Epidemiology

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2.1 Introduction

A rare disease affects a small percentage of the population. There had been several efforts to define rare diseases. Some characteristics of rare diseases have led to the expression "orphan disease" and influenced the definition of rare diseases: rare diseases often show a genetic origin, symptoms appear early in life, while the genetic predisposition lasts; rare diseases are often inadequately diagnosed and treated. The interest of the pharmaceutical industry to develop new drugs for rare diseases is generally low as the rarity of the disease leads to little financial incentive. Apart from this general consideration, a rare disease might be rare in a particular part of the world or in a specific group of people. The US Rare Disease Act of 2002 defines a rare disease as "any disease or condition that affects less than 200,000 persons in the United States," which is a prevalence of 1 in 1500 people or less (National Institutes of Health 2010).

However, this definition is based on prevalence and not incidence, as most rare diseases are chronic conditions. In contrast, cancer is a subacute disease; thus, its occurrence in a population should be measured by incidence. A consensus process within the European oncology community promoted by the RARECARE project defined rare cancers as those malignancies whose incidence is <6/100,000/year (Gatta et al. 2011). According to this definition, all childhood cancers are rare; however, there are some particularly rare pediatric cancers which have not benefited from advances made by the international pediatric oncology network. To establish a shared definition and produce a list of these entities, the European Union "Joint Action on Rare Cancers" (JARC) and the "European Cooperative Study Group for Pediatric Rare Tumors" (EXPERT) promoted a consensus effort. Rare pediatric tumors were listed and defined as those with an annual incidence of <2/1000,000 corresponding to 11% of all cancers in patients aged 0–14 years (Ferrari et al. 2019).

2.2 Classification

The specific spectrum of rare cancers in children is not well described through one of the existing classification systems. The International

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Classification of Diseases for Oncology (ICD-O, third edition) is primarily developed for adult cancers and based on tumor site (Fritz et al. 2000). The International Classification of Childhood Cancer (ICCC, third edition) on the other hand is primarily based on morphology and histology (Steliarova-Foucher et al. 2005). A combination of both systems has to be used, the ICCC and ICD-O morphology and topography codes, in order to comprehensively describe rare tumors in children and adolescents. So far, no uniform classification system for rare pediatric tumor entities has been defined. Anyway, there have been efforts to develop a separate nosologic system for malignant entities occurring in adolescents and young adults (Birch et al. 2002). This system might be used as a basis for the development of a new classification for pediatric rare tumors, which mainly occur in adolescents and therefore show a similar spectrum.

2.3 How to Define Rare Tumors in Children and Adolescents?

Cancers rarely occur before the age of 14 years, and when they do, they raise a range of medical, psychological, ethical, and societal concerns. The age-standardized incidence rates of childhood cancer range from about 120 per million in southeast Asia to 150/160 per million in Europe and in the USA. However, the extent of the cancer burden in this young population is unknown in many low-income and middle-income countries (LMICs), where data on cancer incidence are not collected (Steliarova-Foucher et al. 2017). While according to the above definition of the RARECARE project all tumors are rare in childhood (incidence <6/100,000/year), pediatric oncologists realized that there are several cancers which they might only see once in their lifetime practice but present a major problem as no definite guidelines for diagnosis and treatment exist for pediatric age. Thus, realizing that we are actually dealing with not only very rare but also "orphan" entities, the Italian TREP project (Italian Study on Rare Tumors in Pediatric Age) pragmatically defined rare pediatric tumors as "any malignancies characterized by an annual incidence <2/million and not considered in other trials" (Ferrari et al. 2007). The German Rare Tumor group adopted this definition (Brecht et al. 2009).

However, due to the rarity of these tumors, problems arise in determining the exact incidence of rare pediatric tumors. Because of lacking experience with these tumor types, there might be diagnostic and coding inconsistencies and misclassification problems (Pastore et al. 2009). For example, the incidence of pleuropulmonary blastoma might be underestimated if they are registered as sarcomas. The risk of misclassification may inevitably be high in population-based cancer registries, because they are constructed on community-based pathological diagnoses and not exclusively on expert pathological diagnosis. Also, the classification of entities into benign, borderline, and malignant neoplasms might not be uniform (Stiller 2007). Some patients with rare tumors might not be reported to registries for reasons lying in the organizational structures of pediatric oncology within different countries. For example, an analysis from the population-based German Childhood Cancer Registry (GCCR) revealed 129 rare cases diagnosed between 1998 and 2007 and not being registered with one of the Society of Pediatric Oncology and Hematology (GPOH) studies (Brecht et al. 2010). This accounts for 1.2% of all malignancies or 3.8% of all malignant extracranial tumors registered within the GCCR. The authors concluded that rare pediatric cancers were underregistered due to different reasons lying in the status as an "orphan disease." In the UK, Brennan arbitrary defined rare pediatric tumors as those which have "an age-standardized annual incidence of less than 1 per million children in the U.K., excluding tumors of unspecified morphology" registering 766 patients under the age of 15 between 1991 and 2000 (Brennan and Stiller 2010). In the USA, the US Infrequent Tumor Initiative of the Children's Oncology Group basically deals with tumors "classified as other malignant epithelial neoplasms and melanomas in the International Classification of Childhood Cancer subgroup XI of the SEER database" being predominantly

adult cancer occurring in pediatric age (Pappo et al. 2010). According to this definition, rare tumors compose approximately 15% of all cancers in the age group <15 years and 30% in <20 years (see chapter on national rare tumor groups).

Thus, traditionally, rare pediatric tumors are defined by incidence as well as their characteristics as an orphan disease:

Rare pediatric malignancies are characterized by an annual incidence <2/1,000,000 and/or are considered as "orphan" due to lack of pediatric trials and/or underestimation of incidence. Rare pediatric malignancies might be common in adult age or pediatric subpopulations like a specific age group, a country, or a gender, often an underlying genetic predisposition can be suspected, and they might be inadequately diagnosed and treated.

2.4 Incidence-Based Definition of Rare Tumors in Children and Adolescents

Recently, there have been efforts to define rare pediatric tumors according to incidence rates by using large databases. The Surveillance, Epidemiology, and End Results (SEER) database of the US National Cancer Institute registers patients with cancer of all age groups. Data is provided by 18 registries accounting for 10–14% of the US population during the study period from 1973 to 2004 (SEER 2007) and by 13 registries during the study period from 1992 to 2007 (SEER 2010). Data from the SEER database collected between 1992 and 2007 was used to get a more realistic overview of rare tumor entities in childhood and adolescence. According to the above-provided definition for rare pediatric tumors, all children and adolescents under the age of 20 years with an extracranial solid tumor and an incidence rate of <2/1,000,000 in the age group <15 years and/or <20 years were included in this analysis. Data was sorted by ICCC-3 and ICD-O3 (see Tables 2.1 and 2.2); 2887 patients with a rare solid extracranial tumor were identified within the age group 0–14 years and 6923 patients within the age group 0–19 years. The age-specific incidence rate of rare solid pediatric tumors in the USA was calculated to be 21.1/1,000,000 under the age of 15 and 37.6/1,000,000 under the age of 20. Table 2.1 shows age-specific incidence rates and percentages of rare pediatric tumors. In the age group 0–14 years, rare solid tumors account for 25% of all extracranial solid tumors and in the age group 0–19 years, 41%. Anyway, these numbers include germ cell tumors and rare soft tissue sarcomas, which are registered in pediatric clinical trials in most developed countries and therefore are not considered as rare pediatric tumors according to the above mentioned definition. If rare soft tissue sarcomas and germ cell tumors are excluded, the incidence rate of rare solid pediatric tumors usually not registered in clinical trials is 11.5/1,000,000 under the age of 15 and 21.3/1,000,000 under the age of 20. Consequently, surprisingly high numbers of children and adolescents with rare tumors can be identified through the SEER database.

In 2019, within the frame of a cooperative analysis of the European Union "Joint Action on Rare Cancers" (JARC) and the "European Cooperative Study Group for Pediatric Rare Tumors" (EXPeRT), a definition according to incidence rate could be found for very rare pediatric tumors by listing all pediatric cancers. Due to the strength of a profound epidemiological database, this consensus report succeeded to find a threshold below which a tumor entity is classified as rare – an annual incidence of 2/1,000,000. By doing this 11% of all cancers in patients aged 0–14 years were identified as rare (Ferrari et al. 2019). Within the population aged 0–19 years, three of these rare tumor types had an incidence rate which was >2/1,000,000 (i.e., thyroid and testicular cancers and skin melanoma); however, the consensus experts still considered them as "rare" according to their clinical needs (e.g., shortage of knowledge and clinical expertise as the other rare pediatric cancers) (Ferrari et al. 2019).

Table 2.1 Annual incidence of pediatric cancer and rare pediatric malignant tumors within different age groups (data from the US Surveillance, Epidemiology, and End Results database (1992–2007) (rare tumors defined as all extracranial solid tumors with an incidence rate of <2/1,000,000 in the age groups <15 years and/or <20 years)

	0–14 years		0–19 years		0–4 years		5–9 years		10–14 years		15–19 years	
US population	134,900,815		177,623,103		45,673,629		44,723,693		44,503,493		42,722,288	
	Rate	Count	Rate	Count	Rate	Count	Rate	Count	Rate	Count	Rate	Count
Incidence of all malignant cancer[a]	152.19	19,984	164.58	28,838	206.75	9445	110.57	4945	125.7	5594	207.25	8854
Incidence of all malignant solid tumors[b]	87.12	11,424	96.98	17,019	121.44	5552	58.49	2616	73.16	3256	130.96	5595
Incidence of rare malignant solid tumors[b]	21.06	2887	37.55	6923	20.94	958	11.46	516	31.7	1413	94.47	4036
Percentage of rare entities of all malignant solid tumors[b]	25		41		17		20		43		72	
Incidence of rare malignant solid tumors[b] excluding germ cell tumors and rare soft tissue sarcomas	11.53	1599	21.33	3952	10.04	459	6.77	305	18.72	835	55.08	2353
Percentage of rare entities[b] not registered in clinical studies of all malignant extracranial solid tumors	14		23		8		11		26		42	

[a] Including hematopoietic cancers and cranial tumors

[b] Excluding hematopoietic cancers and cranial tumors

Table 2.2 Rare tumors in children and adolescents: annual incidence rates and numbers of cases of all extracranial solid tumors (hematopoietic cancers excluded) with an incidence rate of <2/1,000,000 in the age group <15 years and/or <20 years sorted by ICCC (third edition) and registered within the US Surveillance, Epidemiology, and End Results database (1992–2007)

Age at diagnosis (years)	0–14 years		0–19 years		0–4 years		5–9 years		10–14 years		15–19 years	
International Classification of Childhood Cancer (third edition)	Rate	Count	Rate	Count	Rate	Count	Rate	Count	Rate	Count	Rate	Count
IV Rare tumors of the peripheral nervous cell												
IV (b) Other peripheral nervous cell tumors	0.19	26	0.26	47	0.15	7	0.18	8	0.25	11	0.49	21
VI Rare renal tumors												
VI (a.2) Rhabdoid renal tumor	0.20	24	0.16	24	0.50	23	0.02	1	0.00	0	0.00	0
VI (a.3) Kidney sarcomas	0.28	34	0.22	35	0.64	29	0.11	5	0.00	0	0.02	1
VI (b) Renal carcinomas	0.25	36	0.48	91	0.11	5	0.20	9	0.49	22	1.29	55
VII Hepatic tumors												
VII (a) Hepatoblastoma	**2.36**	282	1.83	282	**5.68**	260	0.40	18	0.09	4	0.00	0
VII (b) Hepatic carcinomas	0.36	52	0.59	110	0.18	8	0.27	12	0.72	32	1.36	58
VII (c) Unspecified malignant hepatic tumors	0.03	3	0.02	3	0.07	3	0.00	0	0.00	0	0.00	0
VIII Malignant bone tumors												
VIII (b) Chondrosarcomas	0.19	29	0.33	64	0.00	0	0.07	3	0.58	26	0.82	35
VIII (c.1) Ewing tumor and Askin tumor of bone	1.66	239	**2.27**	426	0.55	25	1.61	72	**3.19**	142	**4.38**	187
VIII (c.2) pPNET of bone	0.10	15	0.13	25	0.00	0	0.13	6	0.20	9	0.23	10
VIII (d.1) Malignant fibrous neoplasms of the bone	0.04	5	0.07	13	0.07	3	0.04	2	0.00	0	0.19	8
VIII (d.2) Malignant chordomas	0.15	21	0.23	43	0.11	5	0.20	9	0.16	7	0.51	22
VIII (d.3) Odontogenic malignant tumors	0.01	2	0.06	11	0.00	0	0.04	2	0.00	0	0.21	9
VIII (d.4) Miscellaneous malignant bone tumors	0.06	9	0.09	17	0.02	1	0.02	1	0.16	7	0.19	8
VIII (e) Unspecified malignant bone tumors	0.06	9	0.09	17	0.04	2	0.02	1	0.13	6	0.19	8
IX Rare soft tissue and other extraosseous sarcomas												
IX (b.1) Fibroblastic and myofibroblastic tumors	0.80	102	0.79	134	1.41	65	0.31	14	0.52	23	0.75	32
IX (b.2) Nerve sheath tumors	0.44	63	0.57	108	0.20	9	0.25	11	0.97	43	1.05	45
IX (b.3) Other fibromatous neoplasms	0.01	1	0.01	2	0.00	0	0.02	1	0.00	0	0.02	1
IX (c) Kaposi sarcoma	0.02	3	0.05	9	0.02	1	0.04	2	0.00	0	0.14	6
IX (d.1) Ewing tumor and Askin tumor of soft tissue	0.35	49	0.46	85	0.20	9	0.29	13	0.61	27	0.84	36
IX (d.2) pPNET of soft tissue	0.26	36	0.32	59	0.20	9	0.29	13	0.31	14	0.54	23
IX (d.3) Extrarenal rhabdoid tumor	0.22	27	0.17	28	0.44	20	0.04	2	0.11	5	0.02	1
IX (d.4) Liposarcomas	0.12	18	0.29	55	0.04	2	0.11	5	0.25	11	0.87	37
IX (d.5) Fibrohistiocytic tumors	0.94	133	1.33	247	0.59	27	0.65	29	1.73	77	**2.67**	114

(continued)

Table 2.2 (continued)

Age at diagnosis (years)	0–14 years		0–19 years		0–4 years		5–9 years		10–14 years		15–19 years	
International Classification of Childhood Cancer (third edition)	Rate	Count	Rate	Count	Rate	Count	Rate	Count	Rate	Count	Rate	Count
IX (d.6) Leiomyosarcomas	0.18	25	0.26	48	0.11	5	0.25	11	0.20	9	0.54	23
IX (d.7) Synovial sarcomas	0.59	88	0.96	184	0.11	5	0.29	13	1.57	70	**2.25**	96
IX (d.8) Blood vessel tumors	0.08	11	0.12	22	0.11	5	0.04	2	0.09	4	0.26	11
IX (d.9) Osseous and chondromatous neoplasms of soft tissue	0.08	11	0.11	21	0.02	1	0.07	3	0.16	7	0.23	10
IX (d.10) Alveolar soft parts sarcoma	0.08	12	0.12	23	0.04	2	0.04	2	0.18	8	0.26	11
IX (d.11) Miscellaneous soft tissue sarcomas	0.22	31	0.22	41	0.15	7	0.13	6	0.40	18	0.23	10
IX (e) Unspecified soft tissue sarcomas	0.77	108	1.03	190	0.55	25	0.49	22	1.37	61	1.92	82
X Germ cell tumors, trophoblastic tumors, and neoplasms of gonads												
X (b.1) Germinomas: extracranial/extragonadal	0.08	11	0.18	34	0.07	3	0.02	1	0.16	7	0.54	23
X (b.2) Malignant teratomas: extracranial/extragonadal	1.09	130	0.88	138	**2.70**	124	0.09	4	0.04	2	0.19	8
X (b.3) Embryonal carcinomas: extracranial/extragonadal	0.00	0	0.01	1	0.00	0	0.00	0	0.00	0	0.02	1
X (b.4) Yolk sac tumor: extracranial/extragonadal	0.54	65	0.45	70	1.31	60	0.04	2	0.07	3	0.12	5
X (b.5) Choriocarcinomas: extracranial/extragonadal	0.02	3	0.19	37	0.00	0	0.00	0	0.07	3	0.80	34
X (b.6) Other mixed germ cell: extracranial/extragonadal	0.09	11	0.14	25	0.20	9	0.00	0	0.04	2	0.33	14
X (c.1) Malignant gonadal germinomas	0.37	55	1.34	255	0.04	2	0.29	13	0.90	40	**4.68**	200
X (c.2) Malignant gonadal teratomas	0.85	121	1.86	348	0.52	24	0.60	27	1.57	70	**5.31**	227
X (c.3) Gonadal embryonal carcinomas	0.06	8	0.77	145	0.07	3	0.00	0	0.11	5	**3.21**	137
X (c.4) Gonadal yolk sac tumor	0.77	95	0.85	144	1.60	73	0.16	7	0.34	15	1.15	49
X (c.5) Gonadal choriocarcinoma	0.01	1	0.09	17	0.00	0	0.02	1	0.00	0	0.37	16
X (c.6) Malignant gonadal tumors of mixed forms	0.33	48	2.14	406	0.13	6	0.07	3	0.88	39	**8.38**	358
X (c.7) Malignant gonadal gonadoblastoma	0.00	0	0.01	1	0.00	0	0.00	0	0.00	0	0.02	1
X (d) Gonadal carcinomas	0.07	10	0.35	66	0.00	0	0.00	0	0.22	10	1.31	56
X (e) Other and unspecified malignant gonadal tumors	0.09	12	0.15	28	0.07	3	0.09	4	0.11	5	0.37	16
XI Other malignant epithelial neoplasms and malignant melanomas												
XI (a) Adrenocortical carcinomas	0.24	31	0.26	44	0.39	18	0.16	7	0.13	6	0.30	13
XI (b) Thyroid carcinomas	1.75	262	**5.18**	989	0.04	2	1.16	52	**4.67**	208	**17.02**	727
XI (c) Nasopharyngeal carcinomas	0.20	31	0.48	92	0.00	0	0.02	1	0.67	30	1.43	61
XI (d) Malignant melanomas	1.59	229	**4.63**	874	0.66	30	1.23	55	**3.24**	144	**15.10**	645
XI(e) Skin carcinomas	0.06	9	0.08	16	0.02	1	0.02	1	0.16	7	0.16	7
XI (f.1) Carcinomas of salivary glands	0.43	64	0.76	145	0.07	3	0.20	9	1.17	52	1.90	81

International Classification of Childhood Cancer (third edition)	Rate	Count	Rate	Count	Rate	Count	Rate	Count	Rate	Count	Rate	Count
XI (f.2) Carcinomas of colon and rectum	0.12	18	0.49	94	0.00	0	0.02	1	0.38	17	1.78	76
XI (f.3) Carcinomas of appendix	0.06	9	0.14	27	0.00	0	0.00	0	0.20	9	0.42	18
XI (f.4) Carcinomas of lung	0.11	16	0.25	47	0.02	1	0.04	2	0.29	13	0.73	31
XI (f.5) Carcinomas of thymus	0.04	6	0.06	11	0.00	0	0.04	2	0.09	4	0.12	5
XI (f.6) Carcinomas of breast	0.04	6	0.19	36	0.00	0	0.00	0	0.13	6	0.70	30
XI (f.7) Carcinomas of cervix uteri	0.02	3	0.23	43	0.00	0	0.04	2	0.02	1	0.94	40
XI (f.8) Carcinomas of bladder	0.02	3	0.08	15	0.02	1	0.00	0	0.04	2	0.28	12
XI (f.9) Carcinomas of eye	0.02	3	0.02	4	0.02	1	0.02	1	0.02	1	0.02	1
XI (f.10) Carcinomas of other specified sites	0.40	58	0.93	176	0.15	7	0.27	12	0.88	39	**2.76**	118
XI (f.11) Carcinomas of unspecified site	0.09	13	0.20	37	0.07	3	0.00	0	0.22	10	0.56	24
XII (a.1) Gastrointestinal stromal tumor	0.04	5	0.05	10	0.02	1	0.02	1	0.07	3	0.12	5
XII (a.2) Pancreatoblastoma	0.03	5	0.03	6	0.00	0	0.07	3	0.04	2	0.02	1
XII (a.3) Pulmonary blastoma and pleuropulmonary blastoma	0.10	12	0.08	13	0.22	10	0.00	0	0.04	2	0.02	1
XII (a.4) Other complex mixed and stromal neoplasms	0.03	4	0.05	9	0.00	0	0.02	1	0.07	3	0.12	5
XII (a.5) Mesothelioma	0.00	0	0.02	4	0.00	0	0.00	0	0.00	0	0.09	4
XII (a.6) Other specified malignant tumors	0.01	1	0.01	1	0.00	0	0.00	0	0.02	1	0.00	0
XII (b) Other unspecified malignant tumors	0.19	25	0.28	51	0.22	10	0.13	6	0.20	9	0.61	26
Sum	21.06	2887	37.55	6923	20.94	958	11.46	516	31.7	1413	94.47	4036

Incidence rates of >2/1,000,000 within specific age groups are marked in bold

2.5 Rare Pediatric Cancer Age-Specific Incidence

The overall incidence of rare pediatric tumors rises dramatically within adolescence (Table 2.1 and Fig. 2.1). As shown in Table 2.1, rare pediatric tumors account for 8% of all malignant solid extracranial tumors within the age group 0–4 years; within the age group of 15–19 years, this number rises up to 42%. Also, the European Automated Childhood Cancer Information System (ACCIS) reports an incidence of carcinomas of 3.4/100,000 in the age group 0–14 years, but 9.9/100,000 in children and adolescents up to 19 years (http://wwwdep.iarc.fr/accis.htm). While in younger age groups histotypes typically diagnosed in the pediatric age predominate (i.e., hepatoblastoma, pleuropulmonary blastoma, pancreatoblastoma), tumor types that frequently occur in adults, but rarely on children and adolescents (e.g., melanoma, carcinomas), prevail during adolescence.

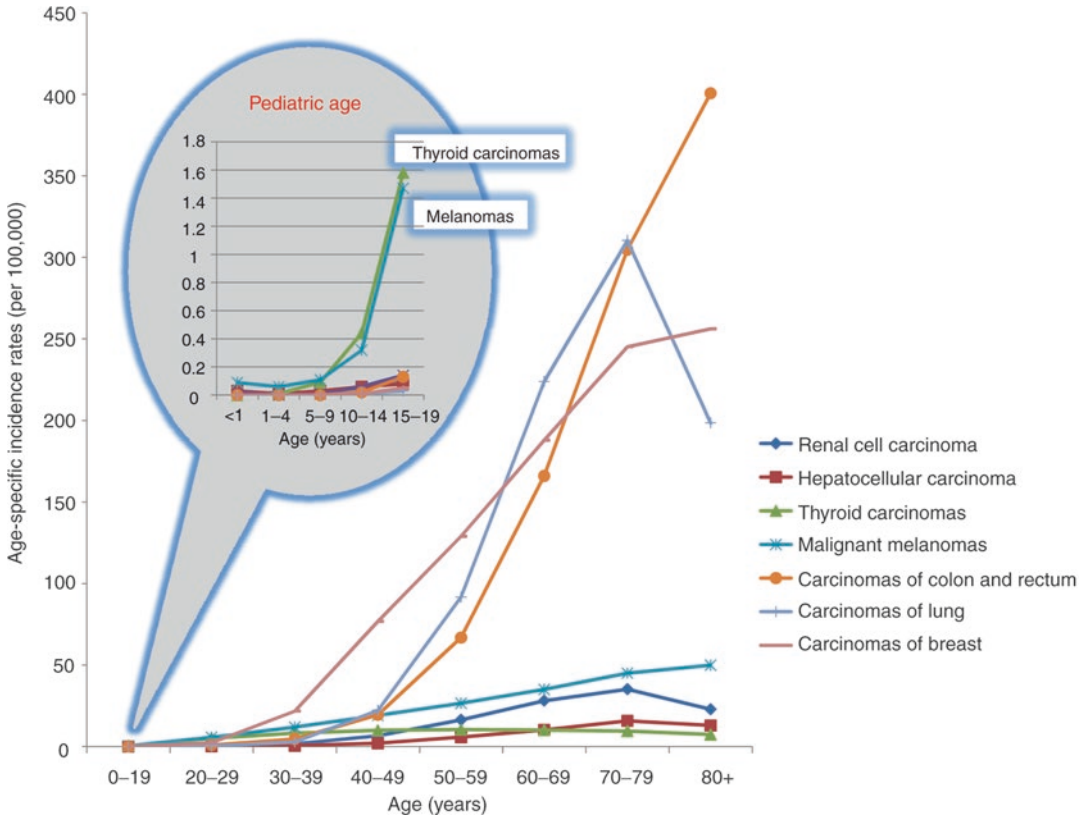

Fig. 2.1 Age-specific incidence rates (per 100,000 population) of selected adult cancers from the United States Surveillance, Epidemiology and End Results database (1973–2006). (Courtesy Dr. Sultan, Dr. Ferrari)

2.6 Conclusion

The JARC and EXPeRT consensus has provided a definition of very rare pediatric cancers based on incidence rates. However, this definition and the categorization and determination of incidence rates of rare tumors have to be considered "work in progress." For example, with the implementation of clinical and scientific structures for rare pediatric cancers, we see a rise in documented cases within registries. Moreover, new tumor entities are discovered by molecular characterization leading to a re-classification. Therefore, facilitated by sustainable clinical structures and scientific progress, the picture of rare pediatric tumors will develop continuously and hopefully become clearer over the next years.

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