

Rare cancers are not rare in Asia as well: The rare cancer burden in East Asia

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ABSTRACT

Introduction: Epidemiologic information on rare cancers is scarce outside of the Western countries. The project “surveillance of rare cancers in Asia” (RARECAREnet Asia) provides, for the first time, the burden of rare cancers in some Asian countries based on the latest list.

Objectives: 1) to assess whether the European list of rare cancers fits the Asian setting and 2) to compare the incidences of rare cancers between Europe and Asian countries.

Material and methods: Population-based cancer registry data on patients diagnosed from 2011 to 2015 in Japan, Korea, and Taiwan and patients diagnosed from 2000 to 2007 in 94 European registries were analysed. The incidences for all cancers were calculated; they were then grouped into several tiers and families according to the rare cancer list, and whether cancers rare was examined.

Results: Rare cancer counts according to the list in the observed population were 196 in Japan, 203 in Korea, 198 in Taiwan, and 198 in the EU. The proportions of rare in overall incidence were 16.3% in Japan, 23.7% in Korea, 24.2% in Taiwan, and 22.2% in the EU. The numbers of newly diagnosed rare cancer cases in 2015 were 140,188 in Japan, 52,071 in Korea, and 24,147 in Taiwan.

Conclusion: Most rare cancers in Europe were also rare in the Asian countries considered. The observed differences were due to well-known risk factors. The European definition and list of rare cancers appear to reflect well cancer incidence in East Asia.

1. Introduction

There has been an overwhelming need for Asian countries where more than 40% of cancers are diagnosed currently to adopt and implement cancer control actions based on reliable population-based cancer registry (PBCR) data [1].

In East Asian countries, the distribution of primary cancer sites is estimated to differ substantially from European countries [2]. However, whether the incidence patterns of rare cancers are also quite different between the continents is unknown. Since the publication by Gatta et al., there has been an internationally agreed definition of rare cancers [3]. The project Surveillance of Rare Cancers in Asia (RARECAREnet Asia) was established by the National Cancer Center, Japan, National Cancer Center, Korea, and Taiwan Cancer Registry Center in

collaboration with the epidemiology unit of the Fondazione IRCCS Istituto Nazionale Tumori, Milan (INT), responsible for the European projects RARECARE and RARECAREnet to measure the burden of rare cancers [4]. This collaboration is a part of initiatives named Rare Cancers Asia (<https://www.esmo.org/newsroom/press-office/rare-cancers-asia-improve-patient-care>).

In the current study, we performed the analysis in several organized steps; data quality check of the Asian data for comparability, calculation of crude incidence rates in the three Asian countries and EU according to the RARECARE list to verify its applicability, and comparison of age-standardized rates among the three countries to analyze the difference.

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2. Material and methods

2.1. Data source and quality control

The RARECAREnet Asia project is based on PBCR data including cancer patients diagnosed from 2011 to 2015 in Japan, Korea, and Taiwan and from 2000 to 2007 in Europe (EU). In Japan, the PBCR covers 100% of the population since 2012; however the high-quality prefectural data (DCO% < 10%) is available in 37 to 43 prefectures out of 47 during the 5-year observation period, which corresponded to 446,045,783. In Korea and Taiwan, the coverage was 100%. The populations in the period were 252,730,670 in Korea and 116,675,104 in Taiwan. In EU, the RARECAREnet database, drawn from the EURO-CARE-5 including 94 PBCRs (www.rarecarenets.eu) was used. The average European population covered during the period was about 207,942,000, corresponding to 48% of the population of countries participating in RARECAREnet and 46% of the population of the EU28.

Systematic data checks were performed to detect errors, inconsistencies, or unusual combinations of site, morphology, sex, and age at diagnosis according to IARC/IACR check logic in each country [5]. The following data quality indicators were calculated for incident malignant cancers collected (Table 1):

- 1 proportion of cases known from Death Certificate Only (DCO);
- 2 proportion of cases diagnosed incidentally at autopsy;
- 3 proportion of Microscopically Verified (MV) cases;
- 4 proportion of Not Otherwise Specified (NOS) morphology (for solid cancers: ICD-O-3 8000 Neoplasm, malignant; 8001 Tumour cells, malignant; 8010 Carcinoma, NOS; for hematological diseases: ICD-O-3 9590 Lymphoma, NOS; 9591 Non-Hodgkin lymphoma, NOS; 9760 Immunoproliferative diseases, NOS; 9820 Lymphoid leukaemia, NOS; 9800 Leukaemia, NOS; 9801 Acute leukaemia, NOS; 9860 Myeloid leukaemia, NOS; and 9989 Myelodysplastic syndrome, NOS)
- 5 proportion of NOS topography (ICD-O-3: C14.0; C14.8; C26.0; C26.8; C26.9; C39.0; C39.8-C39.9; C57.7; C57.8; C57.9; C55.9; C63.2; C63.8; C63.9; C68.8; C68.9; C75.2; C75.4; C75.5; C75.8; C75.9; C76.0-76.8)

In addition, several quality indicators were verified (Tables 4–6 in Annexes).

2.2. List of cancers and definition of rare cancers

The present analyses are based on the updated version (as of

January 2019) of the standard list of rare cancers provided by RARECAREnet expert panel and endorsed by major European cancer organizations [6]. The list is organized into three tiers: the bottom tier (Tier 3) corresponds to the WHO names of individual cancer entities (<http://whobluebooks.iarc.fr/>) and their corresponding ICD-O-3 codes. Tier 3 entities were grouped into categories (Tier 2) by using morphologies and topographies. These entities had to be viewed as clinically relevant by clinicians and correspond to consistent diagnostic and therapeutic approaches. The Tier 2 entities were then assembled into Tier 1 entities, which also included the NOS morphologies of any site. Tier 1 entities were intended to be major cancer entities in a clinical sense and to have an organizational importance: for example, they could underlie patient referral policies. However, focusing on referral of patients, Tier 1 entities have been grouped into gross partitions called “Families” identifying major groups of cancer diseases.

Rare cancers are defined as Tier 2 entities with an incidence < 6/100,000/year according to the EU data, and the Tier 1 and Families of rare/common cancers is fixed according to the study, and will not be modified by time or location. Accordingly, the 12 Families of rare cancers are 1. head and neck, 2. digestive rare, 3. thoracic rare, 4. female genital rare, 5. male genital and urogenital rare, 6. skin rare, 7. pediatric, 8. sarcomas, 9. neuroendocrine, 10. endocrine organ, 11. central nervous system, and 12. hematological rare. Likewise, the 7 families of common cancers are; digestive common, female genital common, thoracic common, breast, male genital and urogenital common, skin common, hematological common.

2.3. Statistical analysis

Crude incidence rates (CRs) were estimated as the number of new cases occurring in 2011–2015 in Asian countries and in 2000–2007 in EU divided by the total person-years in the covered area in the general population of both sexes, over the same period. Age-standardized rates (ASRs) were calculated according to the world standard population in order to compare the incidence risks of rare cancers in the three Asian countries. Analysis was performed in each country using SEER*Stat vers. 8.3.5 (<https://seer.cancer.gov/seerstat/>).

3. Results

3.1. Data quality check for comparability

The proportions of DCO cases were 5.1% in Japan, 1.1% in Korea, and 0.8% in Taiwan. The proportions of cases discovered at autopsy were 0.05% in Japan, 0.0% in Korea, and 0.00% in Taiwan. The

Table 1

Data quality indicators of malignant cancers diagnosed in Asian cancer registries 2011–2015 and included in the analyses.

Registry	No of malignant cases	Quality indicators				
		DCO %	Autopsy %	MV %	Morphology NOS* (%)	Topography NOS** (%)
Japan	3,087,224	5.1%	0.05%	83.7%	16.5%	1.8%
Korea	1,100,891	1.1%	0.0%	90.3%	6.9%	0.9%
Taiwan	497,806	0.8%	0.0%	91.3%	3.1%	0.2%

* ICD-O-3 8000, 8001, 8010 for solid cancers and 9590, 9591, 9760, 9820, 9800, 9801, 9860, 9989 for hematological diseases.

** ICD-O-3: C14.0; C14.8; C26.0; C26.8; C26.9; C39.0; C39.8-C39.9; C57.7; C57.8; C57.9; C55.9; C63.2; C63.8; C63.9; C68.8; C68.9; C75.2; C75.4; C75.5; C75.8; C75.9; C76.0–76.8.

Table 2a
Crude incidence of rare cancers according to the RARECARE net list for 3 Asian countries and the EU.

Families	Tier	List	Japan (2011-15)			Korea (2011-15)			Taiwan (2011-15)			Europe (2000-07)		
			Crude rate	n	Common/Rare	Crude rate	n	Common/Rare	Crude rate	n	Common/Rare	Crude rate	n	Common/Rare
1. HEAD & NECK	1	EPITHELIAL TUMOURS OF NASAL CAVITY AND SINUSES	0.94	4,172		0.41	1,032		0.52	603		0.45	7,046	
	2	Squamous cell carcinoma with variants of nasal cavity and sinuses	0.72	3,232	R	0.33	835	R	0.41	477	R	0.35	5,465	R
	2	Lymphoepithelial carcinoma of nasal cavity and sinuses	0.00	7	R	0.00	10	R	0.01	10	R	0.00	31	R
	2	Undifferentiated carcinoma of nasal cavity and sinuses	0.02	92	R	0.01	33	R	0.03	38	R	0.02	286	R
	2	Intestinal type adenocarcinoma of nasal cavity and sinuses	0.00	7	R	0.00	3	R	0.01	10	R	0.00	42	R
	1	EPITHELIAL TUMOURS OF NASOPHARYNX	0.54	2,430		0.77	1,950		6.66	7,771		0.47	7,439	
	2	Squamous cell carcinoma with variants of nasopharynx	0.43	1,912	R	0.38	958	R	6.50	7,584	C	0.36	5,613	R
	2	Papillary adenocarcinoma of nasopharynx	0.00	10	R	0.00	7	R	0.01	14	R	0.00	17	R
	1	EPITHELIAL TUMOURS OF MAJOR SALIVARY GLANDS AND SALIVARY GLAND TYPE TUMOURS	1.67	7,470		1.33	3,356		1.68	1,962		1.32	20,734	
	2	Epithelial tumour of major salivary glands	1.21	5,389	R	0.94	2,374	R	1.14	1,334	R	0.96	15,053	R
	2	Salivary gland type tumour of head and neck	0.47	2,081	R	0.39	982	R	0.54	628	R	0.36	5,681	R
	1	EPITHELIAL TUMOURS OF HYPOPHARYNX AND LARYNX	7.00	31,214		3.03	7,656		7.30	8,517		6.33	99,176	
	2	Squamous cell carcinoma with variants of hypopharynx	2.70	12,034	R	0.75	1,890	R	4.36	5,087	R	1.27	19,828	R
	2	Squamous cell carcinoma with variants of larynx	3.69	16,441	R	2.10	5,316	R	2.75	3,208	R	4.61	72,210	R
	1	EPITHELIAL TUMOURS OF OROPHARYNX	2.47	11,005		1.31	3,300		6.23	7,270		3.34	52,247	
	2	Squamous cell carcinoma with variants of oropharynx	2.24	10,013	R	1.24	3,136	R	6.08	7,096	C	3.13	49,004	R
	1	EPITHELIAL TUMOURS OF ORAL CAVITY AND LIP	6.49	28,969		1.92	4,841		20.19	23,557		4.78	74,890	
	2	Squamous cell carcinoma with variants of oral cavity	5.74	25,622	R	1.75	4,422	R	18.73	21,849	C	3.51	54,931	R
	2	Squamous cell carcinoma with variants of lip	0.11	475	R	0.07	176	R	1.22	1,427	R	1.02	15,984	R
	1	EPITHELIAL TUMOURS OF EYE AND ADNEXA	0.09	395		0.07	164		0.07	79		0.15	2,364	
	2	Squamous cell carcinoma with variants of eye and adnexa	0.04	171	R	0.03	75	R	0.04	43	R	0.04	659	R
	2	Adenocarcinoma with variants of eye and adnexa	0.03	140	R	0.02	52	R	0.03	29	R	0.01	221	R
2. DIGESTIVE	1	EPITHELIAL TUMOURS OF MIDDLE EAR	0.02	110		0.01	30		0.02	23		0.03	524	
	2	Squamous cell carcinoma with variants middle ear	0.02	82	R	0.01	20	R	0.01	16	R	0.02	377	R
	2	Adenocarcinoma with variants of middle ear	0.00	10	R	0.00	4	R	0.00	4	R	0.00	50	R
			1.86	8,279		0.70	1,772		0.66	772		0.77	12,132	
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Table 2a (continued)

Families	Tier	List	Japan (2011-15)			Korea (2011-15)			Taiwan (2011-15)			Europe (2000-07)		
			Crude rate	n	Common/Rare	Crude rate	n	Common/Rare	Crude rate	n	Common/Rare	Crude rate	n	Common/Rare
EPITHELIAL TUMOURS OF SMALL INTESTINE														
	2	Adenocarcinoma with variants of small intestine	1.52	6,790	R	0.58	1,467	R	0.59	685	R	0.59	9,219	R
	2	Squamous cell carcinoma with variants of small intestine	0.01	27	R	0.01	18	R	0.01	6	R	0.01	133	R
	1	EPITHELIAL TUMOURS OF ANAL CANAL	0.71	3,174		0.49	1,231		0.44	518		1.16	18,155	
	2	Squamous cell carcinoma with variants of anal canal	0.22	972	R	0.27	677	R	0.25	294	R	0.81	12,691	R
	2	Adenocarcinoma with variants of anal canal	0.40	1,776	R	0.19	471	R	0.18	204	R	0.25	3,970	R
	2	Paget s disease of anal canal	0.00	21	R	0.00	11	R	0.01	6	R	0.00	21	R
	1	EPITHELIAL TUMOURS OF GALLBLADDER AND EXTRAHEPATIC BILIARY TRACT (EBT)	18.15	80,946		11.32	28,610		4.09	4,776		4.44	69,633	
	2	Adenocarcinoma with variants of gallbladder	3.07	13,683	R	2.95	7,451	R	0.89	1,040	R	1.35	21,084	R
	2	Adenocarcinoma with variants of EBT	6.90	30,766	C	5.57	14,067	R	2.72	3,171	R	1.44	22,507	R
	2	Squamous cell carcinoma of gallbladder and EBT	0.07	290	R	0.04	90	R	0.01	14	R	0.03	496	R
3. THORACIC	1	EPITHELIAL TUMOURS OF TRACHEA	0.05	240		0.04	112		0.07	81		0.11	1,783	
	2	Squamous cell carcinoma with variants of trachea	0.02	104	R	0.02	47	R	0.03	40	R	0.06	1,017	R
	2	Adenocarcinoma with variants of trachea	0.00	8	R	0.00	6	R	0.01	8	R	0.01	164	R
	2	Salivary gland type tumour of trachea	0.02	84	R	0.02	47	R	0.02	26	R	0.01	175	R
	1	EPITHELIAL TUMOURS OF THYMUS	0.87	3,875		0.71	1,787		1.05	1,230		0.18	2,795	
	2	Malignant thymoma	0.60	2,666	R	0.53	1,336	R	0.90	1,044	R	0.14	2,268	R
	2	Squamous cell carcinoma of thymus	0.17	755	R	0.11	272	R	0.10	116	R	0.01	114	R
	2	Adenocarcinoma with variants of thymus	0.03	112	R	0.02	39	R	0.01	14	R	0.01	89	R
	1	MALIGNANT MESOTHELIOMA	1.27	5,681		0.25	635		0.36	416		2.14	33,552	
	2	Mesothelioma of pleura and pericardium	1.10	4,922	R	0.14	359	R	0.26	298	R	1.83	28,676	R
4. FEMALE GENITAL RARE	2	Mesothelioma of peritoneum and tunica vaginalis	0.12	516	R	0.07	166	R	0.07	83	R	0.13	2,065	R
	1	NON EPITHELIAL TUMOURS OF OVARY	0.30	1,340		0.33	827		0.46	534		0.25	3,977	
	2	Sex cord tumour of ovary	0.03	141	R	0.09	234	R	0.17	203	R	0.13	2,006	R
	2	Malignant/Immature teratoma of ovary	0.16	712	R	0.10	250	R	0.14	160	R	0.05	833	R
	2	Germ cell tumour of ovary	0.11	487	R	0.14	343	R	0.14	168	R	0.07	1,138	R
	1	EPITHELIAL TUMOURS OF VULVA AND VAGINA	0.83	3,718		0.36	910		0.63	736		1.97	30,933	
	2	Squamous cell carcinoma with variants of vulva and vagina	0.52	2,330	R	0.25	626	R	0.49	571	R	1.69	26,416	R
	2	Adenocarcinoma with variants of vulva and vagina	0.05	222	R	0.03	67	R	0.06	64	R	0.07	1,120	R
	2	Paget s disease of vulva and vagina	0.20	872	R	0.06	157	R	0.06	70	R	0.05	746	R
	2	Undifferentiated carcinoma of vulva and vagina	0.00	2	R	0.00	0	R	0.00	1	R	0.01	85	R
2	Mullerian mixed tumour of vulva and vagina	0.00	2	R	0.00	1	R	0.00	2	R	0.00	63	R	

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Table 2a (continued)

Families	Tier	List	Japan (2011-15)			Korea (2011-15)			Taiwan (2011-15)			Europe (2000-07)		
			Crude rate	n	Common/Rare	Crude rate	n	Common/Rare	Crude rate	n	Common/Rare	Crude rate	n	Common/Rare
5. MALE GENITAL	1	1 TROPHOBLASTIC TUMOURS OF PLACENTA	0.04	168		0.08	203		0.04	48		0.03	403	
	2	Chorio carcinoma of placenta	0.03	149	R	0.06	160	R	0.04	41	R	0.02	352	R
	1	1 TESTICULAR AND PARATESTICULAR CANCERS	1.44	6,413		0.48	1,206		0.94	1,094		3.29	51,601	
	2	Paratesticular adenocarcinoma with variants	0.00	14	R	0.00	9	R	0.01	8	R	0.00	22	R
	2	Non seminomatous testicular cancer	0.40	1,781	R	0.19	471	R	0.45	526	R	1.27	19,835	R
	2	Seminomatous testicular cancer	0.96	4,286	R	0.26	650	R	0.45	523	R	1.82	28,516	R
	2	Spermatocytic seminoma	0.01	28	R	0.00	10	R	0.00	4	R	0.03	502	R
	2	Teratoma with malignant transformation	0.00	14	R	0.00	0	R	0.00	0	R	0.00	20	R
	2	Testicular sex cord cancer	0.00	15	R	0.01	18	R	0.00	3	R	0.02	332	R
	1	1 EPITHELIAL TUMOURS OF PENIS	0.38	1,684		0.13	321		0.24	274		0.66	10,371	
	2	Squamous cell carcinoma with variants of penis	0.26	1,180	R	0.10	249	R	0.21	240	R	0.62	9,649	R
	2	Adenocarcinoma with variants of penis	0.08	360	R	0.02	58	R	0.03	30	R	0.01	88	R
6. SKIN	1	1 EPITHELIAL TUMOURS OF PELVIS AND URETER	5.79	25,835		1.88	4,752		5.70	6,645		1.58	24,826	
	2	Transitional cell carcinoma of pelvis and ureter	4.13	18,430	R	1.62	4,103	R	5.29	6,166	R	1.40	21,975	R
	2	Squamous cell carcinoma with variants of pelvis and ureter	0.08	357	R	0.02	40	R	0.06	73	R	0.03	496	R
	2	Adenocarcinoma with variants of pelvis and ureter	0.05	221	R	0.01	35	R	0.17	192	R	0.02	326	R
	1	1 EPITHELIAL TUMOURS OF URETHRA	0.12	536		0.06	162		0.10	113		0.13	2,096	
	2	Transitional cell carcinoma of urethra	0.05	231	R	0.02	59	R	0.06	73	R	0.09	1,382	R
	2	Squamous cell carcinoma with variants of urethra	0.02	99	R	0.01	23	R	0.01	7	R	0.02	343	R
	2	Adenocarcinoma with variants of urethra	0.03	131	R	0.02	56	R	0.02	26	R	0.01	199	R
	1	1 EXTRAGONADAL GERM CELL TUMOURS	0.26	1,170		0.30	753		0.41	476		0.12	1,874	
	2	Non seminomatous germ cell tumour	0.08	372	R	0.10	242	R	0.15	180	R	0.06	927	R
	2	Seminomatous germ cell tumor	0.03	133	R	0.02	46	R	0.02	18	R	0.01	130	R
	2	Germ cell tumour of CNS	0.12	536	R	0.16	411	R	0.18	211	R	0.04	574	R
7. PEDIATRIC	1	1 MALIGNANT MELANOMA OF MUCOSA AND EXTRACUTANEOUS	0.36	1,621		0.19	471		0.22	254		0.15	2,279	
	2	Malignant melanoma of mucosa and extracutaneous	0.36	1,621	R	0.19	471	R	0.22	254	R	0.15	2,279	R
	1	1 MALIGNANT MELANOMA OF UVEA	0.05	211		0.07	181		0.06	66		0.52	8,073	
	2	Malignant melanoma of uvea	0.05	211	R	0.07	181	R	0.06	66	R	0.52	8,073	R
	1	1 ADENEXAL CARCINOMAS OF SKIN	1.01	4,513		0.49	1,238		0.74	868		0.35	5,575	
	2	Adnexal carcinoma of skin	1.01	4,513	R	0.49	1,238	R	0.74	868	R	0.35	5,575	R
	1	1 KAPOSI S SARCOMA	0.04	166		0.12	292		0.41	480		0.25	3,893	
	2	Kaposi's sarcoma	0.04	166	R	0.12	292	R	0.41	480	R	0.25	3,893	R
	1	1 NEUROBLASTOMA AND GANGLIONEUROBLASTOMA	0.12	539		0.16	412		0.13	153		0.14	2,163	
	2	Neuroblastoma and ganglioneuroblastoma	0.12	539	R	0.16	412	R	0.13	153	R	0.14	2,163	R
	1	1 NEPHROBLASTOMA	0.04	169		0.05	127		0.04	50		0.13	1,965	
	2	Nephroblastoma	0.04	169	R	0.05	127	R	0.04	50	R	0.13	1,965	R
	1	1 EMBRYONAL TUMOURS OF EYE	0.04	194		0.06	158		0.06	69		0.06	878	

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Table 2a (continued)

Families	Tier	List	Japan (2011-15)			Korea (2011-15)			Taiwan (2011-15)			Europe (2000-07)		
			Crude rate	n	Common/Rare	Crude rate	n	Common/Rare	Crude rate	n	Common/Rare	Crude rate	n	Common/Rare
8. SARCOMAS	2	Retinoblastoma	0.04	194	R	0.06	158	R	0.06	69	R	0.06	876	R
	2	Medulloepithelioma	0.00	0	R	0.00	0	R	0.00	0	R	0.00	2	R
	1	HEPATOBlastoma	0.04	185	R	0.04	104	R	0.06	65	R	0.02	357	R
	2	Hepatoblastoma	0.04	185	R	0.04	104	R	0.06	65	R	0.02	357	R
	1	PLEUROPULMONARY BLASTOMA	0.00	8	R	0.00	10	R	0.00	4	R	0.00	10	R
	2	Pleuropulmonary blastoma	0.00	8	R	0.00	10	R	0.00	4	R	0.00	10	R
	1	PANCREATOBlastoma	0.00	8	R	0.00	4	R	0.00	3	R	0.00	39	R
	1	Pancreatoblastoma	0.00	8	R	0.00	4	R	0.00	3	R	0.00	39	R
	1	OLFACATORY NEUROBLASTOMA	0.06	269	R	0.04	99	R	0.08	92	R	0.03	511	R
	2	Olfactory neuroblastoma	0.06	269	R	0.04	99	R	0.08	92	R	0.03	511	R
	1	ODONTOGENIC MALIGNANT TUMOURS	0.02	77	R	0.01	32	R	0.01	16	R	0.02	285	R
	2	Odontogenic malignant tumour	0.02	77	R	0.01	32	R	0.01	16	R	0.02	285	R
	1	SOFT TISSUE SARCOMA	4.51	20,127	R	3.90	9,859	R	5.42	6,326	R	4.69	73,440	R
	2	Soft tissue sarcoma of head and neck	0.24	1,079	R	0.23	575	R	0.33	381	R	0.24	3,827	R
	2	Soft tissue sarcoma of limbs	1.12	5,011	R	0.87	2,186	R	1.09	1,273	R	1.10	17,186	R
	2	Soft tissue sarcoma of superficial trunk	0.45	1,997	R	0.40	1,004	R	0.56	657	R	0.50	7,807	R
	2	Soft tissue sarcoma of mediastinum	0.06	266	R	0.03	85	R	0.05	63	R	0.03	465	R
	2	Soft tissue sarcoma of heart	0.03	144	R	0.03	72	R	0.01	16	R	0.01	216	R
	2	Soft tissue sarcoma of breast	0.15	689	R	0.19	478	R	0.33	390	R	0.18	2,858	R
	2	Soft tissue sarcoma of uterus	0.58	2,593	R	0.47	1,188	R	0.70	817	R	0.55	8,652	R
	2	Soft tissue sarcoma of paratestis	0.04	157	R	0.02	41	R	0.04	47	R	0.03	510	R
	2	Soft tissue sarcomas of other genitourinary tract (vulva, vagina, ovary, penis, prostate, testis, kidney, renal pelvis, ureter, bladder, urethra)	0.14	607	R	0.13	326	R	0.15	173	R	0.20	3,155	R
	2	Soft tissue sarcoma of viscera	0.25	1,123	R	0.31	785	R	0.43	506	R	0.38	5,946	R
	2	Soft tissue sarcoma of retroperitoneum and peritoneum	0.51	2,282	R	0.29	730	R	0.47	543	R	0.31	4,908	R
	2	Soft tissue sarcoma of pelvis	0.18	808	R	0.18	463	R	0.24	277	R	0.19	3,033	R
	2	Soft tissue sarcoma of skin	0.36	1,623	R	0.37	940	R	0.57	667	R	0.30	4,734	R
	2	Soft tissue sarcoma of paraorbit	0.01	23	R	0.01	13	R	0.01	7	R	0.01	118	R
	2	Soft tissue sarcoma of brain and other parts of nervous system	0.13	565	R	0.14	345	R	0.13	152	R	0.17	2,704	R
	2	Embryonal rhabdomyosarcoma of soft tissue	0.02	102	R	0.04	93	R	0.05	52	R	0.05	814	R
	2	Alveolar rhabdomyosarcoma of soft tissue	0.02	107	R	0.03	70	R	0.03	38	R	0.03	516	R
9. NEUROENDOCRINE	2	Ewing's sarcoma of soft tissue	0.06	281	R	0.08	210	R	0.09	100	R	0.07	1,002	R
	1	BONE SARCOMA	0.63	2,805	R	0.88	2,219	R	0.73	852	R	0.89	13,870	R
	2	Osteogenic sarcoma	0.21	953	R	0.34	860	R	0.29	341	R	0.24	3,806	R
	2	Chondrogenic sarcoma	0.17	769	R	0.26	654	R	0.17	192	R	0.29	4,572	R
	2	Notochordal sarcoma, chordoma	0.09	421	R	0.10	252	R	0.11	122	R	0.07	1,145	R
	2	Vascular sarcoma	0.01	46	R	0.01	23	R	0.02	26	R	0.01	160	R
	2	Ewing's sarcoma	0.04	161	R	0.07	170	R	0.05	59	R	0.12	1,955	R
	2	Other high grade sarcomas (fibrosarcoma, malignant fibrous histiocytoma)	0.02	110	R	0.01	25	R	0.01	7	R	0.02	322	R
	1	GASTROINTESTINAL STROMAL SARCOMA	1.20	5,336	R	1.34	3,382	R	2.08	2,427	R	0.30	4,706	R
	2	Gastrointestinal stromal sarcoma	1.20	5,336	R	1.34	3,382	R	2.08	2,427	R	0.30	4,706	R
	1	NET GEP	3.85	17,157	R	4.27	10,800	R	2.81	3,273	R	1.71	26,831	R
	2		2.53	11,285	R	3.26	8,229	R	1.95	2,279	R	1.01	15,852	R

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Table 2a (continued)

Families	Tier	List	Japan (2011-15)			Korea (2011-15)			Taiwan (2011-15)			Europe (2000-07)		
			Crude rate	n	Common/Rare	Crude rate	n	Common/Rare	Crude rate	n	Common/Rare	Crude rate	n	Common/Rare
10. ENDOCRINE ORGAN		Well diff not funct endocrine carcinoma of pancreas and digestive tract												
	2	Well diff funct endocrine carcinoma of pancreas and digestive tract	0.02	106	R	0.00	8	R	0.01	9	R	0.03	411	R
	2	Poorly differentiated endocrine carcinoma	1.28	5,707	R	1.01	2,550	R	0.84	975	R	0.67	10,421	R
	2	Malignant mixed pancreatic endocrine and exocrine tumour	0.01	59	R	0.01	13	R	0.01	10	R	0.01	147	R
	1	NET LUNG	0.21	938	R	0.14	357	R	0.17	198	R	0.39	6,160	R
	2	Typical and atypical carcinoid of the lung	0.21	938	R	0.14	357	R	0.17	198	R	0.39	6,160	R
	1	NET OTHER SITES	1.11	4,956	R	0.85	2,142	R	1.11	1,292	R	1.40	21,948	R
	2	Pheochromocytoma, malignant	0.04	181	R	0.05	131	R	0.03	34	R	0.04	645	R
	2	Paraganglioma	0.02	85	R	0.03	65	R	0.02	18	R	0.02	347	R
	2	Endocrine carcinoma of thyroid gland	0.12	531	R	0.31	785	R	0.16	183	R	0.24	3,810	R
11. CENTRAL NERVOUS	2	Neuroendocrine carcinoma of skin	0.15	672	R	0.07	172	R	0.07	84	R	0.19	3,026	R
	2	Neuroendocrine carcinoma of other sites	0.78	3,487	R	0.39	989	R	0.83	973	R	0.90	14,120	R
	1	CARCINOMAS OF PITUITARY GLAND	0.06	258	R	0.05	113	R	0.01	11	R	0.04	584	R
	2	Carcinoma of pituitary gland	0.06	258	R	0.05	113	R	0.01	11	R	0.04	584	R
	1	CARCINOMAS OF THYROID GLAND	10.79	48,129	C	72.83	184,055	C	13.29	15,508	C	5.07	79,420	R
	2	Carcinoma of thyroid gland	10.79	48,129	C	72.83	184,055	C	13.29	15,508	C	5.07	79,420	R
	1	CARCINOMAS OF PARATHYROID GLAND	0.02	91	R	0.03	80	R	0.02	27	R	0.03	410	R
	2	Carcinoma of parathyroid gland	0.02	91	R	0.03	80	R	0.02	27	R	0.03	410	R
	1	CARCINOMAS OF ADRENAL CORTEX	0.16	701	R	0.14	356	R	0.13	149	R	0.22	3,424	R
	2	Carcinoma of adrenal cortex	0.16	701	R	0.14	356	R	0.13	149	R	0.22	3,424	R
12. HEMATOLOGICAL RARE	1	TUMOURS OF CENTRAL NERVOUS SYSTEM (CNS)	4.01	17,887	R	3.19	8,067	R	3.00	3,504	R	7.36	115,255	R
	2	Astrocytic tumors of CNS	2.56	11,439	R	2.09	5,278	R	2.24	2,614	R	4.98	78,007	R
	2	Oligodendroglial tumors of CNS	0.20	878	R	0.27	676	R	0.21	240	R	0.39	6,148	R
	2	Ependymal tumors of CNS	0.11	500	R	0.18	464	R	0.14	168	R	0.19	2,937	R
	2	Neuronal and mixed neuronal-glial tumors	0.00	21	R	0.00	10	R	0.02	18	R	0.00	74	R
	2	Choroid plexus carcinoma of CNS	0.00	18	R	0.01	15	R	0.01	10	R	0.01	144	R
	2	Malignant meningiomas	0.20	882	R	0.13	318	R	0.25	289	R	0.22	3,376	R
	2	Tumours of the pineal gland	0.03	113	R	0.03	72	R	0.02	17	R	0.02	293	R
	1	EMBRYONAL TUMOURS OF CNS	0.09	414	R	0.12	303	R	0.14	160	R	0.20	3,152	R
	2	Embryonal tumour of CNS	0.09	414	R	0.12	303	R	0.14	160	R	0.20	3,152	R
13. HEMATOLOGICAL RARE	1	ACUTE MYELOID LEUKEMIA AND RELATED PRECURSOR NEOPLASMS	4.90	21,836	R	3.02	7,637	R	3.43	4,000	R	4.01	62,767	R
	2	Acute promyelocytic leukemia (AML with t(15;17) with variants	0.39	1,744	R	0.35	890	R	0.26	307	R	0.12	1,876	R
	2	Acute myeloid leukemia	4.50	20,092	R	2.67	6,747	R	3.17	3,693	R	3.89	60,891	R
	1	MYELOID AND LYMPHOID NEOPLASMS	0.23	1,030	R	0.36	908	R	0.05	53	R	0.26	4,076	R
	2	Myeloid and lymphoid neoplasms	0.23	1,030	R	0.36	908	R	0.05	53	R	0.26	4,076	R
	1	MYELOPROLIFERATIVE NEOPLASMS	3.21	14,339	R	2.89	7,306	R	1.88	2,196	R	3.31	51,888	R
	2	Chronic myeloid leukemia	1.42	6,332	R	1.02	2,581	R	0.89	1,042	R	1.12	17,473	R
	2	Other myeloproliferative neoplasms	1.79	8,005	R	1.85	4,668	R	0.99	1,152	R	2.17	33,954	R
	2	Mast cell tumour	0.00	2	R	0.02	57	R	0.00	2	R	0.03	461	R
	1		6.55	29,227	R	1.99	5,023	R	1.68	1,964	R	2.47	38,739	R

(continued on next page)

Table 2a (continued)

Families	Tier	List	Japan (2011-15)			Korea (2011-15)			Taiwan (2011-15)			Europe (2000-07)		
			Crude rate	n	Common/Rare	Crude rate	n	Common/Rare	Crude rate	n	Common/Rare	Crude rate	n	Common/Rare
MYELODYSPLASTIC SYNDROME AND MYELODYSPLASTIC/ MYELOPROLIFERATIVE DISEASES														
	2	Myelodysplastic syndrome with 5q syndrome	0.03	148	R	0.01	21	R	0.02	18	R	0.01	156	R
	2	Other myelodysplastic syndrome	6.18	27,586	C	1.79	4,527	R	1.19	1,385	R	2.14	33,542	R
	2	Chronic Myelomonocytic leukemia	0.29	1,293	R	0.14	340	R	0.16	190	R	0.29	4,542	R
	2	Atypical chronic myeloid leukemia	0.02	97	R	0.03	73	R	0.03	30	R	0.02	239	R
		BCR/ABL negative												
	1	HISTIOCYTIC AND DENDRITIC CELL NEOPLASMS	0.07	331		0.30	748		0.16	190		0.05	828	
	2	Histiocytic malignancies	0.05	215	R	0.27	676	R	0.12	140	R	0.04	656	R
	2	Lymph node accessory cell tumors	0.03	116	R	0.03	72	R	0.04	50	R	0.01	172	R

proportions of morphology NOS were 16.5% in Japan, 6.9 in Korea, and 3.1% in Taiwan (Table 1). The quality of the EU data is reported in Gatta et al. [4]. In the EU, the proportion of all morphologies NOS was 15%. The proportion was comparatively high (>50%) mainly in sites less likely to receive a pathological confirmation (Table 4 in Annex). The myeloid and lymphoid neoplasms tier includes mainly leukemia NOS (ICD-O-3 9800). The proportions of topography NOS overall were 1.8% in Japan, 0.9% in Korea, and 0.2% in Taiwan (Table 1). In EU it was 1%. The topography NOS by site (Table 5 in Annex) ranged from 0.01% to 2.04% in Japan, from 0.03% to 1.57% in Korea, from 0.00% to 3.90% in Taiwan, and from 0.03% to 3.76% in the EU. The topography of soft tissue sarcoma was examined independently (Table 6 in Annex). The overall proportions of MV cases were 83.7% in Japan, 90.3% in Korea, and 91.3% in Taiwan (Table 1). Across different PBCRs, the proportion of MV cases was >85% for most solid cancers, but 70% for CNS tumours, 50–60% for pancreatic, gallbladder, and liver cancers, and 50–70% for eye/uveal tumours (Table 4 in Annex). We concluded that the data in the four areas were of high quality and had no problem to be compared.

3.2. Application of RARECAREnet definition and list of rare cancers in Asia

Rare cancer counts according to Tier 2 in the observed population were 196 in Japan, 203 in Korea, 198 in Taiwan, and 198 in the EU (Tables 2a and 2b). The proportions of rare in overall incidence according to the norm 6/100,000 in each country were 16.3% in Japan, 23.7% in Korea, 24.0% in Taiwan, and 22.2% in the EU. When we apply the rare cancer definition in EU to the Asian countries, the proportions were 26.9% in Japan, 42.1% in Korea and 42.4% in Taiwan. The numbers of newly diagnosed rare cancer cases in 2015 were 140,188 in Japan, 52,071 in Korea, and 24,147 in Taiwan.

The differences between the continents are summarized in Table 3. First, with respect to rare cancers (first column in Table 3), the eight of 12 families included cancers that were rare in both Asian countries and EU, i.e., rare thoracic cancers (epithelial tumours of thymus, trachea and malignant mesothelioma), rare female genital cancers (non-epithelial ovary tumours, vulva and vagina tumours, and trophoblastic tumours), rare skin cancers (mucosal and uveal melanoma, adnexal skin cancers, and Kaposi's sarcoma), pediatric cancers, sarcomas, neuroendocrine tumours, central nervous system tumours, and rare hematological diseases (acute myeloid leukemia, myeloproliferative neoplasms, myelodysplastic syndrome and myelodysplastic/myeloproliferative diseases, and histiocytic and dendritic cell neoplasms). Four families included some cancers that were rare in EU, but not in Asia; in the head and neck cancers family, epithelial tumours of the nasopharynx and oropharynx were not rare in Taiwan, and oral cavity and lip tumours were not rare in Taiwan and Japan; in the family of rare digestive cancers, epithelial tumours of the gallbladder and extrahepatic biliary tract were not rare in Japan and Korea; and of the endocrine tumours, thyroid cancers were not rare in all three Asian countries. As for the common cancers (the second column in Table 3), epithelial tumours of the esophagus and corpus uteri were not common in Korea, epithelial tumours of the ovary were not common in Korea and Taiwan, kidney cancers were not common in Taiwan and Korea, and skin melanoma was not common in all three Asian countries.

When we checked Tier 2 entities in common cancers (the third column in Table 3), differences between Asia and EU were very limited. The clear differences were found in esophagus, hepatocellular carcinoma, poorly differentiated endocrine tumours and breast invasive lobular carcinoma.

3.3. Comparisons of ASRs among the three Asian countries

Figs. 1 and 2 report the ASR for each Tier 1 included in the 12 families of rare cancers. Regarding the head and neck cancer family, Taiwan showed much higher incidences than the other two countries

Table 2b
Crude incidence of common cancers according to the RARECARE net list for 3 Asian countries and the EU.

Families	Tier	List	Japan (2011-15)			Korea (2011-15)			Taiwan (2011-15)			Europe (2000-07)		
			Crude rate	n	Common/rate	Crude rate	n	Common/rate	Crude rate	n	Common/rate	Crude rate	n	Common/rate
DIGESTIVE COMMON	1	EPITHELIAL TUMOURS OF OESOPHAGUS	17.33	77,315		4.62	11,677		10.42	12,161		7.81	122,372	
	2	Squamous cell carcinoma with variants of oesophagus	14.26	63,598	C	4.22	10,664	R	9.79	11,426	C	3.36	52,597	R
	2	Adenocarcinoma with variants of oesophagus	0.98	4,373	R	0.14	354	R	0.40	464	R	3.26	51,138	R
	2	Salivary gland type tumour of oesophagus	0.01	48	R	0.00	9	R	0.01	6	R	0.00	63	R
	2	Undifferentiated carcinoma of oesophagus	0.02	104	R	0.00	3	R	0.01	7	R	0.04	695	R
	1	EPITHELIAL TUMOURS OF STOMACH	100.11	446,553		59.14	149,457		15.15	17,672		17.43	272,978	
	2	Adenocarcinoma with variants of stomach	88.40	394,324	C	56.85	143,665	C	14.62	17,053	C	14.18	222,145	C
	2	Squamous cell carcinoma with variants of stomach	0.16	701	R	0.34	852	R	0.14	160	R	0.12	1,807	R
	2	Salivary gland-type tumour of stomach	0.00	10	R	0.00	1	R	0.00	0	R	0.00	39	R
	2	Undifferentiated carcinoma of stomach	0.08	337	R	0.03	87	R	0.02	25	R	0.21	3,300	R
	1	EPITHELIAL TUMOURS OF COLON (including appendix)	77.94	347,663		35.89	90,695		45.31	52,869		43.15	676,017	
	2	Adenocarcinoma with variants of colon	66.72	297,613	C	33.62	84,974	C	43.53	50,790	C	38.01	595,392	C
	2	Squamous cell carcinoma with variants of colon	0.02	76	R	0.01	35	R	0.01	13	R	0.03	400	R
	2	Fibromixoma and low grade mucinous adenocarcinoma of the appendix	0.24	1060	R	0.18	449	R	0.17	194	R	0.11	1674	R
	1	EPITHELIAL TUMOURS OF RECTUM	25.70	114,619		16.69	42,173		17.98	20,980		18.09	283,461	
	2	Adenocarcinoma with variants of rectum	22.01	98,157	C	15.94	40,282	C	17.66	20,606	C	16.45	257,723	C
	2	Squamous cell carcinoma with variants of rectum	0.03	146	R	0.05	131	R	0.05	60	R	0.11	1,764	R
	1	EPITHELIAL TUMOURS OF PANCREAS	27.96	124,698		10.82	27,349		8.22	9,590		12.92	202,338	
	2	Adenocarcinoma with variants of pancreas	12.67	56,514	C	6.72	16,973	C	6.04	7,049	C	7.96	124,744	C
	2	Squamous cell carcinoma with variants of pancreas	0.04	167	R	0.03	67	R	0.03	33	R	0.02	361	R
FEMALE GENITAL COMMON	2	Acinar cell carcinoma of pancreas	0.07	331	R	0.03	70	R	0.03	39	R	0.03	458	R
	2	Mucinous cystadenocarcinoma of pancreas (invasive)	0.04	168	R	0.01	29	R	0.03	37	R	0.01	109	R
	2	Intraductal papillary mucinous carcinoma of pancreas	0.50	2,222	R	0.14	341	R	0.09	99	R	0.01	173	R
	2	Solid pseudopapillary carcinoma of pancreas	0.01	28	R	0.04	97	R	0.07	81	R	0.00	44	R
	2	Serous cystadenocarcinoma of pancreas	0.00	10	R	0.00	2	R	0.00	4	R	0.00	4	R
	2	Carcinoma with osteoclast-like giant cells of pancreas	0.00	19	R	0.00	2	R	0.00	2	R	0.00	19	R
	1	EPITHELIAL TUMOURS OF LIVER AND INTRAEPATIC BILE TRACT (IBT)	33.09	147,576		31.48	79,546		49.42	57,661		7.10	111,271	
	2	Hepatocellular carcinoma of Liver and IBT	26.39	117,728	C	24.37	61,582	C	44.71	52,162	C	3.22	50,461	R
	2	Hepatocellular carcinoma, fibrolamellar of liver and IBT	0.00	20	R	0.00	6	R	0.01	14	R	0.02	387	R
	2	Cholangiocarcinoma of IBT	2.87	12,816	R	4.34	10,956	R	4.20	4,894	R	0.97	15,201	R
	2	Adenocarcinoma with variants of liver and IBT	0.44	1,949	R	1.61	4,079	R	0.28	331	R	0.41	6,457	R
	2	Undifferentiated carcinoma of liver and IBT	0.01	62	R	0.01	15	R	0.01	6	R	0.02	240	R
	2	Squamous cell carcinoma with variants of liver and IBT	0.02	72	R	0.03	70	R	0.02	25	R	0.01	147	R
	2	Bile duct cystadenocarcinoma of IBT	0.03	134	R	0.01	26	R	0.01	6	R	0.00	38	R
	1	EPITHELIAL TUMOURS OF CORPUS UTERI	10.18	45,409		3.95	9,969		8.25	9,626		11.39	178,482	
	2		8.48	37,804	C	3.34	8,452	R	7.27	8,486	C	10.12	155,771	C
														(continued on next page)

Table 2b (continued)

Families	Tier	List	Japan (2011-15)			Korea (2011-15)			Taiwan (2011-15)			Europe (2000-07)		
			Crude rate	n	Common/rate	Crude rate	n	Common/rate	Crude rate	n	Common/rate	Crude rate	n	Common/rate
		Adenocarcinoma with variants of corpus uteri												
	2	Squamous cell carcinoma with variants of corpus uteri	0.04	192	R	0.04	94	R	0.03	38	R	0.06	1,008	R
	2	Adenoid cystic carcinoma of corpus uteri	0.00	2	R	0.00	0	R	0.00	1	R	0.00	5	R
	2	Clear cell adenocarcinoma, NOS of corpus uteri	0.23	1,019	R	0.07	179	R	0.14	163	R	0.16	2,537	R
	2	Serous (papillary) carcinoma of corpus uteri	0.46	2,040	R	0.19	471	R	0.29	338	R	0.08	1,317	R
	2	Mullerian mixed tumour of corpus uteri	0.43	1,907	R	0.19	467	R	0.40	468	R	0.40	6,293	R
	1	EPITHELIAL TUMOURS OF CERVIX UTERI	8.19	36,530		7.13	18,031		6.54	7,633		6.28	98,321	
	2	Squamous cell carcinoma with variants of cervix uteri	5.83	26,020	R	5.38	13,592	R	4.96	5,782	R	4.73	74,105	R
	2	Adenocarcinoma with variants of cervix uteri	1.61	7,181	R	1.23	3,108	R	1.18	1,382	R	0.91	14,252	R
	2	Undifferentiated carcinoma of cervix uteri	0.01	54	R	0.00	11	R	0.01	9	R	0.03	480	R
	2	Mullerian mixed tumour of cervix uteri	0.02	68	R	0.01	35	R	0.01	13	R	0.02	257	R
	1	EPITHELIAL TUMOURS OF OVARY AND FALLOPIAN TUBE	8.00	35,695		4.38	11,057		5.28	6,162		9.38	146,908	
	2	Adenocarcinoma with variants of ovary	3.78	16,839	R	2.55	6,445	R	3.04	3,546	R	5.95	93,263	R
	2	Mucinous adenocarcinoma of ovary	0.73	3,238	R	0.50	1,267	R	0.71	829	R	0.77	12,066	R
	2	Clear cell adenocarcinoma of ovary	1.41	6,268	R	0.39	985	R	0.88	1,025	R	0.30	4,753	R
	2	Primary peritoneal serous/papillary carcinoma of ovary	0.23	1,044	R	0.12	305	R	0.15	169	R	0.08	1,280	R
	2	Mullerian mixed tumour of ovary	0.11	479	R	0.07	169	R	0.09	106	R	0.15	2,348	R
	2	Adenocarcinoma with variant of fallopian tube	0.27	1,210	R	0.13	333	R	0.19	222	R	0.17	2,694	R
	1	EPITHELIAL TUMOURS OF LUNG	88.42	394,395		45.85	115,872		52.04	60,722		57.39	899,066	
	2	Squamous cell carcinoma with variants of lung	15.36	68,511	C	10.69	27,024	C	8.53	9,953	C	14.10	220,896	C
	2	Adenocarcinoma with variants of lung	39.50	176,180	C	19.49	49,250	C	32.95	38,442	C	11.63	182,175	C
	2	Adenosquamous carcinoma of lung	0.71	3,150	R	0.24	614	R	0.66	766	R	0.29	4,607	R
	2	Large cell carcinoma of lung	0.56	2,504	R	0.10	243	R	0.17	195	R	2.02	31,589	R
	2	Poorly differentiated endocrine carcinoma of lung	8.03	35,809	C	5.33	13,464	R	4.38	5,112	R	7.91	123,888	C
	2	Salivary gland type tumour of lung	0.08	365	R	0.10	240	R	0.09	110	R	0.06	894	R
	2	Sarcomatoid carcinoma of lung	0.62	2,760	R	0.36	920	R	0.41	474	R	0.21	3,255	R
	1	EPITHELIAL TUMOURS OF BREAST	59.29	264,454		34.58	87,399		48.04	56,047		67.17	1,052,250	
	2	Invasive carcinoma of no special type-NST (obs Invasive ductal carcinoma of breast)	48.20	215,016	C	30.11	76,099	C	42.02	49,024	C	48.65	762,142	C
	2	Invasive lobular carcinoma of breast	2.56	11,439	R	1.47	3,706	R	2.21	2,582	R	7.75	121,455	C
	2	Mammary Paget's disease of breast	0.10	445	R	0.16	397	R	0.50	580	R	0.41	6,488	R
	2	Special types of adenocarcinoma of breast	2.97	13,232	R	1.56	3,952	R	1.99	2,322	R	3.31	51,796	R
	2	Metaplastic carcinoma of breast	0.25	1,134	R	0.27	678	R	0.33	383	R	0.12	1,889	R
	2	Salivary gland type tumour of breast	0.05	236	R	0.04	88	R	0.05	55	R	0.06	868	R
	1	EPITHELIAL TUMOURS OF PROSTATE	59.34	264,693		19.03	48,087		20.88	24,357		55.66	872,015	
	2	Adenocarcinoma with variants of prostate	52.35	233,522	C	18.16	45,899	C	20.38	23,778	C	48.86	765,405	C
	2	Squamous cell carcinoma with variants of prostate	0.01	61	R	0.01	12	R	0.01	6	R	0.02	291	R
	2	Infiltrating duct carcinoma of prostate	0.11	504	R	0.04	104	R	0.06	71	R	0.51	8,064	R
	2	Transitional cell carcinoma of prostate	0.03	131	R	0.05	134	R	0.00	3	R	0.06	960	R
	2	Basal cell adenocarcinoma of prostate	0.00	2	R	0.00	0	R	0.00	3	R	0.01	122	R
	1	EPITHELIAL TUMOURS OF KIDNEY	12.82	57,171		8.40	21,223		5.30	6,188		12.71	199,131	

(continued on next page)

Table 2b (continued)

Families	Tier	List	Japan (2011-15)			Korea (2011-15)			Taiwan (2011-15)			Europe (2000-07)		
			Crude rate	n	Common/rate	Crude rate	n	Common/rate	Crude rate	n	Common/rate	Crude rate	n	Common/rate
SKIN COMMON	2	Renal cell carcinoma with variants	10.22	45,604	C	7.59	19,188	C	5.04	5,884	R	10.08	157,885	C
	2	Squamous cell carcinoma spindle cell type of kidney	0.01	48	R	0.00	7	R	0.00	5	R	0.01	190	R
	2	Squamous cell carcinoma with variants of kidney	0.01	49	R	0.01	31	R	0.00	5	R	0.03	533	R
	1	EPITHELIAL TUMOURS OF BLADDER	16.05	71,593		7.51	18,990		9.04	10,551		18.22	285,389	
	2	Transitional cell carcinoma of bladder	12.77	56,975	C	6.74	17,026	C	8.60	10,037	C	15.68	245,681	C
	2	Squamous cell carcinoma with variants of bladder	0.22	962	R	0.04	100	R	0.06	70	R	0.36	5,566	R
	2	Adenocarcinoma with variants of bladder	0.27	1,213	R	0.17	417	R	0.19	222	R	0.30	4,663	R
	2	Salivary gland type tumour of bladder	0.00	0	R	0.00	0	R	0.00	0	R	0.00	7	R
	1	MALIGNANT SKIN MELANOMA	1.30	5,817		1.07	2,701		1.15	1,342		14.06	220,206	
	2	Malignant skin melanoma	1.30	5,817	R	1.07	2,701	R	1.15	1,342	R	14.06	220,206	C
HEMATOLOGICAL COMMON	1	EPITHELIAL TUMOURS OF SKIN	12.34	55,061		7.58	19,150		12.30	14,352		55.03	862,079	
	2	Basal cell carcinoma of skin	7.34	32,760	C	4.95	12,507	R	7.67	8,950	C	40.75	638,347	C
	2	Squamous cell carcinoma with variants of skin	5.00	22,292	R	2.63	6,638	R	4.63	5,397	R	14.28	223,691	C
	1	LYMPHOID DISEASES	30.82	137,479		13.89	35,105		15.55	18,148		29.12	456,219	
	2	Hodgkin lymphoma, classical	0.92	4,111	R	0.52	1,320	R	0.83	964	R	2.46	38,588	R
	2	Hodgkin lymphoma nodular lymphocyte predominance	0.05	232	R	0.02	38	R	0.03	37	R	0.09	1,483	R
	2	Precursor B/T lymphoblastic leuk/lymphoma (and Burkitt leukemia/lymphoma)	1.55	6,924	R	1.36	3,438	R	1.41	1,650	R	1.46	22,795	R
	2	T cutaneous lymphoma (Sezary syn, Mycosis fung)	0.37	1,638	R	0.17	434	R	0.19	223	R	0.35	5,526	R
	2	Other T cell lymphomas and NK cell neoplasms	2.65	11,813	R	1.23	3,103	R	1.20	1,401	R	0.62	9,656	R
	2	Diffuse B lymphoma	9.58	42,727	C	4.28	10,808	R	5.58	6,510	R	4.32	67,645	R
	2	Follicular B lymphoma	3.19	14,238	R	0.49	1,239	R	1.11	1,292	R	2.19	34,346	R
	2	Hairy cell leukaemia	0.04	172	R	0.01	25	R	0.02	19	R	0.28	4,375	R
	2	Plasmacytoma/Multiple Myeloma (and Heavy chain diseases)	5.11	22,799	R	2.60	6,562	R	2.38	2,776	R	5.71	89,440	R
	2	Other non Hodgkin, Mature B cell lymphoma	3.19	14,220	R	2.33	5,899	R	2.10	2,452	R	6.37	99,729	C
	2	Mantle cell lymphoma	0.41	1,808	R	0.18	450	R	0.26	307	R	0.56	8,748	R
	2	Prolymphocytic leukaemia, B cell	0.01	59	R	0.02	53	R	0.01	10	R	0.05	804	R

Table 3
Summary of application of the rare/common cancer definition to the data in Asia.

Rare cancer families	Rare cancer based on tier-1 in EU and Asia	Common cancer based on tier-1 in EU and Asia	Tier-2 rare cancer among Tier-1 common cancer in EU and Asia
HEAD & NECK	Epithelial tumors of nasal cavity and sinuses Epithelial tumors of nasopharynx (not rare only in TW) Epithelial tumors of major salivary gland and salivary gland tumors Epithelial tumors of hypopharynx Epithelial tumors of larynx Epithelial tumors of oropharynx (not rare only in TW) Epithelial tumors of oral cavity and lip (not rare in JP and TW) Epithelial tumour of eye and adnexa Epithelial tumour of middle ear Epithelial tumors of small intestine	NONE	NONE
DIGESTIVE (RARE/COMMON)	Epithelial tumors of anal canal Epithelial tumors of gallbladder and extrahepatic biliary tract (EBT) (not rare in JP and KR)	Epithelial tumors of esophagus (not common only in KR) Epithelial tumors of stomach Epithelial tumors of colon Epithelial tumors of rectum Epithelial tumors of pancreas Epithelial tumors of liver and intrahepatic and bile tract (IBT) Epithelial tumors of lung	Squamous cell carcinoma with variants of oesophagus (not rare in JP and TW); all other the tier-2 rare in EU are rare in Asia All the tier-2 rare in EU are rare in Asia All the tier-2 rare in EU are rare in Asia All the tier-2 rare in EU are rare in Asia All the tier-2 rare in EU are rare in Asia Hepatocellular carcinoma (not rare in Asia, in Europe most likely there are issues with the quality of the diagnosis); all the other tiers 2 rare in EU and Asia All the tier-2 rare in EU are rare in Asia; Poorly differentiated endocrine tumors (not rare in Europe but rare in KR and TW)
THORACIC (RARE/COMMON)	Thymomas and thymic carcinomas		
FEMALE GENITAL (RARE/COMMON)	Epithelial tumors of trachea Malignant Mesothelioma Non epithelial tumors of ovary Epithelial tumors of vulva and vagina Trophoblastic tumors of placenta	Epithelial tumors of breast Epithelial tumors of corpus uteri (not common in KR) Epithelial tumors of cervix uteri Epithelial tumour of ovary (not common in KR and TW) Epithelial tumors of prostate Epithelial tumors of kidney (not common in KR and TW) Epithelial tumors of bladder	All the tier-2 rare in EU are rare in Asia; Invasive lobular carcinoma (not rare in EU but rare in Asia) All the tier-2 rare in EU are rare in JP and TW All the tier-2 rare in EU are rare in Asia All the tier-2 rare in EU are rare in JP
MALE GENITAL & UROGENITAL (RARE/COMMON)	Tumors of testis and paratestis Epithelial tumors of penis Epithelial tumors of renal pelvis and ureter and urethra (not rare in TW and JP) to discuss Extragenital germ cell tumor		All the tier-2 rare in EU are rare in Asia All the tier-2 rare in EU are rare in JP All the tier-2 rare in EU are rare in Asia
SKIN (RARE/COMMON)	Mucosal melanoma Uveal melanoma Adnexa carcinomas of skin Kaposi sarcoma Hepatoblastoma Neuroblastoma & ganglioneuroblastoma Nephroblastoma Odontogenic malignant tumors Olfactory neuroblastoma Pancreatoblastoma Pleuropulmonary blastoma Myelodysplastic syndrome and myelodysplastic/ myeloproliferative diseases	Skin melanoma (not common in Asia) Epithelial tumors of skin	Squamous cell carcinoma (not rare in Asia)
PEDIATRIC	Soft tissue sarcoma Bone sarcoma Gastrointestinal stromal sarcoma NET GEP NET lung NET other sites Thyroid cancers (not rare in Asia) Parathyroid cancer Adrenal cortex cancer Pituitary gland cancer CNS tumors (exception in EU)	NONE NONE NONE NONE	NONE NONE NONE NONE
SARCOMAS			
NEUROENDOCRINE			
ENDOCRINE ORGAN			

(continued on next page)

Table 3 (continued)

Rare cancer families	Rare cancer based on tier-1 in EU and Asia	Common cancer based on tier-1 in EU and Asia	Tier-2 rare cancer among Tier-1 common cancer in EU and Asia
CENTRAL NERVOUS SYSTEM (CNS)	Embryonal tumour of CNS		
HAEMATOLOGICAL (RARE/COMMON)	Acute myeloid leukemia Myeloproliferative neoplasms Myelodysplastic syndrome and myelodysplastic/myeloproliferative diseases Histiocytic and dendritic cell neoplasms	Lymphomas	All the tier-2 rare in EU are rare in Asia

JP = Japan, KR = Korea, TW = Taiwan.

for epithelial tumours of the nasopharynx, hypopharynx and larynx, oropharynx, and oral cavity and lip. On the other hand, looking at the family of digestive rare cancers, Taiwan showed much lower ASRs for epithelial tumours of the gallbladder and extrahepatic biliary tract (EBT). Looking at the family of rare thoracic cancers, the ASR of malignant mesothelioma was clearly higher in Japan, whereas the ASR of epithelial tumours of the thymus was higher in Taiwan. Regarding the family of male genital and urogenital rare cancers, the ASR of epithelial tumours of the pelvis and ureter was higher in Taiwan. Of the cancers included in the family of rare skin cancers, the ASRs of Kaposi's sarcoma and adnexal carcinoma of the skin were higher in Taiwan. Considering the family of neuroendocrine tumours, in Korea, the ASR of gastroenteropancreatic neuroendocrine tumour (NET-GEP) was higher than in the other two countries. The ASR of soft tissue sarcoma was higher in Taiwan. Of the cancers included in the family of rare endocrine tumours, the ASR of carcinoma of the thyroid gland was 5–10 times higher in Korea than in the others. Carcinoma of the pituitary gland was very rare in Taiwan. Finally, of the hematological rare cancers, myelodysplastic syndrome and myelodysplastic/myeloproliferative diseases were the highest in Japan, and the lowest in Taiwan. Fig. 3 shows the ASR for each Tier 1 for common cancers. The ASRs of IBT, epithelial tumours of lung and epithelial tumours of skin in Taiwan and epithelial tumours of prostate in Japan were higher than the other countries. Epithelial tumours of corpus uteri in Korea showed lower ASR.

4. Discussion

4.1. Study design under regulation on data exchange

The data security policies in the world are becoming stricter, even for anonymous data especially after the General Data Protection Regulation affected cancer registration and cancer research [7]. A number of countries have specific regulation on data exchange in place. Accordingly, we planned a non-centralized international study design with standard data quality checks and a standard statistical package. Even with this remote international setting, reliable data comparison could be performed supported by routine teleconferences and several in-person meetings. This study design can be referred as a model for future research.

4.2. Data quality check for comparability

It was assumed that the populations in this study were representative of the respective populations, since they are the national registries. In Japan, when the incidence of rare cancer was estimated in Japan a decade ago [8], the researchers had problem of data quality, however, the Act on Promotion of Cancer Registries was enacted in 2016, and the current PBCR is nationwide [9]. The Korea Central Cancer Registry (KCCR) was established in 1980 as a nationwide hospital-based database. Since 1999, the KCCR has collected cancer incidence data for the entire nation, the Korea National Cancer Incidence Data Bases (KNCIDB), by compiling a nationwide hospital-based KCCR database and 9 PBCRs [10]. The Taiwan Cancer Registry, a PBCR, was founded in 1979 [11,12]. To assess the extent of registration bias, each country reviewed the data according to the preceding study [13]. No systematic reason for inaccurate classification was found.

4.3. Application of RARECAREnet definition and list of rare cancers in Asia

The present results showed that most of the rare cancers in EU were also rare in Asia with few exceptions due mainly to well-known risk factors. Though age structures in the four areas vary proportion of the population above 65 years old are 28.5% in Japan, 14.2% in Korea, 12.3% in Taiwan, and 18.9% in EU according to the latest census in each area, rarity of cancer was not so different. Cancer incidence varies considerably between the countries and by ethnic groups. However, it is known that most of the contributing risk factors are acquired and related to environment and lifestyle habits. The international study on childhood cancers found a wide variety of incidence [14], however, the authors emphasized the variety in registration techniques, diagnostic standardization, coding system, access to medical institutes and other artifacts. In fact the incidence in high income groups are much more similar. The situation in rare cancers may be the same, genetic difference do exist but has a much less impact compared with the acquired factors.

4.4. Difference in risk factors of rare cancers in Asia

In addition to smoking and alcohol drinking, these high rates of oral and pharyngeal cancers in Taiwan are largely associated with the

Table 4
Data quality indicators and of malignant cancers (Tier 1) diagnosed in the 3 East Asian countries and in EU.

Tier	List	Difference between Tier 1 and 2 (%)					Microscopically Verified cases (%)					Morphologically NOS (%)				
		Japan (2011- 2015)	Korea (2011- 2015)	Taiwan (2011- 2015)	Europe (2000- 2007)		Japan (2011- 2015)	Korea (2011- 2015)	Taiwan (2011- 2015)	Europe (2000- 2007)		Japan (2011- 2015)	Korea (2011- 2015)	Taiwan (2011- 2015)	Europe (2000- 2007)	
1	EPITHELIAL TUMOURS OF NASAL CAVITY AND SINUSES	20.0	14.6	11.3	17.3		85.0	93.5	98.2	90.4		19.9	14.1	10.1	16.4	
1	EPITHELIAL TUMOURS OF NASOPHARYNX	20.9	50.5	2.2	24.3		90.0	96.1	99.3	92.5		20.8	50.3	2.2	22.9	
1	EPITHELIAL TUMOURS OF MAJOR SALIVARY GLANDS AND SALIVARY-GLAND TYPE TUMOURS	NA	NA	NA	NA		93.7	98.0	98.5	94.2		11.4	10.3	5.8	11.6	
1	EPITHELIAL TUMOURS OF HYPOPHARYNX AND LARYNX	8.8	5.9	2.6	7.2		92.9	96.1	98.3	94.6		8.8	5.7	2.5	7.0	
1	EPITHELIAL TUMOURS OF OROPHARYNX	9.0	5.0	2.4	6.2		93.3	97.8	99.0	95.7		9.0	4.9	2.3	6.0	
1	EPITHELIAL TUMOURS OF ORAL CAVITY AND LIP	9.9	5.0	1.2	5.3		92.2	96.9	99.5	95.6		9.9	4.9	0.9	5.2	
1	EPITHELIAL TUMOURS OF OESOPHAGUS	11.9	5.5	2.1	14.6		90.4	96.0	98.9	89.8		11.9	5.5	1.9	14.3	
1	EPITHELIAL TUMOURS OF STOMACH	11.5	3.2	2.5	16.7		90.6	97.8	98.7	87.3		11.5	3.2	2.4	16.7	
1	EPITHELIAL TUMOURS OF SMALL INTESTINE	17.7	16.2	10.5	22.9		85.7	89.4	95.3	85.3		17.6	15.1	9.1	22.5	
1	EPITHELIAL TUMOURS OF COLON (including appendix)	14.1	5.8	3.5	11.6		87.9	95.7	97.4	90.7		14.1	5.8	3.5	11.6	
1	EPITHELIAL TUMOURS OF RECTUM	14.2	4.2	1.5	8.5		88.4	97.0	99.1	93.4		14.2	4.2	1.5	8.4	
1	EPITHELIAL TUMOURS OF ANAL CANAL	12.8	5.8	2.7	8.1		89.7	96.7	98.6	94.0		12.7	5.8	2.7	8.0	
1	EPITHELIAL TUMOURS OF PANCREAS	52.3	35.7	23.4	37.8		52.5	68.4	71.0	53.6		54.1	37.7	31.4	56.6	
1	EPITHELIAL TUMOURS OF LIVER AND INTRAHEPATIC BILE TRACT (IBT)	10.0	3.5	0.4	34.5		36.5	38.1	47.8	53.0		10.0	3.5	0.3	34.4	
1	EPITHELIAL TUMOURS OF GALLBLADDER AND EXTRAHEPATIC BILIARY TRACT (EBT)	44.7	24.5	11.5	36.7		60.3	73.5	80.0	67.8		44.7	24.2	11.3	36.5	
1	EPITHELIAL TUMOURS OF TRACHEA	18.3	10.7	8.6	23.9		86.7	91.1	97.5	85.4		16.7	9.8	7.4	21.5	
1	EPITHELIAL TUMOURS OF LUNG	26.7	20.8	9.3	36.9		78.7	86.5	94.7	77.8		24.3	15.3	6.3	29.2	
1	EPITHELIAL TUMOURS OF THYMUS	8.8	7.8	4.6	11.6		94.1	95.6	91.8	93.2		7.4	7.4	4.3	10.6	
1	EPITHELIAL TUMOURS OF BREAST	8.7	2.8	2.0	10.2		94.4	99.0	99.5	95.7		7.8	2.5	1.2	7.8	
1	EPITHELIAL TUMOURS OF CORPUS UTERI	5.4	3.1	1.4	6.5		96.4	98.6	99.6	96.9		5.0	2.7	1.0	4.5	
1	EPITHELIAL TUMOURS OF CERVIX UTERI	8.8	7.1	5.9	9.4		95.8	97.5	99.1	96.4		6.0	4.3	2.9	6.7	
1	EPITHELIAL TUMOURS OF OVARY AND FALLOPIAN TUBE	18.5	14.0	4.3	20.8		86.3	92.0	97.1	87.2		17.0	12.3	4.5	19.1	
1	NON EPITHELIAL TUMOURS OF OVARY	0.0	0.0	0.6	0.0		99.9	99.9	92.5	98.9		NA	NA	NA	NA	
1	EPITHELIAL TUMOURS OF VULVA AND VAGINA	7.8	6.5	3.8	8.1		94.4	97.4	98.9	94.8		7.5	5.6	3.4	7.6	

(continued on next page)

Table 4 (continued)

Tier	List	Difference between Tier 1 and 2 (%)				Microscopically Verified cases (%)				Morphologically NOS (%)			
		Japan (2011- 2015)	Korea (2011- 2015)	Taiwan (2011- 2015)	Europe (2000- 2007)	Japan (2011- 2015)	Korea (2011- 2015)	Taiwan (2011- 2015)	Europe (2000- 2007)	Japan (2011- 2015)	Korea (2011- 2015)	Taiwan (2011- 2015)	Europe (2000- 2007)
1	TROPHOBLASTIC TUMOURS OF PLACENTA	11.3	21.2	14.6	12.7	61.9	82.3	77.1	88.3	9.5	15.3	2.1	8.4
1	EPITHELIAL TUMOURS OF PROSTATE	11.5	4.0	2.0	11.1	90.3	97.3	98.2	92.0	11.5	4.0	2.0	11.0
1	TESTICULAR AND PARATESTICULAR CANCERS	4.3	4.0	2.7	4.6	97.5	98.6	99.1	96.9	2.9	2.3	0.9	2.8
1	EPITHELIAL TUMOURS OF PENIS	8.6	4.4	1.5	6.1	92.6	97.8	99.3	95.7	8.3	4.0	1.5	5.9
1	EPITHELIAL TUMOURS OF KIDNEY	20.1	9.4	4.8	20.3	81.5	91.6	92.1	80.3	20.0	9.3	4.4	20.2
1	EPITHELIAL TUMOURS OF PELVIS AND UTERUS	26.4	12.1	3.2	8.2	79.6	90.5	96.3	93.1	26.3	11.8	2.8	7.8
1	EPITHELIAL TUMOURS OF URETHRA	14.0	14.8	6.2	8.2	89.9	90.1	99.1	95.1	13.6	14.2	3.5	8.1
1	EPITHELIAL TUMOURS OF BLADDER	17.4	7.6	2.1	10.3	86.1	94.2	98.7	92.0	17.3	7.6	2.0	10.1
1	EPITHELIAL TUMOURS OF EYE AND ADNEXA	21.3	22.6	8.9	62.8	85.1	87.8	92.4	44.4	20.8	22.0	7.6	62.3
1	EPITHELIAL TUMOURS OF MIDDLE EAR	16.4	20.0	13.0	18.5	87.3	90.0	100.0	84.9	15.5	16.7	13.0	17.4
1	MALIGNANT MESOTHELIOMA	4.3	17.3	8.4	8.4	98.6	95.1	98.6	90.9	NA	NA	NA	NA
1	MALIGNANT SKIN MELANOMA	NA	NA	NA	NA	93.2	98.1	99.0	98.4	NA	NA	NA	NA
1	MALIGNANT MELANOMA OF MUCOSA AND EXTRACUTANEOUS	NA	NA	NA	NA	99.9	99.8	97.6	99.3	NA	NA	NA	NA
1	MALIGNANT MELANOMA OF UVEA	NA	NA	NA	NA	61.1	45.3	56.1	73.8	NA	NA	NA	NA
1	EPITHELIAL TUMOURS OF SKIN	NA	NA	NA	NA	99.9	100.0	99.7	98.7	NA	NA	NA	NA
1	ADNEXAL CARCINOMAS OF SKIN	NA	NA	NA	NA	99.8	100.0	99.8	99.5	NA	NA	NA	NA
1	NEUROBLASTOMA AND GANGLIONEUROBLASTOMA	NA	NA	NA	NA	91.3	95.1	97.4	96.7	NA	NA	NA	NA
1	NEPHROBLASTOMA	NA	NA	NA	NA	92.9	98.4	98.0	96.8	NA	NA	NA	NA
1	EMBRYONAL TUMOURS OF EYE	NA	NA	NA	NA	66.0	50.0	76.8	75.1	NA	NA	NA	NA
1	HEPATOBLASTOMA	NA	NA	NA	NA	98.9	99.0	95.4	95.0	NA	NA	NA	NA
1	PLEUROPULMONARY BLASTOMA	NA	NA	NA	NA	100.0	100.0	100.0	100.0	NA	NA	NA	NA
1	PANCREATOBLASTOMA	NA	NA	NA	NA	100.0	100.0	66.7	97.4	NA	NA	NA	NA
1	OLFATORY NEUROBLASTOMA	NA	NA	NA	NA	99.6	99.0	98.9	98.0	NA	NA	NA	NA
1	ODONTOGENIC MALIGNANT TUMOURS	NA	NA	NA	NA	100.0	100.0	100.0	98.2	NA	NA	NA	NA
1	EXTRAGONADAL GERM CELL TUMOURS	11.0	7.2	14.1	13.0	98.6	91.4	87.2	97.9	NA	NA	NA	NA
1	SOFT TISSUE SARCOMA	3.3	2.6	2.6	6.8	96.4	99.4	98.4	97.5	8.5	6.7	7.9	12.9
1	BONE SARCOMA	12.3	10.6	12.3	13.8	98.8	99.0	97.4	97.0	2.7	1.6	2.0	5.9
1	GASTROINTESTINAL STROMAL SARCOMA	NA	NA	NA	NA	99.6	100.0	96.5	99.4	NA	NA	NA	NA
1	KAPOSI S SARCOMA	NA	NA	NA	NA	98.2	97.3	97.9	93.1	NA	NA	NA	NA
1	NET GEP	NA	NA	NA	NA	99.5	100.0	99.4	98.3	NA	NA	NA	NA
1	NET LUNG	NA	NA	NA	NA	100.0	100.0	100.0	98.6	NA	NA	NA	NA

(continued on next page)

Table 4 (continued)

Tier	List	Difference between Tier 1 and 2 (%)					Microscopically Verified cases (%)					Morphologically NOS (%)				
		Japan (2011- 2015)	Korea (2011- 2015)	Taiwan (2011- 2015)	Europe (2000- 2007)	Japan (2011- 2015)	Korea (2011- 2015)	Taiwan (2011- 2015)	Europe (2000- 2007)	Japan (2011- 2015)	Korea (2011- 2015)	Taiwan (2011- 2015)	Europe (2000- 2007)	Japan (2011- 2015)	Korea (2011- 2015)	Taiwan (2011- 2015)
1	NET OTHER SITES	NA	NA	NA	NA	99.7	100.0	98.8	97.5	NA	NA	NA	NA	NA	NA	NA
1	CARCINOMAS OF PITUITARY GLAND	NA	NA	NA	NA	18.6	11.5	27.3	33.0	82.6	83.2	36.4	72.9	82.6	83.2	36.4
1	CARCINOMAS OF THYROID GLAND	NA	NA	NA	NA	95.3	99.4	99.5	96.4	6.5	1.1	1.2	6.2	6.5	1.1	1.2
1	CARCINOMAS OF PARATHYROID GLAND	NA	NA	NA	NA	85.7	98.8	100.0	87.6	74.7	91.3	88.9	72.2	74.7	91.3	88.9
1	CARCINOMAS OF ADRENAL CORTEX	NA	NA	NA	NA	50.4	71.6	88.6	62.4	55.8	37.1	15.4	55.5	55.8	37.1	15.4
1	TUMOURS OF CENTRAL NERVOUS SYSTEM (CNS)	22.6	15.3	4.2	21.1	69.1	69.1	85.6	72.0	24.4	16.9	4.6	21.8	24.4	16.9	4.6
1	EMBRYONAL TUMOURS OF CNS	NA	NA	NA	NA	96.1	98.7	98.8	98.3	NA	NA	NA	NA	NA	NA	NA
1	LYMPHOID DISEASES	10.6	4.9	2.8	16.0	90.6	97.5	98.2	93.3	10.5	4.9	2.7	16.0	10.5	4.9	2.7
1	ACUTE MYELOID LEUKEMIA AND RELATED PRECURSOR NEOPLASMS	NA	NA	NA	NA	98.4	98.9	98.3	89.8	5.9	6.3	2.4	9.7	5.9	6.3	2.4
1	MYELOID AND LYMPHOID NEOPLASMS	NA	NA	NA	NA	26.9	38.8	71.7	58.3	99.7	100.0	88.7	100.0	99.7	100.0	88.7
1	MYELOPROLIFERATIVE NEOPLASMS	NA	NA	NA	NA	99.3	98.8	90.3	90.8	NA	NA	NA	NA	NA	NA	NA
1	MYELODYSPLASTIC SYNDROME AND MYELODYSPLASTIC/MYELOPROLIFERATIVE DISEASES	0.4	1.2	17.4	0.7	98.6	98.9	92.5	87.7	0.5	0.4	0.9	0.4	0.5	0.4	0.9
1	HISTIOCYTIC AND DENDRITIC CELL NEOPLASMS	NA	NA	NA	NA	99.4	99.1	98.4	89.7	NA	NA	NA	NA	NA	NA	NA
NOS for solid tumor		8000 Neoplasm, malignant; 8001 Tumor cells, malignant; 8010 Carcinoma, NOS														
NOS for hematological		9590 Lymphoma, NOS, 9591 Non-Hodgkin lymphoma, NOS, 9760 Immunoproliferative diseases, NOS, 9820 Lymphoid leukemia, NOS, 9800 Leukemia, NOS, 9801 Acute leukemia, NOS, 9860 Myeloid leukemia, NOS, 9989 Myelodysplastic syndrome, NOS														
NOS for sarcoma		8800														

Table 5
Data quality indicators in the 3 East Asian countries and in EU: Proportion of topography NOS.

Topography Group	Japan (2011-2015)	Korea (2011-2015)	Taiwan (2011-2015)	Europe (2000-2007)
LIP,ORAL CAVITY, PHARYNX	2.04	1.57	0.31	3.76
DIGESTIVE ORGANS	0.06	0.04	0.06	0.77
RESPIRATORY SYSTEM	0.01	0.01	0.00	0.11
FEMALE GENITAL ORGANS	1.93	1.24	0.15	1.87
MALE GENITAL ORGANS	0.45	0.03	0.02	0.03
URINARY ORGANS	0.33	0.81	2.47	0.63
ENDOCRINE ORGANS	0.08	0.01	0.02	0.37

Table 6
Data quality indicators in the 3 East Asian countries and in EU: Topography in soft tissue sarcoma.

Tier	List	Japan (2011-2015)			Korea (2011-2015)			Taiwan (2011-2015)			Europe (2000-2007)		
		All sites	C49	Not C49	All sites	C49	Not C49	All sites	C49	Not C49	All sites	C49	Not C49
1	SOFT TISSUE SARCOMA	20,127	9,121	11,006	9,853	4,332	5,521	6,324	2,605	3,719	73,936	34,485	39,451
2	Soft tissue sarcoma of head and neck	1,079	786	293	575	397	178	381	226	155	3,847	2,746	1,101
2	Soft tissue sarcoma of limbs	5,011	5,004	7	2,186	2,176	10	1,273	1,273	0	17,237	16,616	621
2	Soft tissue sarcoma of superficial trunk	1,997	1,921	76	1,004	983	21	657	653	4	7,836	7,280	556
2	Soft tissue sarcoma of mediastinum	266	0	266	85	0	85	63	0	63	468	0	468
2	Soft tissue sarcoma of heart	144	0	144	72	0	72	16	0	16	218	0	218
2	Soft tissue sarcoma of breast	689	0	689	478	0	478	390	0	390	2,872	0	2,872
2	Soft tissue sarcoma of uterus	2,593	0	2,593	1,188	0	1,188	817	0	817	8,664	0	8,664
2	Soft tissue sarcoma of paratestis	157	0	157	41	0	41	47	0	47	510	0	510
2	Soft tissue sarcomas of other genitourinary tract (vulva, vagina, ovary, penis, prostate, testis, kidney, renal pelvis, ureter, bladder, urethra)	607	0	607	326	0	326	173	0	173	3,169	0	3,169
2	Soft tissue sarcoma of viscera	1,123	0	1,123	785	0	785	506	0	506	5,972	0	5,972
2	Soft tissue sarcoma of retroperitoneum and peritoneum	2,282	0	2,282	730	0	730	543	0	543	4,924	0	4,924
2	Soft tissue sarcoma of pelvis	808	790	18	463	455	8	277	276	1	3,050	2,820	230
2	Soft tissue sarcoma of skin	1,623	0	1,623	940	0	940	667	0	667	4,744	0	4,744
2	Soft tissue sarcoma of paraorbit	23	0	23	13	0	13	7	0	7	121	0	121
2	Soft tissue sarcoma of brain and other parts of nervous system	565	0	565	345	0	345	152	0	152	2,730	0	2,730
2	Embryonal rhabdomyosarcoma of soft tissue	102	40	62	93	46	47	52	21	31	819	336	483
2	Alveolar rhabdomyosarcoma of soft tissue	107	67	40	70	41	29	38	27	11	516	346	170
2	Ewing's sarcoma of soft tissue	281	126	155	204	87	117	98	49	49	1,088	603	485

consumption of betel quid [15–17]. Recently, the prevalence of human papillomavirus is considered to be a possible risk factor in Taiwan [17,18]. Epstein-Barr virus (EBV) infection, genetic susceptibility, and environment factors are considered the major etiological factors for nasopharyngeal carcinoma (NPC) pathogenesis [19]. The decreasing trend of NPC incidence in Hong Kong, Taiwan, and Singapore suggests that changes in dietary habits [20–22].

The risk factors for esophageal squamous cell carcinoma, the predominant histologic subtype in East Asia [23], include smoking, alcohol, diet, and genetic predisposition; typical of black men and white women. The risk factors for adenocarcinoma include gastroesophageal reflux disease (GERD) and Barrett's esophagus; the prevalence of GERD in the Western population is about 10–20%. In addition one must include obesity, smoking, and genetic predisposition. A high prevalence of HBV and HCV carriers in the area has been known as the main factor for the extremely high incidence of liver cancer compared with EU data [24]. However, the large difference between Asia and the

EU is most likely due to the quality of diagnosis (low MV%), since there is a widespread use of diagnostic imaging that can also provide the morphologies in Asian countries.

Regarding cancer of the gallbladder, there is a high incidence in Korea and Japan that is already known to be most likely because of an anomalous pancreatobiliary duct junction (APBDJ) [25].

Ultrasound screening of the thyroid in Korea is also a well-known “artificial” risk factor for the high incidence rate of thyroid cancer [26].

The notion of GEP-NET was proposed in 2010 by the WHO classification, which may result in confusion in the clinical setting in Asian countries similar to several haematological malignancies [27]. It has been reported that the incidence of NET is increasing in Japan [28], and the same tendency has been observed in Korea and Taiwan [29,30].

4.5. Limitation of the study

Although the data in the four areas followed the same methods and



Fig. 1. Age-standardized rates (ASRs) (world population, per 100,000) of rare cancers in Asia based on the cancer families.

cleared the standard quality check, we are not completely sure of the quality of case finding and coding systems. In EU, it was found that the few unspecified morphology in data, after the review, changed to a more specific diagnosis and modified the incidence [13]. Diagnostic

techniques and the experience of tumor registrars are not controllable in the current study which may lead to differences in incidence patterns.

In EU, available data were drawn from the EUROcare-5 from 2000

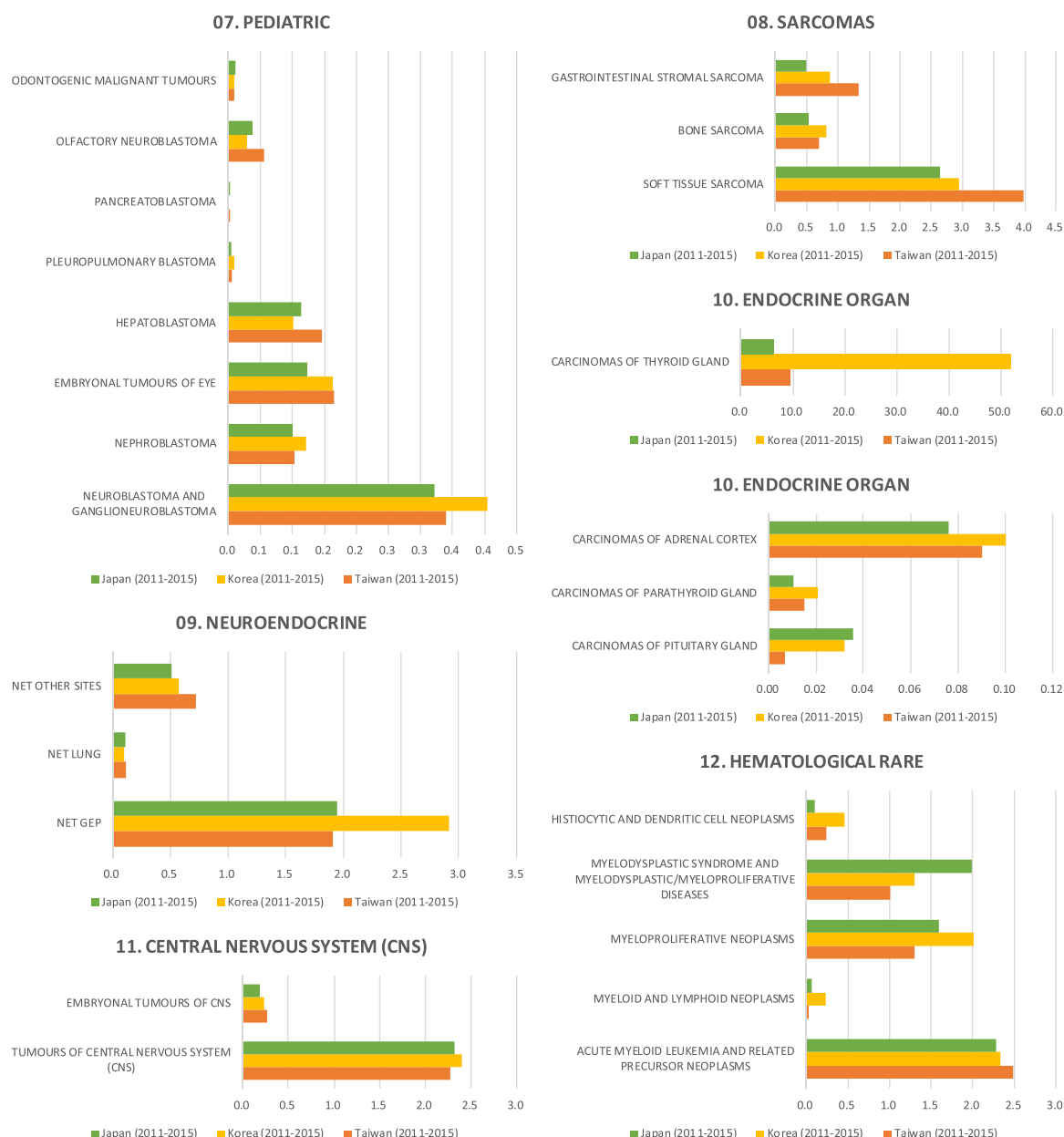


Fig. 2. ASRs (world population, per 100,000) of rare cancers in Asia based on the cancer families.

to 2007 which did not match the incidence period in the Asian countries. This discordance may result in slightly different statistics, but as long as we know, the incidence of rare cancers is more or less stable over time.

4.6. Need for international collaboration on rare cancer control

The International Agency for Research on Cancer (IARC) have launched an international project called Global Initiative of Cancer Registry (GICR) to improve PBCR data quality since 2011 [31].

Especially for rare cancers, an effective and nationwide cancer control program could only be conducted based on reliable data [32]. The results of RARECAREnet Asia also contribute to clinical trials crossing the borders between epidemiology and clinical research; the MASTER KEY project in Japan, which is a biomarker-driven basket/umbrella trial receives PBCR data regularly to determine the size of the affected population [33].



Fig. 3. ASRs (world population, per 100,000) of common cancers in Asia based on the cancer families.

5. Conclusion

We have at last put numbers to the previously unknown status of rare cancers in Asia. Most rare cancers in EU are also rare in Asia and we found that the rare cancer list developed based on the European data was well applicable to the Asian data. Most of the continental differences found in the current study were well known and did not affect validity or reliability of the rare cancer list. The first collaborative study using population-based data under standard data quality check and non-centralized protocol, RARECAREnet Asia, will continue to contribute to the improvement of rare cancer care in the region. RARECAREnet Asia, as a part of Rare Cancers Asia, is currently analysing

survival for rare cancers in Europe and Asia. The results will be soon released.

Authorship contribution statement

Study concepts: TM, YW, RC
 Study design: TM, YW, RC, AT
 Data acquisition: TM, YW, RC, AT
 Quality control of data and algorithms: JL, KS, KF, LB
 Data analysis and interpretation: TM, YW, RC, WL, AT, AB
 Statistical analysis: JL, KS, KF, LB
 Manuscript preparation: TM, YW, RC

Manuscript editing: TM, YW, RC, WL, AB

Manuscript review: AT, AB

Declaration of Competing Interest

The authors declare no conflicts of interest.

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CRediT authorship contribution statement

Tomohiro Matsuda: Conceptualization, Methodology, Investigation, Resources, Writing - original draft, Writing - review & editing, Funding acquisition. **Young-Joo Won:** Conceptualization, Methodology, Investigation, Resources, Writing - original draft, Writing - review & editing, Funding acquisition. **RuRu Chun-ju Chiang:** Conceptualization, Methodology, Investigation, Resources, Software, Validation, Formal analysis, Writing - original draft, Writing - review & editing. **Jiwon Lim:** Software, Validation, Formal analysis. **Kumiko Saika:** Software, Validation, Formal analysis. **Keisuke Fukui:** Software, Validation, Formal analysis. **Wen-Chung Lee:** Funding acquisition. **Laura Botta:** Software, Validation, Formal analysis. **Alice Bernasconi:** Software, Validation, Formal analysis. **Annalisa Trama:** Conceptualization, Methodology, Investigation, Resources, Writing - original draft, Writing - review & editing, Funding acquisition, Supervision.

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