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Time trend analysis of rare cancer incidence 2011–2018: Nationwide population-based cancer registries in Japan

Hiromi Sugiyama[1] | Manami Konda[1] | Kumiko Saika[2] | Tomohiro Matsuda[2]

[1]Department of Epidemiology, Radiation Effects Research Foundation, Hiroshima, Japan

[2]Division of International Health Policy Research, Institution for Cancer Control, National Cancer Center, Tokyo, Japan

Correspondence
Hiromi Sugiyama, Department of Epidemiology, Radiation Effects Research Foundation, 5-2 Hijiyama Park, Minami-ku, Hiroshima City, Hiroshima, 732-0815, Japan.
Email: sugi@rerf.or.jp

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Abstract

Rare cancers collectively account for a significant proportion of the overall cancer burden in Japan. We aimed to describe and examine the incidence of each rare cancer and the temporal changes using the internationally agreed rare cancer classification. Cancer cases registered in regional population-based cancer registries from 2011 to 2015 and the National Cancer Registry (NCR) from 2016 to 2018 were classified into 18 families, 68 Tier-1 cancer groupings, and 216 single cancer entities based on the RARECAREnet list. Crude incidence rates and age-standardized incidence rates (ASR) were calculated for Tier-1 and Tier-2 cancers. The annual percent change and the 95% and 99% confidence limits for annual ASR for each of the 68 Tier-1 cancers were estimated using the log-linear regression of the weighted least squares method. The differences in ASRs between 2011 and 2018 were evaluated as an absolute change. A total of 5,640,879 cases were classified into Tier-1 and Tier-2 cancers. The ASRs of 18 out of 52 Tier-1 cancers in the rare cancer families increased, whereas the ASR for epithelial tumors of gallbladder decreased. The ASRs of 6 out of the 16 Tier-1 cancers in the common cancer families increased, whereas those of epithelial tumors of stomach and liver decreased. There was no significant change in the incidence of the other 40 Tier-1 cancers. The incidence of several cancers increased due to the dissemination of diagnostic concepts, improved diagnostic techniques, changes in coding practice, and the initiation of the NCR.

KEYWORDS
incidence, National Cancer Registry, population-based cancer registry, rare cancer, time trend

1 | INTRODUCTION

Since 2012, there has been an impetus on the control of rare cancers in Japan based on the Basic Plan to Cancer Control Program.[1] The cancer incidence statistics based on the PBCRs have been provided according to ICD-10 to ensure comparability with cancer mortality.[2] However, the ICD-10 classification does not include definitions for each rare cancer with a combination of topography and histological type. Thus, there was a paucity of comprehensive epidemiological analyses focusing on rare cancers until around 2010.

Abbreviations: APC, annual percent change; ASR, age-standardized incidence rate; CI, confidence interval; CL, confidence limit; CNS, central nervous system; CR, crude rate; DCO, death certificate only; EU, European Union; FL, follicular lymphoma; GIST, gastrointestinal stromal tumor; HBV, hepatitis B virus; HCV, hepatitis C virus; ICD-10, International Classification of Diseases, 10th Revision; ICD-O-3, International Classification of Disease for Oncology, 3rd Edition; MDS, myelodysplastic syndrome; MI, mortality incidence; NCR, National Cancer Registry; NET, neuroendocrine tumor; NOS, not otherwise specified; PBCR, population-based cancer registry; PNET, pancreatic neuroendocrine tumor; SEER, Surveillance Epidemiology and End Results.

The RARECARE, the rare cancer network project in the EU, developed the RARECARE list to classify all cancers and measured the burden of rare cancers diagnosed between 1988 and 2002 in the EU in 2011.[3] Subsequently, a study published in 2014 investigated the incidence of rare cancer in Japan between 1998 and 2007 based on the data from 12 PBCRs using the RARECARE list.[4] The RARECAREnet was the second project of the RARECARE, which evaluated the burden and centralized treatment in the EU using the RARECAREnet list.[5,6] Accordingly, the RARECAREnet Asia team reported the rare cancer incidence between 2011 and 2015 and compared the rates among Japan, Korea, Taiwan, and the EU in 2020.[7] They also verified the usefulness of the RARECAREnet list for the analysis of the Japanese PBCR data and confirmed the data quality using the same methods as the RARECAREnet. Recently, we published the Rare Cancer Data Book based on the PBCRs in Japan,[8] which describes the epidemiology of the incidence of both rare and common cancers by age, time, and geography based on the high-quality PBCRs and the latest NCR data in Japan.

This study aimed to undertake a comprehensive analysis of the time trend of the incidence of rare and common cancers and to examine the factors that impacted the incidence trend of each rare cancer, adding a more detailed discussion on the Rare Cancer Data Book.[8]

2 | METHODS

2.1 | Population-based regional cancer registries and the NCR in Japan

In Japan, 46 of the 47 prefectures operationalized their respective regional PBCR in 2011 under the Health Promotion Act and the Cancer Control Act. The Cancer Registry Promotion Act was promulgated in 2016, and the NCR, a nationwide PBCR covering a population of 126,933,000, was initiated. The NCR requires mandatory reporting of information regarding cancer patients by all hospitals and designated clinics to the National Cancer Center through the regional cancer registry office (i.e., personal information, cancer diagnosis, extent of disease, treatment, and vital status). The vital status and cause of death obtained from the local municipalities are registered in the centralized NCR database. Cancer patients are identified using personal information (e.g., name, date of birth, sex, address) in the database. For the cases initiated to register by death certificate (death certificate initiated [DCI]), the regional cancer registry offices carry out a follow-back survey of the hospitals that have diagnosed the cause of death. All cancers are coded using ICD-O-3 and summarized using the international rules for multiple primary cancers of the International Association of Cancer Registries/IARC.

2.2 | Definition of rare and common cancers

The RARECAREnet list was used to group all cancer cases.[3] In brief, the list is organized into three tiers: the bottom tier (Tier-3) includes pathological cancer entities corresponding to ICD-O-3 morphological codes (ICD-O-3-M), which are grouped into Tier-2 as "cancer entities" with a clinical and pathological meaning. Based on the PBCRs covered by the EUROCARE study, Tier-2 cancer with a CR of ≤6/100,000 was regarded as a "rare cancer." Tier-2 cancer entities and cases for which the morphology was NOS are grouped into Tier-1, which corresponds to "cancer grouping" with organizational importance (e.g., to describe epidemiological features of each cancer). Finally, 52 Tier-1 cancer groupings (hereinafter referred to as "Tier-1 cancer") with CR of ≤6/100,000 are grouped into 12 families of rare cancers, and 16 other Tier-1 cancers with CR of >6/100,000 are grouped into six families of common cancers, as proposed by the EU Joint Action on Rare Cancers.[3] Although the rarity of cancer varies depending on the area, race, and country, most rare cancers are consistent across Europe and Japan.[7] We used 52 Tier-1 cancers included in the 12 rare cancer families as "rare cancer" and 16 Tier-1 cancers included in the 6 common cancer families as "common cancer," to ensure the comparability with the incidence of each cancer among EU and Asian countries and in the time trend analyses, too.[7]

2.3 | Patients, quality indicators, and population

We obtained data pertaining to patients diagnosed with a primary malignancy (ICD-O-3, behavior: 3) between 2011 and 2015 and registered in the prefectural PBCRs and those registered in the NCR from 2016 to 2018. Data by year of diagnosis and prefecture satisfied the good criteria (MI ratio <0.45 and the proportion of cases registered by DCO <10%) and were selected. Then, cases for analysis were assessed using qualitative measures to examine the accuracy of pathological diagnosis and coding (details in Appendix S1). We used the total population by year, 5-year age group (0–4, 5–9, ..., 85+), and prefecture estimated by the Statistics Bureau of Japan using the National Census (e-stat: https://www.e-stat.go.jp/). The total population for Japan and for each prefecture were the sum of the population in each of the age groups.

2.4 | Statistical analysis

All cases were grouped into 68 Tier-1 cancers and 216 Tier-2 cancers. The number of incident cases, CRs, and ASRs per 100,000 population standardized for the Japanese 1985 model population and Segi's world standard population were calculated for 68 Tier-1 cancers and 216 Tier-2 cancers by 2011–2015, 2016–2018, and over the study period. The logarithmic APCs of the ASRs adjusted for the Japanese model population in 68 Tier-1 cancers from 2011 to 2018 were estimated using a weighted least squares regression. The 95% and 99% CIs of APCs were calculated as the standard error of APC ±2.447 and ±3.707, respectively, following *t*-distribution (degrees of freedom: 6). The funnel plot of the APCs for the 68 Tier-1 cancers were plotted with precision as the inverse of standard errors of the APCs. The significant increase or decrease of each APC was decided based on whether the APC was beyond the 99% CLs of the funnel plot. The difference in the ASRs for each of the 68 Tier-1 cancers between 2011 and 2018 was also calculated to examine the absolute changes in the ASRs.

SEER*Stat version 8.4.0.1 (https://seer.cancer.gov/seerstat), SAS version 9.4 (SAS Institute Inc.), and Microsoft Excel 365 (Microsoft Corporation) were used for all analyses and data visualization.

3 | RESULTS

3.1 | Data quality

Data pertaining to 7,331,235 primary malignancies registered in 46 out of the 47 prefectural PBCRs (2011–2015) and the NCR (2016–2018) were obtained. After excluding the cases that were not residents of Japan or for whom the address was unknown, the data quality for 7,327,422 cases was assessed. We selected the 5,705,916 cases diagnosed from 2011 to 2015, which satisfied the criteria (MI ratio <0.45 and DCO% <10%) with accurate ICD-O-3 coding from 16 prefectural PBCRs (Miyagi, Yamagata, Gunma, Niigata, Fukui, Nagano, Aichi, Shiga, Osaka, Tottori, Shimane, Hiroshima, Yamaguchi, Kagawa, Nagasaki, and Kumamoto) covering a population of 38,300,000 in 2011 to 42 prefectural PBCRs (Hokkaido, Aomori, Iwate, Miyagi, Akita, Yamagata, Fukushima, Ibaraki, Tochigi, Gunma, Saitama, Chiba, Tokyo, Kanagawa, Niigata, Ishikawa, Fukui, Yamanashi, Nagano, Gifu, Shizuoka, Aichi, Mie, Shiga, Kyoto, Osaka, Hyogo, Nara, Wakayama, Tottori, Shimane, Hiroshima, Yamaguchi, Tokushima, Kagawa, Ehime, Fukuoka, Saga, Kumamoto, Oita, Kagoshima, and Okinawa) covering a population of 120,893,000 in 2015. All cases from the NCR covering the whole population (average population: 126,704,333 during 2016–2018) were selected because the quality of data from PBCRs of all prefectures was satisfactory over the period (Tables S1 and S2). Overall, the data quality for all indicators was satisfactory in both periods (2011–2015 and 2016–2018) and improved over time (i.e., MI ratio: 0.412–0.374; proportion of DCO: 5.44%–2.34%; proportion of MV: 84.3%–86.5%) (Table 1). Finally, according to the RARECAREnet list, 5,640,879 cancers (98.9%) were classified as Tier-1 cancers. Other 65,037 cancers (1.1%), such as topography NOS cases and cases with a biologically implausible combination of topography and morphology, could not be classified as Tier-1.

3.2 | Age-standardized incidence rates by Tier-1 cancer grouping and Tier-2 cancer

The number of cases, CRs, and ASRs by Tier-1 and Tier-2 cancer by period are shown in Table 2. Of the 5,640,879 cancer cases, 1,059,541 cases (18.8%) and 4,581,338 cases (81.2%) were classified into 52 Tier-1 cancers in the rare cancer families and 16 Tier-1 cancers in common cancer families, respectively.

Over the observation period from 2011 to 2018, the CRs of most Tier-1 cancers were lower than 6/100,000 in the rare cancer families (Table 2). However, the CRs of epithelial tumors of the hypopharynx and larynx (7.44/100,000), oral cavity and lip (7.20/100,000), gallbladder and extrahepatic biliary tract (17.96/100,000), pelvis and ureter (6.39/100,000), thyroid gland (12.64/100,000), lymphoid diseases (34.01/100,000), and myelodysplastic syndrome and myelodysplastic/myeloproliferative diseases (7.33/100,000) were higher than 6/100,000. In the common cancer families, the ASRs of all Tier-1 cancers were higher than 6/100,000.

TABLE 1 Number of cases, person-years, and quality indicators by period (2011-2015 and 2016-2018).

	2011–2015	2016–2018
PBCR system	Regional	National
Number of prefectures	16–42	47
Number of cases	2,709,099	2,996,817
Person-years	387,815,000	380,113,000
MI ratio	0.412	0.374
DCO (%)	5.44	2.43
Autopsy only (%)	0.045	0.054
MV (%)	84.3	86.5
Morphology NOS (%)	16.3	14.2
Topography NOS (%)	0.24	0.20
Not classified into Tier-1	1.19	1.10

Note: Cases are all malignant (ICD-O-3] behavior: 3). Morphology not otherwise specified (NOS): ICD-O-3-M: 8000: 8001, 8010 (solid cancer); 9590, 9591, 9760, 9800, 9801, 9820, 9860, 9989 (hematological cancer). Topography NOS: ICD-O-3-T: C14.0, C14.8, C26.0, C26.8, C26.9, C39.0, C39.8, C39.9, C55.9, C57.7, C57.8, C57.9, C63.2, C63.8, C63.9, C68.8, C68.9, C75.2, C75.4, C75.5, C75.8, C75.9, C76.0–C76.8.

Abbreviations: DCO, death certificate only; MI, mortality incidence; MV, microscopically verified; PBCR, population-based cancer registry.

3.3 | Time trend of ASRs of whole rare cancer families and whole common cancer families

The ASR of whole rare cancer families progressively increased from 70.4/100,000 in 2011 to 84.2/100,000 in 2018 (APC=3.50%; 95% CI, 2.25%–4.76%). The ASR of whole common cancer families decreased from 289.9/100,000 in 2011 to 287.2/100,000 in 2014. Then the rate showed an abrupt increase to 316.8/100,000 in 2016 followed by a decrease to 301.0/100,000 in 2018 (APC=1.2%; 95% CI, −0.1% to 2.51%) (Figure 1). The proportion of whole rare cancer families showed a slight increase from 18.2% in 2011 to 19.6% in 2018 (Figure 2).

3.4 | Relative change of ASRs between 2011 and 2018 for each Tier-1 cancer

Of the 52 Tier-1 cancers in 12 rare cancer families, the ASRs of 18 Tier-1 cancers increased, whereas the ASR of epithelial tumors of

TABLE 2 Number of rare cancer cases in Japan, crude rates, age-standardized incidence rates (ASRs) by RARECAREnet list Tier-1 cancer grouping and Tier-2 cancer by period (2011–2015 and 2016–2018).

			2011–2015			
			Person-years: 387,815,000			
Family	Tier	RARECAREnet list	Number of cases	Crude rate	ASR Japanese population[a]	ASR World population[b]
Head and neck	**1**	**Epithelial tumors of nasal cavity and sinuses**	**3655**	**0.94**	**0.52**	**0.39**
	2	Squamous cell carcinoma with variants of nasal cavity and sinuses	2854	0.74	0.43	0.32
	2	Lymphoepithelial carcinoma of nasal cavity and sinuses	6	0.00	0.00	0.00
	2	Undifferentiated carcinoma of nasal cavity and sinuses	77	0.02	0.01	0.01
	2	Intestinal type adenocarcinoma of nasal cavity and sinuses	5	0.00	0.00	0.00
	1	**Epithelial tumors of nasopharynx**	**2127**	**0.55**	**0.38**	**0.30**
	2	Squamous cell carcinoma with variants of nasopharynx	1691	0.44	0.31	0.24
	2	Papillary adenocarcinoma of nasopharynx	7	0.00	0.00	0.00
	1	**Epithelial tumors of major salivary glands and salivary gland type tumors**	**6519**	**1.68**	**1.07**	**0.83**
	2	Epithelial tumor of major salivary glands	4676	1.21	0.77	0.60
	2	Salivary gland type tumor of head and neck	1843	0.48	0.30	0.23
	1	**Epithelial tumors of hypopharynx and larynx**	**27,324**	**7.05**	**3.68**	**2.66**
	2	Squamous cell carcinoma with variants of hypopharynx	10,611	2.74	1.51	1.11
	2	Squamous cell carcinoma with variants of larynx	14,454	3.73	1.92	1.38
	1	**Epithelial tumors of oropharynx**	**9784**	**2.52**	**1.48**	**1.11**
	2	Squamous cell carcinoma with variants of oropharynx	8986	2.32	1.38	1.03
	1	**Epithelial tumors of oral cavity and lip**	**25,444**	**6.56**	**3.55**	**2.60**
	2	Squamous cell carcinoma with variants of oral cavity	22,601	5.83	3.27	2.40
	2	Squamous cell carcinoma with variants of lip	409	0.11	0.04	0.03
	1	**Epithelial tumors of eye and adnexa**	**336**	**0.09**	**0.05**	**0.04**
	2	Squamous cell carcinoma with variants of eye and adnexa	143	0.04	0.02	0.01
	2	Adenocarcinoma with variants of eye and adnexa	121	0.03	0.02	0.02
	1	**Epithelial tumors of middle ear**	**94**	**0.02**	**0.01**	**0.01**
	2	Squamous cell carcinoma with variants of middle ear	71	0.02	0.01	0.01
	2	Adenocarcinoma with variants of middle ear	10	0.00	0.00	0.00
Digestive (rare)	**1**	**Epithelial tumors of small intestine**	**7227**	**1.86**	**0.96**	**0.69**
	2	Adenocarcinoma with variants of small intestine	6004	1.55	0.84	0.61
	2	Squamous cell carcinoma with variants of small intestine	25	0.01	0.00	0.00
	1	**Epithelial tumors of anal canal**	**2846**	**0.73**	**0.37**	**0.27**
	2	Squamous cell carcinoma with variants of anal canal	875	0.23	0.13	0.09
	2	Adenocarcinoma with variants of anal canal	1597	0.41	0.21	0.15
	2	Paget's disease of anal canal	20	0.01	0.00	0.00
	1	**Epithelial tumors of gallbladder and extrahepatic biliary tract (EBT)**	**70,165**	**18.09**	**7.15**	**4.78**
	2	Adenocarcinoma with variants of gallbladder	11,874	3.06	1.45	0.99
	2	Adenocarcinoma with variants of EBT	26,992	6.96	3.09	2.09
	2	Squamous cell carcinoma of gallbladder and EBT	259	0.07	0.03	0.02
Thoracic (rare)	**1**	**Epithelial tumors of trachea**	**200**	**0.05**	**0.03**	**0.02**
	2	Squamous cell carcinoma with variants of trachea	83	0.02	0.01	0.01
	2	Adenocarcinoma with variants of trachea	8	0.00	0.00	0.00
	2	Salivary gland type tumor of trachea	74	0.02	0.01	0.01

2016–2018				2011–2018			
Person-years: 380,113,000				Person-years: 767,928,000			
Number of cases	Crude rate	ASR Japanese population[a]	ASR World population[b]	Number of cases	Crude rate	ASR Japanese population[a]	ASR World population[b]
3851	**1.01**	**0.54**	**0.40**	**7506**	**0.98**	**0.53**	**0.39**
3048	0.80	0.45	0.33	5902	0.77	0.44	0.33
3	0.00	0.00	0.00	9	0.00	0.00	0.00
101	0.03	0.02	0.01	178	0.02	0.02	0.01
9	0.00	0.00	0.00	14	0.00	0.00	0.00
2222	**0.58**	**0.40**	**0.31**	**4349**	**0.57**	**0.39**	**0.30**
1779	0.47	0.33	0.26	3470	0.45	0.32	0.25
13	0.00	0.00	0.00	20	0.00	0.00	0.00
7662	**2.02**	**1.27**	**0.99**	**14,181**	**1.85**	**1.17**	**0.91**
5480	1.44	0.90	0.70	10,156	1.32	0.83	0.65
2182	0.57	0.37	0.29	4025	0.52	0.34	0.26
29,795	**7.84**	**3.90**	**2.80**	**57,119**	**7.44**	**3.79**	**2.73**
13,174	3.47	1.84	1.34	23,785	3.10	1.67	1.22
14,406	3.79	1.83	1.30	28,860	3.76	1.88	1.34
12,179	**3.20**	**1.84**	**1.37**	**21,963**	**2.86**	**1.66**	**1.24**
11,298	2.97	1.74	1.29	20,284	2.64	1.56	1.16
29,824	**7.85**	**4.11**	**3.03**	**55,268**	**7.20**	**3.83**	**2.81**
27,029	7.11	3.84	2.84	49,630	6.46	3.55	2.62
488	0.13	0.05	0.03	897	0.12	0.05	0.03
466	**0.12**	**0.07**	**0.05**	**802**	**0.10**	**0.06**	**0.04**
204	0.05	0.03	0.02	347	0.05	0.02	0.02
175	0.05	0.03	0.02	296	0.04	0.02	0.02
88	**0.02**	**0.01**	**0.01**	**182**	**0.02**	**0.01**	**0.01**
64	0.02	0.01	0.00	135	0.02	0.01	0.01
5	0.00	0.00	0.00	15	0.00	0.00	0.00
9254	**2.43**	**1.20**	**0.87**	**16,481**	**2.15**	**1.08**	**0.78**
7958	2.09	1.08	0.79	13,962	1.82	0.96	0.70
28	0.01	0.00	0.00	53	0.01	0.00	0.00
3204	**0.84**	**0.42**	**0.30**	**6050**	**0.79**	**0.39**	**0.28**
1065	0.28	0.15	0.11	1940	0.25	0.14	0.10
1819	0.48	0.24	0.17	3416	0.44	0.22	0.16
14	0.00	0.00	0.00	34	0.00	0.00	0.00
67,723	**17.82**	**6.53**	**4.38**	**137,888**	**17.96**	**6.84**	**4.58**
12,880	3.39	1.48	1.02	24,754	3.22	1.47	1.00
29,917	7.87	3.20	2.15	56,909	7.41	3.15	2.12
265	0.07	0.03	0.02	524	0.07	0.03	0.02
267	**0.07**	**0.04**	**0.03**	**467**	**0.06**	**0.03**	**0.03**
91	0.02	0.01	0.01	174	0.02	0.01	0.01
16	0.00	0.00	0.00	24	0.00	0.00	0.00
91	0.02	0.02	0.01	165	0.02	0.02	0.01

(Continues)

TABLE 2 (Continued)

Family	Tier	RARECAREnet list	2011–2015 Person-years: 387,815,000 Number of cases	Crude rate	ASR Japanese population[a]	ASR World population[b]
	1	**Epithelial tumors of thymus**	**3618**	**0.93**	**0.61**	**0.46**
	2	Malignant thymoma	2547	0.66	0.45	0.34
	2	Squamous cell carcinoma of thymus	689	0.18	0.11	0.08
	2	Adenocarcinoma with variants of thymus	100	0.03	0.02	0.01
	1	**Malignant mesothelioma**	**5072**	**1.31**	**0.63**	**0.45**
	2	Mesothelioma of pleura and pericardium	4412	1.14	0.55	0.38
	2	Mesothelioma of peritoneum and tunica vaginalis	453	0.12	0.07	0.05
Female genital (rare)	**1**	**Nonepithelial tumors of ovary**	**1159**	**0.30**	**0.36**	**0.38**
	2	Sex cord tumor of ovary	129	0.03	0.03	0.02
	2	Malignant/immature teratoma of ovary	614	0.16	0.19	0.20
	2	Germ cell tumor of ovary	416	0.11	0.14	0.16
	1	**Epithelial tumors of vulva and vagina**	**3288**	**0.85**	**0.37**	**0.26**
	2	Squamous cell carcinoma with variants of vulva and vagina	2063	0.53	0.24	0.17
	2	Adenocarcinoma with variants of vulva and vagina	187	0.05	0.03	0.02
	2	Paget's disease of vulva and vagina	782	0.20	0.08	0.06
	2	Undifferentiated carcinoma of vulva and vagina	2	0.00	0.00	0.00
	2	Mullerian mixed tumor of vulva and vagina	2	0.00	0.00	0.00
	1	**Trophoblastic tumors of placenta**	**148**	**0.04**	**0.04**	**0.04**
	2	Choriocarcinoma of placenta	128	0.03	0.04	0.03
Male genital and urogenital (rare)	**1**	**Testicular and paratesticular cancers**	**5600**	**1.44**	**1.64**	**1.43**
	2	Paratesticular adenocarcinoma with variants	12	0.00	0.00	0.00
	2	Nonseminomatous testicular cancer	1537	0.40	0.50	0.47
	2	Seminomatous testicular cancer	3786	0.98	1.08	0.90
	2	Spermatocytic seminoma	22	0.01	0.00	0.00
	2	Teratoma with malignant transformation	11	0.00	0.00	0.00
	2	Testicular sex cord cancer	15	0.00	0.00	0.00
	1	**Epithelial tumors of penis**	**1474**	**0.38**	**0.17**	**0.12**
	2	Squamous cell carcinoma with variants of penis	1027	0.26	0.13	0.09
	2	Adenocarcinoma with variants of penis	325	0.08	0.04	0.02
	1	**Epithelial tumors of pelvis and ureter**	**22,877**	**5.90**	**2.52**	**1.69**
	2	Transitional cell carcinoma of pelvis and ureter	16,426	4.24	1.94	1.32
	2	Squamous cell carcinoma with variants of pelvis and ureter	320	0.08	0.04	0.03
	2	Adenocarcinoma with variants of pelvis and ureter	201	0.05	0.03	0.02
	1	**Epithelial tumors of urethra**	**480**	**0.12**	**0.06**	**0.04**
	2	Transitional cell carcinoma of urethra	218	0.06	0.02	0.02
	2	Squamous cell carcinoma with variants of urethra	86	0.02	0.01	0.01
	2	Adenocarcinoma with variants of urethra	108	0.03	0.01	0.01
	1	**Extragonadal germ cell tumors**	**1026**	**0.26**	**0.35**	**0.40**
	2	Nonseminomatous germ cell tumor	325	0.08	0.10	0.11
	2	Seminomatous germ cell tumor	121	0.03	0.04	0.04
	2	Germ cell tumor of CNS	474	0.12	0.18	0.22

2016–2018				2011–2018			
Person-years: 380,113,000				Person-years: 767,928,000			
Number of cases	Crude rate	ASR Japanese population[a]	ASR World population[b]	Number of cases	Crude rate	ASR Japanese population[a]	ASR World population[b]
5725	**1.51**	**0.98**	**0.75**	**9343**	**1.22**	**0.80**	**0.61**
4166	1.10	0.76	0.58	6713	0.87	0.60	0.46
979	0.26	0.15	0.11	1668	0.22	0.13	0.10
114	0.03	0.02	0.01	214	0.03	0.02	0.01
5337	**1.40**	**0.63**	**0.44**	**10,409**	**1.36**	**0.63**	**0.44**
4678	1.23	0.54	0.38	9090	1.18	0.55	0.38
464	0.12	0.07	0.05	917	0.12	0.07	0.05
1330	**0.35**	**0.44**	**0.45**	**2489**	**0.32**	**0.40**	**0.41**
183	0.05	0.04	0.03	312	0.04	0.03	0.03
691	0.18	0.23	0.24	1305	0.17	0.21	0.22
456	0.12	0.17	0.18	872	0.11	0.16	0.17
3650	**0.96**	**0.40**	**0.28**	**6938**	**0.90**	**0.39**	**0.27**
2351	0.62	0.26	0.18	4414	0.57	0.25	0.18
229	0.06	0.03	0.03	416	0.05	0.03	0.02
793	0.21	0.08	0.06	1575	0.21	0.08	0.06
6	0.00	0.00	0.00	8	0.00	0.00	0.00
7	0.00	0.00	0.00	9	0.00	0.00	0.00
141	**0.04**	**0.05**	**0.04**	**289**	**0.04**	**0.05**	**0.04**
134	0.04	0.04	0.04	262	0.03	0.04	0.04
6285	**1.65**	**1.90**	**1.66**	**11,885**	**1.55**	**1.77**	**1.54**
3	0.00	0.00	0.00	15	0.00	0.00	0.00
1704	0.45	0.57	0.55	3241	0.42	0.53	0.51
4296	1.13	1.26	1.05	8082	1.05	1.17	0.97
26	0.01	0.00	0.00	48	0.01	0.00	0.00
11	0.00	0.00	0.00	22	0.00	0.00	0.00
12	0.00	0.00	0.00	27	0.00	0.00	0.00
1624	**0.43**	**0.19**	**0.13**	**3098**	**0.40**	**0.18**	**0.12**
1125	0.30	0.14	0.09	2152	0.28	0.13	0.09
350	0.09	0.04	0.03	675	0.09	0.04	0.02
26,194	**6.89**	**2.68**	**1.79**	**49,071**	**6.39**	**2.60**	**1.74**
19,038	5.01	2.12	1.43	35,464	4.62	2.04	1.38
287	0.08	0.03	0.02	607	0.08	0.03	0.02
203	0.05	0.03	0.02	404	0.05	0.03	0.02
549	**0.14**	**0.06**	**0.04**	**1029**	**0.13**	**0.06**	**0.04**
284	0.07	0.03	0.02	502	0.07	0.03	0.02
95	0.02	0.01	0.01	181	0.02	0.01	0.01
99	0.03	0.01	0.01	207	0.03	0.01	0.01
1237	**0.33**	**0.44**	**0.50**	**2263**	**0.29**	**0.39**	**0.45**
375	0.10	0.12	0.14	700	0.09	0.11	0.12
143	0.04	0.04	0.04	264	0.03	0.04	0.04
607	0.16	0.24	0.29	1081	0.14	0.21	0.25

(Continues)

TABLE 2 (Continued)

Family	Tier	RARECAREnet list	2011–2015 Person-years: 387,815,000 Number of cases	Crude rate	ASR Japanese population[a]	ASR World population[b]
Skin (rare)	**1**	**Malignant melanoma of mucosa and extracutaneous**	**1463**	**0.38**	**0.18**	**0.13**
	2	Malignant melanoma of mucosa and extracutaneous	1463	0.38	0.18	0.13
	1	**Malignant melanoma of eye**	**271**	**0.07**	**0.04**	**0.03**
	2	Malignant melanoma of conjunctiva	52	0.01	0.01	0.01
	2	Malignant melanoma of uvea	202	0.05	0.03	0.03
	1	**Adnexal carcinomas of skin**	**3970**	**1.02**	**0.46**	**0.32**
	2	Adnexal carcinoma of skin	3970	1.02	0.46	0.32
	1	**Kaposi's sarcoma**	**150**	**0.04**	**0.03**	**0.03**
	2	Kaposi's sarcoma	150	0.04	0.03	0.03
Pediatric	**1**	**Neuroblastoma and ganglioneuroblastoma**	**481**	**0.12**	**0.20**	**0.33**
	2	Neuroblastoma and ganglioneuroblastoma	481	0.12	0.20	0.33
	1	**Nephroblastoma**	**152**	**0.04**	**0.06**	**0.10**
	2	Nephroblastoma	152	0.04	0.06	0.10
	1	**Retinoblastoma**	**184**	**0.05**	**0.08**	**0.13**
	2	Retinoblastoma	184	0.05	0.08	0.13
	1	**Hepatoblastoma**	**154**	**0.04**	**0.07**	**0.11**
	2	Hepatoblastoma	154	0.04	0.07	0.11
	1	**Pleuropulmonary blastoma**	**8**	**0.00**	**0.00**	**0.01**
	2	Pleuropulmonary blastoma	8	0.00	0.00	0.01
	1	**Pancreatoblastoma**	**7**	**0.00**	**0.00**	**0.00**
	2	Pancreatoblastoma	7	0.00	0.00	0.00
	1	**Olfactory neuroblastoma**	**245**	**0.06**	**0.05**	**0.04**
	2	Olfactory neuroblastoma	245	0.06	0.05	0.04
	1	**Odontogenic malignant tumors**	**65**	**0.02**	**0.01**	**0.01**
	2	Odontogenic malignant tumor	65	0.02	0.01	0.01
Sarcomas	**1**	**Soft tissue sarcoma**	**17,596**	**4.54**	**3.25**	**2.66**
	2	Soft tissue sarcoma of head and neck	924	0.24	0.15	0.12
	2	Soft tissue sarcoma of limbs	4347	1.12	0.76	0.61
	2	Soft tissue sarcoma of superficial trunk	1750	0.45	0.30	0.25
	2	Soft tissue sarcoma of mediastinum	241	0.06	0.05	0.04
	2	Soft tissue sarcoma of heart	131	0.03	0.03	0.02
	2	Soft tissue sarcoma of breast	609	0.16	0.14	0.11
	2	Soft tissue sarcoma of uterus	2282	0.59	0.46	0.36
	2	Soft tissue sarcoma of paratestis	143	0.04	0.02	0.02
	2	Soft tissue sarcomas of other genitourinary tract (vulva, vagina, ovary, penis, prostate, testis, kidney, renal pelvis, ureter, bladder, urethra)	515	0.13	0.09	0.08
	2	Soft tissue sarcoma of viscera	982	0.25	0.15	0.12
	2	Soft tissue sarcoma of retroperitoneum and peritoneum	2037	0.53	0.34	0.26
	2	Soft tissue sarcoma of pelvis	707	0.18	0.12	0.10
	2	Soft tissue sarcoma of skin	1460	0.38	0.30	0.25
	2	Soft tissue sarcoma of paraorbit	20	0.01	0.01	0.01
	2	Soft tissue sarcoma of brain and other parts of nervous system	474	0.12	0.10	0.09
	2	Embryonal rhabdomyosarcoma of soft tissue	90	0.02	0.03	0.05

2016–2018				2011–2018			
Person-years: 380,113,000				Person-years: 767,928,000			
Number of cases	Crude rate	ASR Japanese population[a]	ASR World population[b]	Number of cases	Crude rate	ASR Japanese population[a]	ASR World population[b]
1541	**0.41**	**0.18**	**0.13**	**3004**	**0.39**	**0.18**	**0.13**
1541	0.41	0.18	0.13	3004	0.39	0.18	0.13
347	**0.09**	**0.06**	**0.05**	**618**	**0.08**	**0.05**	**0.04**
76	0.02	0.01	0.01	128	0.02	0.01	0.01
241	0.06	0.04	0.03	443	0.06	0.04	0.03
4311	**1.13**	**0.49**	**0.34**	**8281**	**1.08**	**0.47**	**0.33**
4311	1.13	0.49	0.34	8281	1.08	0.47	0.33
148	**0.04**	**0.03**	**0.03**	**298**	**0.04**	**0.03**	**0.03**
148	0.04	0.03	0.03	298	0.04	0.03	0.03
495	**0.13**	**0.22**	**0.36**	**976**	**0.13**	**0.21**	**0.35**
495	0.13	0.22	0.36	976	0.13	0.21	0.35
146	**0.04**	**0.07**	**0.11**	**298**	**0.04**	**0.06**	**0.11**
146	0.04	0.07	0.11	298	0.04	0.06	0.11
242	**0.06**	**0.11**	**0.19**	**426**	**0.06**	**0.09**	**0.16**
242	0.06	0.11	0.19	426	0.06	0.09	0.16
161	**0.04**	**0.07**	**0.12**	**315**	**0.04**	**0.07**	**0.12**
161	0.04	0.07	0.12	315	0.04	0.07	0.12
9	**0.00**	**0.00**	**0.01**	**17**	**0.00**	**0.00**	**0.01**
9	0.00	0.00	0.01	17	0.00	0.00	0.01
5	**0.00**	**0.00**	**0.00**	**12**	**0.00**	**0.00**	**0.00**
5	0.00	0.00	0.00	12	0.00	0.00	0.00
368	**0.10**	**0.08**	**0.06**	**613**	**0.08**	**0.06**	**0.05**
368	0.10	0.08	0.06	613	0.08	0.06	0.05
126	**0.03**	**0.03**	**0.02**	**191**	**0.02**	**0.02**	**0.02**
126	0.03	0.03	0.02	191	0.02	0.02	0.02
20,127	**5.30**	**3.71**	**3.03**	**37,723**	**4.91**	**3.48**	**2.84**
1045	0.27	0.16	0.13	1969	0.26	0.16	0.13
5212	1.37	0.90	0.71	9559	1.24	0.83	0.66
2222	0.58	0.40	0.32	3972	0.52	0.35	0.28
228	0.06	0.04	0.03	469	0.06	0.04	0.04
121	0.03	0.03	0.02	252	0.03	0.03	0.02
691	0.18	0.16	0.13	1300	0.17	0.15	0.12
2591	0.68	0.53	0.42	4873	0.63	0.50	0.39
181	0.05	0.03	0.02	324	0.04	0.03	0.02
523	0.14	0.10	0.09	1038	0.14	0.10	0.09
1140	0.30	0.18	0.15	2122	0.28	0.17	0.13
2389	0.63	0.39	0.30	4426	0.58	0.36	0.28
798	0.21	0.14	0.11	1505	0.20	0.13	0.10
1600	0.42	0.32	0.27	3060	0.40	0.31	0.26
29	0.01	0.01	0.01	49	0.01	0.01	0.01
538	0.14	0.11	0.10	1012	0.13	0.11	0.09
111	0.03	0.04	0.06	201	0.03	0.04	0.05

(Continues)

TABLE 2 (Continued)

Family	Tier	RARECAREnet list	2011–2015 Person-years: 387,815,000 Number of cases	Crude rate	ASR Japanese population[a]	ASR World population[b]
	2	Alveolar rhabdomyosarcoma of soft tissue	97	0.03	0.03	0.04
	2	Ewing sarcoma of soft tissue	245	0.06	0.07	0.08
	1	**Bone sarcoma**	**2529**	**0.65**	**0.58**	**0.56**
	2	Osteogenic sarcoma	858	0.22	0.24	0.25
	2	Chondrogenic sarcoma	671	0.17	0.13	0.11
	2	Notochordal sarcoma, chordoma	382	0.10	0.07	0.05
	2	Vascular sarcoma	41	0.01	0.01	0.01
	2	Ewing sarcoma	152	0.04	0.05	0.06
	2	Other high grade sarcomas (fibrosarcoma, malignant fibrous histiocytoma)	100	0.03	0.02	0.01
	1	**Gastrointestinal stromal sarcoma**	**4613**	**1.19**	**0.67**	**0.49**
	2	Gastrointestinal stromal sarcoma	4613	1.19	0.67	0.49
Neuroendocrine	1	**NET GEP**	**15,347**	**3.96**	**2.64**	**2.01**
	2	Well diff not funct endocrine carcinoma of pancreas and digestive tract	10,164	2.62	1.87	1.44
	2	Well diff funct endocrine carcinoma of pancreas and digestive tract	93	0.02	0.02	0.01
	2	Poorly differentiated endocrine carcinoma	5040	1.30	0.74	0.55
	2	Malignant mixed pancreatic endocrine and exocrine tumor	50	0.01	0.01	0.01
	1	**NET lung**	**870**	**0.22**	**0.15**	**0.12**
	2	Typical and atypical carcinoid of the lung	870	0.22	0.15	0.12
	1	**NET other sites**	**4321**	**1.11**	**0.68**	**0.51**
	2	Pheochromocytoma, malignant	149	0.04	0.03	0.02
	2	Paraganglioma	74	0.02	0.02	0.01
	2	Endocrine carcinoma of thyroid gland	462	0.12	0.09	0.08
	2	Neuroendocrine carcinoma of skin	568	0.15	0.05	0.03
	2	Neuroendocrine carcinoma of other sites	3068	0.79	0.49	0.37
Endocrine organ	1	**Carcinomas of pituitary gland**	**229**	**0.06**	**0.04**	**0.04**
	2	Carcinoma of pituitary gland	229	0.06	0.04	0.04
	1	**Carcinomas of thyroid gland**	**42,609**	**10.99**	**8.14**	**6.44**
	2	Carcinoma of thyroid gland	42,609	10.99	8.14	6.44
	1	**Carcinomas of parathyroid gland**	**77**	**0.02**	**0.01**	**0.01**
	2	Carcinoma of parathyroid gland	77	0.02	0.01	0.01
	1	**Carcinomas of adrenal cortex**	**584**	**0.15**	**0.09**	**0.07**
	2	Carcinoma of adrenal cortex	584	0.15	0.09	0.07
CNS	1	**Tumors of CNS**	**15,595**	**4.02**	**2.76**	**2.35**
	2	Astrocytic tumors of CNS	10,165	2.62	1.89	1.60
	2	Oligodendroglial tumors of CNS	766	0.20	0.18	0.15
	2	Ependymal tumors of CNS	454	0.12	0.13	0.15
	2	Neuronal and mixed neuronal-glial tumors	20	0.01	0.00	0.00
	2	Choroid plexus carcinoma of CNS	16	0.00	0.01	0.01
	2	Malignant meningiomas	752	0.19	0.10	0.08
	2	Tumors of the pineal gland	99	0.03	0.03	0.03
	1	**Embryonal tumors of CNS**	**364**	**0.09**	**0.14**	**0.20**
	2	Embryonal tumor of CNS	364	0.09	0.14	0.20
	2	Medulloepithelioma	0	0.00	0.00	0.00

2016–2018				2011–2018			
Person-years: 380,113,000				Person-years: 767,928,000			
Number of cases	Crude rate	ASR Japanese population[a]	ASR World population[b]	Number of cases	Crude rate	ASR Japanese population[a]	ASR World population[b]
94	0.02	0.03	0.04	191	0.02	0.03	0.04
236	0.06	0.07	0.07	481	0.06	0.07	0.07
2958	**0.78**	**0.69**	**0.65**	**5487**	**0.71**	**0.63**	**0.60**
875	0.23	0.26	0.27	1733	0.23	0.25	0.26
778	0.20	0.16	0.13	1449	0.19	0.15	0.12
472	0.12	0.09	0.07	854	0.11	0.08	0.06
72	0.02	0.01	0.01	113	0.01	0.01	0.01
161	0.04	0.06	0.07	313	0.04	0.06	0.07
97	0.03	0.02	0.01	197	0.03	0.02	0.01
4475	**1.18**	**0.66**	**0.49**	**9088**	**1.18**	**0.67**	**0.49**
4475	1.18	0.66	0.49	9088	1.18	0.67	0.49
22,323	**5.87**	**3.89**	**2.97**	**37,670**	**4.91**	**3.26**	**2.48**
17,328	4.56	3.22	2.48	27,492	3.58	2.54	1.96
56	0.01	0.01	0.01	149	0.02	0.01	0.01
4889	1.29	0.66	0.47	9929	1.29	0.70	0.51
50	0.01	0.01	0.00	100	0.01	0.01	0.01
1091	**0.29**	**0.19**	**0.14**	**1961**	**0.26**	**0.17**	**0.13**
1091	0.29	0.19	0.14	1961	0.26	0.17	0.13
5468	**1.44**	**0.88**	**0.67**	**9789**	**1.27**	**0.78**	**0.59**
415	0.11	0.09	0.07	564	0.07	0.06	0.05
160	0.04	0.03	0.03	234	0.03	0.03	0.02
638	0.17	0.14	0.11	1100	0.14	0.11	0.09
692	0.18	0.06	0.04	1260	0.16	0.05	0.04
3563	0.94	0.56	0.42	6631	0.86	0.52	0.39
205	**0.05**	**0.04**	**0.03**	**434**	**0.06**	**0.04**	**0.04**
205	0.05	0.04	0.03	434	0.06	0.04	0.04
54,419	**14.32**	**10.83**	**8.61**	**97,028**	**12.64**	**9.47**	**7.51**
54,419	14.32	10.83	8.61	97,028	12.64	9.47	7.51
119	**0.03**	**0.02**	**0.02**	**196**	**0.03**	**0.02**	**0.01**
119	0.03	0.02	0.02	196	0.03	0.02	0.01
641	**0.17**	**0.10**	**0.09**	**1225**	**0.16**	**0.10**	**0.08**
641	0.17	0.10	0.09	1225	0.16	0.10	0.08
17,099	**4.50**	**3.14**	**2.69**	**32,694**	**4.26**	**2.95**	**2.52**
10,758	2.83	2.04	1.73	20,923	2.72	1.96	1.66
1017	0.27	0.26	0.21	1783	0.23	0.22	0.18
605	0.16	0.17	0.18	1059	0.14	0.15	0.17
14	0.00	0.00	0.00	34	0.00	0.00	0.00
10	0.00	0.00	0.00	26	0.00	0.00	0.01
855	0.22	0.12	0.09	1607	0.21	0.11	0.08
141	0.04	0.04	0.04	240	0.03	0.04	0.04
367	**0.10**	**0.14**	**0.20**	**731**	**0.10**	**0.14**	**0.20**
367	0.10	0.14	0.20	731	0.10	0.14	0.20
0	0.00	0.00	0.00	0	0.00	0.00	0.00

(Continues)

TABLE 2 (Continued)

Family	Tier	RARECAREnet list	2011–2015 Person-years: 387,815,000 Number of cases	Crude rate	ASR Japanese population[a]	ASR World population[b]
Hematological	1	**Lymphoid diseases**	**120,860**	**31.16**	**17.33**	**13.37**
	2	Hodgkin lymphoma, classical	3671	0.95	0.75	0.65
	2	Hodgkin lymphoma nodular lymphocyte predominance	207	0.05	0.04	0.04
	2	Precursor B/T lymphoblastic leukemia/lymphoma (and Burkitt leukemia/lymphoma)	6139	1.58	1.63	1.89
	2	T cutaneous lymphoma (Sezary syndrome, mycosis fungoides)	1465	0.38	0.24	0.19
	2	Other T cell lymphomas and NK cell neoplasms	10,201	2.63	1.50	1.14
	2	Diffuse B lymphoma	38,131	9.83	5.12	3.68
	2	Follicular B lymphoma	12,639	3.26	2.10	1.59
	2	Hairy cell leukemia	161	0.04	0.02	0.02
	2	Plasmacytoma/multiple myeloma (and heavy chain diseases)	20,004	5.16	2.41	1.67
	2	Other non-Hodgkin, mature B cell lymphoma	12,588	3.25	1.84	1.34
	2	Mantle cell lymphoma	1606	0.41	0.21	0.15
	2	Prolymphocytic leukemia, B cell	52	0.01	0.01	0.01
	1	**Acute myeloid leukemia and related precursor neoplasms**	**18,827**	**4.85**	**3.03**	**2.50**
	2	Acute promyelocytic leukemia (AML with t(15;17) with variants)	1503	0.39	0.31	0.26
	2	Acute myeloid leukemia	17,324	4.47	2.72	2.24
	1	**Myeloid and lymphoid neoplasms**	**869**	**0.22**	**0.09**	**0.06**
	2	Myeloid and lymphoid neoplasms	869	0.22	0.09	0.06
	1	**Myeloproliferative neoplasms**	**12,862**	**3.32**	**2.12**	**1.65**
	2	Chronic myeloid leukemia	5634	1.45	1.04	0.84
	2	Other myeloproliferative neoplasms	7225	1.86	1.08	0.81
	2	Mast cell tumor	3	0.00	0.00	0.00
	1	**Myelodysplastic syndrome and myelodysplastic/ myeloproliferative diseases**	**26,137**	**6.74**	**2.93**	**2.07**
	2	Myelodysplastic syndrome with 5q syndrome	114	0.03	0.01	0.01
	2	Other myelodysplastic syndrome	24,702	6.37	2.75	1.93
	2	Chronic myelomonocytic leukemia	1139	0.29	0.14	0.12
	2	Atypical chronic myeloid leukemia BCR/ABL negative	83	0.02	0.01	0.01
	1	**Histiocytic and dendritic cell neoplasms**	**308**	**0.08**	**0.09**	**0.11**
	2	Histiocytic malignancies	202	0.05	0.07	0.10
	2	Lymph node accessory cell tumors	106	0.03	0.02	0.02
Digestive (common)	1	**Epithelial tumors of esophagus**	**66,991**	**17.27**	**8.93**	**6.43**
	2	Squamous cell carcinoma with variants of esophagus	55,699	14.36	7.57	5.47
	2	Adenocarcinoma with variants of esophagus	3766	0.97	0.53	0.39
	2	Salivary gland type tumor of esophagus	42	0.01	0.01	0.00
	2	Undifferentiated carcinoma of esophagus	94	0.02	0.01	0.01
	1	**Epithelial tumors of stomach**	**388,958**	**100.29**	**47.64**	**33.28**
	2	Adenocarcinoma with variants of stomach	345,059	88.98	43.66	30.61
	2	Squamous cell carcinoma with variants of stomach	615	0.16	0.08	0.06
	2	Salivary gland-type tumor of stomach	9	0.00	0.00	0.00
	2	Undifferentiated carcinoma of stomach	293	0.08	0.03	0.02

2016–2018				2011–2018			
Person-years: 380,113,000				Person-years: 767,928,000			
Number of cases	Crude rate	ASR Japanese population[a]	ASR World population[b]	Number of cases	Crude rate	ASR Japanese population[a]	ASR World population[b]
140,329	**36.92**	**19.50**	**15.03**	**261,189**	**34.01**	**18.41**	**14.20**
4189	1.10	0.83	0.70	7860	1.02	0.79	0.67
228	0.06	0.05	0.05	435	0.06	0.05	0.04
6506	1.71	1.79	2.09	12,645	1.65	1.71	1.99
1839	0.48	0.30	0.24	3304	0.43	0.27	0.21
11,402	3.00	1.61	1.21	21,603	2.81	1.55	1.17
44,022	11.58	5.68	4.08	82,153	10.70	5.40	3.88
16,041	4.22	2.52	1.90	28,680	3.73	2.31	1.74
177	0.05	0.03	0.02	338	0.04	0.03	0.02
21,903	5.76	2.55	1.77	41,907	5.46	2.48	1.72
16,556	4.36	2.39	1.74	29,144	3.80	2.11	1.54
1870	0.49	0.24	0.17	3476	0.45	0.22	0.16
49	0.01	0.01	0.01	101	0.01	0.01	0.01
19,416	**5.11**	**3.09**	**2.56**	**38,243**	**4.98**	**3.06**	**2.53**
1836	0.48	0.39	0.32	3339	0.43	0.35	0.29
17,580	4.62	2.71	2.25	34,904	4.55	2.71	2.24
1592	**0.42**	**0.18**	**0.15**	**2461**	**0.32**	**0.13**	**0.11**
1592	0.42	0.18	0.15	2461	0.32	0.13	0.11
19,425	**5.11**	**3.18**	**2.46**	**32,287**	**4.20**	**2.65**	**2.05**
7320	1.93	1.34	1.07	12,954	1.69	1.19	0.96
12,095	3.18	1.83	1.38	19,320	2.52	1.45	1.09
10	0.00	0.00	0.00	13	0.00	0.00	0.00
30,160	**7.93**	**3.24**	**2.27**	**56,297**	**7.33**	**3.08**	**2.17**
257	0.07	0.03	0.02	371	0.05	0.02	0.01
27,876	7.33	2.96	2.06	52,578	6.85	2.86	1.99
1286	0.34	0.16	0.13	2425	0.32	0.15	0.12
131	0.03	0.02	0.01	214	0.03	0.01	0.01
611	**0.16**	**0.21**	**0.28**	**919**	**0.12**	**0.15**	**0.19**
503	0.13	0.19	0.26	705	0.09	0.13	0.18
108	0.03	0.02	0.01	214	0.03	0.02	0.02
76,268	**20.06**	**9.92**	**7.09**	**143,259**	**18.66**	**9.43**	**6.76**
65,390	17.20	8.59	6.15	121,089	15.77	8.08	5.81
5415	1.42	0.77	0.57	9181	1.20	0.65	0.48
22	0.01	0.00	0.00	64	0.01	0.00	0.00
66	0.02	0.01	0.01	160	0.02	0.01	0.01
387,959	**102.06**	**45.06**	**31.28**	**776,917**	**101.17**	**46.38**	**32.30**
358,844	94.40	42.68	29.68	703,903	91.66	43.21	30.18
842	0.22	0.10	0.07	1457	0.19	0.09	0.06
7	0.00	0.00	0.00	16	0.00	0.00	0.00
441	0.12	0.05	0.04	734	0.10	0.04	0.03

(Continues)

TABLE 2 (Continued)

Family	Tier	RARECAREnet list	2011–2015 Person-years: 387,815,000 Number of cases	Crude rate	ASR Japanese population[a]	ASR World population[b]
	1	**Epithelial tumors of colon (including appendix)**	**305,966**	**78.89**	**38.40**	**27.20**
	2	Adenocarcinoma with variants of colon	262,834	67.77	34.49	24.53
	2	Squamous cell carcinoma with variants of colon	69	0.02	0.01	0.01
	2	Fibromyxoma and low grade mucinous adenocarcinoma of the appendix	968	0.25	0.16	0.12
	1	**Epithelial tumors of rectum**	**100,198**	**25.84**	**13.98**	**10.21**
	2	Adenocarcinoma with variants of rectum	86,153	22.21	12.47	9.17
	2	Squamous cell carcinoma with variants of rectum	127	0.03	0.02	0.01
	1	**Epithelial tumors of pancreas**	**109,115**	**28.14**	**12.74**	**8.86**
	2	Adenocarcinoma with variants of pancreas	50,093	12.92	6.73	4.80
	2	Squamous cell carcinoma with variants of pancreas	158	0.04	0.02	0.02
	2	Acinar cell carcinoma of pancreas	297	0.08	0.05	0.03
	2	Mucinous cystadenocarcinoma of pancreas (invasive)	149	0.04	0.02	0.02
	2	Intraductal papillary mucinous carcinoma invasive of pancreas	1964	0.51	0.24	0.16
	2	Solid pseudopapillary carcinoma of pancreas	23	0.01	0.01	0.01
	2	Serous cystadenocarcinoma of pancreas	10	0.00	0.00	0.00
	2	Carcinoma with osteoclast-like giant cells of pancreas	15	0.00	0.00	0.00
	1	**Epithelial tumors of liver and intrahepatic bile tract (IBT)**	**128,332**	**33.09**	**15.22**	**10.46**
	2	Hepatocellular carcinoma of liver and IBT	103,106	26.59	12.51	8.61
	2	Hepatocellular carcinoma, fibrolamellar of liver and IBT	19	0.00	0.00	0.00
	2	Cholangiocarcinoma of IBT	11,533	2.97	1.40	0.98
	2	Adenocarcinoma with variants of liver and IBT	1608	0.41	0.21	0.15
	2	Undifferentiated carcinoma of liver and IBT	53	0.01	0.01	0.00
	2	Squamous cell carcinoma with variants of liver and IBT	67	0.02	0.01	0.01
	2	Bile duct cystadenocarcinoma of IBT	108	0.03	0.01	0.01
Female genital (common)	1	**Epithelial tumors of corpus uteri**	**39,931**	**10.30**	**7.54**	**5.81**
	2	Adenocarcinoma with variants of corpus uteri	33,254	8.57	6.58	5.10
	2	Squamous cell carcinoma with variants of corpus uteri	173	0.04	0.03	0.02
	2	Adenoid cystic carcinoma of corpus uteri	2	0.00	0.00	0.00
	2	Clear cell adenocarcinoma, NOS of corpus uteri	904	0.23	0.13	0.10
	2	Serous (papillary) carcinoma of corpus uteri	1827	0.47	0.26	0.19
	2	Mullerian mixed tumor of corpus uteri	1694	0.44	0.27	0.20
	1	**Epithelial tumors of cervix uteri**	**32,052**	**8.26**	**6.85**	**5.40**
	2	Squamous cell carcinoma with variants of cervix uteri	22,883	5.90	4.94	3.90
	2	Adenocarcinoma with variants of cervix uteri	6334	1.63	1.40	1.10
	2	Undifferentiated carcinoma of cervix uteri	49	0.01	0.01	0.01
	2	Mullerian mixed tumor of cervix uteri	55	0.01	0.01	0.01
	1	**Epithelial tumors of ovary and fallopian tube**	**31,312**	**8.07**	**5.71**	**4.41**
	2	Adenocarcinoma with variants of ovary	14,924	3.85	2.82	2.17
	2	Mucinous adenocarcinoma of ovary	2797	0.72	0.60	0.48
	2	Clear cell adenocarcinoma of ovary	5523	1.42	1.19	0.93
	2	Primary peritoneal serous/papillary carcinoma of ovary	973	0.25	0.15	0.12
	2	Mullerian mixed tumor of ovary	415	0.11	0.07	0.05
	2	Adenocarcinoma with variant of fallopian tube	1060	0.27	0.18	0.13

2016–2018				2011–2018			
Person-years: 380,113,000				Person-years: 767,928,000			
Number of cases	Crude rate	ASR Japanese population[a]	ASR World population[b]	Number of cases	Crude rate	ASR Japanese population[a]	ASR World population[b]
346,542	**91.17**	**42.27**	**29.95**	**652,508**	**84.97**	**40.35**	**28.58**
309,736	81.49	39.26	27.88	572,570	74.56	36.89	26.21
114	0.03	0.01	0.01	183	0.02	0.01	0.01
1299	0.34	0.23	0.17	2267	0.30	0.19	0.15
107,142	**28.19**	**14.70**	**10.74**	**207,340**	**27.00**	**14.34**	**10.48**
95,604	25.15	13.54	9.94	181,757	23.67	13.01	9.55
170	0.04	0.02	0.02	297	0.04	0.02	0.01
120,448	**31.69**	**13.45**	**9.33**	**229,563**	**29.89**	**13.10**	**9.10**
63,270	16.65	8.23	5.83	113,363	14.76	7.48	5.31
159	0.04	0.02	0.01	317	0.04	0.02	0.01
365	0.10	0.06	0.04	662	0.09	0.05	0.04
156	0.04	0.03	0.02	305	0.04	0.03	0.02
2310	0.61	0.27	0.19	4274	0.56	0.26	0.18
142	0.04	0.04	0.04	165	0.02	0.02	0.02
8	0.00	0.00	0.00	18	0.00	0.00	0.00
14	0.00	0.00	0.00	29	0.00	0.00	0.00
121,090	**31.86**	**13.45**	**9.24**	**249,422**	**32.48**	**14.34**	**9.86**
100,181	26.36	11.20	7.68	203,287	26.47	11.86	8.15
14	0.00	0.00	0.00	33	0.00	0.00	0.00
15,613	4.11	1.75	1.21	27,146	3.53	1.58	1.10
1022	0.27	0.12	0.08	2630	0.34	0.16	0.12
18	0.00	0.00	0.00	71	0.01	0.00	0.00
53	0.01	0.01	0.01	120	0.02	0.01	0.01
46	0.01	0.00	0.00	154	0.02	0.01	0.01
47,302	**12.44**	**9.06**	**6.99**	**87,233**	**11.36**	**8.30**	**6.39**
39,165	10.30	7.89	6.12	72,419	9.43	7.23	5.61
154	0.04	0.02	0.02	327	0.04	0.02	0.02
0	0.00	0.00	0.00	2	0.00	0.00	0.00
1036	0.27	0.15	0.11	1940	0.25	0.14	0.10
2549	0.67	0.37	0.27	4376	0.57	0.31	0.23
2026	0.53	0.33	0.25	3720	0.48	0.30	0.22
32,699	**8.60**	**7.00**	**5.48**	**64,751**	**8.43**	**6.93**	**5.44**
22,797	6.00	4.90	3.84	45,680	5.95	4.92	3.87
7002	1.84	1.59	1.24	13,336	1.74	1.49	1.17
51	0.01	0.01	0.01	100	0.01	0.01	0.01
77	0.02	0.01	0.01	132	0.02	0.01	0.01
33,738	**8.88**	**6.15**	**4.75**	**65,050**	**8.47**	**5.93**	**4.58**
16,125	4.24	3.07	2.37	31,049	4.04	2.94	2.27
2801	0.74	0.59	0.47	5598	0.73	0.59	0.48
5871	1.54	1.27	1.00	11,394	1.48	1.23	0.97
1394	0.37	0.21	0.16	2367	0.31	0.18	0.14
468	0.12	0.08	0.06	883	0.11	0.08	0.06
1402	0.37	0.24	0.18	2462	0.32	0.21	0.16

(Continues)

TABLE 2 (Continued)

Family	Tier	RARECAREnet list	2011–2015 Person-years: 387,815,000 Number of cases	Crude rate	ASR Japanese population[a]	ASR World population[b]
Thoracic (common)	1	**Epithelial tumors of lung**	**348,154**	**89.77**	**41.54**	**28.89**
	2	Squamous cell carcinoma with variants of lung	60,371	15.57	7.25	4.94
	2	Adenocarcinoma with variants of lung	156,242	40.29	21.07	15.08
	2	Adenosquamous carcinoma of lung	2778	0.72	0.35	0.25
	2	Large cell carcinoma of lung	2206	0.57	0.31	0.22
	2	Poorly differentiated endocrine carcinoma of lung	31,574	8.14	4.01	2.81
	2	Salivary gland type tumor of lung	322	0.08	0.06	0.05
	2	Sarcomatoid carcinoma of lung	2465	0.64	0.35	0.25
Breast	1	**Epithelial tumors of breast**	**233,632**	**60.24**	**43.00**	**33.04**
	2	Invasive carcinoma of no special type-NST (obs Invasive ductal carcinoma of breast)	190,137	49.03	36.10	27.85
	2	Invasive lobular carcinoma of breast	10,253	2.64	1.86	1.43
	2	Mammary Paget's disease of breast	367	0.09	0.06	0.04
	2	Special types of adenocarcinoma of breast	11,814	3.05	1.99	1.49
	2	Metaplastic carcinoma of breast	1013	0.26	0.18	0.14
	2	Salivary gland type tumor of breast	209	0.05	0.03	0.03
Male genital and urogenital (common)	1	**Epithelial tumors of prostate**	**233,482**	**60.20**	**27.78**	**19.07**
	2	Adenocarcinoma with variants of prostate	206,517	53.25	25.60	17.72
	2	Squamous cell carcinoma with variants of prostate	57	0.01	0.01	0.00
	2	Infiltrating duct carcinoma of prostate	454	0.12	0.06	0.04
	2	Transitional cell carcinoma of prostate	108	0.03	0.01	0.01
	2	Basal cell adenocarcinoma of prostate	2	0.00	0.00	0.00
	1	**Epithelial tumors of kidney**	**50,377**	**12.99**	**7.49**	**5.51**
	2	Renal cell carcinoma with variants	40,256	10.38	6.43	4.80
	2	Squamous cell carcinoma spindle cell type of kidney	39	0.01	0.01	0.00
	2	Squamous cell carcinoma with variants of kidney	41	0.01	0.01	0.00
	1	**Epithelial tumors of bladder**	**63,069**	**16.26**	**7.04**	**4.83**
	2	Transitional cell carcinoma of bladder	50,635	13.06	5.94	4.09
	2	Squamous cell carcinoma with variants of bladder	838	0.22	0.09	0.06
	2	Adenocarcinoma with variants of bladder	1053	0.27	0.15	0.11
	2	Salivary gland type tumor of bladder	0	0.00	0.00	0.00
Skin (common)	1	**Malignant skin melanoma**	**5097**	**1.31**	**0.77**	**0.58**
	2	Malignant skin melanoma	5097	1.31	0.77	0.58
	1	**Epithelial tumors of skin**	**48,088**	**12.40**	**5.14**	**3.53**
	2	Basal cell carcinoma of skin	28,849	7.44	3.40	2.36
	2	Squamous cell carcinoma with variants of skin	19,230	4.96	1.74	1.17

Note: Rates are per 100,000. The International Classification of Disease for Oncology, 3rd Edition morphology (ICD-O-3-M) codes of 9599 (B cell lymphoma, not otherwise specified [NOS]) and 9988 (acute myeloid leukemia with myelodysplastic-related changes), which Japanese population-based cancer registries have historically used as unique codes, were converted to 9591 and 9895, respectively.

Abbreviations: CNS, central nervous system; diff, differenciated; funct, functioning; GEP, gastroenteropancreatic; NET, neuroendocrine tumor; NK, natural killer.

[a]Age-standardized rate adjusted for the Japanese 1985 model population.

[b]Age-standardized rate adjusted for Segi's world standard population.

2016–2018				2011–2018			
Person-years: 380,113,000				Person-years: 767,928,000			
Number of cases	Crude rate	ASR Japanese population[a]	ASR World population[b]	Number of cases	Crude rate	ASR Japanese population[a]	ASR World population[b]
374,199	**98.44**	**43.06**	**29.93**	**722,353**	**94.07**	**42.32**	**29.42**
63,490	16.70	7.37	5.00	123,861	16.13	7.31	4.97
173,801	45.72	22.73	16.19	330,043	42.98	21.91	15.64
2642	0.70	0.32	0.22	5420	0.71	0.34	0.23
1352	0.36	0.19	0.14	3558	0.46	0.25	0.18
33,276	8.75	4.13	2.89	64,850	8.44	4.07	2.85
325	0.09	0.06	0.04	647	0.08	0.06	0.05
2489	0.65	0.34	0.25	4954	0.65	0.35	0.25
280,888	**73.90**	**50.52**	**38.68**	**514,520**	**67.00**	**46.75**	**35.85**
226,959	59.71	42.17	32.42	417,096	54.31	39.13	30.12
13,067	3.44	2.31	1.77	23,320	3.04	2.09	1.60
372	0.10	0.05	0.04	739	0.10	0.05	0.04
15,029	3.95	2.44	1.83	26,843	3.50	2.21	1.66
1218	0.32	0.21	0.16	2231	0.29	0.19	0.15
232	0.06	0.04	0.03	441	0.06	0.04	0.03
272,786	**71.76**	**30.92**	**21.09**	**506,268**	**65.93**	**29.37**	**20.09**
236,874	62.32	28.33	19.49	443,391	57.74	26.97	18.61
74	0.02	0.01	0.00	131	0.02	0.01	0.00
567	0.15	0.06	0.04	1021	0.13	0.06	0.04
156	0.04	0.02	0.01	264	0.03	0.01	0.01
1	0.00	0.00	0.00	3	0.00	0.00	0.00
61,181	**16.10**	**9.01**	**6.65**	**111,558**	**14.53**	**8.24**	**6.08**
48,439	12.74	7.76	5.80	88,695	11.55	7.09	5.29
45	0.01	0.01	0.00	84	0.01	0.01	0.00
35	0.01	0.00	0.00	76	0.01	0.00	0.00
69,347	**18.24**	**7.34**	**5.04**	**132,416**	**17.24**	**7.20**	**4.94**
56,503	14.86	6.29	4.33	107,138	13.95	6.12	4.21
811	0.21	0.08	0.06	1649	0.21	0.09	0.06
1163	0.31	0.16	0.11	2216	0.29	0.15	0.11
0	0.00	0.00	0.00	0	0.00	0.00	0.00
5535	**1.46**	**0.79**	**0.59**	**10,632**	**1.38**	**0.78**	**0.58**
5535	1.46	0.79	0.59	10,632	1.38	0.78	0.58
59,460	**15.64**	**6.08**	**4.20**	**107,548**	**14.00**	**5.62**	**3.87**
36,136	9.51	4.13	2.89	64,985	8.46	3.77	2.62
23,317	6.13	1.95	1.32	42,547	5.54	1.85	1.24

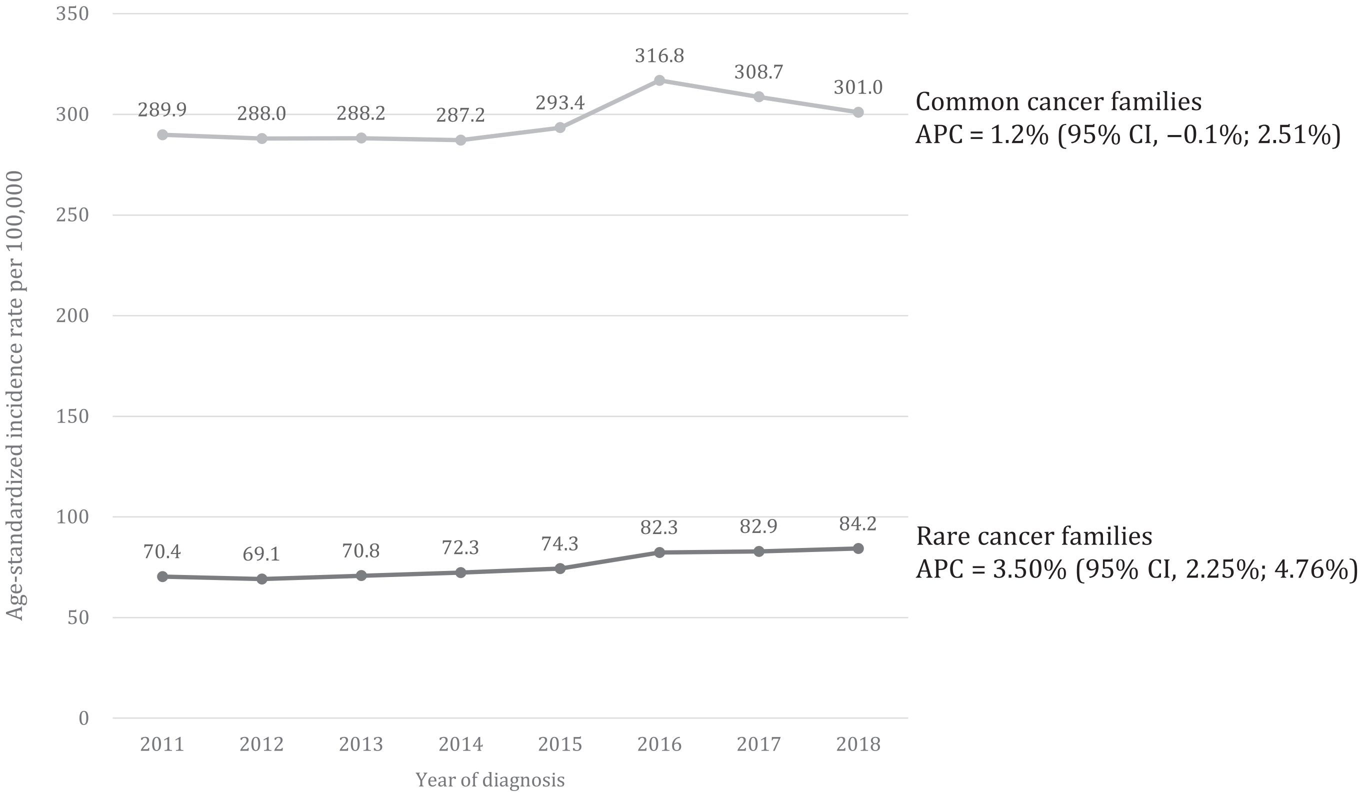

FIGURE 1 Time trend of age-standardized incidence rates of rare cancer families and common cancer families in Japan from 2011 to 2018. The rates were adjusted using the Japanese 1985 model population. APC, annual percent change; CI, confidence interval.

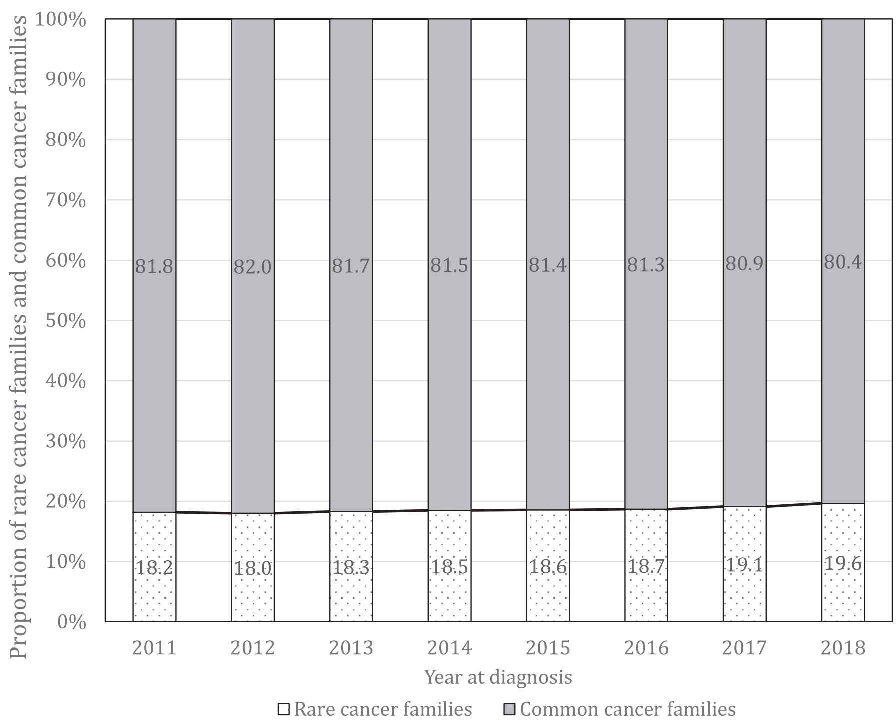

FIGURE 2 Proportion of rare cancer families and common cancer families in Japan, 2011–2018.

the gallbladder and the extrahepatic biliary tract was significantly decreased. The APCs for 32 Tier-1 cancers were within the 99% CL (Table 3 and Figure 3).

Of the 16 Tier-1 cancers in common cancer families, the ASRs of 6 Tier-1 cancers were significantly increased, whereas the ASRs of epithelial tumors of the stomach and liver and intrahepatic bile tract

TABLE 3 Age-standardized incidence rates of rare cancer in Japan, annual percent change (APC), and the difference in age-standardized rates (ASRs) between 2011 and 2018 by RARECAREnet list.

		ASR (per 100,000) in year at diagnosis								Relative change				Absolute change
Family	RARECAREnet list Tier-1 cancer grouping	2011	2012	2013	2014	2015	2016	2017	2018	APC (%)	Standard error	95% CI	99% CI	Difference in ASRs between 2011 and 2018
Head and neck	Epithelial tumors of nasal cavity and sinuses	0.56	0.48	0.50	0.53	0.53	0.55	0.53	0.54	0.88	0.66	−0.71 to 2.5	−1.55 to 3.31	0.02
	Epithelial tumors of nasopharynx	0.40	0.37	0.36	0.39	0.39	0.42	0.40	0.38	0.64	0.87	−1.46 to 2.78	−2.57 to 3.85	0.02
	Epithelial tumors of major salivary glands and salivary-gland type tumors	1.01	1.03	1.04	1.13	1.09	1.27	1.29	1.27	4.14	0.78	2.24 to 6.08	1.23 to 7.05	0.26
	Epithelial tumors of hypopharynx and larynx	3.64	3.58	3.59	3.63	3.82	3.92	3.93	3.86	1.51	0.38	0.59 to 2.44	0.11 to 2.91	0.22
	Epithelial tumors of oropharynx	1.42	1.31	1.48	1.50	1.57	1.77	1.81	1.94	5.77	0.62	4.26 to 7.3	3.47 to 8.07	0.52
	Epithelial tumors of oral cavity and lip	3.45	3.39	3.55	3.56	3.65	4.07	4.14	4.13	3.51	0.57	2.12 to 4.93	1.38 to 5.64	0.68
	Epithelial tumors of eye and adnexa	0.06	0.03	0.05	0.04	0.06	0.06	0.07	0.06	7.29	3.19	−0.23 to 15.37	−4.53 to 19.11	0.00
	Epithelial tumors of middle ear	0.01	0.01	0.01	0.01	0.01	0.01	0.01	0.01	−4.03	3.17	−11.48 to 4.04	−15.79 to 7.73	0.00
Digestive (rare)	Epithelial tumors of small intestine	0.90	0.96	0.95	0.93	1.01	1.19	1.23	1.19	5.21	1.06	2.65 to 7.84	1.28 to 9.14	0.29
	Epithelial tumors of anal canal	0.42	0.34	0.37	0.38	0.37	0.42	0.39	0.44	2.40	1.13	−0.34 to 5.21	−1.8 to 6.6	0.02
	Epithelial tumors of gallbladder and extrahepatic biliary tract (EBT)	7.67	7.46	7.34	6.98	6.85	6.79	6.58	6.24	−2.73	0.22	−3.26 to −2.2	−3.53 to −1.93	−1.43
Thoracic (rare)	Epithelial tumors of trachea	0.04	0.03	0.03	0.03	0.03	0.04	0.03	0.04	1.46	2.47	−4.4 to 7.69	−7.7 to 10.62	0.00
	Epithelial tumors of thymus	0.62	0.52	0.58	0.64	0.66	0.71	0.74	1.50	16.56	5.09	4.76 to 29.68	−2.32 to 35.44	0.88
	Malignant mesothelioma	0.69	0.66	0.63	0.59	0.64	0.65	0.64	0.60	−0.76	0.70	−2.46 to 0.97	−3.36 to 1.84	0.09
Female genital (rare)	Nonepithelial tumors of ovary	0.34	0.37	0.38	0.34	0.38	0.42	0.46	0.44	4.31	1.12	1.6 to 7.1	0.14 to 8.48	0.10
	Epithelial tumors of vulva and vagina	0.35	0.36	0.36	0.40	0.37	0.41	0.39	0.41	1.99	0.65	0.4 to 3.6	−0.43 to 4.41	0.06
	Trophoblastic tumors of placenta	0.04	0.06	0.05	0.05	0.04	0.04	0.05	0.05	−0.64	2.70	−7.04 to 6.19	−10.66 to 9.38	0.01
Male genital and urogenital (rare)	Testicular and paratesticular cancers	1.44	1.52	1.64	1.73	1.70	1.93	1.86	1.93	3.90	0.70	2.2 to 5.63	1.3 to 6.5	0.49
	Epithelial tumors of penis	0.18	0.16	0.17	0.18	0.17	0.19	0.19	0.18	1.40	0.84	−0.65 to 3.48	−1.73 to 4.53	0.00
	Epithelial tumors of pelvis and ureter	2.46	2.43	2.47	2.60	2.53	2.74	2.71	2.59	1.35	0.58	−0.07 to 2.79	−0.82 to 3.52	0.13
	Epithelial tumors of urethra	0.05	0.06	0.05	0.06	0.05	0.06	0.06	0.06	0.87	1.17	−1.95 to 3.77	−3.46 to 5.2	0.01
	Extragonadal germ cell tumors	0.30	0.34	0.31	0.37	0.37	0.43	0.45	0.44	6.04	1.02	3.58 to 8.55	2.28 to 9.8	0.14
Skin (rare)	Malignant melanoma of mucosa and extracutaneous	0.19	0.17	0.16	0.18	0.19	0.18	0.18	0.19	0.81	0.86	−1.27 to 2.94	−2.38 to 4	0.00
	Malignant melanoma of eye	0.04	0.04	0.04	0.04	0.05	0.06	0.07	0.05	7.27	3.50	−0.95 to 16.18	−5.71 to 20.25	0.01
	Adnexal carcinomas of skin	0.49	0.46	0.45	0.45	0.48	0.48	0.50	0.48	0.95	0.61	−0.54 to 2.46	−1.32 to 3.22	0.01
	Kaposi's sarcoma	0.04	0.04	0.03	0.04	0.03	0.04	0.04	0.03	−1.67	2.24	−6.99 to 3.96	−9.96 to 6.62	0.01

(Continues)

TABLE 3 (Continued)

Family	RARECAREnet list Tier-1 cancer grouping	ASR (per 100,000) in year at diagnosis 2011	2012	2013	2014	2015	2016	2017	2018	Relative change APC (%)	Standard error	95% CI	99% CI	Absolute change Difference in ASRs between 2011 and 2018
Pediatric	Neuroblastoma and ganglioneuroblastoma	0.14	0.14	0.18	0.21	0.24	0.24	0.22	0.20	4.32	2.87	−2.46 to 11.58	−6.31 to 14.95	0.06
	Nephroblastoma	0.06	0.05	0.04	0.06	0.08	0.07	0.07	0.06	2.55	3.40	−5.43 to 11.2	−10.05 to 15.15	0.00
	Retinoblastoma	0.07	0.09	0.08	0.07	0.08	0.11	0.12	0.10	7.14	2.80	0.5 to 14.21	−3.24 to 17.52	0.03
	Hepatoblastoma	0.05	0.06	0.07	0.08	0.06	0.08	0.08	0.06	1.65	3.27	−6.04 to 9.98	−10.48 to 13.78	0.01
	Pleuropulmonary blastoma	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.01	5.51	5.49	−7.08 to 19.8	−14.85 to 25.87	0.01
	Pancreatoblastoma	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	NA	NA	NA	NA	NA
	Olfactory neuroblastoma	0.05	0.03	0.06	0.04	0.06	0.09	0.08	0.08	10.10	3.78	1.24 to 19.74	−3.91 to 24.11	0.03
	Odontogenic malignant tumors	0.02	0.01	0.01	0.01	0.01	0.03	0.02	0.03	15.83	5.28	3.63 to 29.47	−3.74 to 35.4	0.01
Sarcomas	Soft tissue sarcoma	3.33	2.97	3.10	3.32	3.40	3.66	3.75	3.73	3.36	0.67	1.73 to 5.02	0.87 to 5.85	0.40
	Bone sarcoma	0.60	0.54	0.57	0.61	0.59	0.71	0.67	0.69	3.54	1.08	0.92 to 6.22	−0.47 to 7.55	0.09
	Gastrointestinal stromal sarcoma	0.81	0.75	0.69	0.67	0.58	0.60	0.58	0.81	−0.66	2.51	−6.62 to 5.68	−9.98 to 8.66	0.00
Neuroendocrine	NET GEP	2.02	2.30	2.41	2.73	3.07	3.71	3.94	4.03	11.04	1.03	8.55 to 13.58	7.23 to 14.85	2.01
	NET lung	0.13	0.15	0.15	0.14	0.17	0.19	0.18	0.19	5.32	1.10	2.66 to 8.05	1.24 to 9.4	0.06
	NET other sites	0.66	0.66	0.65	0.66	0.72	0.81	0.80	1.03	7.26	1.52	3.6 to 11.05	1.62 to 12.9	0.37
Endocrine organ	Carcinomas of pituitary gland	0.06	0.05	0.05	0.04	0.03	0.04	0.04	0.04	−4.09	2.06	−9.01 to 1.09	−11.74 to 3.56	0.02
	Carcinomas of thyroid gland	8.20	7.58	7.80	8.14	8.62	10.74	10.71	11.02	6.73	1.30	3.61 to 9.95	1.93 to 11.53	2.82
	Carcinomas of parathyroid gland	0.02	0.01	0.01	0.01	0.02	0.02	0.02	0.02	11.35	4.18	1.6 to 22.04	−4.13 to 26.83	0.00
	Carcinomas of adrenal cortex	0.07	0.10	0.10	0.10	0.09	0.11	0.10	0.10	2.43	1.60	−1.41 to 6.42	−3.5 to 8.36	0.03
Central nervous system (CNS)	Tumors of CNS	2.54	2.64	2.78	2.79	2.86	3.32	3.05	3.06	2.95	0.99	0.55 to 5.4	−0.72 to 6.62	0.52
	Embryonal tumors of CNS	0.12	0.14	0.13	0.12	0.16	0.14	0.16	0.13	2.07	1.92	−2.53 to 6.89	−5.07 to 9.21	0.01
Hematological	Lymphoid diseases	16.82	16.86	17.25	17.43	17.71	19.31	19.58	19.63	2.83	0.42	1.8 to 3.86	1.27 to 4.39	2.81
	Acute myeloid leukemia and related precursor neoplasms	3.12	3.11	3.04	3.04	2.96	3.04	3.15	3.09	0.17	0.38	−0.74 to 1.1	−1.22 to 1.56	0.03
	Myeloid and lymphoid neoplasms	0.08	0.09	0.10	0.09	0.08	0.15	0.16	0.23	18.52	3.81	9.55 to 28.22	4.38 to 32.66	0.15
	Myeloproliferative neoplasms	1.66	1.80	2.01	2.19	2.42	2.86	3.22	3.45	11.85	0.53	10.56 to 13.16	9.88 to 13.82	1.79
	Myelodysplastic syndrome and myelodysplastic/ myeloproliferative diseases	2.87	2.74	2.91	2.89	3.07	3.30	3.22	3.19	2.44	0.62	0.95 to 3.96	0.16 to 4.72	0.32
	Histiocytic and dendritic cell neoplasms	0.05	0.05	0.04	0.08	0.16	0.19	0.20	0.23	27.78	5.69	14.61 to 42.47	6.68 to 48.88	0.18

TABLE 3 (Continued)

Family	RARECAREnet list Tier-1 cancer grouping	ASR (per 100,000) in year at diagnosis								Relative change				Absolute change
		2011	2012	2013	2014	2015	2016	2017	2018	APC (%)	Standard error	95% CI	99% CI	Difference in ASRs between 2011 and 2018
Digestive (common)	Epithelial tumors of esophagus	9.10	8.70	8.92	8.86	9.05	10.03	9.87	9.85	2.19	0.62	0.69 to 3.71	−0.1 to 4.48	0.75
	Epithelial tumors of stomach	51.74	50.11	48.85	46.81	45.03	47.53	45.14	42.57	−2.27	0.49	−3.46 to −1.06	−4.09 to −0.45	-9.17
	Epithelial tumors of colon (including appendix)	36.69	38.01	38.14	38.25	39.36	43.56	42.33	40.93	2.05	0.70	0.36 to 3.78	−0.54 to 4.64	4.24
	Epithelial tumors of rectum	14.10	13.99	14.05	13.90	13.95	15.40	14.50	14.21	0.68	0.66	−0.93 to 2.31	−1.77 to 3.13	0.11
	Epithelial tumors of pancreas	12.45	12.74	12.67	12.68	12.91	13.48	13.47	13.39	1.24	0.26	0.61 to 1.88	0.28 to 2.2	0.94
	Epithelial tumors of liver and intrahepatic bile tract (IBT)	17.23	16.24	15.58	14.79	14.22	14.65	13.30	12.42	−4.04	0.51	−5.27 to −2.79	−5.92 to −2.16	−4.81
Female genital (common)	Epithelial tumors of corpus uteri	6.94	7.11	7.38	7.63	7.96	8.77	9.09	9.32	4.91	0.38	3.97 to 5.85	3.49 to 6.33	2.38
	Epithelial tumors of cervix uteri	6.89	6.94	6.84	6.79	6.85	7.06	7.00	6.94	0.32	0.22	−0.21 to 0.86	−0.49 to 1.13	0.05
	Epithelial tumors of ovary and fallopian tube	5.25	5.51	5.56	5.74	6.04	6.26	6.14	6.05	2.08	0.53	0.79 to 3.38	0.12 to 4.04	0.80
Thoracic (common)	Epithelial tumors of lung	42.29	41.74	41.42	41.42	41.33	44.15	43.50	41.55	0.42	0.50	−0.79 to 1.65	−1.43 to 2.27	0.74
Breast	Epithelial tumors of breast	38.85	39.23	41.37	42.69	47.27	51.50	49.91	50.12	4.38	0.84	2.33 to 6.46	1.25 to 7.51	11.27
Male genital and urogenital (common)	Epithelial tumors of prostate	28.72	27.84	27.08	26.99	28.52	30.87	31.08	30.82	2.26	0.67	0.64 to 3.91	−0.22 to 4.74	2.10
	Epithelial tumors of kidney	6.98	7.03	7.28	7.67	7.84	8.89	9.16	8.98	4.67	0.68	3.02 to 6.35	2.15 to 7.19	2.00
	Epithelial tumors of bladder	7.32	7.20	6.96	7.01	6.96	7.56	7.32	7.15	0.41	0.56	−0.95 to 1.78	−1.66 to 2.48	0.17
Skin (common)	Malignant skin melanoma	0.73	0.75	0.79	0.76	0.78	0.83	0.80	0.75	0.64	0.71	−1.07 to 2.39	−1.98 to 3.26	0.02
	Epithelial tumors of skin	4.59	4.85	5.30	5.17	5.33	6.26	6.05	5.93	3.92	1.00	1.51 to 6.39	0.22 to 7.62	1.34

Abbreviations: CI, confidence interval; GEP, gastroenteropancreatic; NA, not available; NET, neuroendocrine tumor.

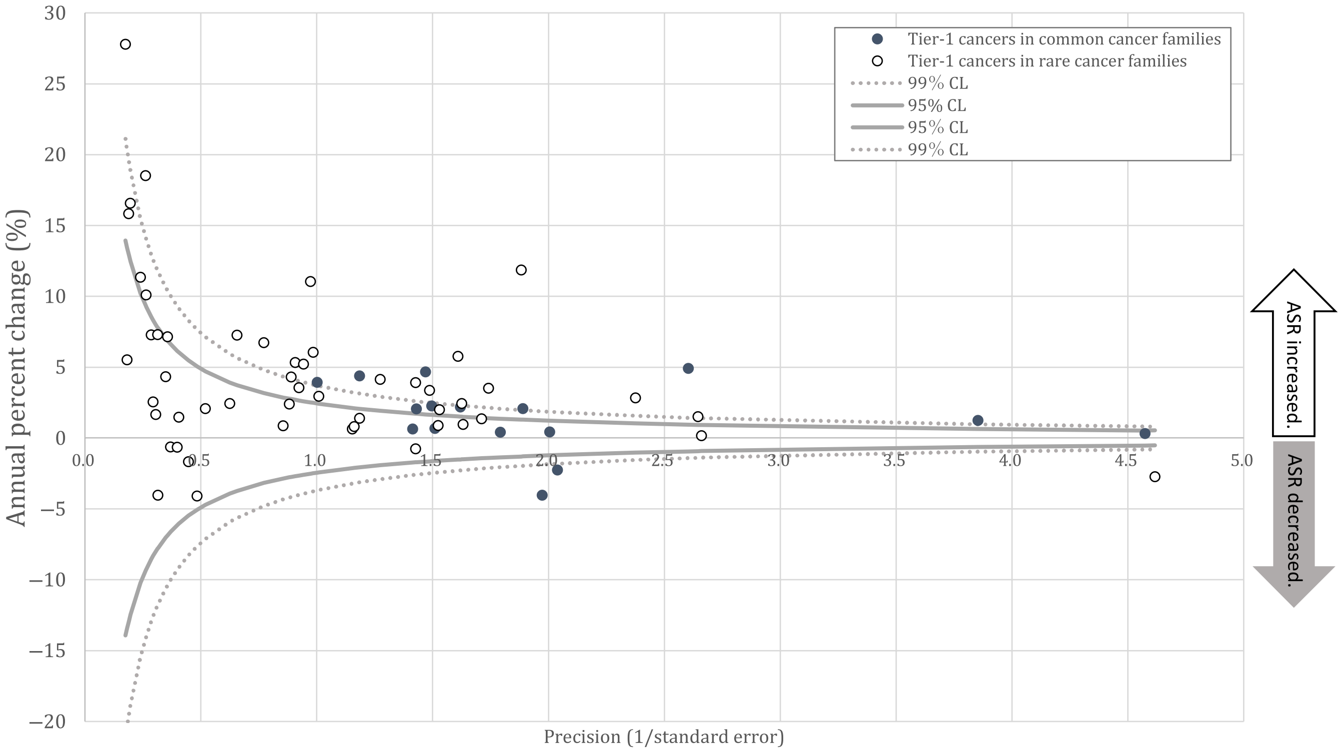

FIGURE 3 Plot showing the annual percent change (APC) in the age-standardized incidence rates (ASRs) for 68 Tier-1 cancers based on the Japanese population-based cancer registries from 2011 to 2018. The 95% and 99% confidence limits (CLs) of APCs were calculated as standard error ±2.447 and ±3.707, respectively, following *t*-distribution (degrees of freedom: 6). Precision indicates the inverse of the standard error of APC.

were significantly decreased. The APCs of 8 Tier-1 cancers were within the 99% CL. In 2016, a notable increase in the incidence of all Tier-1 cancers in common cancer families was observed (Table 3 and Figure 3).

3.5 | Absolute change of ASRs between 2011 and 2018 for each Tier-1 cancer

The difference in the ASRs between 2011 and 2018 as absolute changes of ASRs for 68 Tier-1 cancers are shown in Table 3. The APCs of Tier-1 cancers in rare cancer families varied widely (APC range, −4.09% to 27.78%), while the absolute changes in the ASRs were small (range of difference in ASRs between 2011 and 2018, −1.43 to 2.82). The APCs of many Tier-1 cancers in common cancer families were small (range, −4.04% to 4.91%), whereas the absolute changes in ASRs were great (range of difference in ASRs between 2011 and 2018, −9.17 to 11.27). Tier-1 cancers that showed an increase or decrease in APC at the 1% significant level are shown in Figure 4.

4 | DISCUSSION

Based on the high-quality Japanese regional PBCR and NCR data, we found an increase in the ASRs of 18 Tier-1 cancers and a decrease in the ASR of one Tier-1 cancer among rare cancer families. Consequently, the proportion of rare cancers increased by 1.4% point because of the decrease in the incidence of two Tier-1 common cancers (i.e., epithelial tumors of stomach and liver). The APCs of 18 Tier-1 cancers in rare cancer families increased, whereas the absolute change was small because the ASRs of each rare cancer were essentially low.

4.1 | Rare cancer families

4.1.1 | Head and neck cancer families

The ASRs of epithelial tumors of major salivary glands and salivary gland type tumors, hypopharynx and larynx, oropharynx, and oral cavity and lip increased during the study reference period. As the incidence of laryngeal cancer in Japanese men has shown a progressive decrease from 1985 to 2015 due to the reduction in smoking rate,[10] the increased incidence of hypopharynx cancer may be attributable to the increase in epithelial tumors of the hypopharynx and larynx. The widespread use of narrow-band imaging endoscopy, specifically in Japan,[11,12] and the promotion of aggressive surveillance for multiple tumors among patients with esophageal and lung cancers might have contributed to the increasing ASRs of hypopharyngeal and oral and lip cancers.[11] Alcohol consumption is a known risk factor for hypopharyngeal cancer, however, the prevalence of net alcohol consumption above the recommended limits (i.e., 40 g or more per day

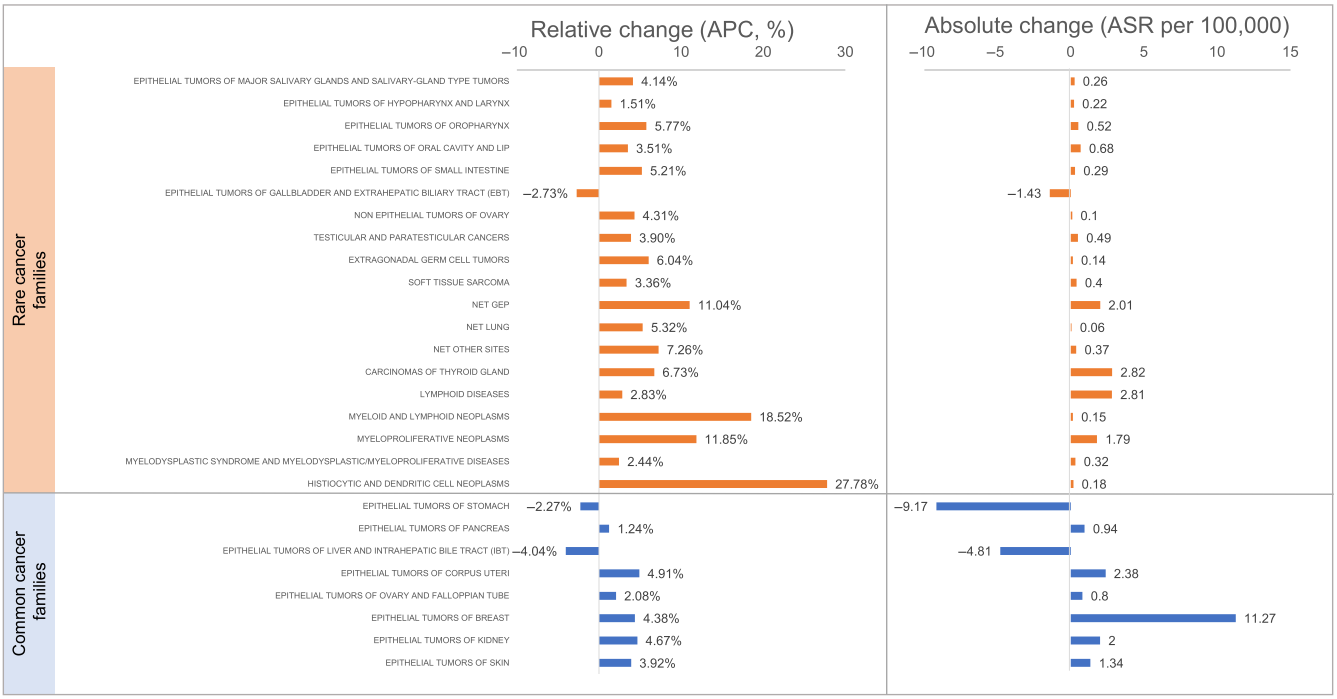

FIGURE 4 Relative change (annual percent change [APC]) and absolute change (difference in age-standardized incidence rates [ASRs] from 2011 to 2018) in rare and common Tier-1 cancers. Tier-1 cancers whose APC increased or decreased at the 1% significance level are shown. GEP, gastroenteropancreatic; NET, neuroendocrine tumor.

for men and 20g or more per day for women) did not change during the study period (i.e., from 16.3% in 2011 to 15.0% in 2018 for men, and from 8.2% in 2011 to 9.1% in 2018 for women).[13] An increased prevalence of human papillomavirus type 16 in patients with oropharynx cancer might affect the increase of oropharyngeal cancer.[14]

4.1.2 | Digestive (rare)

An increasing trend of adenocarcinoma of the small intestine from 2005 to 2015 was reported by Hiroshima PBCR in Japan.[15] This was likely due to the early detection of cases owing to the recent standardization and wider use of improved upper gastrointestinal endoscopy techniques (e.g., endoscopy with a combination of narrow-band imaging, balloon-assisted endoscopy, and capsule endoscopy[16,17]). Of note, the decreasing ASR of epithelial tumors of the gallbladder and the extrahepatic biliary tract may be attributable to the rapid increase in laparoscopic cholecystectomy for cholecystitis and gallstone, which are risk factors for gallbladder cancer.[18]

4.1.3 | Female genital (rare)

Although the incidence of nonepithelial tumors of the ovary showed an increase (APC = 4.31%), the absolute change in ASRs was small at 0.1 (0.34 in 2011 to 0.44 in 2018). Namely, the change in the number of cases over successive years ranged within 36 (number of cases: 430 in 2016, 466 in 2017, 434 in 2018).

4.1.4 | Male genital (rare)

Hispanics, US Black Africans, and Asians (including Japanese) have a lower incidence of testicular cancer compared to Caucasians in the EU and United States.[19,20] Our study showed an increase in the incidence of testicular and paratesticular tumors in Japan, similar to that in lower-risk countries in Europe.[21] A Canadian study suggested that the birth-cohort effects impacted the testicular cancer incidence rather than diagnostic improvements usually observed as period effects.[22] The risk factors for testicular cancer are not well-characterized other than race (i.e., Northern European ancestry), cryptorchidism, and personal or family history of testicular cancer; thus, further studies are required to explore the environmental and socioeconomic risk factors and to identify high-risk groups of the birth cohort. The ASR of extragonadal germ cell tumors significantly increased as the relative change, while the absolute change was small at 0.14. The change in the number of cases over successive years was within the range of 17 (number of cases: 406 in 2016, 423 in 2017, 408 in 2018).

4.1.5 | Sarcoma

There are many histological types of soft tissue sarcoma and bone sarcoma. Unfortunately, the RARECAREnet list does not group Tier-1 soft tissue sarcoma into Tier-2 cancer by topography and histological type. Therefore, we could not identify the histological types that contribute to the increase in the soft tissue sarcoma entity. The

ASR of GIST decreased from 2011 to 2017 but showed an abrupt increase in 2018 due to the change in the coding system from ICD-O-3.1 to ICD-O-3.2, in which all GIST were coded as malignant (i.e., ICD-O-3.1-M/behavior: 8936/0, 8936/1 to ICD-O-3.2-M/behavior: 8936/3).

4.1.6 | Neuroendocrine tumors

The incidence of all NET GEP, NET lung, and NET other sites increased. A nationwide survey of PNETs and gastrointestinal NETs revealed an increasing trend in the estimated incidence rates. This phenomenon was attributed to the wider dissemination of the disease concept of NETs among general clinicians and the increased availability of endoscopic ultrasound-guided fine-needle aspiration, contributing to a more accurate pathologic diagnosis, particularly for PNETs.[23] An increasing trend of neuroendocrine cancers was also reported in Norway,[24] the United States,[25] Australia,[26] and Taiwan.[27] In the ICD-O-3.2, the behavior code of NETs with benign and behavior NOS were changed to malignant (i.e., ICD-O-3.1-M/behavior: 8150–8151/0; 8150/1; 8152–3/1; 8155–6/1; 8158/1, 8240/1; 8242/1 to ICD-O-3.2-M/behavior: 8150–3/3; 8156/3; 8158/3; 8241–2/3). These tumors diagnosed before 2017 were not reported to the PBCR according to ICD-O 3.1 because the behavior was benign or uncertain whether benign or malignant. However, these tumors diagnosed after 2018 were coded as malignant tumors using ICD-O-3.2 and became reportable cancers to be counted as incident cases. Since benign or behavior NOS NETs are extremely rare, reporting these tumors as malignant after 2018 is unlikely to have had a significant impact on the incidence of NETs; however, this may explain the increased incidence in 2018.

4.1.7 | Endocrine tumors

Municipalities in Japan do not have formal programs for thyroid cancer screening. The increased incidence of thyroid cancer is likely attributable to the improvement of ultrasound diagnosis and the increase in the number of hospitals and clinics that can diagnose using ultrasound.[28]

4.1.8 | Hematological

Increasing trends of lymphoid disease can be explained by increasing ASRs of diffuse large B-cell lymphoma, FL, and plasma cell neoplasms.[29] The number of FLs in the small intestine and duodenum has increased since Yoshino et al. first reported a primary FL of the duodenum.[30] Older adult patients with MDS (i.e., age >65 years) were not eligible for hematopoietic stem cell transplantation in Japan. New drugs (e.g., lenalidomide in 2010, azacitidine in 2011, and darbepoetin in 2014)[31] enabled the treatment for older adult patients, thereby increasing the ASR trend of MDS with the promotion of aggressively definitive diagnoses. The change in the ASR of histiocytic and dendritic cell neoplasm (APC = 27.78%) was the greatest among all Tier-1 cancers. The ASR before 2014 was approximately 0.05/100,000, then increased from 0.08/100,000 in 2014 to 0.23/100,000. The changes in morphology and behavior code of several tumors might have resulted in the sudden increase after the adoption of the ICD-O-3 updated version in 2012 (i.e., 9752–4/1 to 9751–4/3).

4.1.9 | Thoracic (rare), skin (rare), CNS, and pediatric

The ASRs of all Tier-1 cancers in the thoracic rare family, skin rare family, and CNS family showed no significant change. Among the Tier-1 cancers of pediatric families, the ASR of neuroblastoma and ganglioneuroblastoma was 0.21, while for others the ASR was <0.1; thus, the CIs of APCs were too wide to evaluate the temporal trend of the incidence. As we did not restrict the subjects to children, further analyses focusing on children are warranted.

4.2 | Common cancer families

We also observed a reduction in the ASR of epithelial tumors of the stomach, liver, and intrahepatic bile duct, similar to a previous study using ICD-10.[2] The reduced incidence of stomach cancers was thought to be related to the reduced prevalence of *Helicobacter pylori* in younger birth cohorts (e.g., the predicted prevalence was >60% in individuals born before 1940, followed by a gradual decrease to 6.6% in individuals born in 2000).[32] The decrease in prevalence of *H. pylori* in younger birth cohorts has been attributed to improved sanitary conditions (e.g., water and sewer services) in early childhood and changes in lifestyle eating behaviors (parent-to-child oral transmission).[33] The health insurance coverage for *H. pylori* eradication therapy for gastritis was initiated in 2013 and this might have contributed to the reduced prevalence.[34] Approximately 65% and 15% of hepatocellular carcinoma cases in Japan were estimated to be caused by persistent HCV and HBV infection, respectively.[35] The prevalence of HCV and HBV decreased because the carrier rates decreased with younger birth cohorts.[35] In addition, the incidence reduction was accelerated by therapeutic improvements such as pegylated interferon in 2004 and a protease inhibitor in 2011.[2]

We observed an increase in the incidence of epithelial tumors of the ovary. In contrast, postmenopausal ovarian cancer decreased in many countries due largely to the widespread use of oral contraceptive pills (e.g., prevalence of contraceptive pill use: Europe, 19.1%; North America, 15.1%; Australia, 22.0%; Japan, 2.9%[36]) and changes in cancer registry practices (i.e., change of coding system).[37] As there are several risk factors for ovarian cancer (e.g., ethnicity, higher maternal age at childbirth, family history),[38] further analyses are required to examine the relationship between the incidence of epithelial tumors of the ovary and risk factors.

A previous study has reported an increasing trend in the diagnosis of breast cancer until 2015 due to the higher participation rate in screening and improved diagnosis.[2] Breast cancer incidence showed geographical variation by prefecture.[8] Especially in Kumamoto Prefecture, the ASR for the period 2016–2018 was the highest (63.28/100,000) among the 47 prefectures (ASR in Japan: 50.52/100,000) due to the artificial effect related to the initiation of the NCR.

4.3 | Effects of initiation of NCR and coding change

For all Tier-1 cancers in common cancer families, the ASR in 2016 showed an abrupt increase because of the initiation of mandatory reporting from hospitals in 2016 due to the setting up of the NCR.[8] In contrast, we did not observe such an apparent increase in ASRs for Tier-1 rare cancers. The ASRs of several cancers were affected by the changes in the definitions of reportable cancers due to the adoption of the ICD-O-3 updated version and ICD-O-3.2. Especially the incidence of thymoma and GIST showed a remarkable increase in 2018 because the Japanese hospital-based cancer registry changed the coding to ICD-O-3.2. Changes in the coding system, especially behavior code, affect the cancer incidence rates and may make the epidemiological interpretation difficult; therefore, the adoption and timing of any change in the coding system should be in sync with the international standard.

4.4 | Limitations and strengths

Some limitations of this study should be acknowledged. We did not evaluate the incidence by sex. Our selected PBCR data covered 30.0% of the Japanese population in 2011. Possible heterogeneity in cancer incidence across prefectures was not considered. The abrupt increase in the ASR for whole common cancer families observed in 2016 was an artificial effect due to the initiation of the NCR in that year.

However, there are several strengths of this study. First, the comprehensive statistics of 68 Tier-1 rare and common cancer incidence were evaluated using the RARECAREnet list. Second, the use of high-quality PBCR data validated by quantitative and qualitative assessment ensured the representativeness of our findings at the national level. Third, the population size was large. Since 2016, the NCR has covered the entire population of Japan (126 million in 2020), which is the 11th largest population in the world and equivalent to approximately 60.6% of the population covered by the RARECAREnet (average population was 207,942,000 during 2000–2007[7]) and approximately 79.1% of the population covered by the US SEER program (159,193,310 in 2020).[39]

The increasing trend in the incidence of 18 Tier-1 cancers in rare cancer families is likely attributable to a better understanding of the disease, dissemination of the disease concept, and aggressive diagnosis due to the availability of new drugs. The decreasing trend in the incidence of gallbladder cancer is due to an increase in the rates of cholecystectomy. Changes in the behavior and morphology code system affected the incidence of rare cancers during the study reference period. Due to the paucity of knowledge regarding risk factors for each rare cancer, further studies are required to evaluate the relationship between each cancer and its risk factors (e.g., virus infection, environmental factors, reproductive factors, lifestyle) with time trends to enable more effective control of rare cancers.

AUTHOR CONTRIBUTIONS

Hiromi Sugiyama: Conceptualization; data curation; formal analysis; investigation; methodology; validation; writing – original draft; writing – review and editing. **Manami Konda:** Data curation; formal analysis; software; validation; writing – review and editing. **Kumiko Saika:** Data curation; investigation; software; validation; writing – review and editing. **Tomohiro Matsuda:** Conceptualization; data curation; funding acquisition; resources; software; supervision; writing – review and editing.

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CONFLICT OF INTEREST STATEMENT

The authors declare no conflict of interest.

ETHICS STATEMENTS

Approval of the research protocol by an institutional review board: This study was approved by the Institutional Review Board of the National Cancer Center (2019-202).

Registry and the registration no. of the study/trial: N/A. Usage of regional cancer registry data were approved by each municipality. In accordance with Article 21 of the Act on Promotion of Cancer Registry, anonymized National Cancer Registry information usage was approved (A2020-0018R2). The data were processed and analyzed by the authors as approved users. According to the terms of use of the National Cancer Registry information in Japan, when the aggregated cell value is less than 10, the aggregated value must be kept confidential. In this study, since the aggregate units were Japan and both sexes, the possibility of individual identification was extremely low. Therefore, it was approved by the National Cancer Registry Information Provision Advisory Committee of the National Cancer Center that the aggregated value can be shown as it is.

Informed consent: N/A.

Animal studies: N/A.

ORCID

Hiromi Sugiyama https://orcid.org/0000-0003-2536-0865
Kumiko Saika https://orcid.org/0000-0002-4164-4430
Tomohiro Matsuda https://orcid.org/0000-0002-7311-1233

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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