RARE CHILDHOOD CANCERS

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- No significant financial interests to disclose
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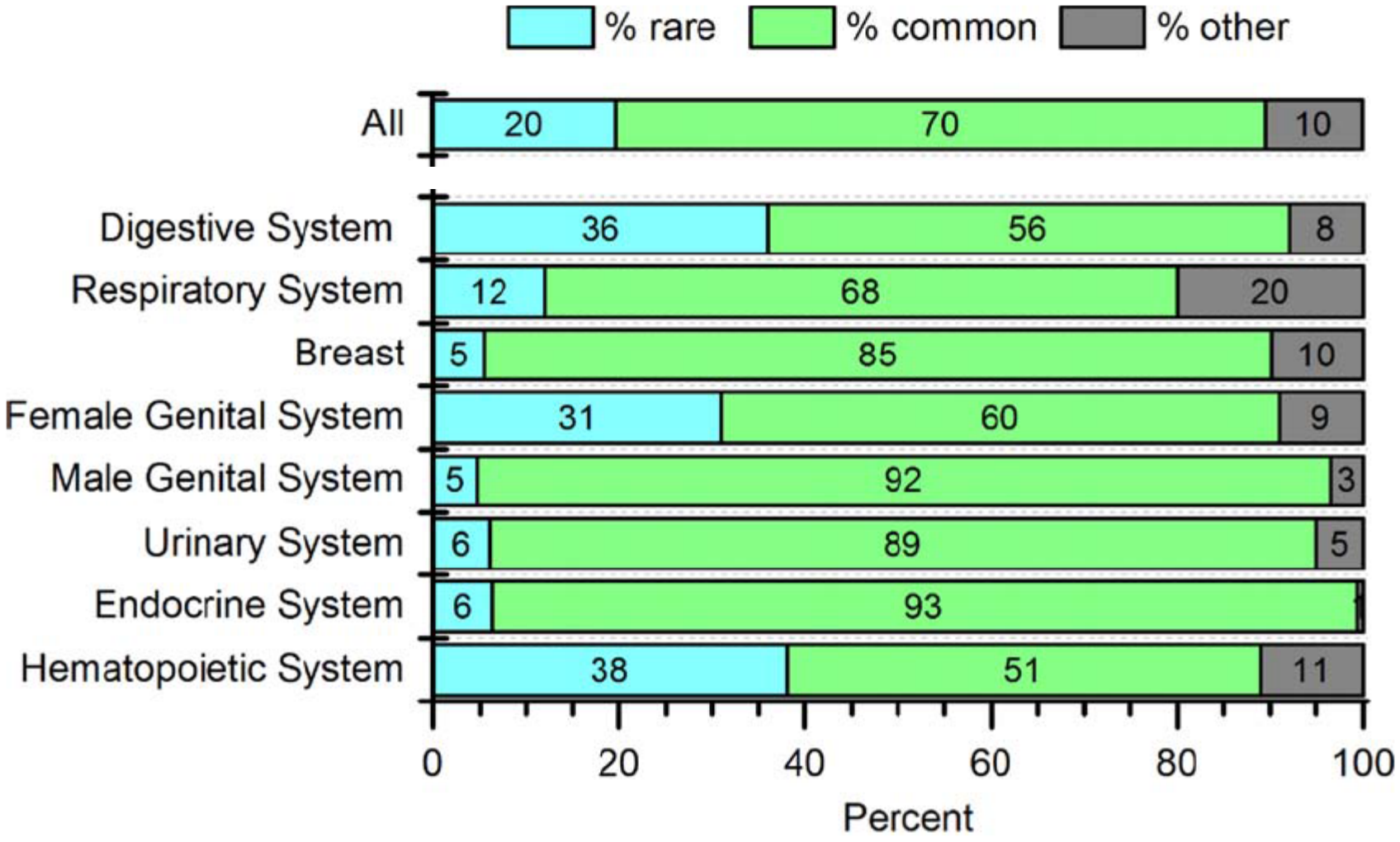
Rare Cancers

- General cancer incidence: 1.7 million cases/year in US
- Rare disease: < 200,000 cases/year (US Orphan Drug Act of 1983)
- Rare cancer:
  - < 15 per 100,000/year (National Cancer Institute 2004)
  - < 6 per 100,000/year (European RARECARE consortium 2011)
- 181 cancers meet RARECARE definition in US
  - 119 are very rare (≤ 0.5 per 100,000): 3% of all cancers
- Overall 20% of cancers in US considered rare
- **Rare cancers are not so rare**

CA Cancer J Clin 2017; 67; 261-272

Rare Cancers



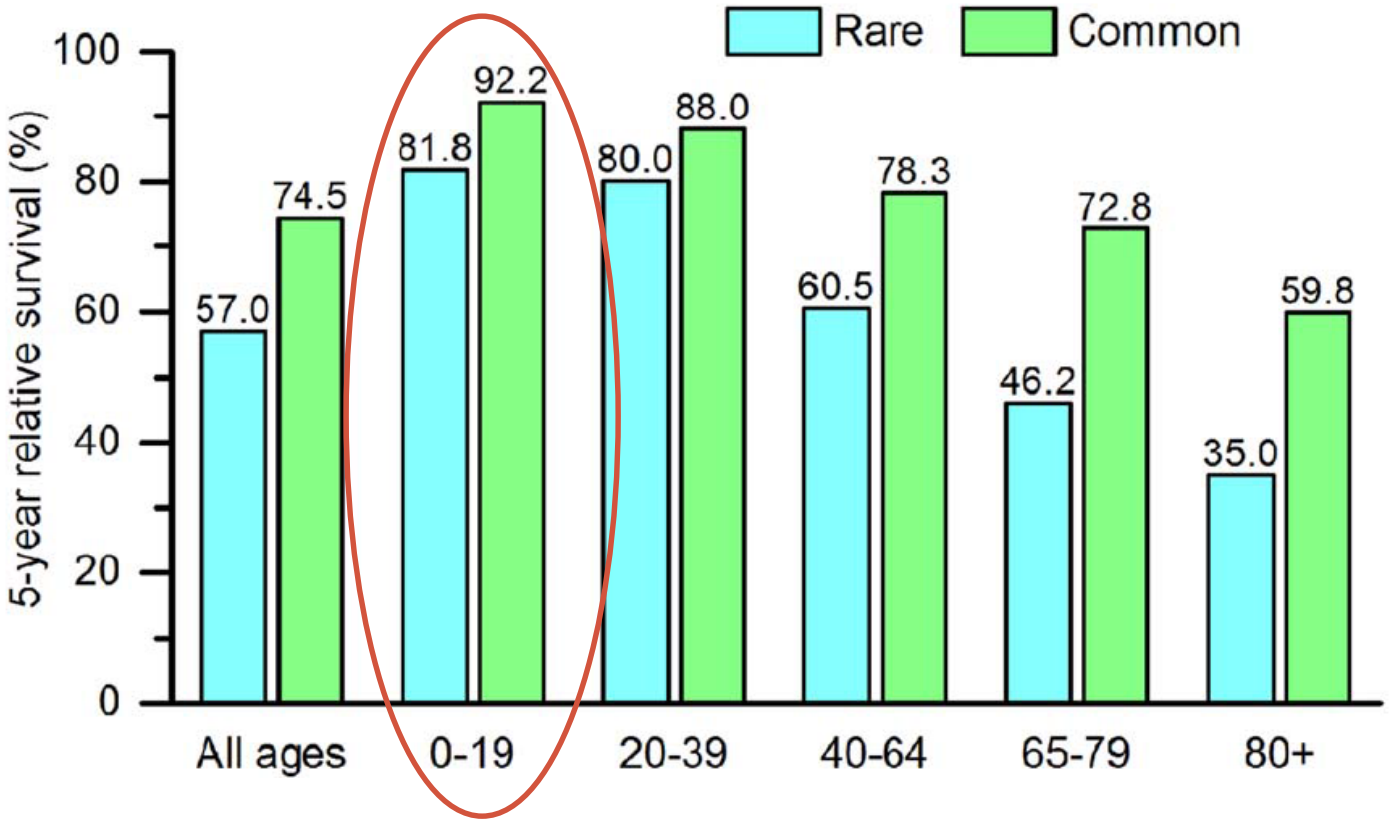
CA Cancer J Clin 2017; 67; 261-272

Rare Cancers

- Unique challenges of studying rare cancers:
  - Difficult to conduct clinical research
    - Logistics of identifying and enrolling patients
    - Lack of funding and awareness
    - Barriers to collaborative/international trials
  - Paucity of basic research
    - Limited biologic specimens
    - Few resources devoted to uncommon diseases
  - Delays in recognition and diagnosis
  - Limited treatment options due to lack of evidence
- 59% of rare tumors advanced stage at diagnosis (vs 45%)
- Decreased survival rates for rare vs common cancers

Rare Cancers

Survival: rare vs common (by age)



CA Cancer J Clin 2017; 67; 261-272

Childhood Cancer

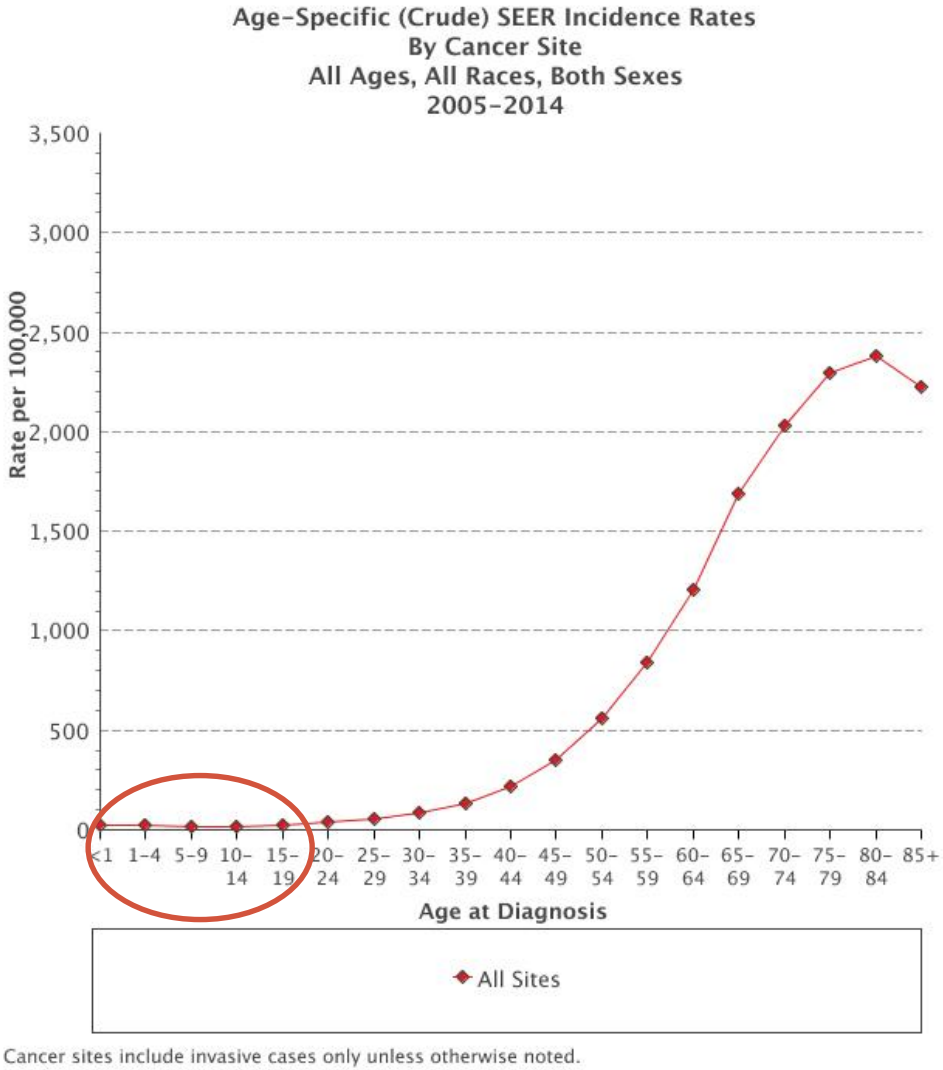
- 1,688,780 new cancers diagnosed in US in 2017
- Only 15,270 in children <20 years old
- Less than 1% of all US cancers are pediatric
- **All childhood cancer is rare**
- Second leading cause of mortality in children ages 1-14: estimated 1,190 cancer deaths in 2017
- Relative 5-year survival rate for pediatric cancer has increased from 58% in 1975 to 84% today

CA Cancer J Clin 2017; 67: 7-30

Childhood Cancer

Estimated New Cancer Cases, United States, 2017[1]

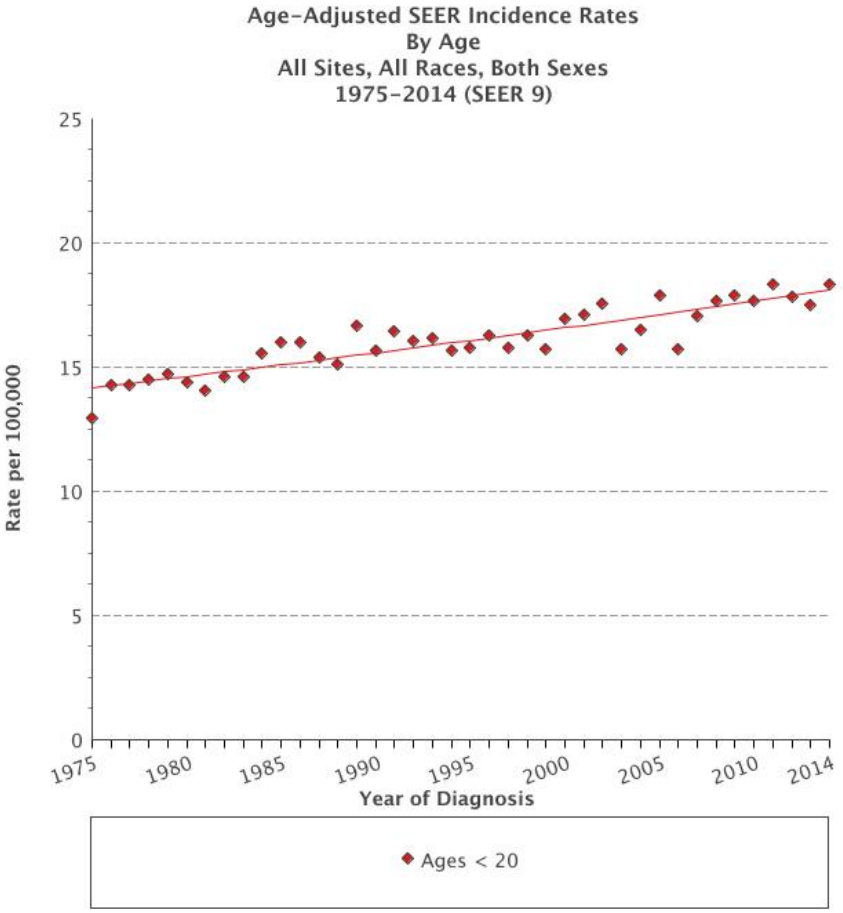
Site	New cases
All	1,688,780
Digestive	310,440
Genital	279,800
Breast	255,180
Respiratory	243,170
Urinary	146,650
Skin	95,360
Lymphoma	80,500
Leukemia	62,130
Endocrine	59,250
Oral	49,670
Other	33,770
Myeloma	30,280
Brain/CNS	26,930
Bone/soft tissue	15,650
All Pediatric	**15,270**



Cancer sites include invasive cases only unless otherwise noted.

[1]*CA Cancer J Clin* 2017; 67: 7-30

Childhood Cancer



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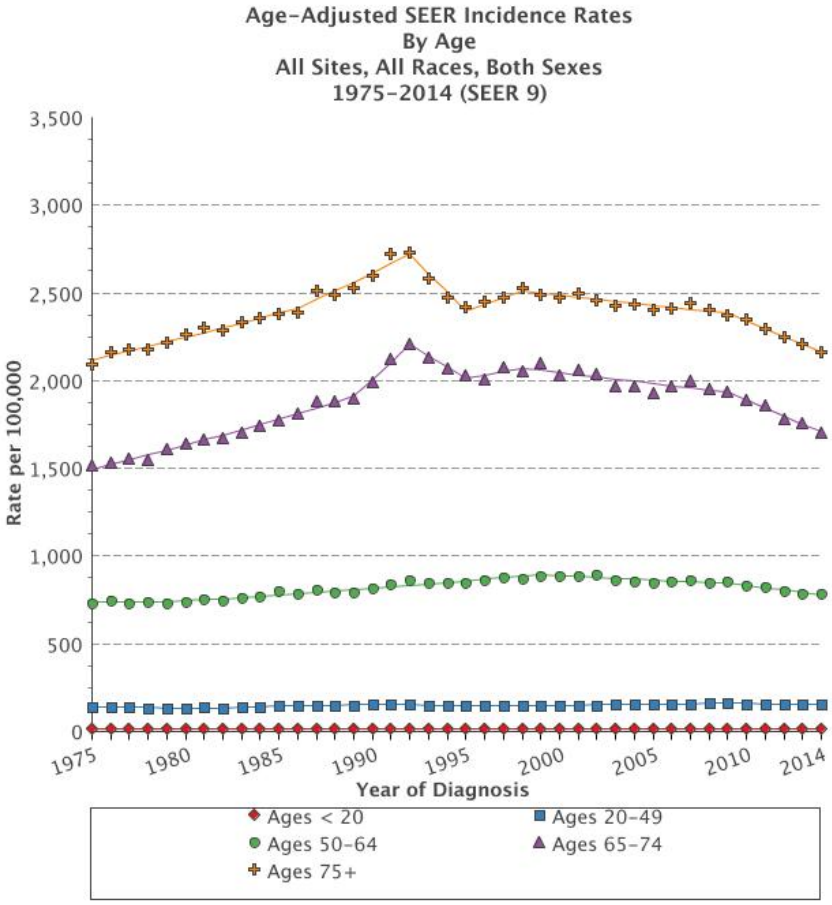

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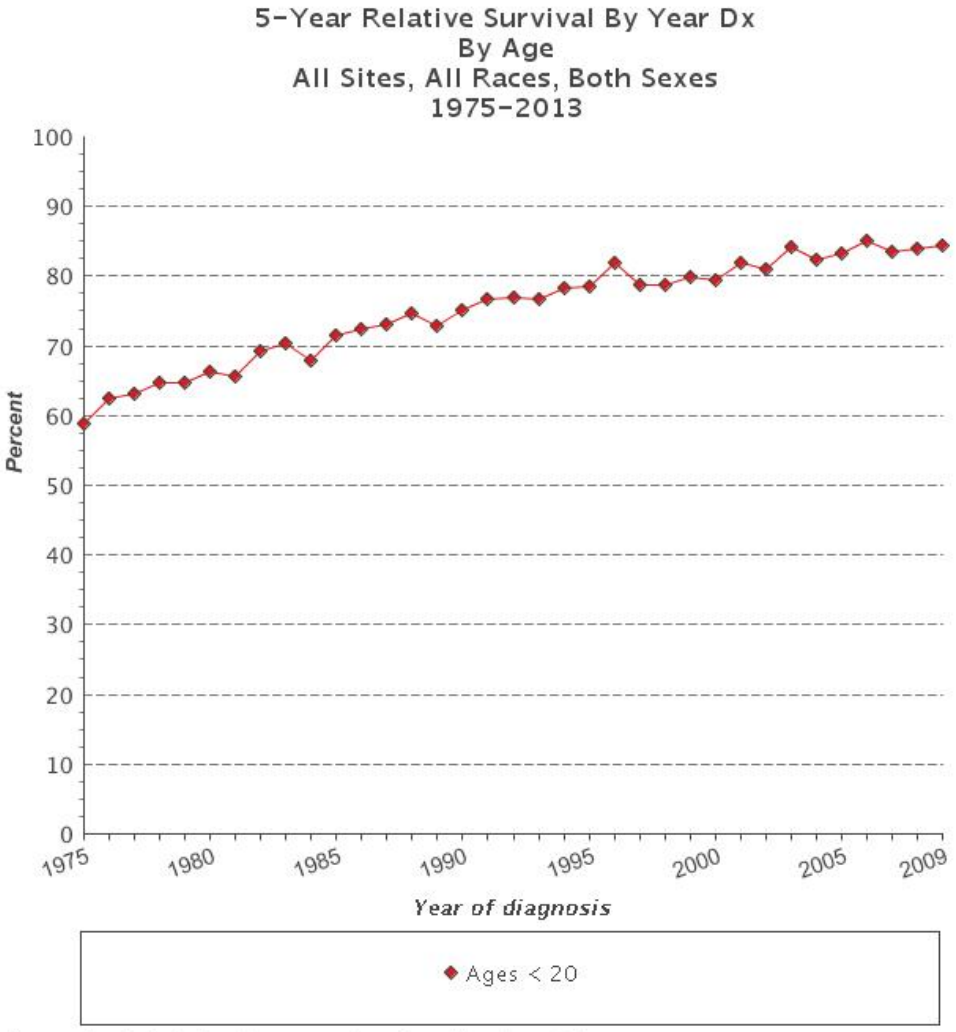
Childhood Cancer



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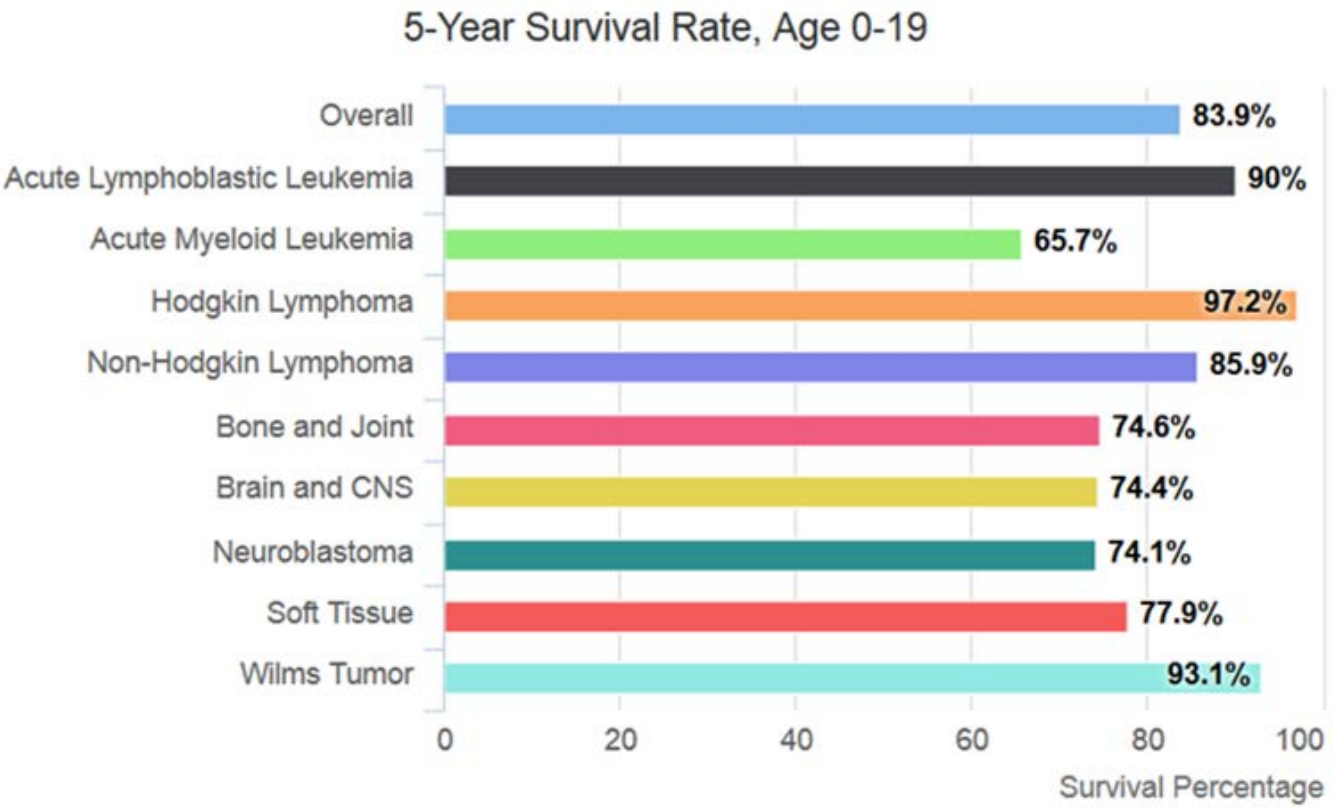
Childhood Cancer



Source: Surveillance, Epidemiology, and End Results (SEER) Program (www.seer.cancer.gov)

SEER 9 area. Based on follow-up of patients into 2012

Childhood Cancer

- **Children are not little adults**
  - >90% of adult cancers are epithelial (carcinoma, melanoma)
  - >85% of pediatric cancers are mesenchymal (sarcoma, lymphoid, embryonal)
  - No link to environmental exposures in most childhood cancer
  - 8.5% of pediatric cancer associated with germline mutations in cancer-predisposing genes
- Adolescent/young adult (AYA) age represents some overlap
  - 21% of cancers in 15-19 year olds are epithelial tumors
  - Increased cancer incidence in AYA versus younger children
    - 1 per 100,000 for ages 0-14
    - 71 per 100,000 for ages 15-39
  - Decreased survival compared with younger children for some diagnoses
    - Leukemia: 74% ages 15-19 vs 91% ages 1-14

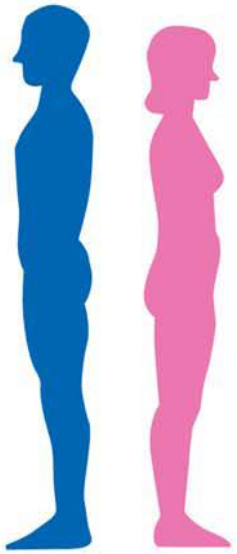
Unusual Cancers of Childhood Treatment (PDQ®)–Health Professional Version was originally published by the National Cancer Institute

N Enlg J Med 2015; 373: 2336-2346

Cancer Distribution: Adults

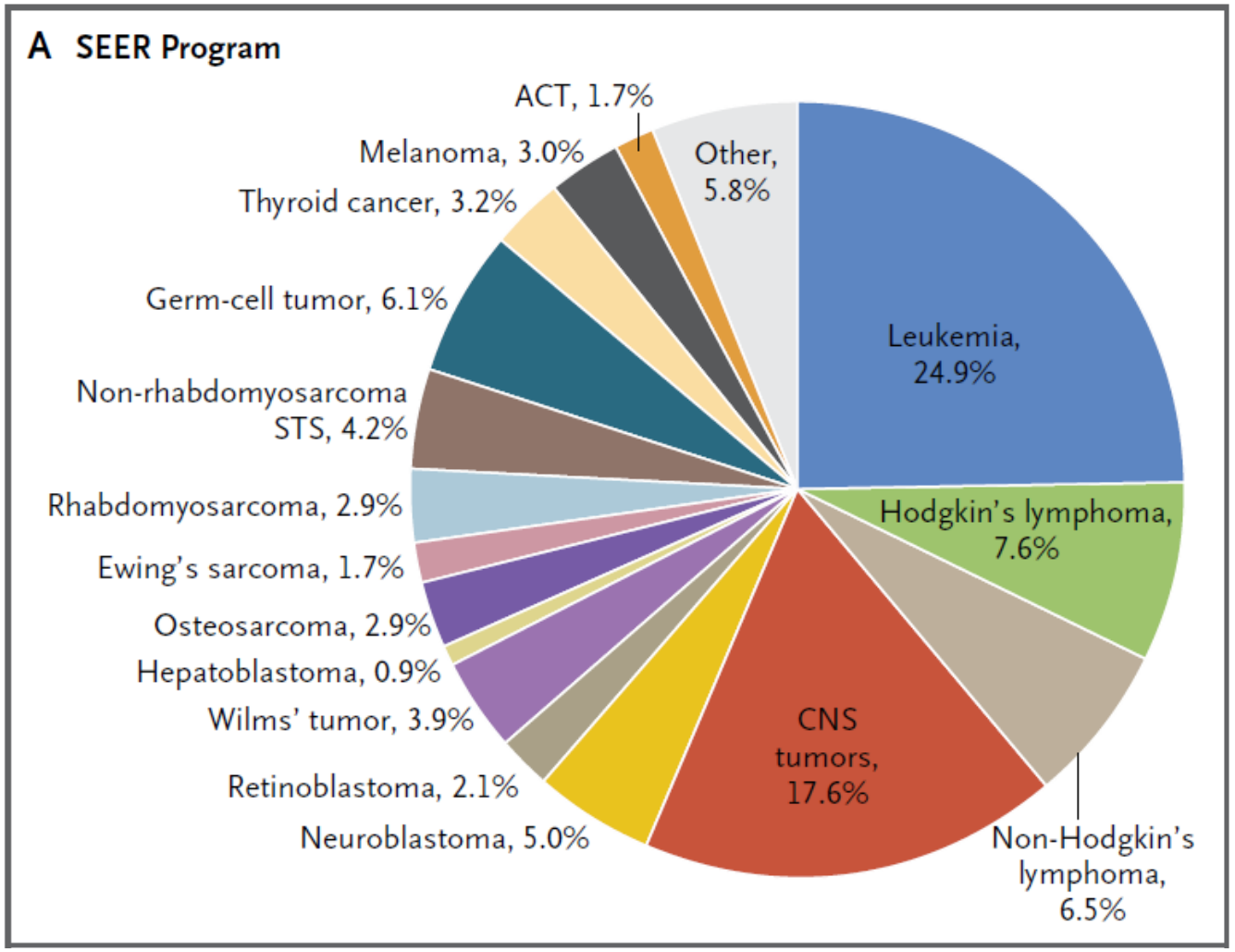
Estimated New Cases

Males				Females		
Prostate	161,360	19%		Breast	252,710	30%
Lung & bronchus	116,990	14%		Lung & bronchus	105,510	12%
Colon & rectum	71,420	9%		Colon & rectum	64,010	8%
Urinary bladder	60,490	7%		Uterine corpus	61,380	7%
Melanoma of the skin	52,170	6%		Thyroid	42,470	5%
Kidney & renal pelvis	40,610	5%		Melanoma of the skin	34,940	4%
Non-Hodgkin lymphoma	40,080	5%		Non-Hodgkin lymphoma	32,160	4%
Leukemia	36,290	4%		Leukemia	25,840	3%
Oral cavity & pharynx	35,720	4%		Pancreas	25,700	3%
Liver & intrahepatic bile duct	29,200	3%		Kidney & renal pelvis	23,380	3%
All Sites	**836,150**	**100%**		**All Sites**	**852,630**	**100%**



CA Cancer J Clin 2017; 67: 7-30

Cancer Distribution: All Children



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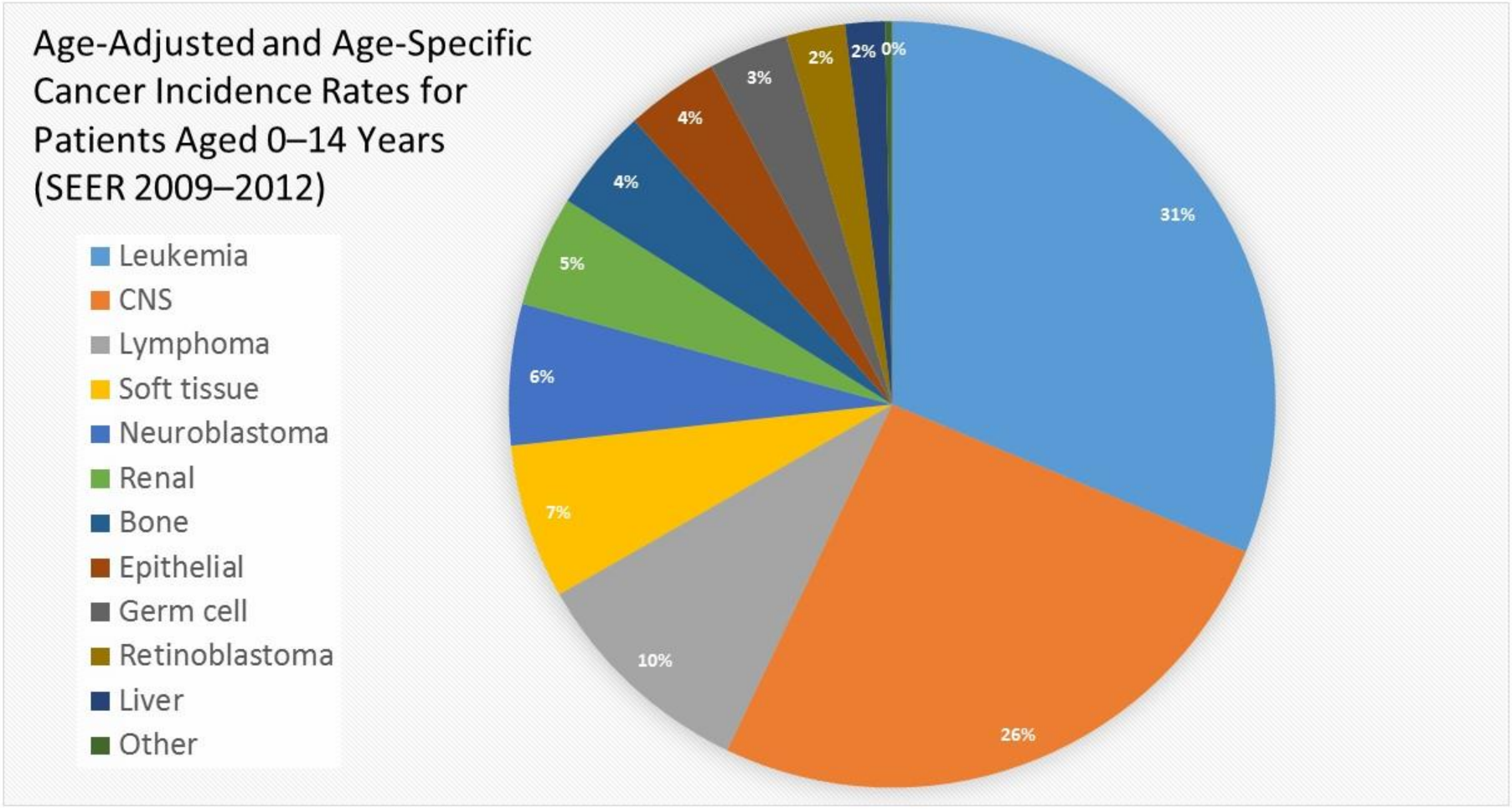
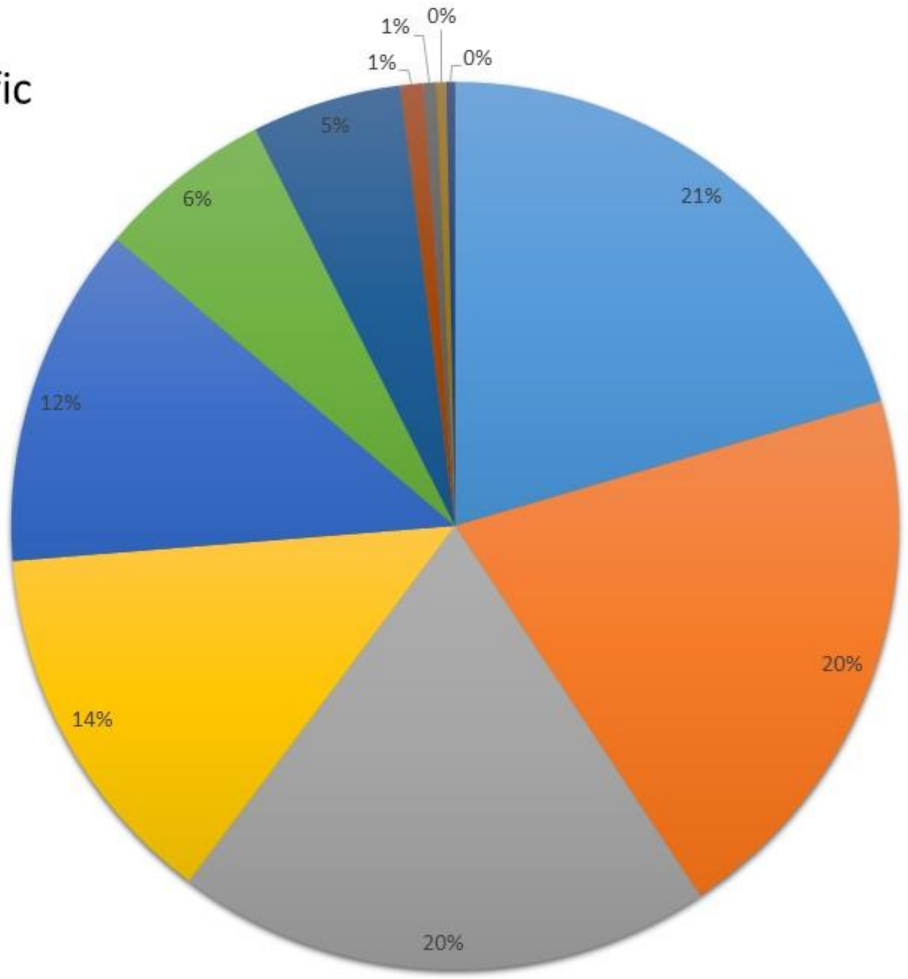
Cancer Distribution: Young Children



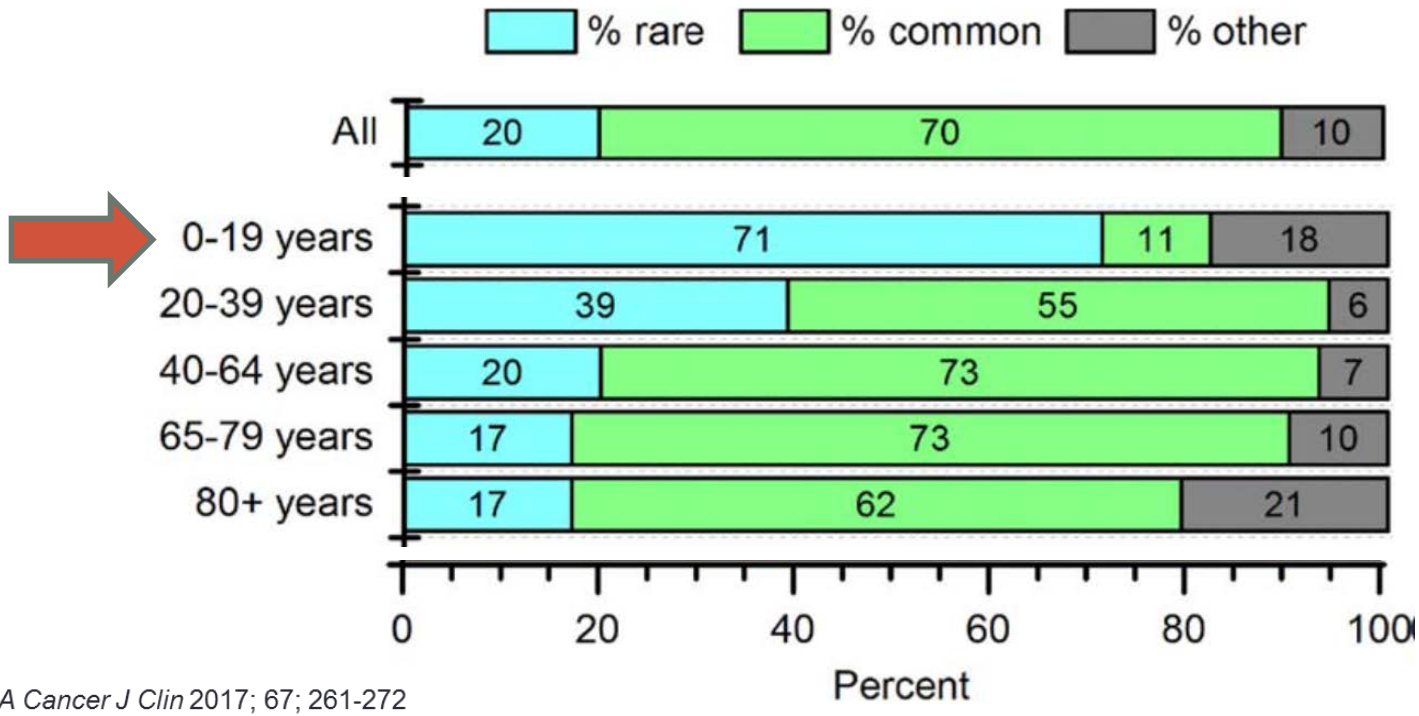
Cancer Distribution: Adolescents

Age-Adjusted and Age-Specific Cancer Incidence Rates for Patients Aged 15–19 Years (SEER 2009–2012)



Rare Childhood Cancers

- What is a rare pediatric cancer?
  - 71% of childhood/adolescent cancers considered rare by RARECARE definition (< 6 per 100,000/year)
  - **All childhood cancer is rare**



CA Cancer J Clin 2017; 67; 261-272

Defining Rare Childhood Cancers

- Underrepresented in pediatric oncology
  - Rare in childhood, not seen in adults
  - Rare in childhood, more common in adults
  - Rare variants of more common childhood cancers
- COG definition
  - Low prevalence in young patients, higher incidence in adults, epithelial origin
  - “Other malignant epithelial neoplasms and melanomas” in ICCC* subgroup of SEER database
  - Does not include some rare cancers seen only in children: pancreatoblastoma, pleuropulmonary blastoma
- EXPeRT** definition
  - Incidence ≤ 2 per million per year
  - Not considered in clinical trials

*International Classification of Childhood Cancer
**European Cooperative Study Group for Pediatric Rare Tumors
J Clin Oncol 2015; 33: 3047-3054

Defining Rare Childhood Cancers

- **Rare cancers are not that rare**
  - 11% of childhood cancers <age 20 (COG definition)
  - 75% occur in patients age 15-19 years

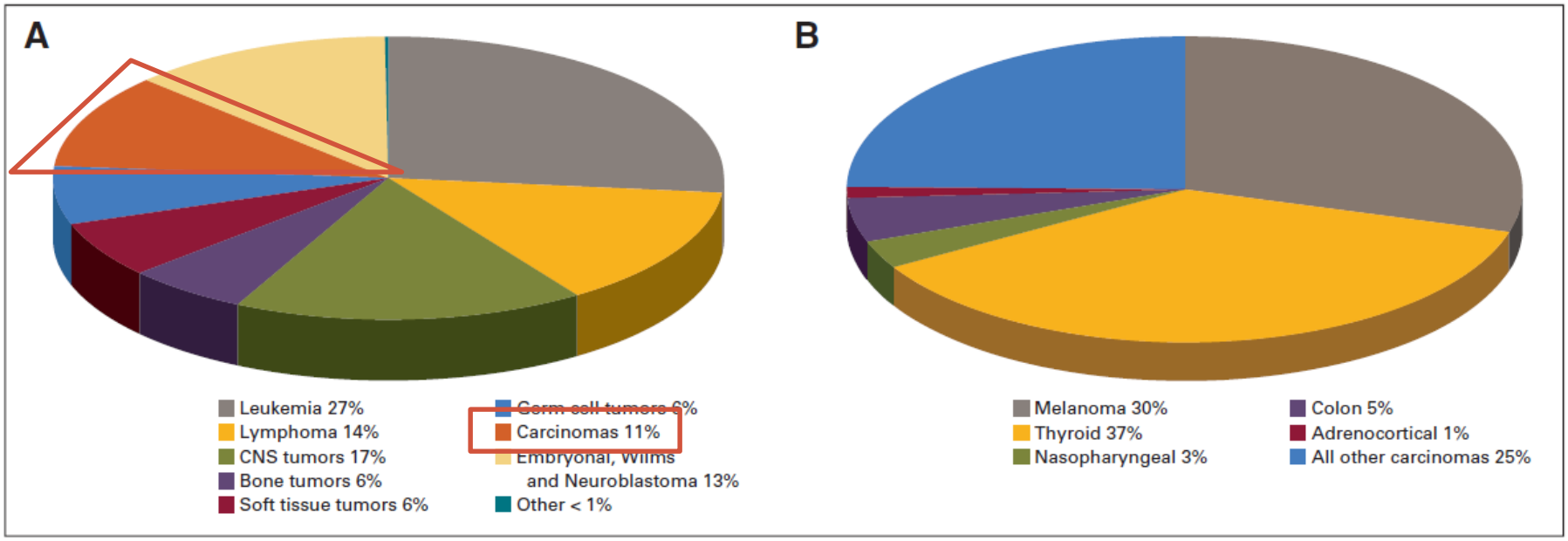
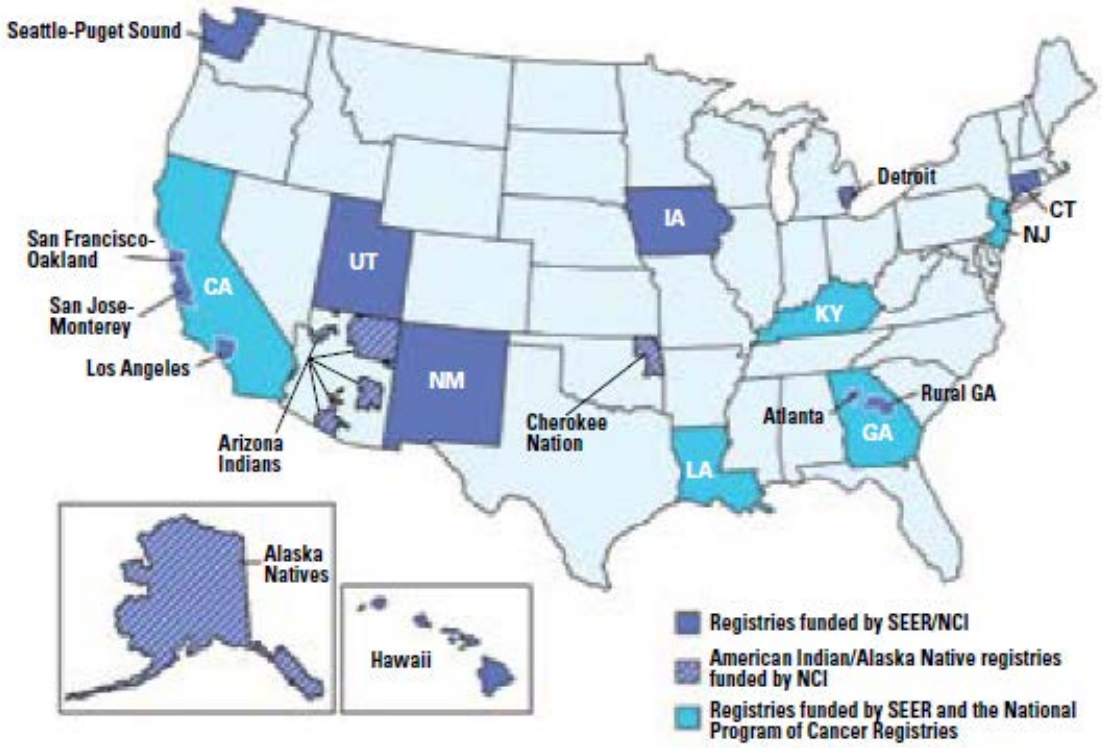


Fig 1. Annual incidence of (A) malignancies and (B) carcinomas and melanomas in those age < 20 years with proportion of specific histologies as coded according to SEER adolescent and young adult classification of International Classification of Diseases for Oncology (version 3), standardized to the 2000 US standard population.[4]

J Clin Oncol 2015; 33: 3047-3054

Studying Rare Childhood Cancers

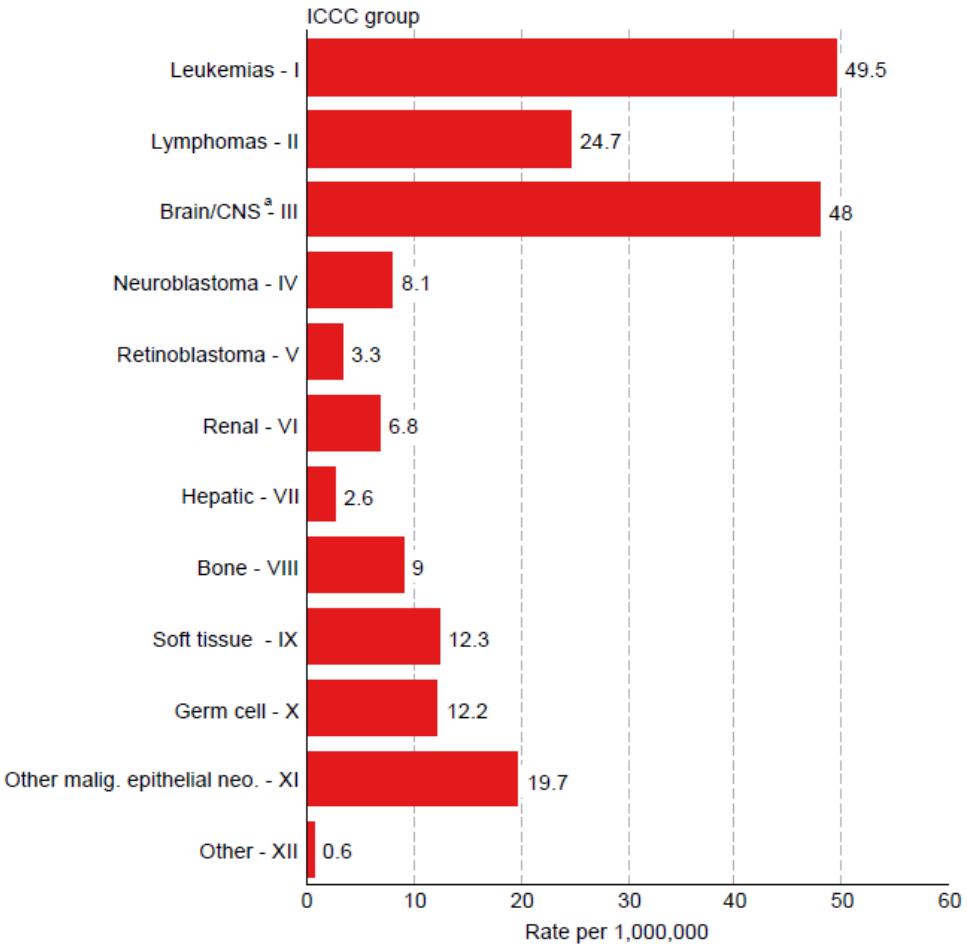
- Surveillance, Epidemiology and End Results (SEER)
  - NCI program for studying cancer epidemiology since 1973
  - Incidence and survival statistics from registries covering 28% of U.S. population
  - 20 geographical regions
  - Represents ethnic mix of U.S. population
  - Database includes
    - Demographics
    - Cancer site
    - Tumor markers
    - Stage
    - Treatment
    - Survival
  - Childhood cancers listed by
    - Site (like adults)
    - ICCC* grouping



*International Classification of Childhood Cancer

Studying Rare Childhood Cancers

Childhood Cancer : SEER Incidence Rates 2010-2014 by ICCC Group
(includes myelodysplastic syndromes and Group III benign brain)
Under 20 Years of Age, Both Sexes, All Races



Age-Adjusted SEER Cancer Incidence[a] and U.S. Death[b] Rates, 2010-2014

By Primary Cancer Site

All Races, Males and Females

	Ages 0-19					
	Incidence			Mortality		
Site	Total	Males	Females	Total	Males	Females
All Sites						
All Races	17.8	18.5	17.0	2.3	2.6	2.1
Whites	18.9	19.7	18.1	2.4	2.6	2.1
Blacks	13.7	13.8	13.6	2.2	2.4	2.1
Bone & Joint	0.9	1.0	0.8	0.2	0.2	0.2
Brain & Other nervous	3.1	3.3	3.0	0.7	0.7	0.6
Hodgkin lymphoma	1.2	1.3	1.1	0.0	0.0	0.0
Kidney & Renal pelvis	0.7	0.6	0.8	0.1	0.1	0.1
Leukemia	4.7	5.1	4.3	0.6	0.7	0.6
Acute lymphocytic	3.5	3.8	3.2	0.3	0.3	0.2
Non-Hodgkin lymphoma	1.3	1.7	0.9	0.1	0.1	0.1
Soft tissue	1.1	1.0	1.1	0.2	0.2	0.2

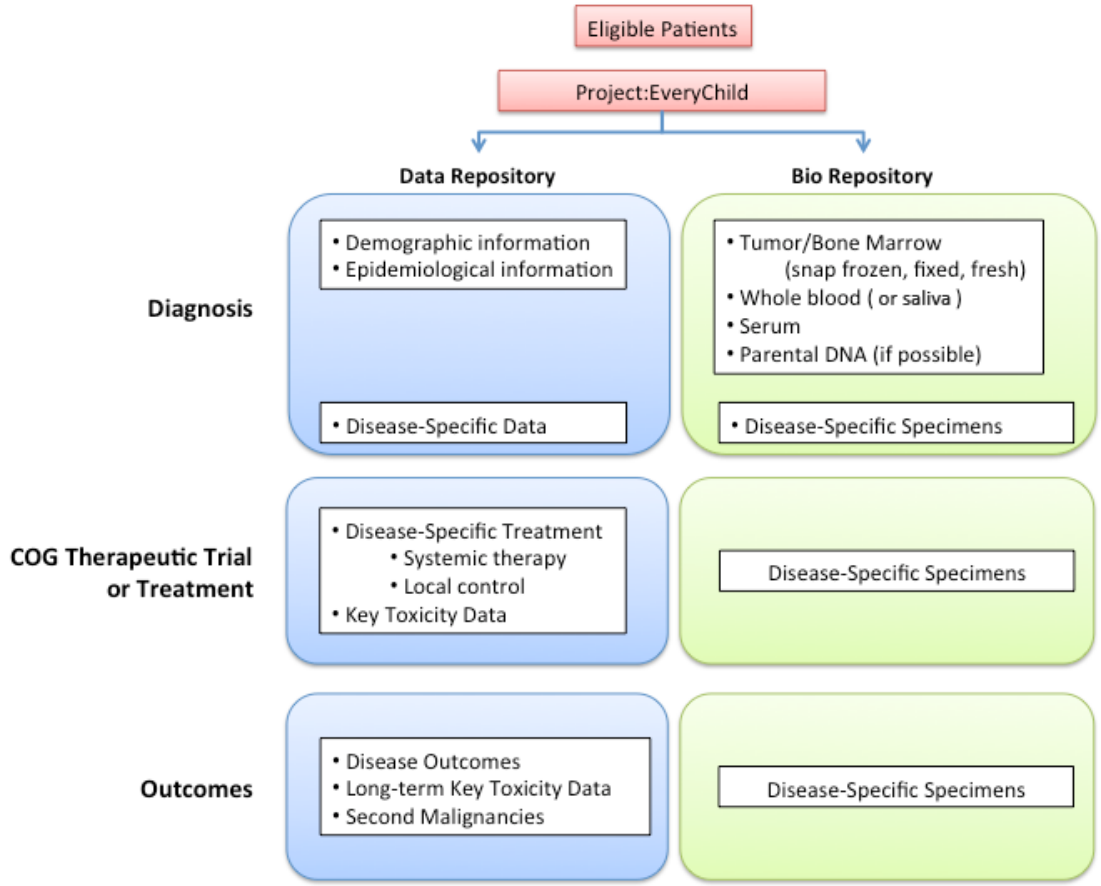
Studying Rare Childhood Cancers

- Children's Oncology Group (COG)
  - Only NCI-sponsored cooperative group in N. America
  - 80% of eligible children with cancer are enrolled on COG trials
  - Children's Cancer Research Network (CCRN)
    - Registry for all pediatric cancer patients at US/Canadian COG centers
    - 42% of all pediatric oncology patients registered in first 2 years
    - 56,886 patients enrolled 2007-2017
  - Project:EveryChild
    - New master protocol with combined registry and biospecimen repository
    - Starting 2017: replaces CCRN and individual disease-specific biology studies
- COG Rare Tumors Committee – since 2002
  - Liver tumors
  - Germ cell tumors
  - Retinoblastoma (since 2008)
  - **Infrequent tumors**

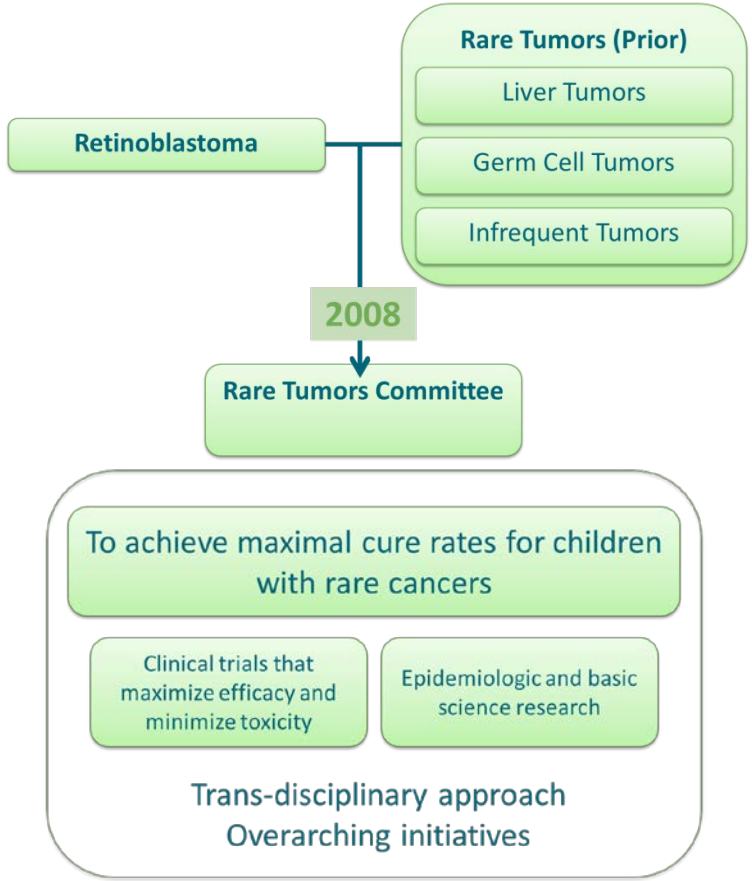
CHILDREN'S ONCOLOGY GROUP
The world's childhood cancer experts

Studying Rare Childhood Cancers

COG Project:Every Child



COG Rare Tumors Committee



Studying Rare Childhood Cancers

- EXPeRT (European Cooperative Study Group for Pediatric Rare Tumors) – since 2008
  - International collaboration: Italy, France, UK, Poland, Germany
  - Aims:
    - Develop recommendations
    - Collect clinical data
    - Identify experts
    - Establish collaborative networks
    - Conduct clinical, pathological, biological studies
  - Examples:
    - Pancreatoblastoma
    - Sertoli-Leydig cell tumors
    - Pleuropulmonary blastoma

Studying Rare Childhood Cancers

- Individual registries

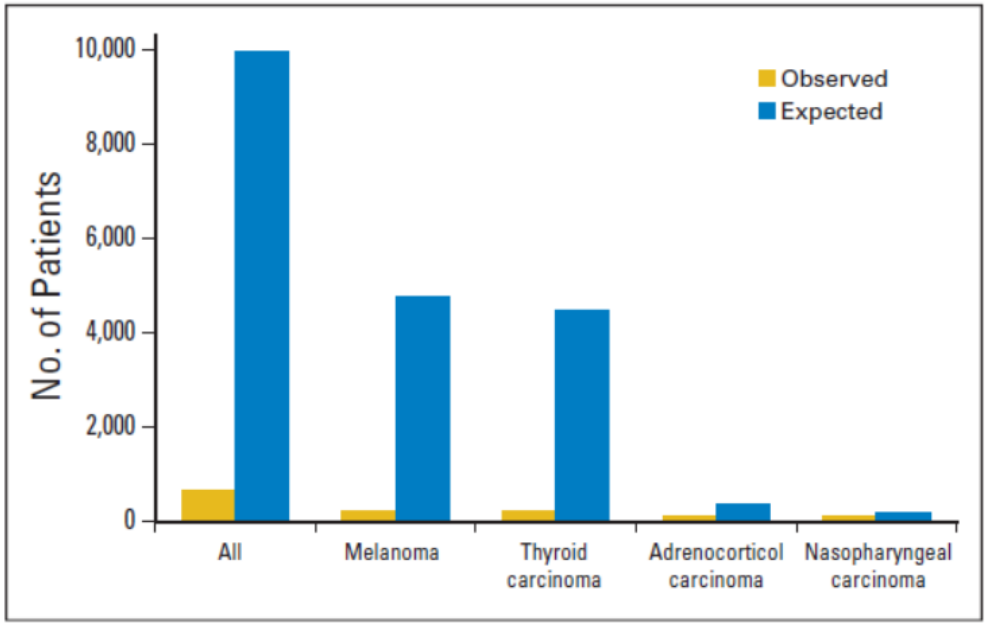
International Pediatric Adrenocortical Tumors Registry

IRHDR

Ovarian and Testicular Stromal Tumor Registry

Studying Rare Childhood Cancers

- **Challenges:**
  - Registry data
    - Only 7% of expected number captured in original COG registry (2002-2007)
    - Only 2.4% of expected rare tumor cases in CCRN (2008-2013)
    - Lack of awareness of individual registries
  - Biospecimen respository gap
    - Only 11% of rare tumors in COG registry (9% in CCRN) have banked tissue available
    - Need for molecular studies to understand pathophysiology and therapeutic targets



J Clin Oncol 2010; 28: 5011-5016
J Clin Oncol 2015; 33: 3047-3054

Studying Rare Childhood Cancers

- **Challenges:**
  - AYA patients (ages 15-19 years)
    - 75% of rare childhood tumors
    - Cancer incidence double that in younger children
    - Participation in NCI-sponsored trials ¼ the rate in children <15
    - Cooperative group registration rate 24% vs 71% for younger
    - Less likely to be seen in pediatric cancer centers
    - More likely to managed exclusively by surgeons/other specialties

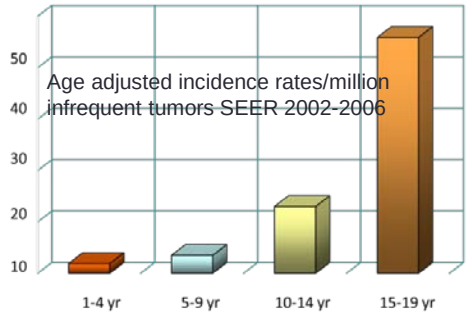


Table 1. Patient Cases Registered in CCRN COG Trial From 2008 to 2013 Compared With Expected Patient Cases During Same Time Period Based on SEER Estimates

	Age Group (years)									
	0 to 4		5 to 9		10 to 14		15 to 19		All	
Diagnosis	Observed	Expected	Observed	Expected	Observed	Expected	Observed	Expected	Observed	Expected
Adrenocortical carcinoma	29	162	9	36	17	66	9	72	64	336
Colon carcinoma	13	84	13	186	37	786	47	3,396	110	4,452
Melanoma (cutaneous)	20	324	41	582	54	1,464	47	5,922	162	8,292
Naospharyngeal carcinoma	27	18	36	162	77	906	53	1,692	193	2,778
Thyroid carcinoma	0	66	14	444	44	2,202	47	7,854	105	10,566

Abbreviations: COG, Children's Oncology Group; CCRN, Children's Cancer Research Network.

J Clin Oncol 2010; 28: 5011-5016

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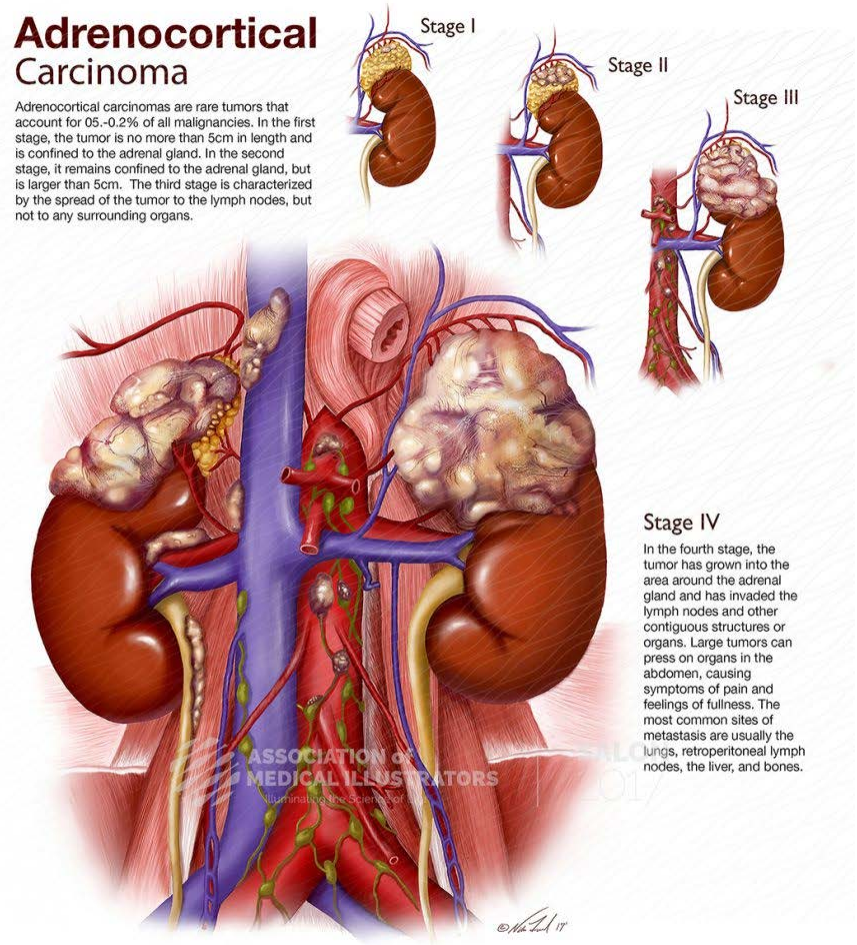
Studying Rare Childhood Cancers

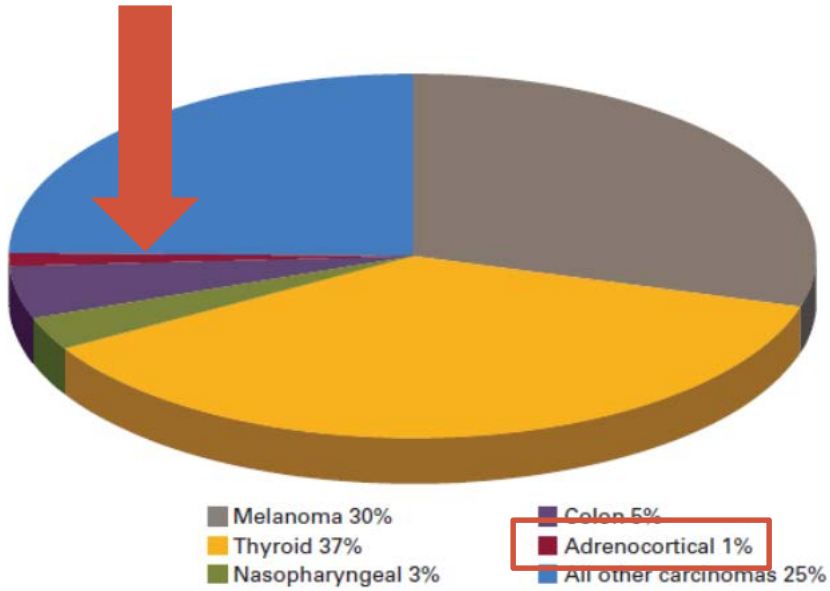
- **Challenges:**
  - Clinical trial development
    - Low participation among COG centers for rare tumor trials
    - Low participation among non-COG centers for pediatric patients
    - Children excluded from clinical trials oriented to “adult” malignancies
    - Numbers too small for randomized trials
    - Barriers to international cooperation
  - COG Infrequent Tumor Subcommittee trials
    - Melanoma
      - COG collaboration with ECOG and SWOG for 2 randomized trials
      - Only 4 children enrolled over 4 years
    - Nasopharyngeal carcinoma: ARAR0331
      - Slow accrual: 111 patients enrolled 2006-2012
    - Adrenocortical carcinoma: ARAR0332
      - 78 patients enrolled 2006-2013
      - Required significant participation by collaborating Brazilian centers

Rare Childhood Cancers: Examples

- Adrenocortical Carcinoma
- Colon cancer
- Melanoma
- Desmoid Tumors
- Gastrointestinal Stromal Tumors (GIST)
- Germ Cell Tumors
- Liver Tumors
- Malignant rhabdoid tumors
- Nasopharyngeal Carcinoma
- Neuroendocrine Tumors
- NUT Midline Carcinoma
- Pancreatic Tumors
- Pleuropulmonary Blastoma (PPB)
- Retinoblastoma
- Sex Cord-Stromal Tumors
- Thyroid Tumors

Adrenocortical Carcinoma

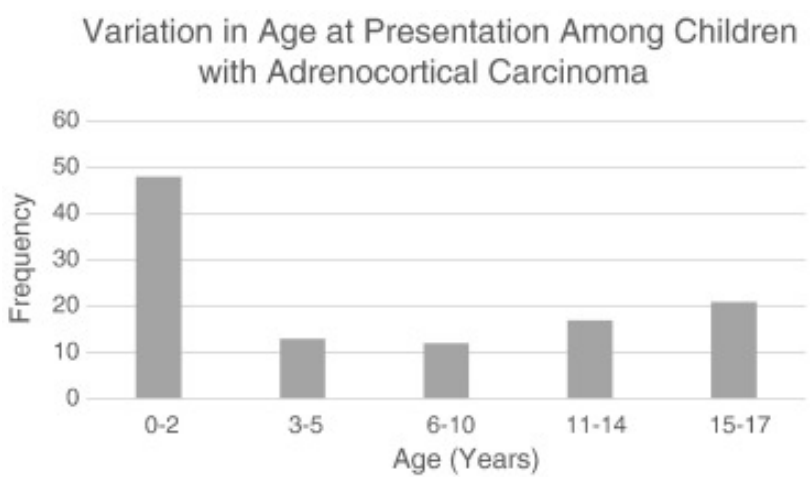


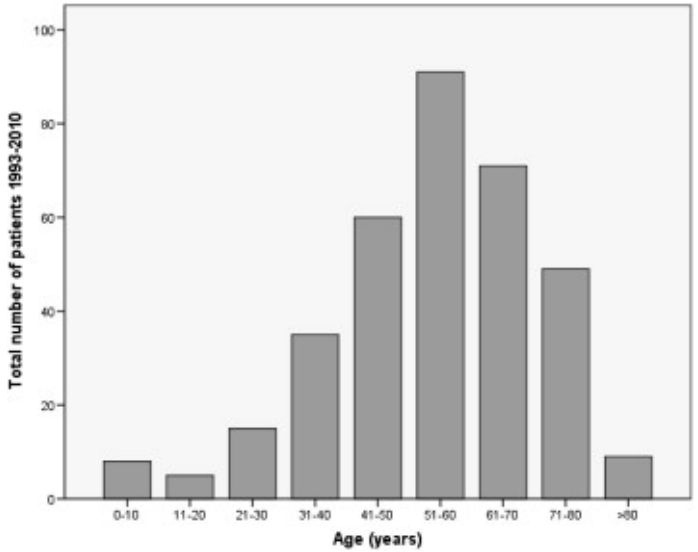


Adrenocortical Carcinoma

- Incidence in US: 0.72 per million
- Incidence in children: 0.2 per million
  - 25 cases per year
  - 0.2% of pediatric cancers
- Age distribution
  - Bimodal peaks in 1st and 4th decades of life
  - Median age in children: 3-4 years (second peak in adolescence)
- Geographical variation: 10-15 x higher incidence in Brazil

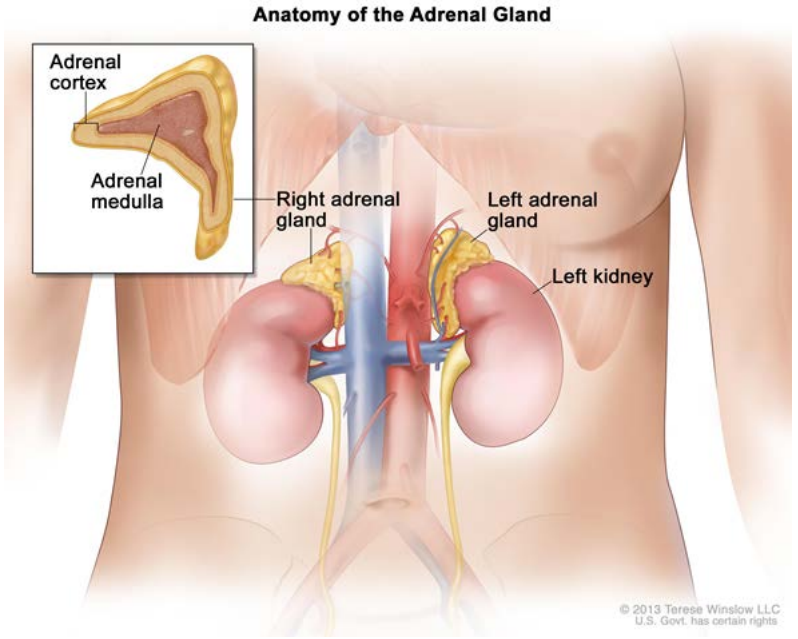
Unusual Cancers of Childhood Treatment (PDQ®)–Health Professional Version was originally published by the National Cancer Institute





Adrenocortical Carcinoma

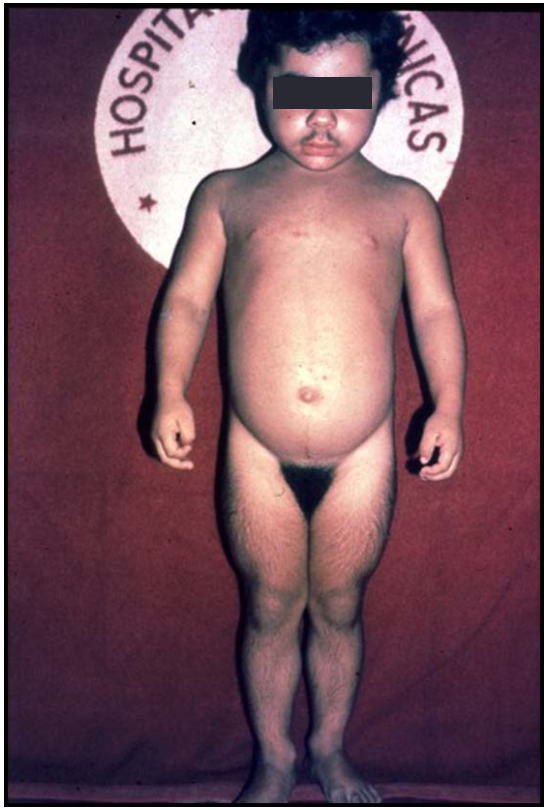
- Biology
  - Adrenal cortex produces:
    - Cortisol/aldosterone
    - Testosterone/estrogen
  - Adrenal medulla
    - Produces adrenaline/noradrenaline
    - Medullary tumors:
      - Pheochromocytoma
      - Neuroblastoma
- Genetics
  - Germline *TP53* mutation
    - Li-Fraumeni syndrome: risk for ACC, sarcomas, leukemia, breast, brain cancer
    - Over 50% of American/European cases
    - 95% of Brazilian cases (unique mutation, no increased risk of other cancers)
  - Beckwith-Wiedemann syndrome, MEN type 1



Adrenocortical Carcinoma

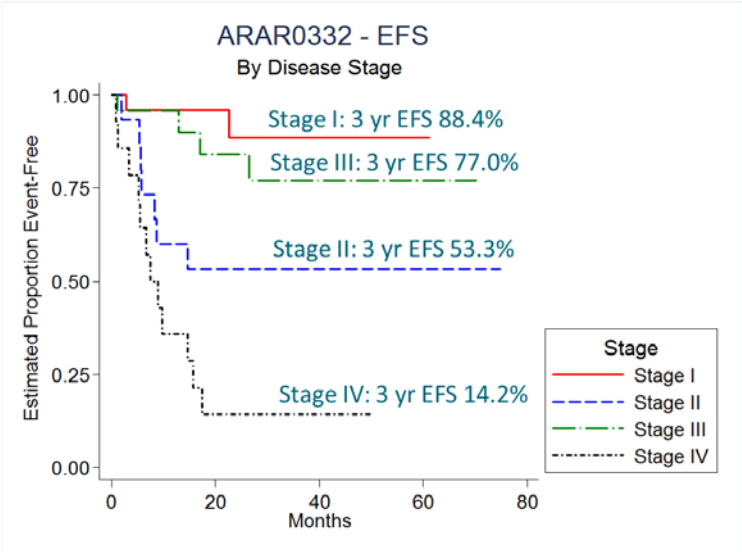
- Clinical features
  - Virilization +/- Cushing syndrome in 80%
  - Hypertensive crisis in 10%
  - Abdominal pain
  - Two-thirds present with localized disease
- Prognosis: 5-year survival 54-74% in children
- Risk factors
  - Larger tumor size
  - Age over 4-5 years
  - Stage/metastases
  - Incomplete resection
- Treatment
  - Surgery (avoid tumor spillage)
  - Mitotane/chemo for incomplete resection
  - Little data in children

Unusual Cancers of Childhood Treatment (PDQ®)–Health Professional Version was originally published by the National Cancer Institute

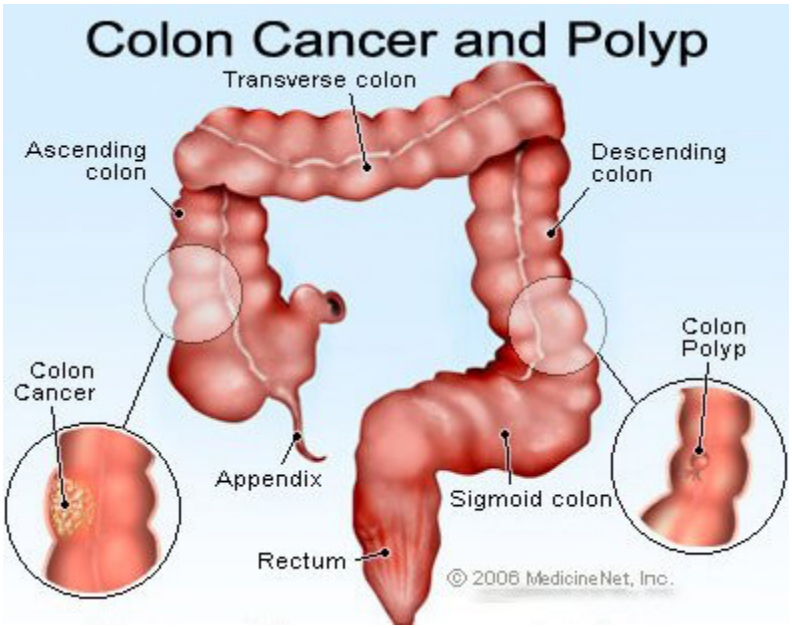


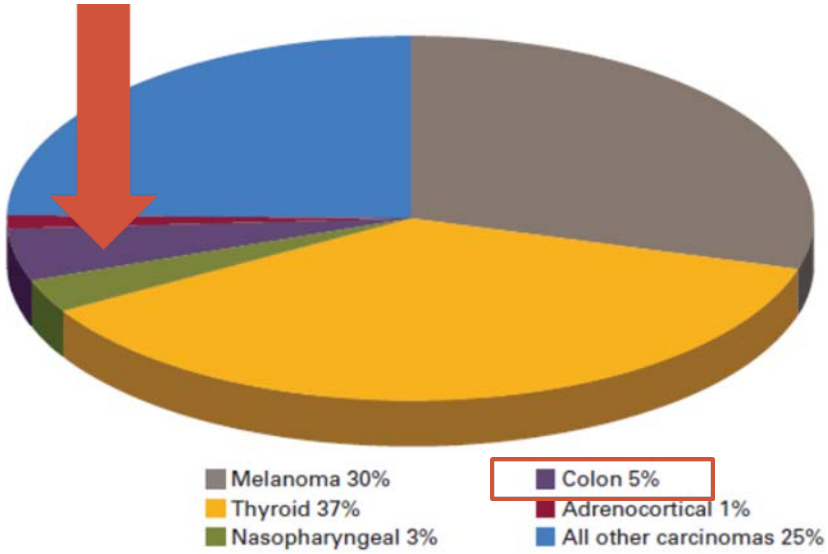
Adrenocortical Carcinoma

- COG trial ARAR0332
  - Open 2006-2013 in US and Brazil
  - 78 patients enrolled
  - Strategy:
    - Stage I: surgery
    - Stage II: extended surgery (RPLND)
    - Stage III/IV: surgery + chemo
  - Conclusions (unpublished):
    - Excellent outcome for stage I: 3-year EFS 88.9%/OS 92.3%
    - RPLND for stage II did not improve outcome: 53.3%/86.2%
    - Good outcome for stage III with surgery + chemo: 77%/100%
    - Poor outcome for stage IV: 13% OS
    - Highly toxic chemotherapy regimen (mitotane + cisplatin/etoposide/doxorubicin)
- Future Trial
  - Mitotane/chemotherapy for stage II?
  - New chemotherapy regimen for stage III/IV?



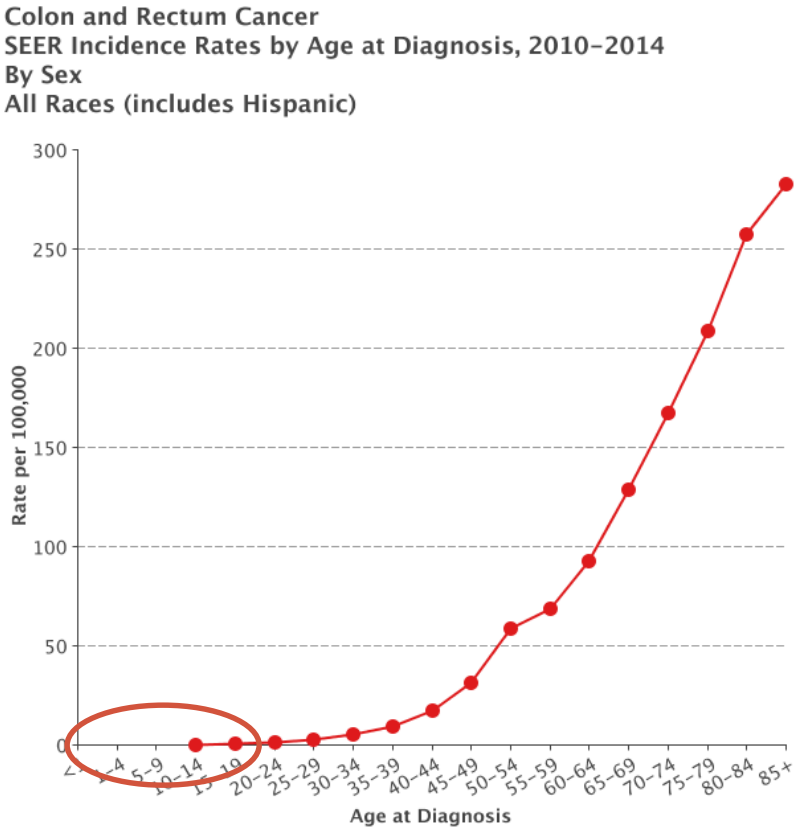
Colorectal Cancer





Colorectal Cancer

- Adults
  - Third most common malignant tumor
  - 90% of cases present > age 50 years
  - Preceded by adenomatous polyps
  - Slow malignant transformation
  - Risk factors:
    - Age, family history, race
    - IBD, FAP, HNPCC, prior radiation
    - Obesity, alcohol, tobacco
- Children/adolescents
  - Annual incidence 1 per million < age 20 in US
  - 1% of all pediatric malignancies
  - Fewer than 100 cases/year in US
  - Predisposing syndromes more common than adults but unknown rate



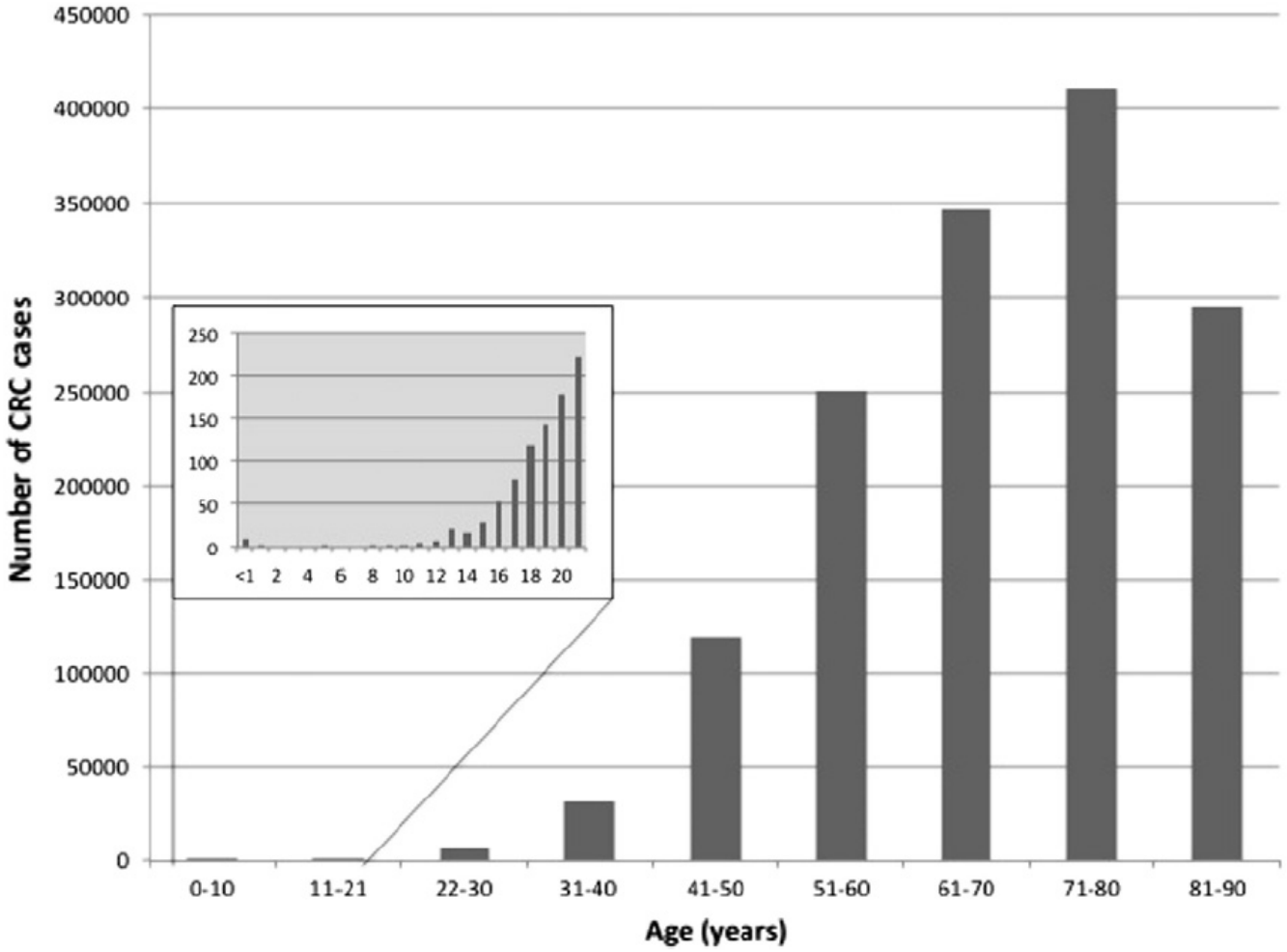
Unusual Cancers of Childhood Treatment (PDQ®)–Health Professional Version was originally published by the National Cancer Institute

Pediatric Colorectal Cancer

- SEER review
  - 159 pediatric cases 1973-2005
- National Cancer Database review
  - 918 pediatric cases 1998-2011
- High risk features more common than in adults:
  - Mucinous/signet ring histology
  - High grade/poorly differentiated
  - Microsatellite instability
  - FAP: 10% vs 0.1% (SEER)
  - Stage III/IV: 62% vs 37% (NCD)
- Outcome
  - Inferior survival for children vs adults <50
  - Inferior outcome for rectal vs colon cancer
  - Inferior survival for higher grade/stage

Cancer 2010;116:758–65
J Pediatric Surg 51 (2016) 1061–1066

Pediatric Colorectal Cancer



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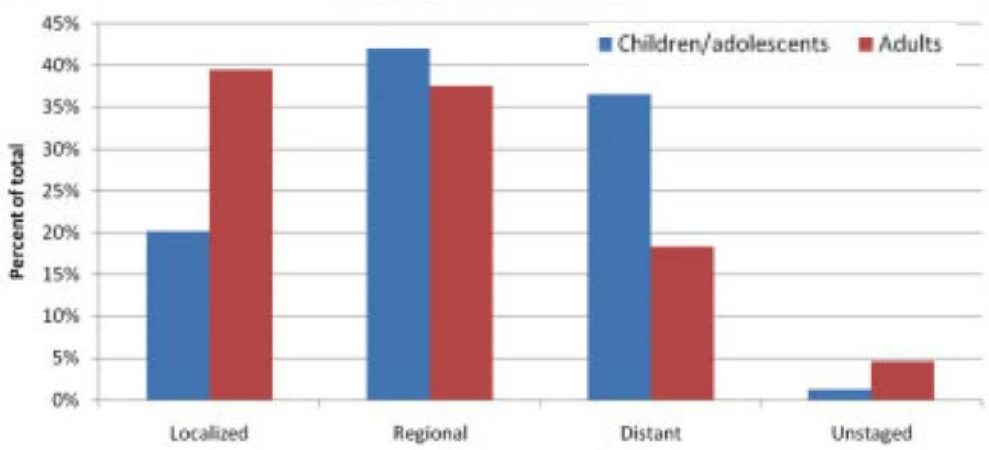
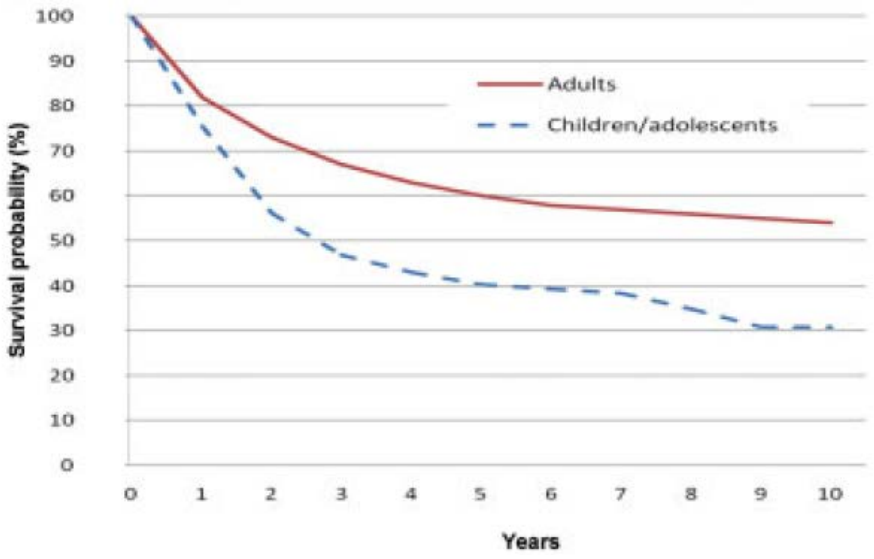
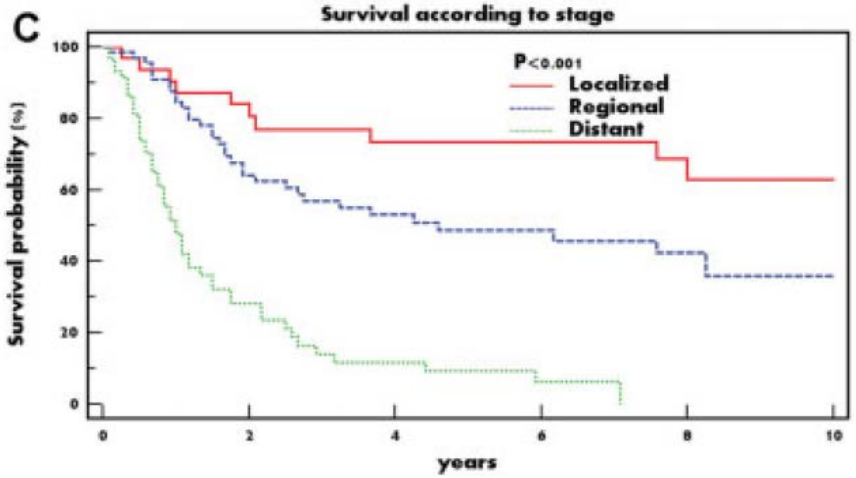
Pediatric Colorectal Cancer



Cancer 2010;116:758–65

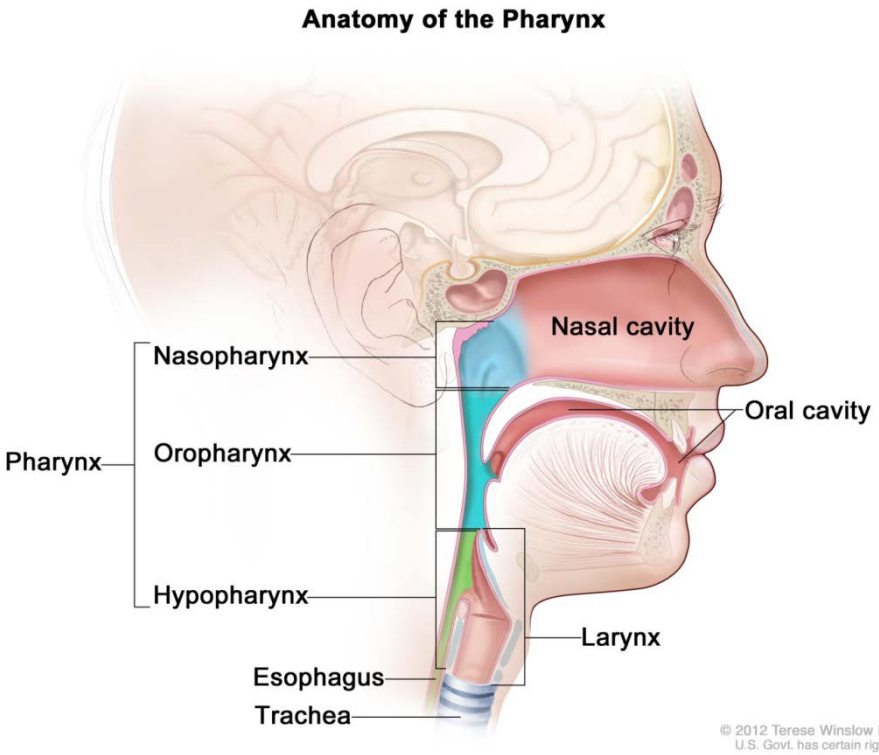


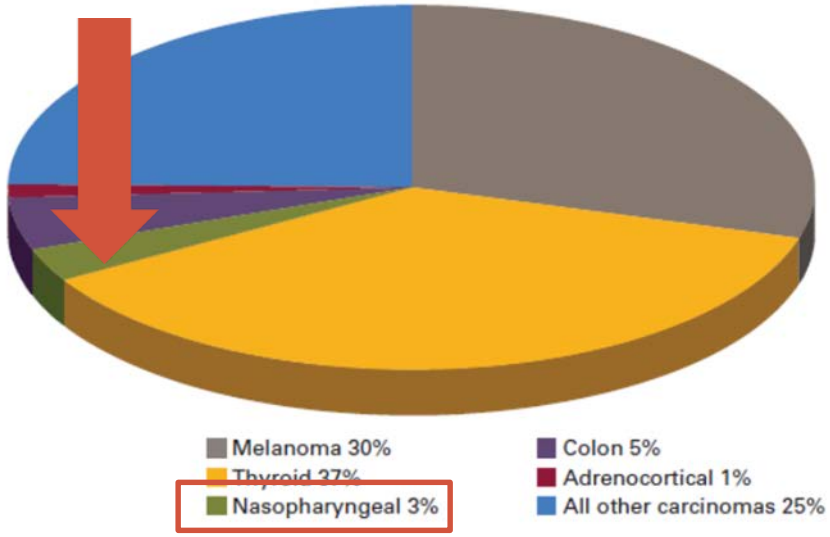


Pediatric Colorectal Cancer

- Unanswered questions:
  - Difference in mechanism of carcinogenesis?
  - Proportion with predisposing syndromes?
  - Undiscovered genetic risk factors?
  - Reasons for advanced grade/stage?
    - No screening
    - Delay in diagnosis
    - Differences in tumor biology
  - Optimal treatment approach?

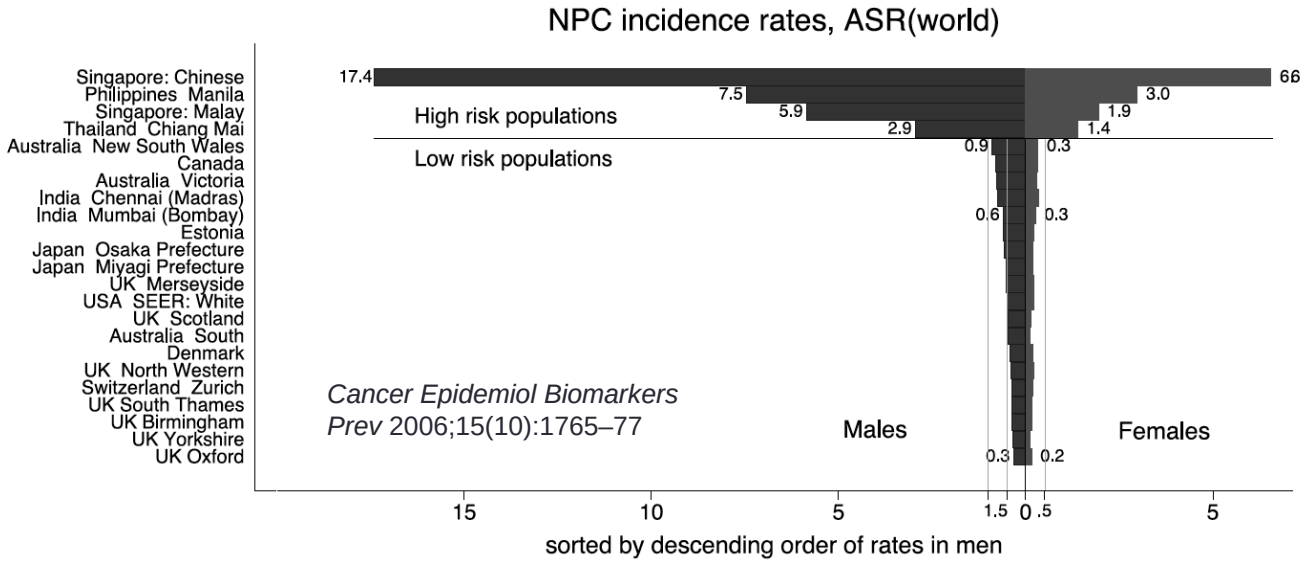
Nasopharyngeal Carcinoma





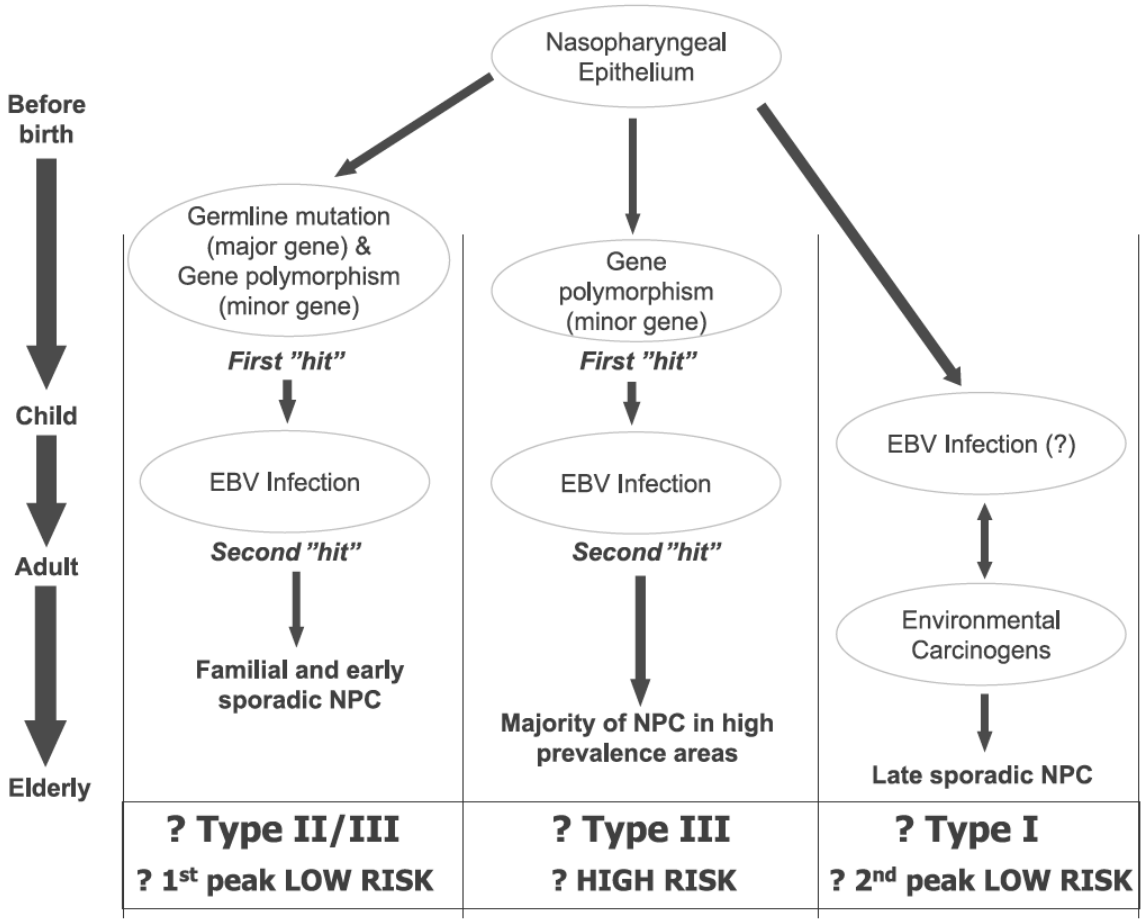
Nasopharyngeal Carcinoma

- Annual incidence: 0.5-2 cases per 100,000 in US
  - Extremely rare <10 years
  - 0.8 cases per million ages 10-14 years
  - 1.3 cases per million ages 15-19 years
  - Peak incidence in 5th-6th decade
  - 2-3 times more common in males
- Geographical/ethnic variation



Nasopharyngeal Carcinoma

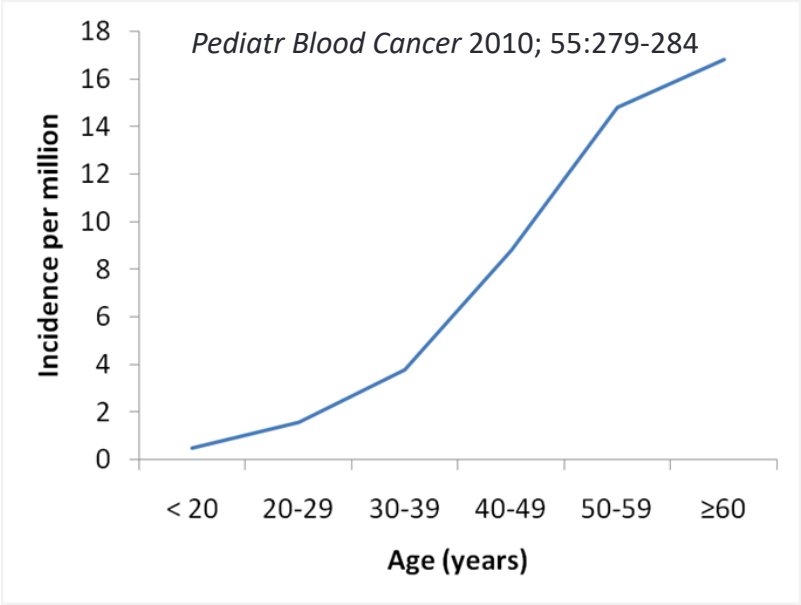
- Risk factors
  - EBV infection
  - Tobacco, alcohol
  - Salted fish
- Classification (WHO)
  - Type I: keratinizing
  - Type II: non-keratinizing
  - Type III: undifferentiated
- Biology:
- Treatment
  - Chemotherapy
  - Radiation
  - Little role for surgery
- Toxicity
  - Acute: mucositis, nausea/vomiting, renal
  - Late: hearing loss, xerostomia, second malignancy, renal, endocrine

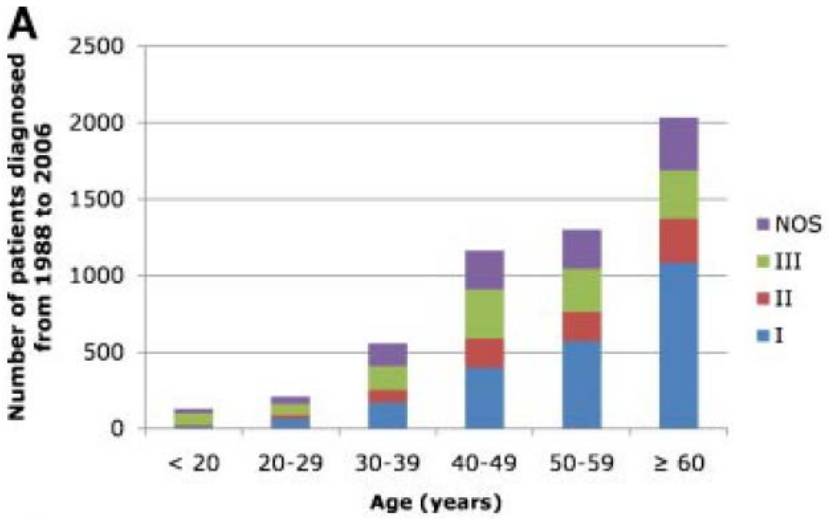


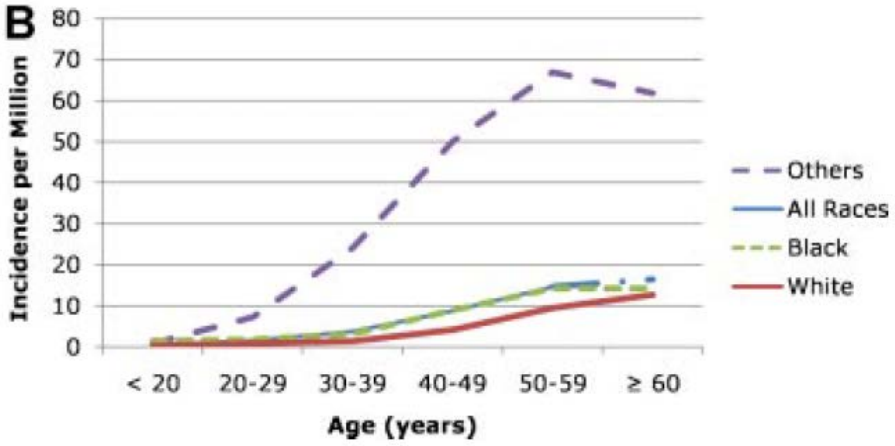
Cancer Epidemiol Biomarkers Prev 2008;17(9):2356–65

Nasopharyngeal Carcinoma

- SEER registry data
  - 1998-2006
  - 6,129 cases
    - 129 children and adolescents (2%)
    - Median age 16 years (range 7-19)
  - Incidence:
    - Children: 0.5/million person-years
    - Adults: 8.4/million person-years







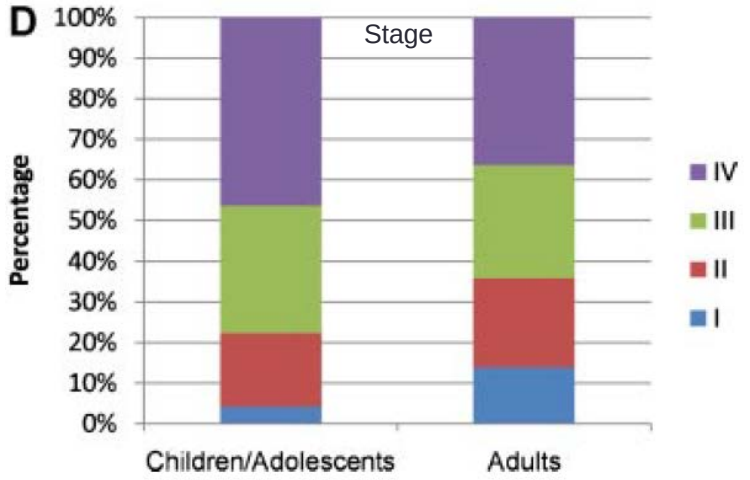
Nasopharyngeal Carcinoma

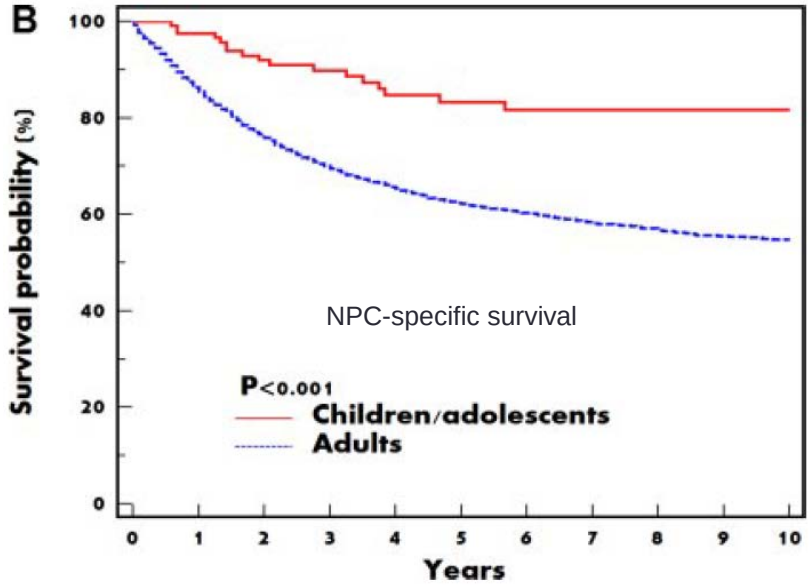
Variable	Children/Adolescents	Adults	*p*
Sex			
Female	34 (26.4%)	1,543 (29.3%)	0.52
Male	**95 (73.6%)**	**3,715 (70.7%)**	
Race			
Native American	1 (0.8%)	101 (1.9%)	
Asian/Pacific	**20 (15.5%)**	**2,271 (43.25)**	
Black	**45 (34.9%)**	**477 (9.1%)**	<0.001
White	63 (48.8%)	2,381 (45.3%)	
Other	0 (0.0%)	28 (0.5%)	
WHO Type			
I	**13 (10.1%)**	**2,280 (43.4%)**	
II	8 (6.25)	778 (14.8%)	<0.001
III	**80 (62.0%)**	**1,150 (21.9%)**	
NOS	28 (21.7%)	1.050 (20.0%)	

Pediatr Blood Cancer 2010; 55:279-284

Nasopharyngeal Carcinoma

- Clinical features
  - Advanced (stage III/IV) disease in:
    - 31/46% of children
    - 29/36% of adults
  - 62% WHO Type III histology
- Prognosis
  - 5/10-year NPC-specific survival:
    - 83/82% in children
    - 62/55% in adults
- Second malignancies
  - O/E ratio in children: 4.36
  - O/E ratio in adults: 1.41

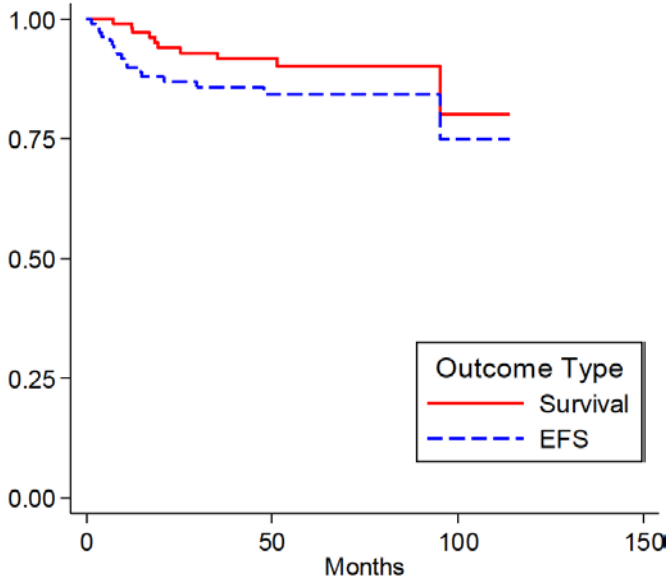




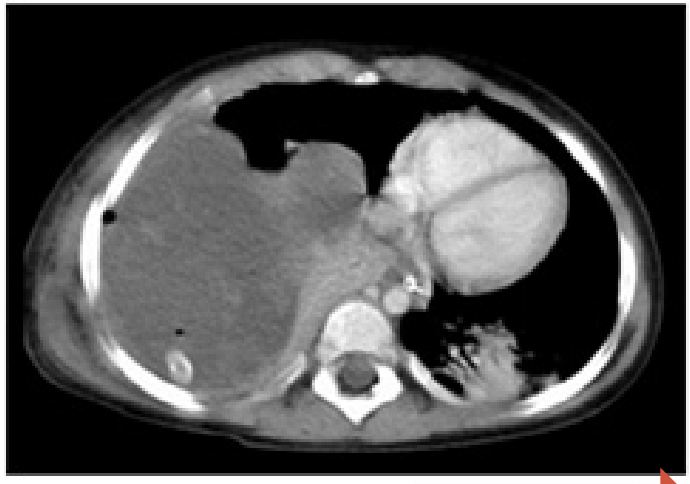
Pediatr Blood Cancer 2010; 55:279-284

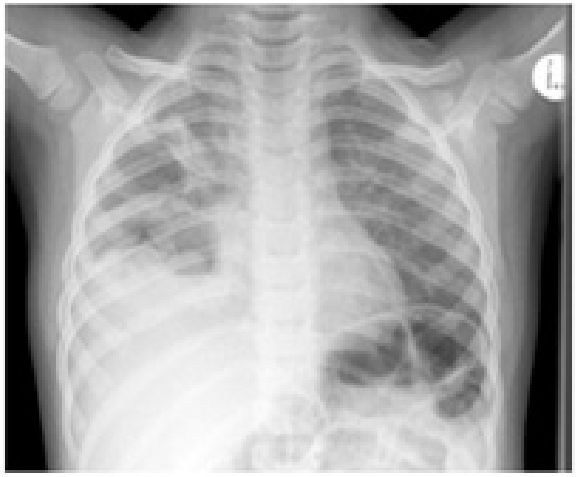
Nasopharyngeal Carcinoma

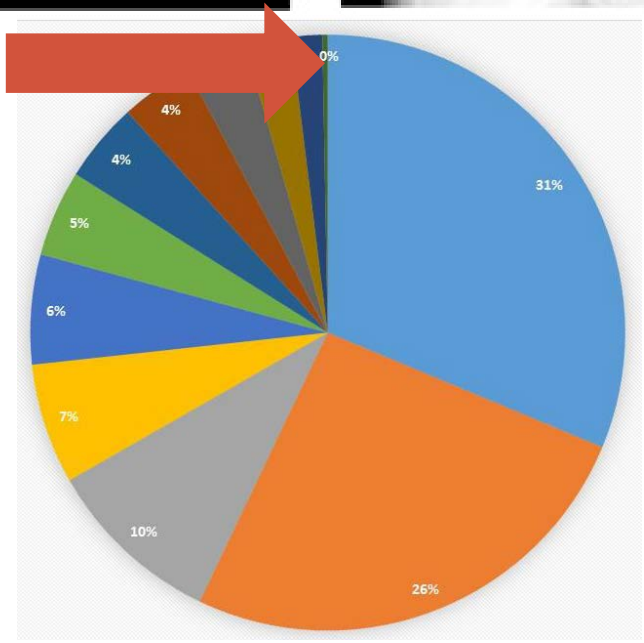
- COG trial ARAR0331
  - Open 2006-2012
  - Cisplatin/5FU + XRT (60 Gy) with amifostine
  - 111 patients enrolled (slow accrual)
    - Median age 14 years (3-18)
    - 46.8% African American
  - Results (unpublished):
    - Excellent 5-year EFS/OS: 84.3/94.1%
    - Significant toxicity with cisplatin/XRT
    - Inferior outcome with cisplatin dose reduction
    - Radiation dose reduction to 60 Gy is feasible
    - Amifostine effect on reducing ototoxicity/xerostomia not yet reported
  - Future plans
    - EBV-specific cytotoxic T lymphocytes?
    - Beta interferon maintenance therapy?
    - Further radiation dose reduction?



Pleuropulmonary Blastoma







Pleuropulmonary Blastoma

- Rare aggressive malignancy of pleuropulmonary mesenchyme
- Epidemiology
  - Extremely rare:
    - 37 cases in SEER 18 from 2000-2011 (~15 cases/year in US)
    - 350 cases in IPPBR* from 1962-2012
  - Most common primary malignancy of lung in children
  - Peak age 1-4 years (median 38 months)
- Classification - reflects a spectrum of malignant evolution over time:
  - Type I: purely cystic with subtle malignant changes
  - Type Ir (regressed): purely cystic with no malignant components
  - Type II: mixed cystic and solid
  - Type III: purely solid malignant neoplasm

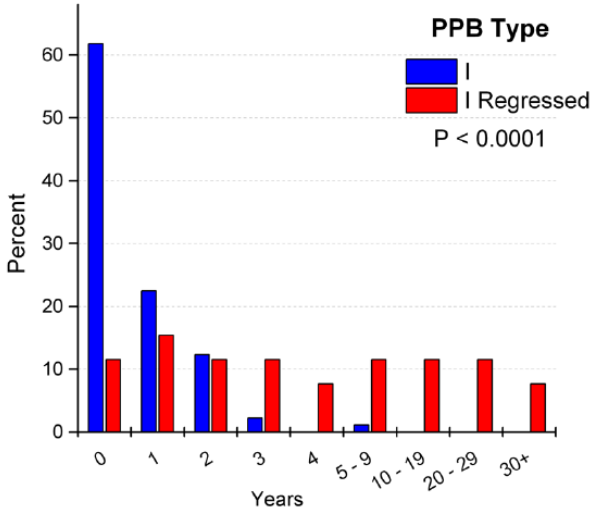
	Type I	Type Ir	Type II	Type II/III + III
Relative proportion	25%	7%	35%	32%
Median age (months)	8	47	35	41
5 year overall survival	89%	100%	71%	53%

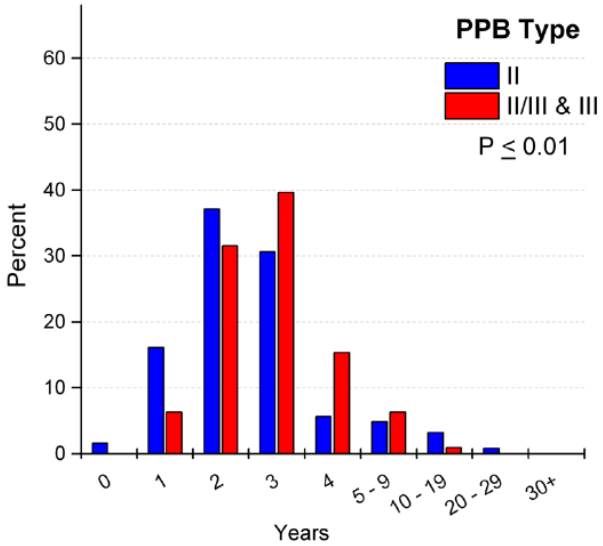
*International Pleuropulmonary Plastoma Registry, established 1998

Cancer 2015 January 15; 121(2): 276–285

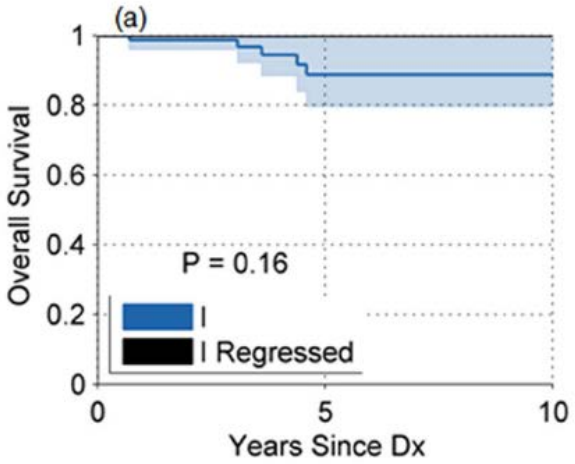
Unusual Cancers of Childhood Treatment (PDQ®)–Health Professional Version was originally published by the National Cancer Institute

Pleuropulmonary Blastoma

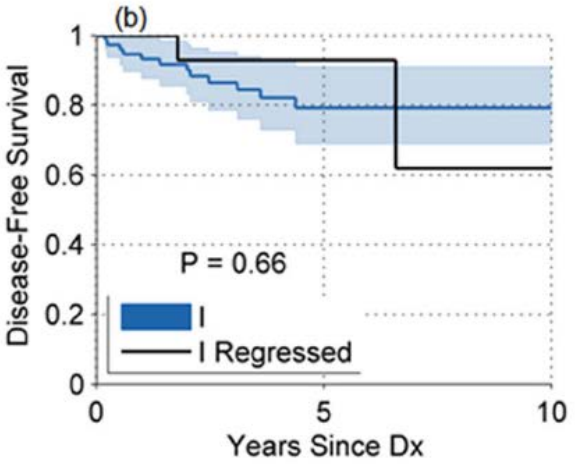


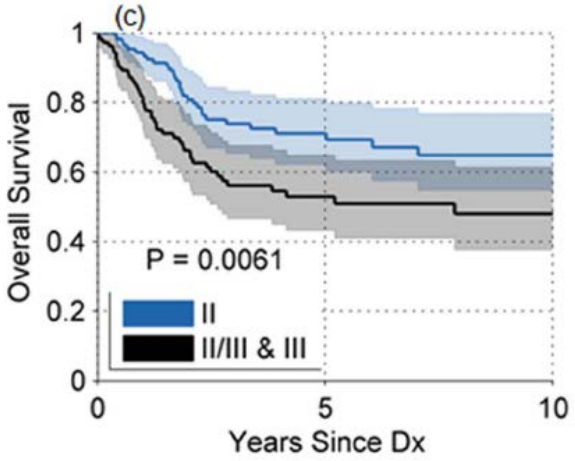


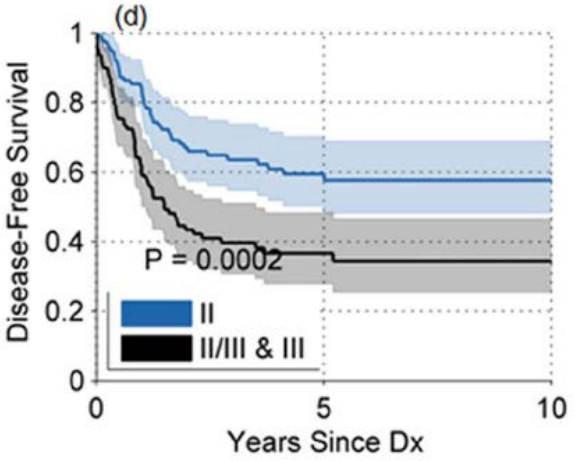
PPB overall survival by type



PPB disease-free survival by type







Cancer 2015 January 15; 121(2): 276–285

Pleuropulmonary Blastoma

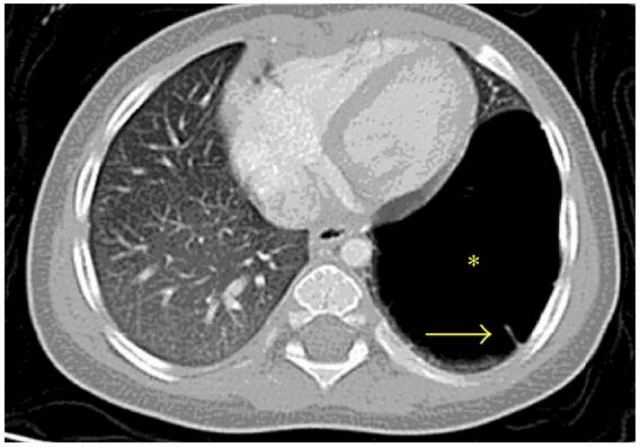
- Genetics
  - Germline mutations in *DICER1* present in 66% of PPB cases
  - One third of cases have *PPB family tumor and dysplasia syndrome*
    - Increased risk in patients and relatives of:
      - Cystic nephroma (up to 10%) or Wilms tumor
      - Sex cord-stromal tumors
      - Multinodular goiters and thyroid cancer
      - Bilateral lung cysts and nodules
    - Low penetrance: not all families with *DICER1* mutations develop PPB
  - *DICER1* status does not correlate with tumor type or outcome
- Prognostic factors
  - Tumor Type
  - Metastases
  - Complete surgical resection

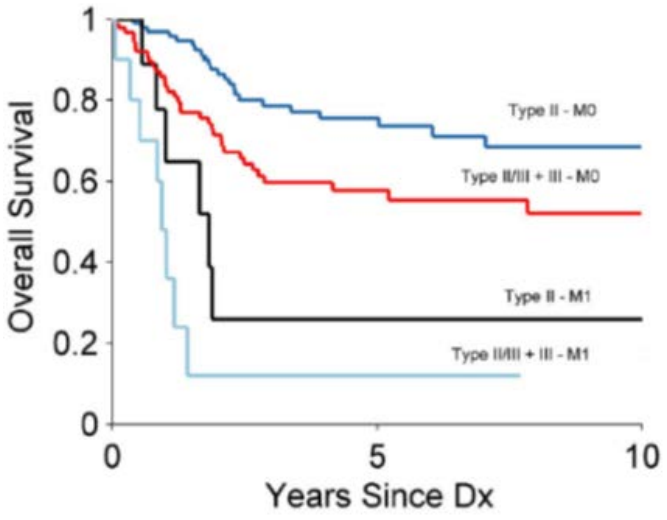
Unusual Cancers of Childhood Treatment (PDQ®)–Health Professional Version was originally published by the National Cancer Institute

Cancer 2015 January 15; 121(2): 276–285

Pleuropulmonary Blastoma

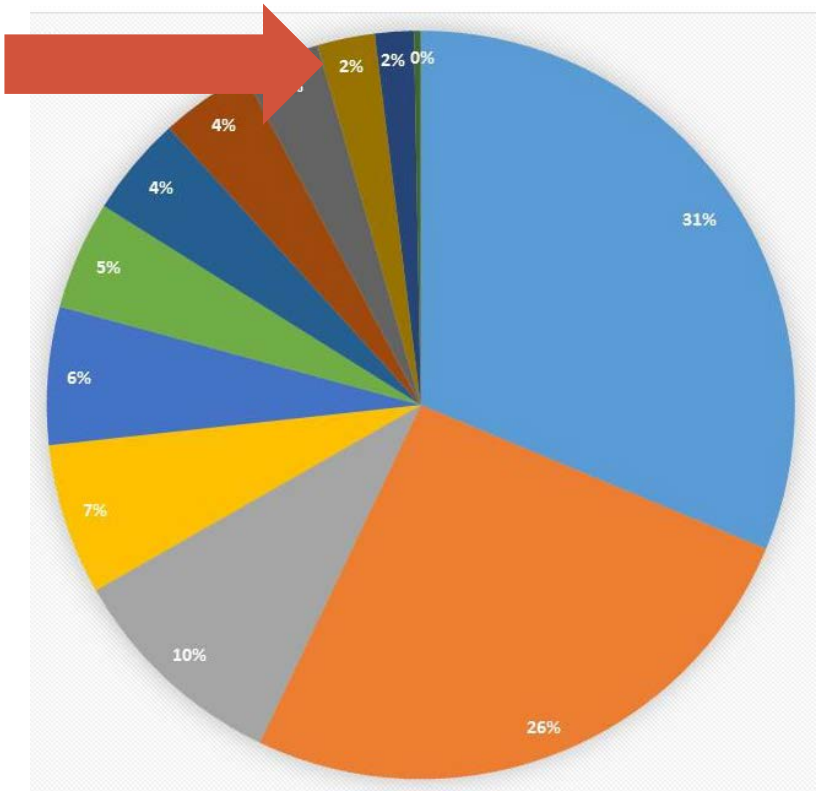
- Clinical features
  - Respiratory distress/chest pain
  - Pneumothorax
  - Incidental pulmonary cysts
  - Multiple lesions in 50% (33% bilateral)
  - Metastases
    - To brain in 11% of type II, 54% of type III
    - Other sites: bone, liver, vascular invasion
- Treatment
  - Chemotherapy may reduce recurrence risk
  - Sarcoma regimens appear effective
  - IPPBR recommendations:
    - Surgery + VAC chemotherapy for Type I
    - Surgery + IVADo chemotherapy for Type II/III
    - Consider radiation for incomplete resection
  - Surveillance is important





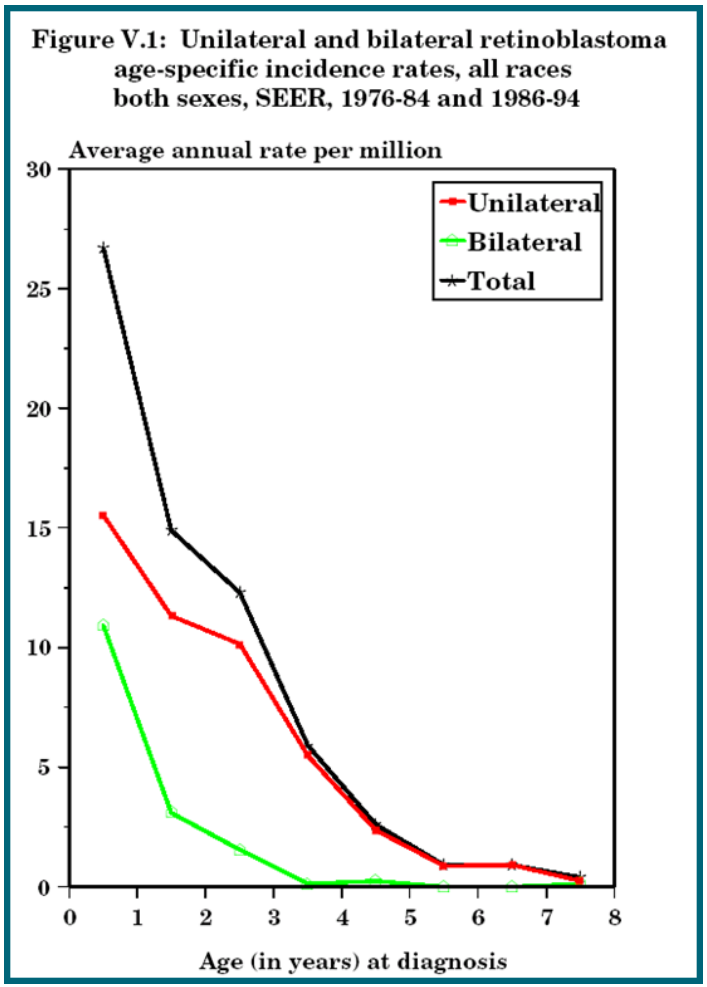
Cancer 2015 January 15; 121(2): 276–285

Retinoblastoma

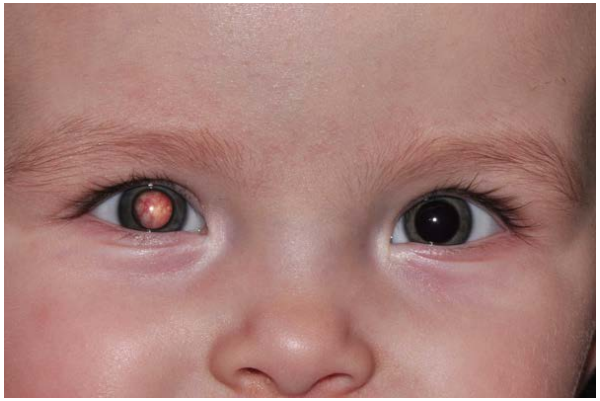


Retinoblastoma

- Incidence: 3.7 cases per million children <15 years
- 300 new cases/year in US
  - 3% of all pediatric cancers
  - 11% of cancers <1 year
- Age at presentation
  - 63% <2 years
  - 95% <5 years
- Laterality
  - <1 yr: 42% bilateral – 58% unilateral
  - >2 yr: 9% bilateral – 91% unilateral
- Prognosis
  - Highly curable: 97% survival
  - High incidence of late effects (87%):
    - Vision loss
    - Hearing loss
    - Second malignancy (leading cause of death)



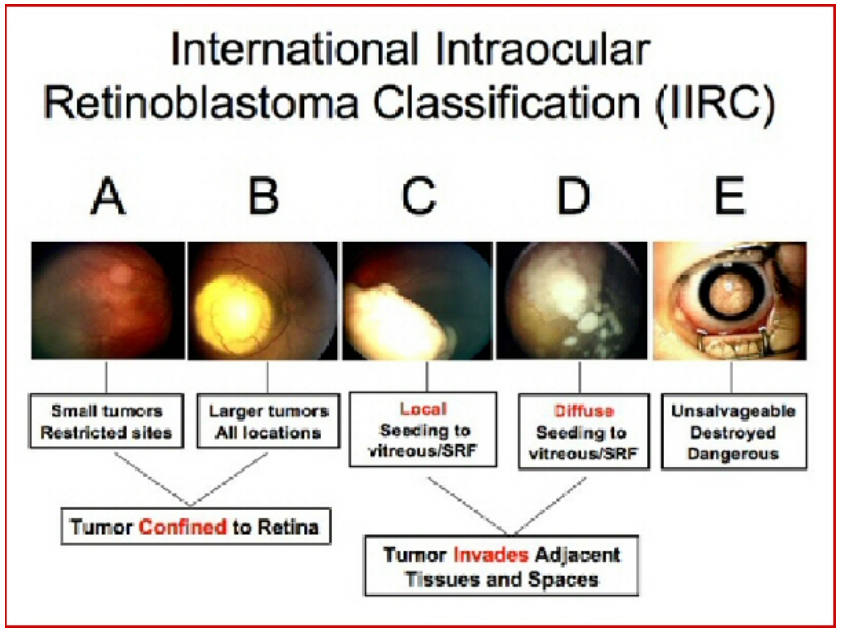
Retinoblastoma



- Presentation: leukocoria or strabismus
- Genetics
  - 25-30% heritable
    - Germline mutation in *RB1* tumor suppressor gene
    - Younger onset and bilateral disease
    - Risk for other cancers: osteosarcoma, pineoblatoma, soft tissue sarcomas, melanoma (especially following radiation)
  - 70-75% sporadic
    - Somatic mutations in *RB1*
  - “Second hit” necessary to cause disease
- Treatment goals
  - Save life/cure disease
  - Preserve vision
  - Minimize late effects

Retinoblastoma

- Staging/Grouping
  - Stage: extent of disease in the body (intraocular/extraocular)
  - Group: extent of disease in the eye (predicts salvage)
- Multidisciplinary approach
- Treatment options
  - Enucleation
  - Systemic chemotherapy
  - Local chemotherapies
    - Arterial chemotherapy
    - Vitreal/subconjunctival chemotherapy
  - Other local therapies
    - Laser therapy
    - Cryotherapy
  - Radiation

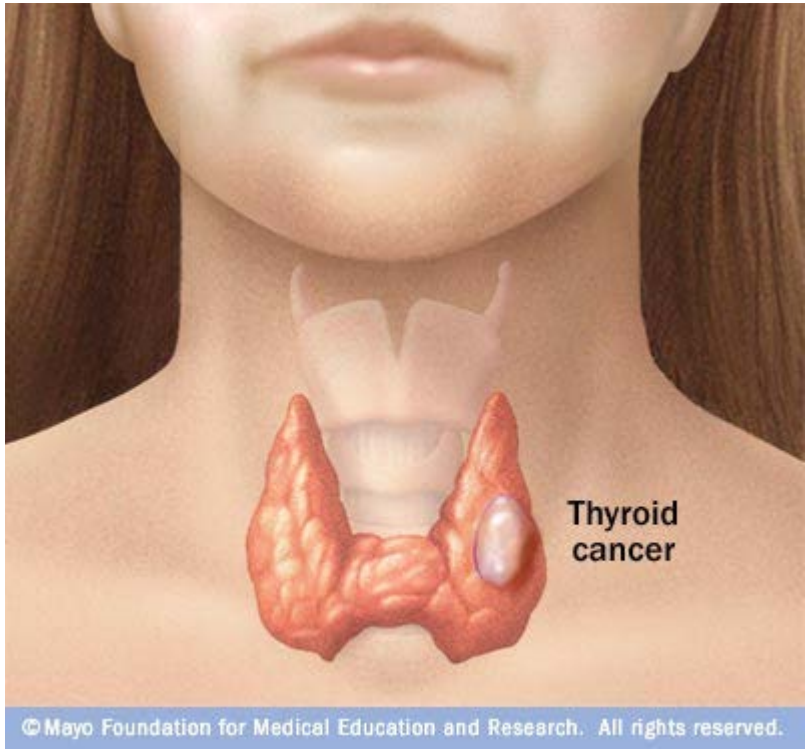


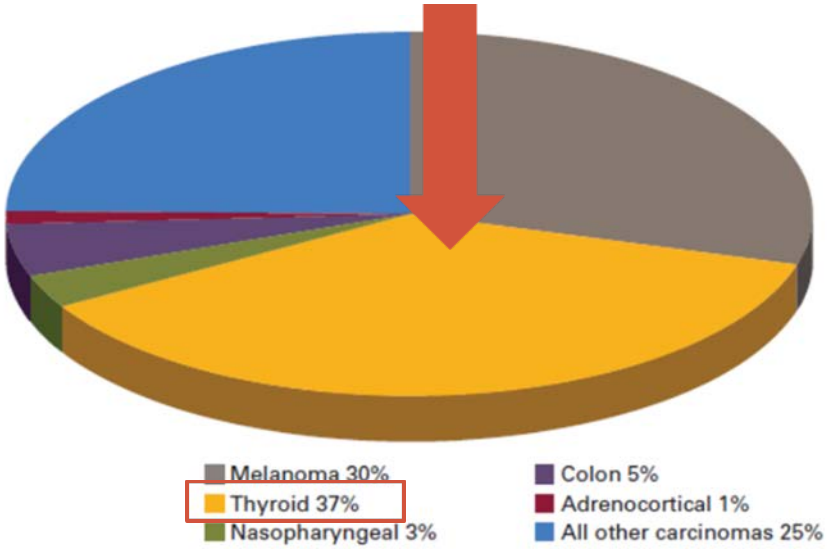
Retinoblastoma: COG trials

Study	Title	Status	Comments
ARET0231	A Single Arm Trial of Systemic and Subtenon Chemotherapy for Groups C and D Intraocular Retinoblastoma	Closed 2011	Terminated early for poor accrual: 22 patients
ARET0332*	A Study of Unilateral Retinoblastoma With and Without Histopathologic High-Risk Features and the Role of Adjuvant Chemotherapy	Completed 2010	Low recurrence risk after enucleation +/- chemo for patients +/- risk factors
ARET0331	Trial of Systemic Neoadjuvant Chemotherapy for Group B Intraocular Retinoblastoma	Closed 2009	Higher than expected local failure rate with 2-drug chemo
ARET0321**	A Trial of Intensive Multi-Modality Therapy for Extra-Ocular Retinoblastoma	Completed May 2017	Improved survival for all but those with CNS disease (trilateral)
ARET12P1	A Multi-Institutional Feasibility Study of Intra-Arterial Chemotherapy Given in the Ophthalmic Artery of Children with Retinoblastoma	Completed April 2017	Not feasible: will pursue systemic + intravitreal therapy next

*participating centers: US, India
**participating centers: Argentina, Australia, Brazil, Canada, Egypt, New Zealand, US

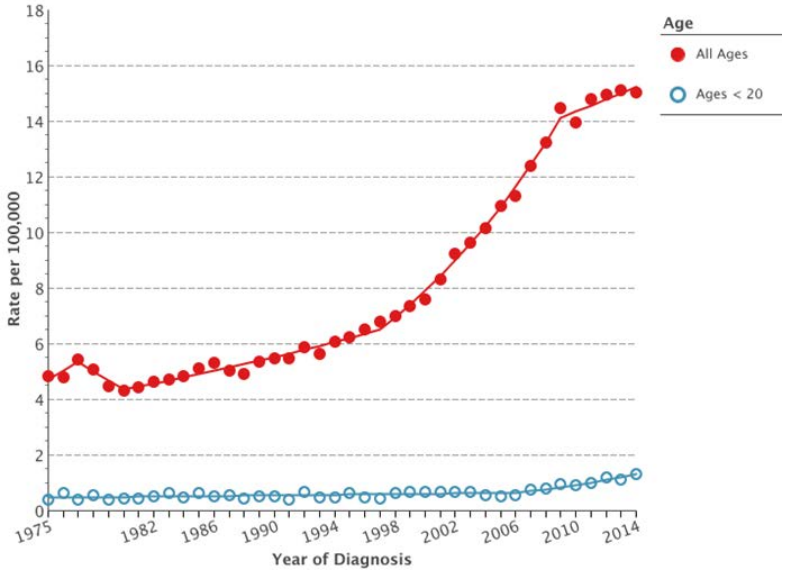
Thyroid Carcinoma

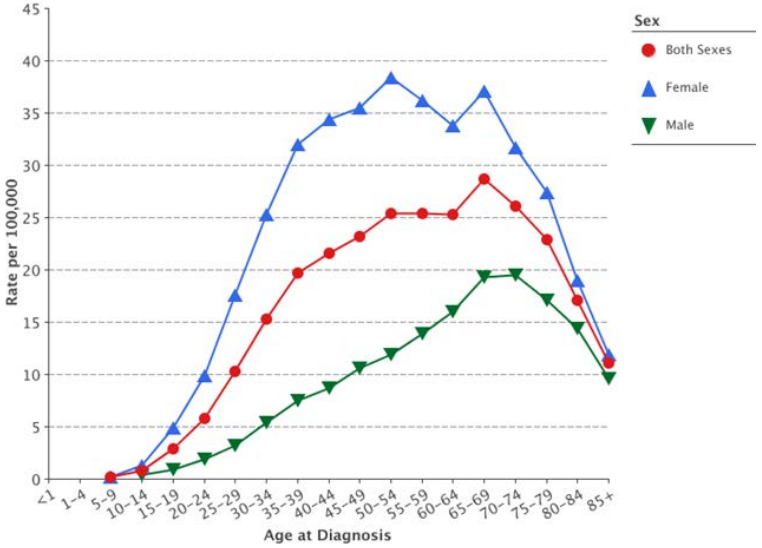




Thyroid Carcinoma

- Epidemiology
  - Incidence: 14.6 per 100,000 (all ages)
  - Children <20 years: 1.1 per 100,000
    - <15 years: 2 cases per million
      - 1.5% of all cancers
    - 15-19 years: 17.6 cases per million
      - 8% of all cancers
  - Incidence in children increasing 1% per year since 1973
  - Female-to-male ratio: 4.4:1
- Risk Factors
  - Radiation exposure
  - Cancer predisposition syndromes
    - MEN2A and MEN2B
    - Carney complex
    - *DICER1* syndrome





Inter J Ped Otorhinolaryngology 89 (2016) 121e126

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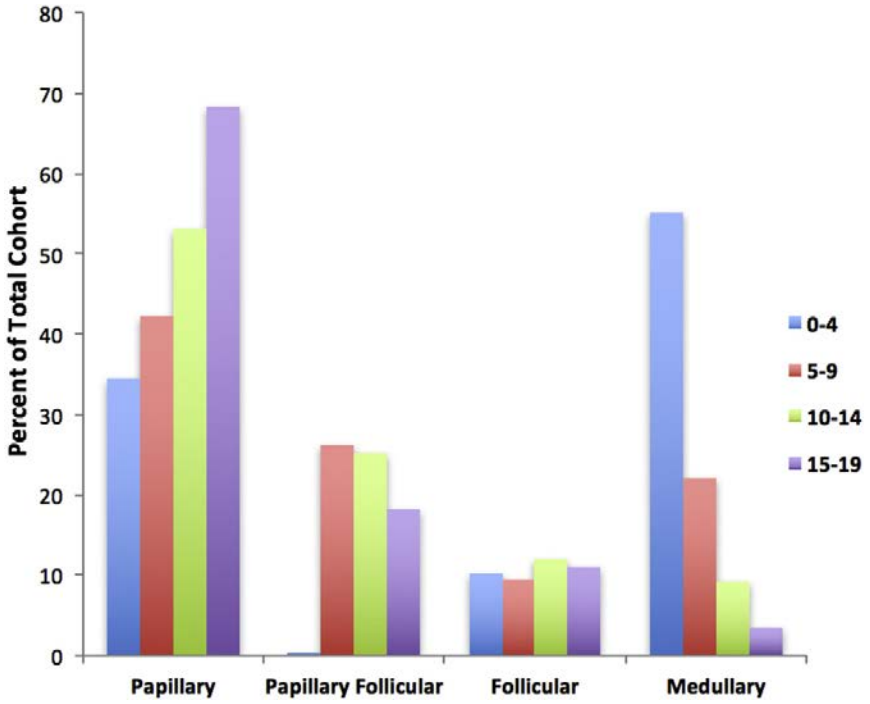
Thyroid Carcinoma

- Histology
  - Papillary (60-75%)
    - Lymph node metastases common
    - Excellent prognosis
  - Follicular (10-20%)
    - Bone/lung metastases common
    - Excellent prognosis
  - Medullary (5-10%)
    - Most often familial (MEN2), younger age
    - Inferior prognosis
  - Anaplastic (<1%)
    - Extremely rare, aggressive
  - Benign lesions
    - Adenomas, goiters
    - 60-80% of thyroid nodules in children are benign (vs 95% in adults)

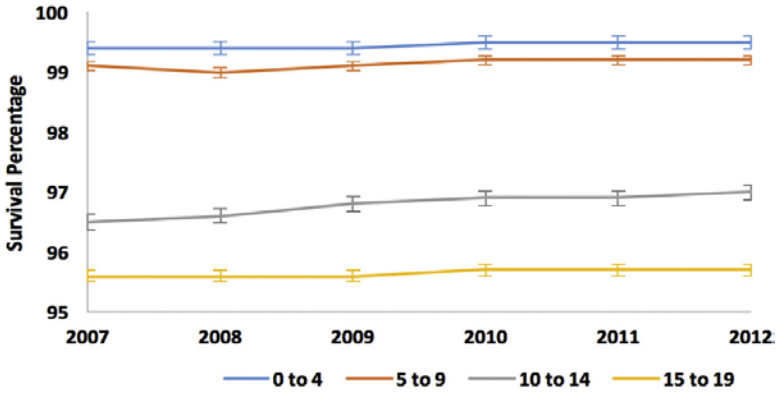


Inter J Ped Otorhinolaryngology 89 (2016) 121e126

Unusual Cancers of Childhood Treatment (PDQ®)–Health Professional Version was originally published by the National Cancer Institute

Thyroid Carcinoma

- Presenting Symptoms
  - Cervical adenopathy
  - Thyroid mass
  - Hyperthyroidism (rare)
- Metastases
  - More common in children than adults
    - Lymph nodes: 40-90% vs 20-50%
    - Lungs: 20-30% vs 2%
  - Most common in younger vs older children
- Outcome
  - Overall: all-stage 5-year survival 99.5% in children (98.2% in adults)
  - Advanced disease
    - 15-year DFS in children: 85-92% with metastases (98-99% for localized)
    - Only 50% survival at 15 years for children with medullary carcinoma
  - Risk factors: male sex, large/multifocal tumor, metastases
  - Similar prognosis +/- prior radiation therapy



15-year disease-specific survival by age (SEER 2007-2012)

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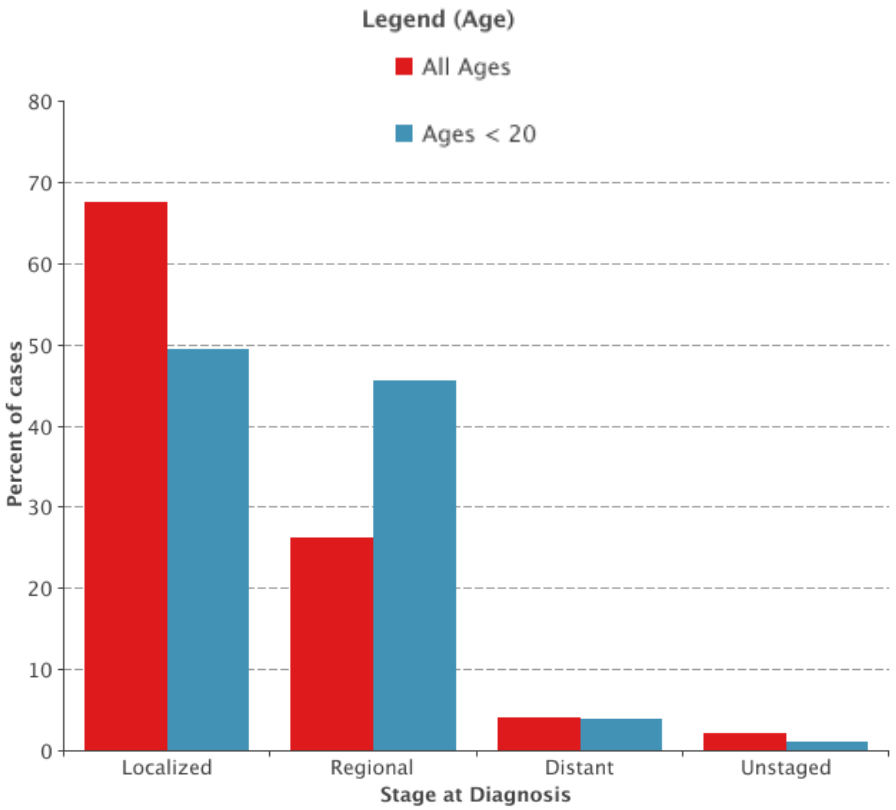
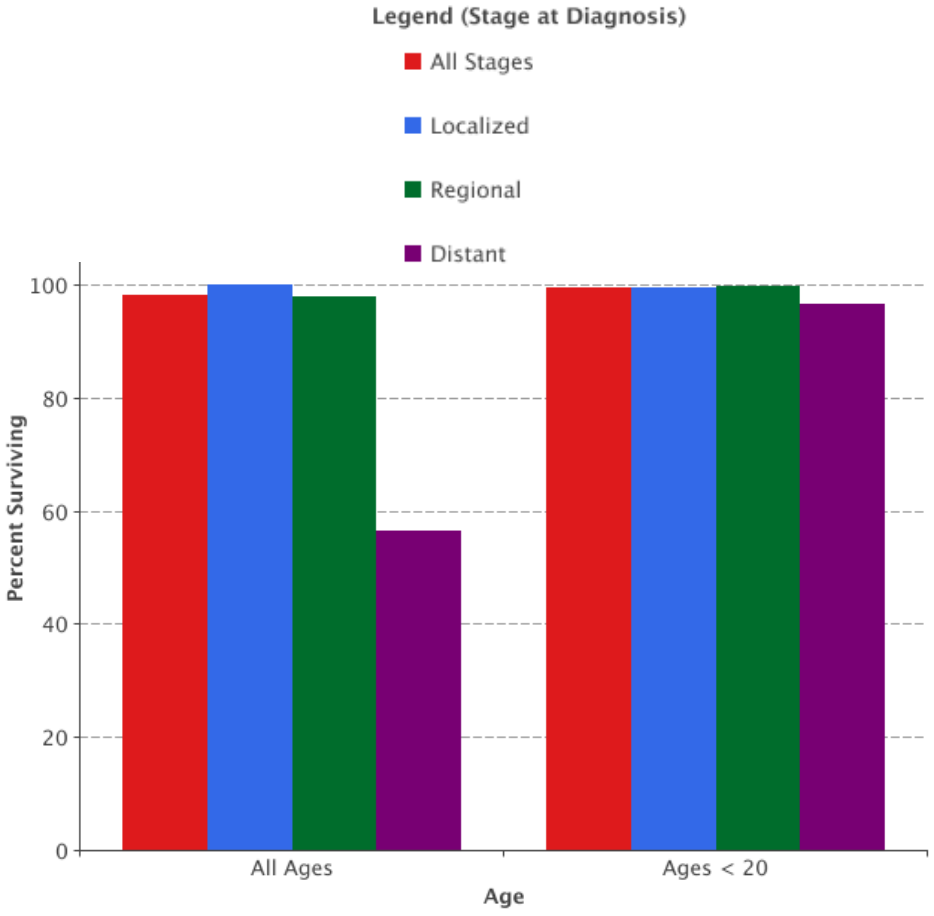
Thyroid Carcinoma



SEER thyroid cancer stage 2005-2014



5 year SEER relative survival 2007-2013

Thyroid Carcinoma

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- Treatment
  - Differentiated (papillary/follicular) carcinoma
    - Surgery: thyroidectomy and lymph node dissection
    - Radioactive iodine (^{131}I): for residual/metastatic disease
  - Medullary carcinoma
    - Surgery: prophylactic thyroidectomy for MEN2
    - Chemotherapy (tyrosine kinase inhibitors):
      - Cabozantinib, vandetanib approved in adults with recurrent/refractory disease
      - Response rate 44% in small pediatric trial of vandetanib
- Toxicity
  - Hypothyroidism: lifelong thryoxine replacement
  - Surgical complications: recurrent laryngeal nerve damage
  - Radiotherapy:
    - Short-term: transient bone marrow suppression, pain, nausea/vomiting
    - Long-term: infertility, leukemia, pulmonary fibrosis, salivary gland dysfunction

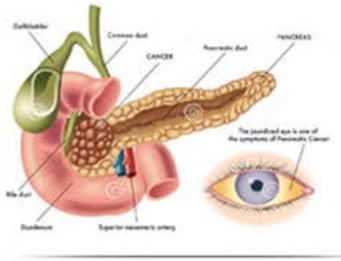
RARE CHILDHOOD CANCERS

CANCERS ONLY IN CHILDREN

MELANOTIC NEUROECTODERMAL
TUMORS OF INFANCY
MALIGNANT RHABDOID TUMORS
PANCREATOBLASTOMA

A 2009 STUDY FOUND THAT THE LEAST COMMON CANCERS IN CHILDREN WHERE THYROID CARCINOMAS AND MUCOEPIDERMOID CARCINOMA.

TYPICALLY ONLY IN ADULTS



PANCREATIC CANCER

DIGESTIVE CANCER

RARELY, CANCERS THAT ARE TYPICAL FOR ONLY ADULTS ARE FOUND IN CHILDREN

ADRENAL CANCER

HEAD AND **NECK CANCERS** IN **CHILDREN** ARE RARE, LIKE ATYPICAL TERATOID AND **GANGIOGLIOMA.**

FORTUNATELY, THERE ARE TREATMENTS AVAILABLE FOR THESE TYPES OF CANCERS.

Conclusions

- All childhood cancer is rare
- Rare tumors are not all that rare
- Children are not little adults
- Infrequent childhood cancers are important
- Defining rare childhood cancer is challenging
- Studying rare childhood cancers is more challenging
- More research is needed to improve understanding and outcomes
- The children are worth it

Rare Childhood **Cancers**