

The hallmarks of cancer: Perspectives for cancer medicine

Stefan Bielack

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Principles of AYA oncology

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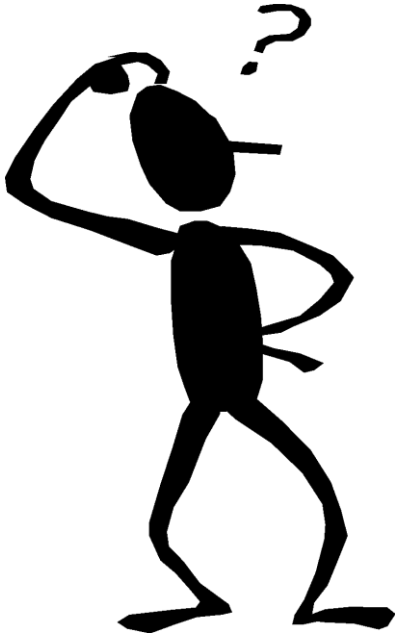
Conflict of Interest Statement

<u>Advisory Board/Consultancy</u>

Bayer, Boehringer Ingelheim, EISAI, Hoffmann LaRoche,

Lilly, MAP Biopharma, Y-mAbs

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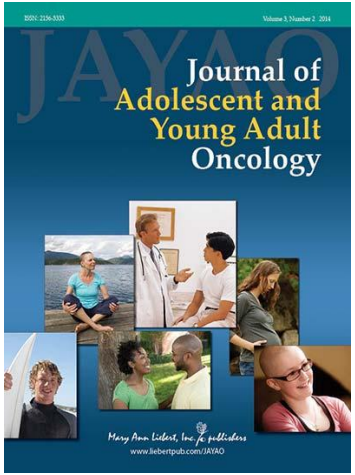
Who is „AYA“?



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AYA = Adolesents and young adults

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JOURNAL OF ADOLESCENT AND YOUNG ADULT ONCOLOGY
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Controversies

What Should the Age Range Be for AYA Oncology?

The field of adolescent and young adult oncology (AYAO) is developing and evolving, providing fertile ground for debate, discussion, and the exchange of opinions. In the "Controversies" feature of each issue of **Journal of Adolescent and Young Adult Oncology**, *we will pose a key AYAO question to people from a wide range of organizations, geographical locations, and professions.*

Those working with pediatric or older adult patients must only concern themselves with either the upper or lower age bounds, respectively, of their field. However, those working in AYAO must consider both ends of the spectrum, and the implications of any answer. Both between and within countries there is much variation in the definitions, and indeed even in the terminology, used to describe the AYA cancer population. In the United States, the 2006 Surveillance, Epidemiology and End Results (SEER) program report used the 15–29 age range,[1] while the 2006 Adolescent and Young Adult Oncology Progress Review Group (AYAO PRG) report used 15–39[2]—now the standard used by the National Cancer Institute (NCI) as well as the age range generally used by **JAYAO**. *Canada generally uses the same 15–29 age range as SEER,[3] while Australia tends to favor 15–25.[4] In the United Kingdom, the Teenage Cancer Trust focuses on teenagers and young adults (TYAs) aged 13–24,[5] though European members of EUROCARE employ the 15–24 bracket.[6] In this first issue, we asked "If you were solely in charge of AYAO for a day, what age range would choose for AYAO, and why?"*

—Editors

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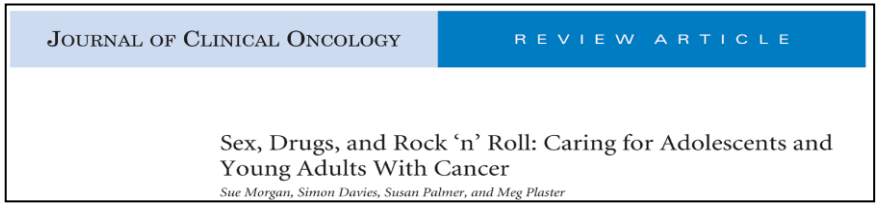
AYA are somewhere inbetween





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AYA: distinct needs and requirements


JOURNAL OF CLINICAL ONCOLOGY | REVIEW ARTICLE

Sex, Drugs, and Rock 'n' Roll: Caring for Adolescents and Young Adults With Cancer

Sue Morgan, Simon Davies, Susan Palmer, and Meg Plaster

- increasing autonomy
- peers, friends
- school => professional life
- love, family, parenthood

Approximate Age	Virtues	Psychosocial crisis[2]
0-2 years	Hope	Basic trust vs. mistrust
2–4 years	Will	Autonomy vs. shame and doubt
4–5 years	Purpose	Initiative vs. guilt
5–12 years	Competence	Industry vs. inferiority
13–19 years	Fidelity	Identity vs. role confusion
20–39 years	Love	Intimacy vs. isolation
40–64 years	Care	Generativity vs. stagnation
65-death	Wisdom	Ego integrity vs. despair

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AYA: distinct pharmacology

Table 1. Summary of the Pharmacology Studies Published in Adolescents

Drug and Study	No. of Patients	Age Range (years)	Sex		Summary of Findings
			M	F	
Temozolomide[68]	39	0.7-21.9	20	19	No difference in Cl between adolescents (older than 10 years of age) and younger children
Dexamethasone[69]	214	1.0-18.8	115	99	Age (younger or older than 10 years) a significant predictor of Cl in children with low albumin; lower apparent oral Cl in adolescents consistent with increased toxicity
Topotecan[70]	162	0.04-22	110	52	No differences in systemic Cl between adolescents and younger children
Vincristine[71]	54	0.2-18	NA	NA	Cl normalized to BW differed significantly between adolescents and children younger than 10 years of age
Vincristine[72]	98	1.3-17.3	NA	NA	No relationship between age and pharmacokinetics
Imatinib[73]	26	7.0-24	17	9	Median Cl greater in children older than 12 years of age, but no statistically significant correlation with age observed
Imatinib[73]	15	6.0-22	NA	NA	
Etoposide[86]	29	1.58-23.9	NA	NA	No correlation between age and etoposide Cl after adjusting for body size
Etoposide[76]	16	0.3-22	NA	NA	AUC normalized to BW correlated to age
Etoposide[75]	31	0.8-23.7	NA	NA	No correlation between Cl normalized for BSA and age, but significant inverse relationship between Cl normalized for BW and age
Etoposide[74]	18	1.1-17	10	8	Inverse relationship between Cl and age
Etoposide[77]	109	0.4-18.7	NA	NA	Age negatively correlated with Cl normalized for BSA
Methotrexate[79]	134	0.33-18.5	76	58	Age negatively correlated with plasma concentration
Methotrexate[80]	122	0.25-15	NA	NA	Cl faster in children younger than 10 years of age than in adolescents
Methotrexate[81]	49	0.5-17	NA	NA	Cl in children younger than 10 years of age two-fold greater than in those older than 10 years of age
Actinomycin D[82]	31	1.0-20	18	13	Higher AUC in younger children (< 40 kg) than in adolescents
Busulfan[83]	27	1.3-50	10	17	Shorter elimination half-life and higher clearance values in children younger than 5 years of age versus children age 5-16 years
Busulfan[96]	25	0.5-54	15	10	Significant increase in busulfan apparent oral clearance expressed relative to body surfac... 4 years versus older children (≥ 1

Abbreviations: NA, not available; Cl, clearance; BW, body weight; AUC, area under the curve; BSA, body-surface area.

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JOURNAL OF CLINICAL ONCOLOGY REVIEW ARTICLE

Clinical Pharmacology in the Adolescent Oncology Patient

Gareth J. Veal, Christine M. Hartford, and Clinton F. Stewart

AYA: trial participation

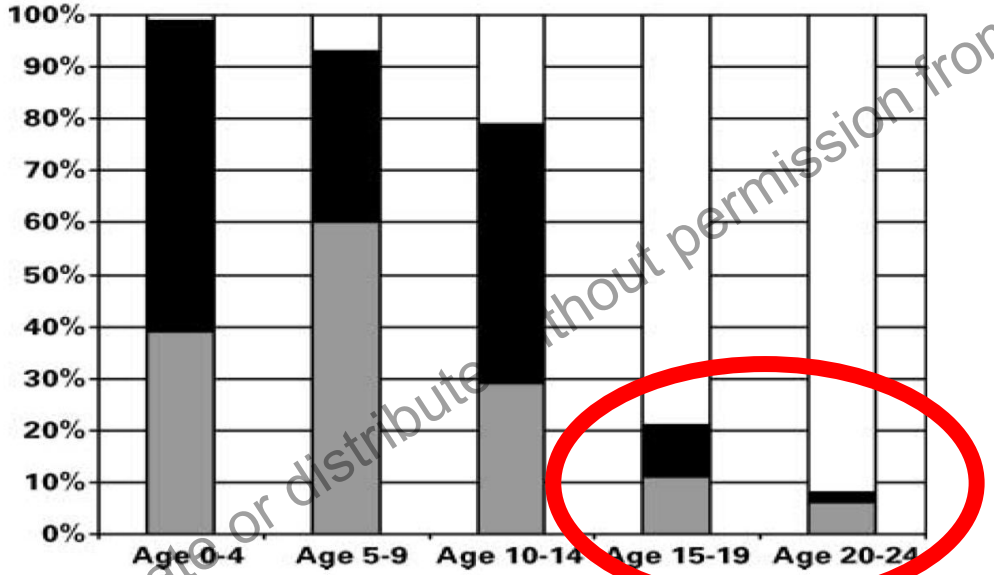


Figure 4. Participation of children, adolescents and young adults with cancer in clinical trials and cooperative treatment protocols in the USA [48]. White area: neither protocol nor trial. Mid-shading: only cooperative group protocol. Darkest shading: entered into both protocol and trial.

Bleyer WA.
The adolescent gap in cancer treatment.
J Registry Manage 1996; 23: 114-5

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Who should be responsible for AYA oncology?



med. oncology ped.

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A message to non-pediatricians

Adolescents and young adults are not little grown-ups



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A message to pediatricians

Adolescents and young adults are not big children



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Fighting is no good

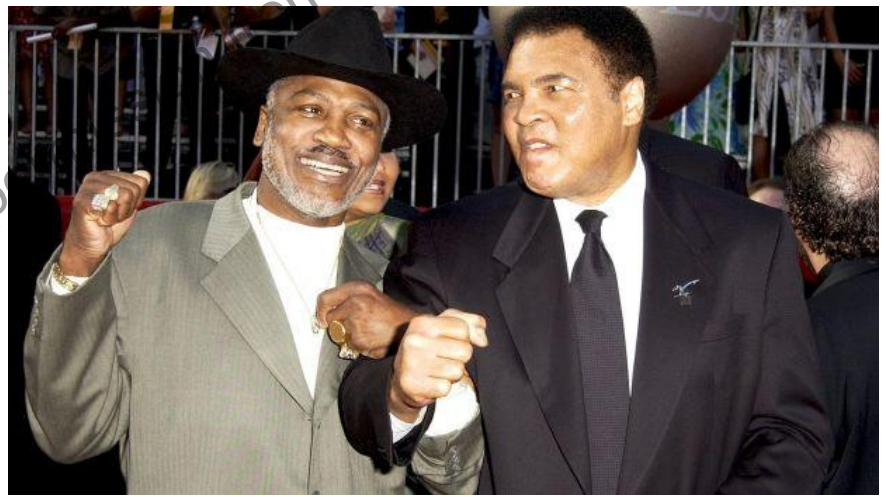


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Ped. & med. together for AYAs!

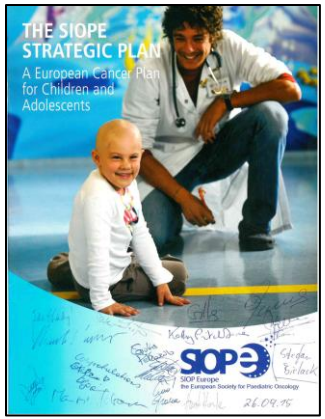






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SIOPE & adult oncology



Overall goals and objectives

The overall goals over the next 10 years

- To increase the cure rate for young people who have a cancer with a poor prognosis.
- To increase the quality of life for survivors of childhood cancer.

The measure of success will be 10 years free of disease and late side effects.

5. **Teenagers and Young Adults**: to address the specific needs of teenagers and young adults (TYA), in cooperation with adult oncology.

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ESMO & SIOPE for AYAs



The Joint ESMO-SIOPE Working Group on Cancer in Adolescents and Young Adults (AYA)

Chairs
- Giannis Mountzios, Greece (ESMO)
- Stefan Bielack, Germany (SIOPE)

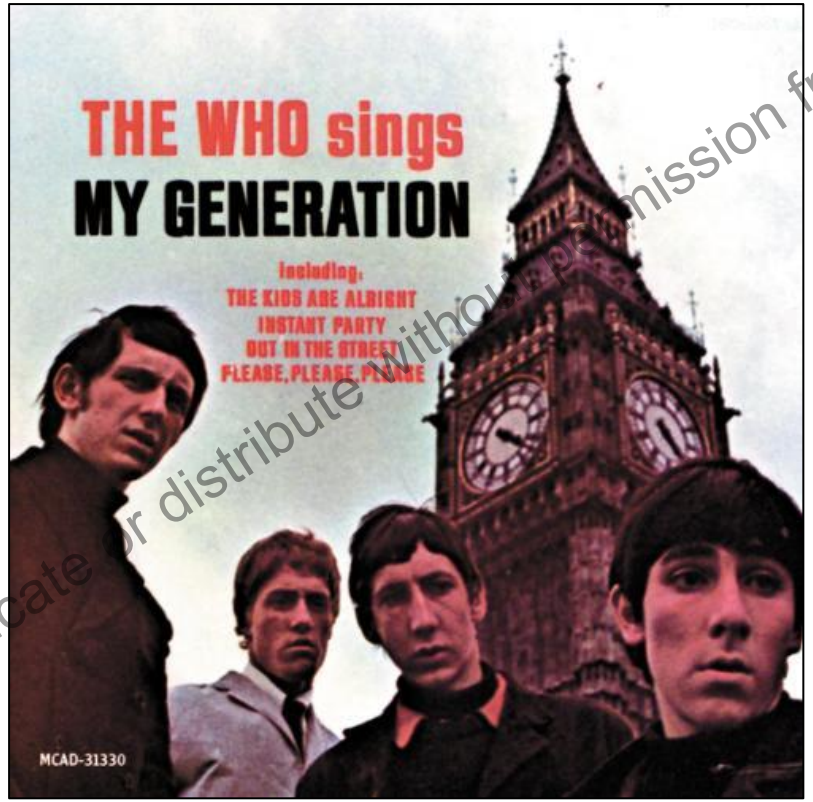
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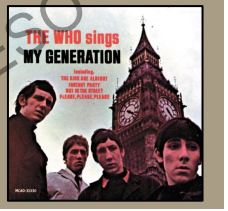
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How big of a problem is cancer in AYAs?



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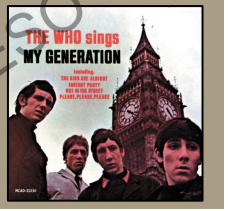
Cancer
Age specific incidence

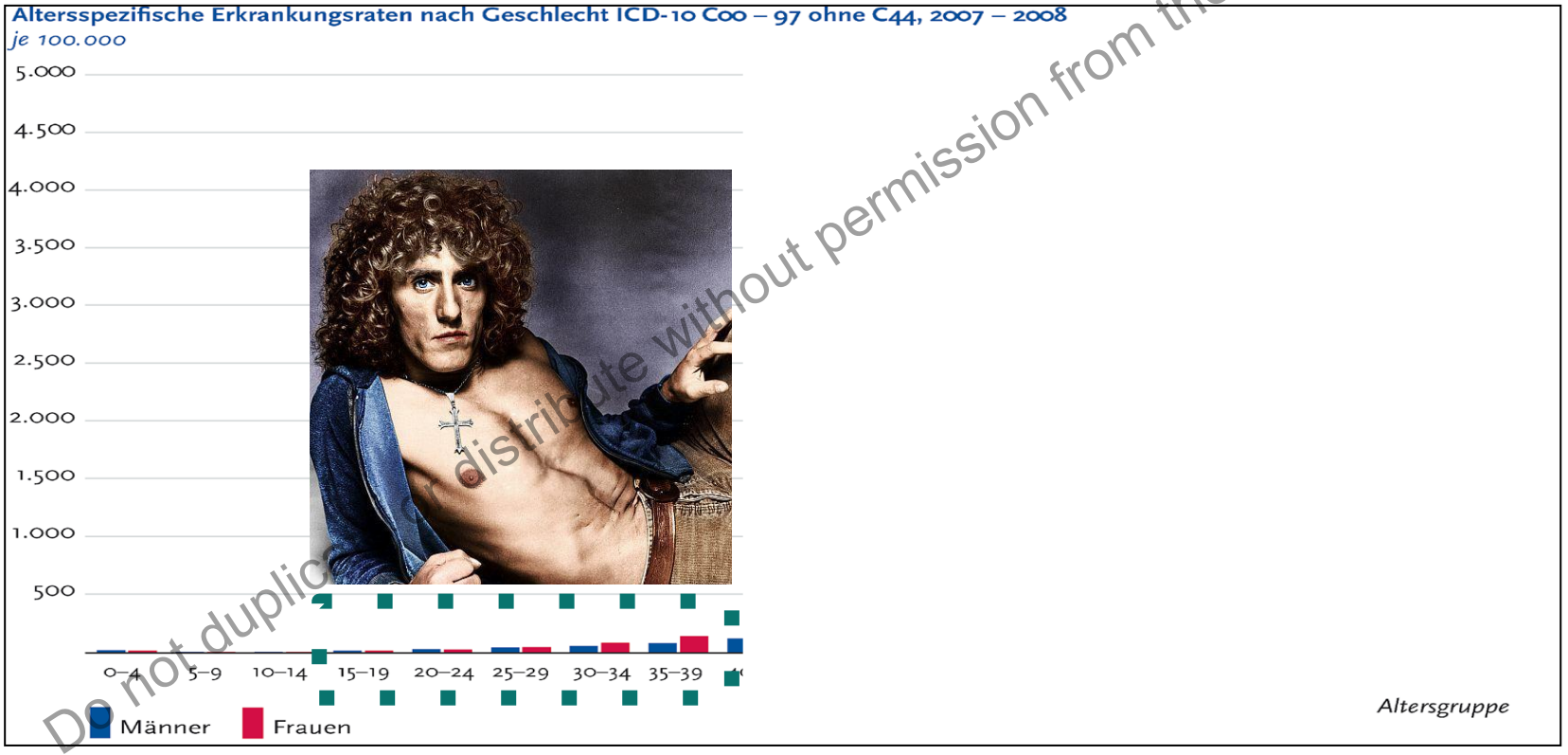




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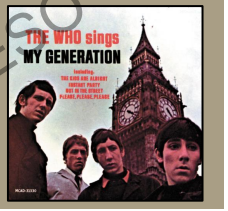
Cancer
Age specific incidence

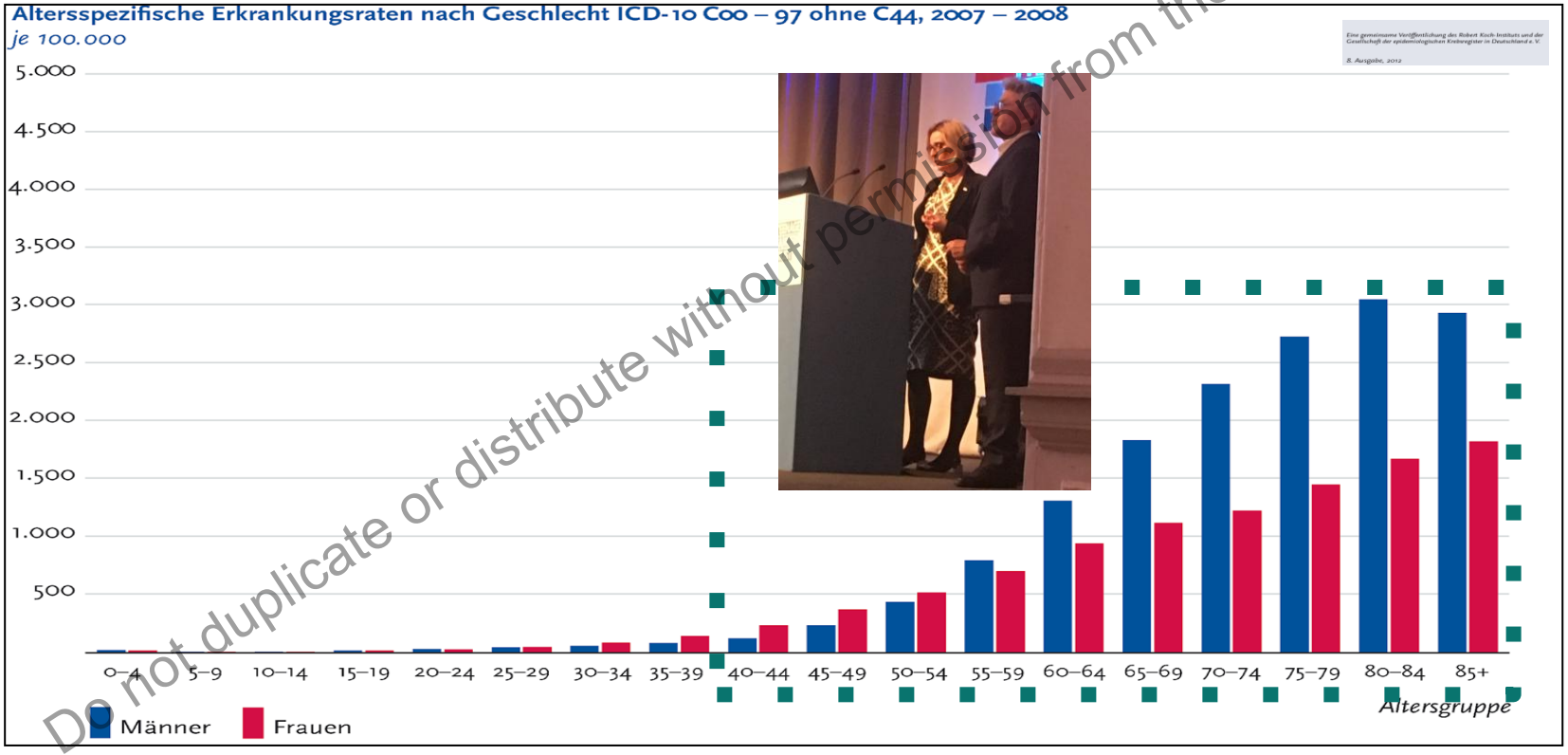




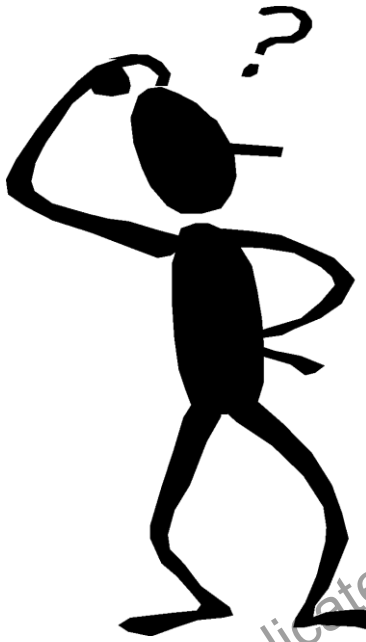
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Cancer
Age specific incidence





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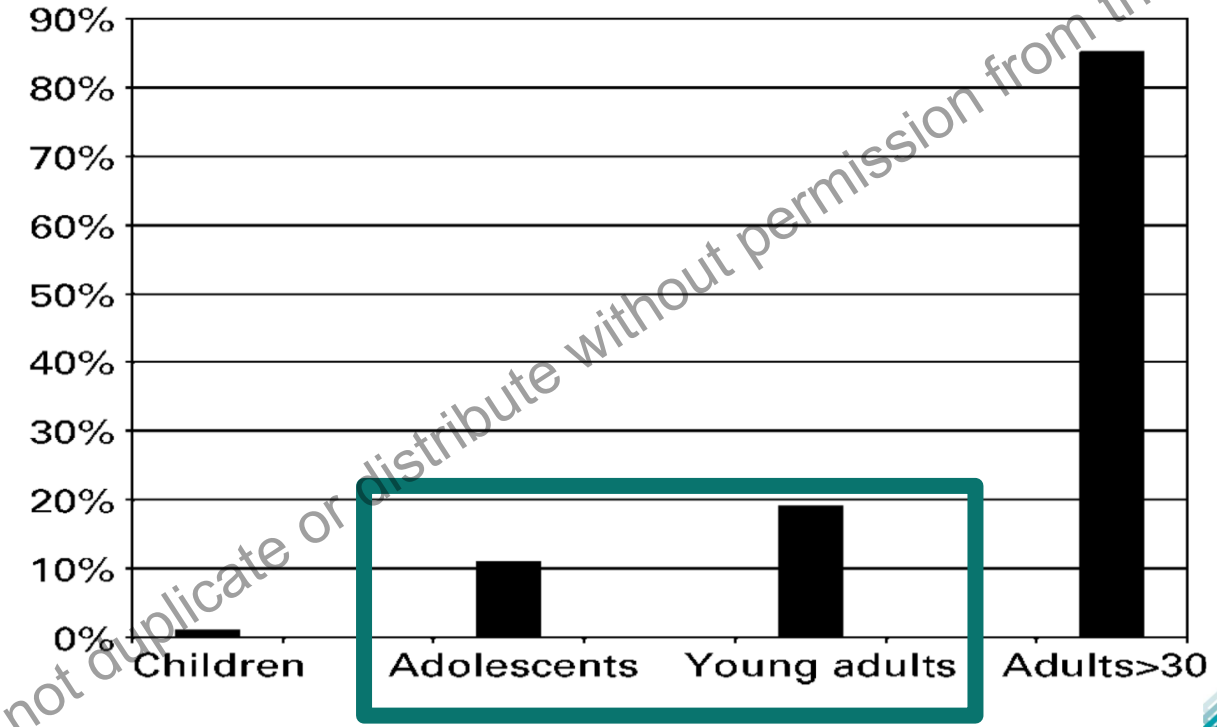


AYAs

Which cancers?

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Relative frequency of epithelial cancers (carcinomas) by age



G. Pentheroudakis & N. Pavlidis* *Annals of Oncology* 16: 181–188, 2005

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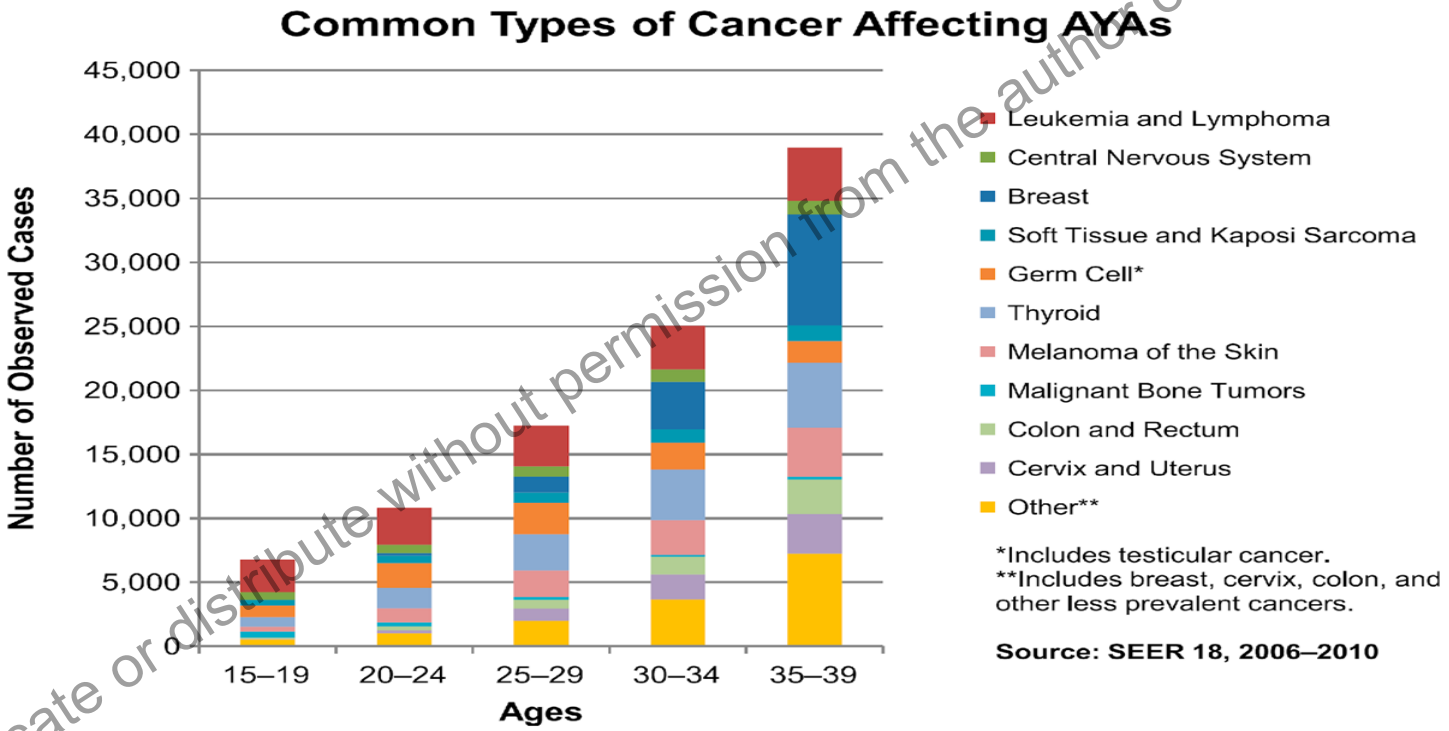


Figure 1. The prevalence of cancer histology by age, 15–39 years. Abbreviation: AYAs, adolescents and young adults.

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Leukemia and lymphoma

Nass, Beaupin, Demark-Wahnefried et al.

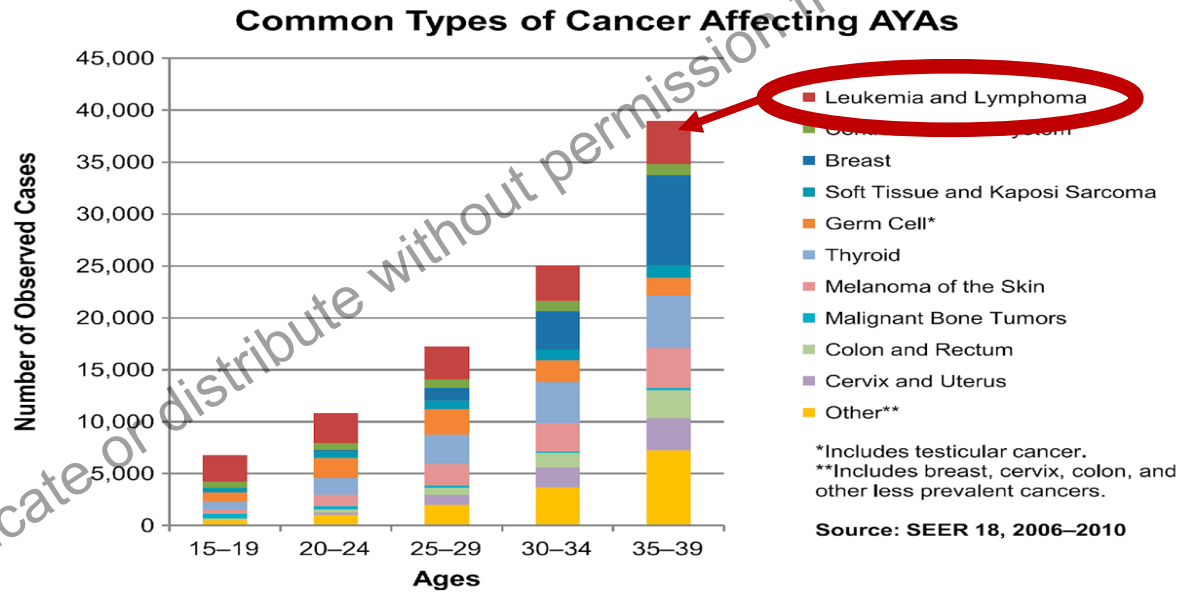


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Leukemia and lymphoma

Children	**AYA**
almost always acute	mainly acute
mostly **ALL** up	**AML** catches
favorable cytogenetics cytogenetics ↑	more **high-risk**
excellent prognosis	prognosis **poorer**

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AYA: Prognostic

changing biology

- disease
- host

treatment

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Treatment affects outcomes: ALL

Pediatric	n	DFS	Adult
	n	DFS	
FRALLE 83	84	48% (6 years)	LALA 85
31	32% (4 years)		
FRALLE 93	77	72% (5 years)	LALA 94
100	49% (5 years)		
CCG 1800	196	64% (6 years)	CALGB
103	38% (6 years)		
AIEOP	150	80% (OS, 2 years)	GIMEMA

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Pediatr Blood Cancer 2006;47:748–756
REVIEW
Adolescents With Acute Lymphoblastic Leukaemia: Emerging From the Shadow of Paediatric and Adult Treatment Protocols

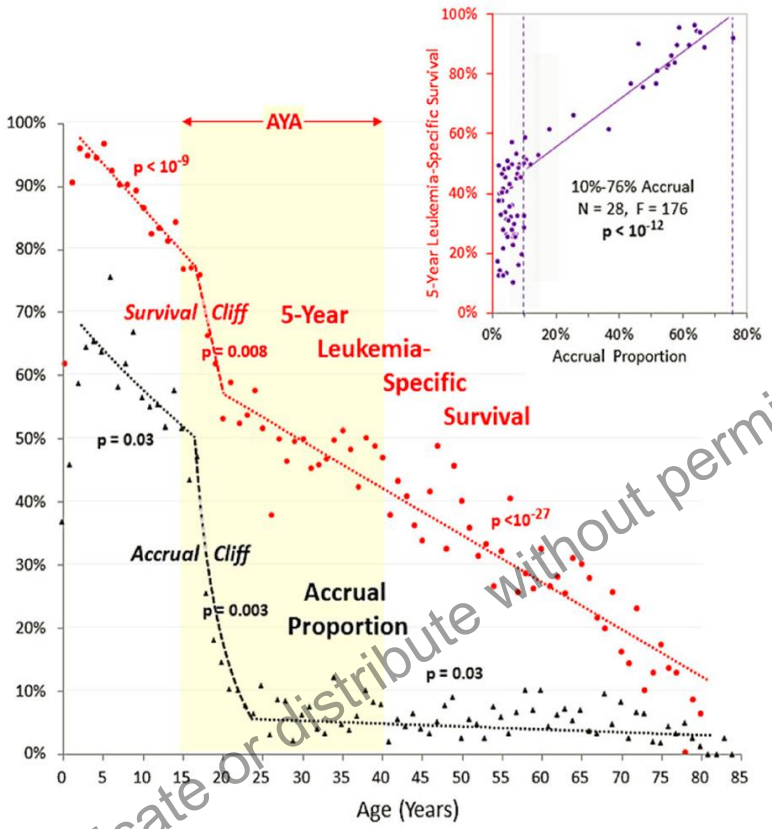


FIGURE 3 Joinpoint analysis of 5-year leukemia-specific survival of patients with ALL, 2000–2014, SEER18, and estimated treatment trial accrual proportion for 2000–2004, by single year of age. Joinpoint analysis was performed with the National Cancer Institute Joinpoint Regression Program.[9] Survival regressions are for 2–17, 17–20, and 20–81 years. Accrual proportion regressions are for 2–16, 16–23, and 23–80 years. *P*-values refer to the linear regression of the corresponding age segment. The inset shows all of the annual data of survival rates and accrual proportions as a function of survival with accrual proportion, demonstrating a linear regression for accrual proportion values >10%. Accrual data source is the same as in Figure 1

Received: 12 April 2017 | Revised: 19 February 2018 | Accepted: 26 February 2018
DOI: 10.1002/pbc.27074

SPECIAL REPORT

WILEY Pediatric Blood & Cancer | aspho

Role of clinical trials in survival progress of American adolescents and young adults with cancer—and lack thereof

Archie Bleyer[1,2] | Eric Tai[3] | Stuart Siegel[4]

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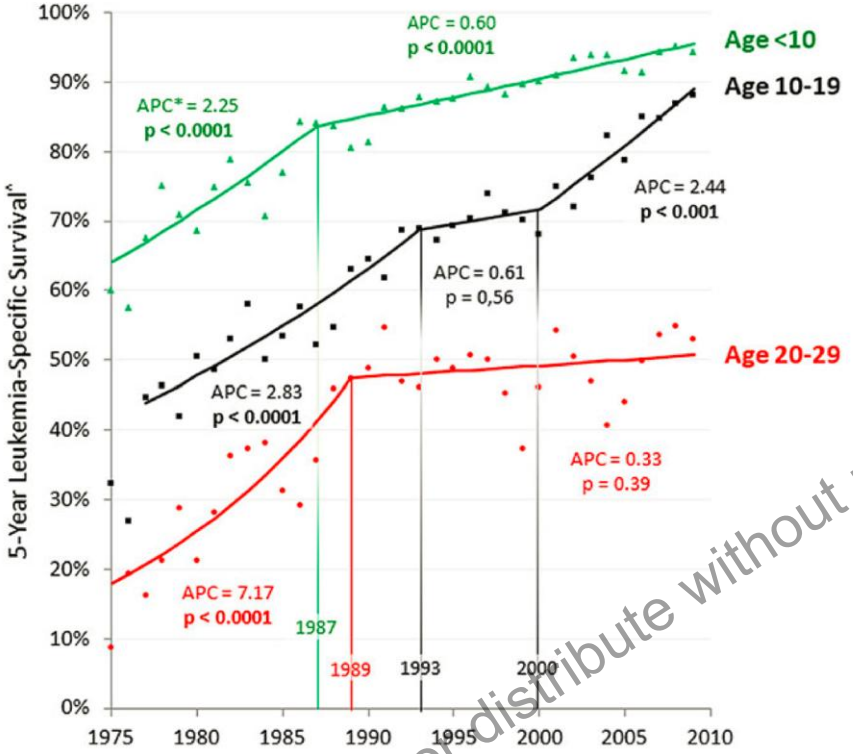


FIGURE 4 Annual ALL 5-year leukemia-specific survival, age < 30, 1975–2009, SEER, by 10 year age intervals. Joinpoint analysis was performed with the National Cancer Institute Joinpoint Regression Program.[9] Survival data were obtained from the SEER program.[3] APC, average annual percent change. Annual values are assessed from two consecutive years (year of and year before)

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The messages

- learn from each another
- put your patients onto trials



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Central nervous system

Nass, Beaupin, Demark-Wahnefried et al.

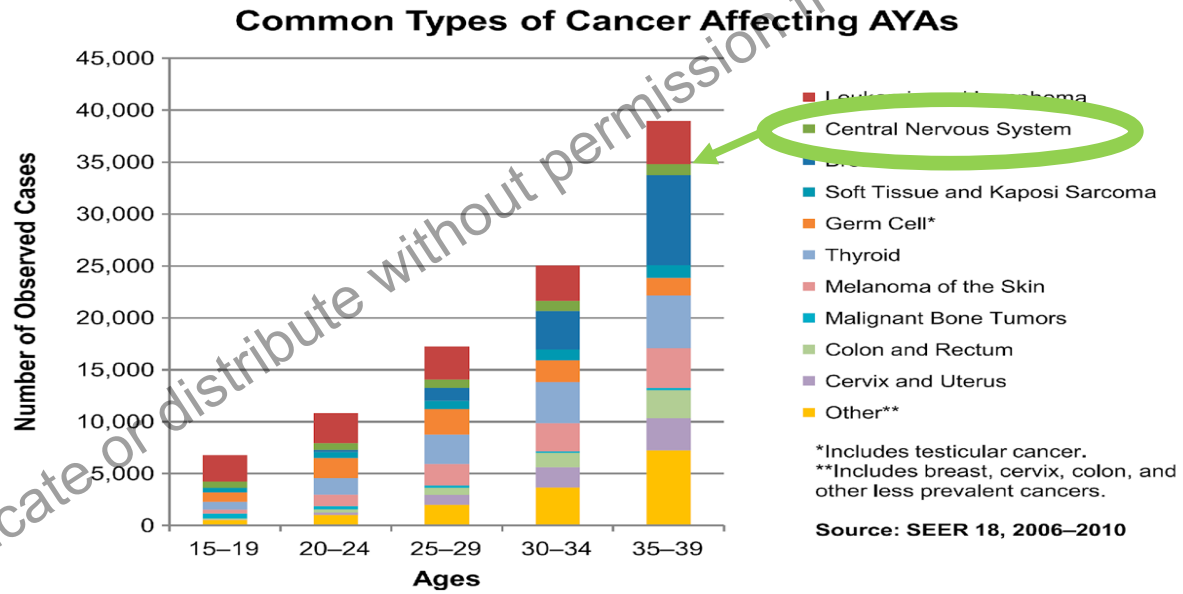


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Abbreviation: AYAs, adolescents and young adults.

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Breast cancer

Nass, Beaupin, Demark-Wahnefried et al.

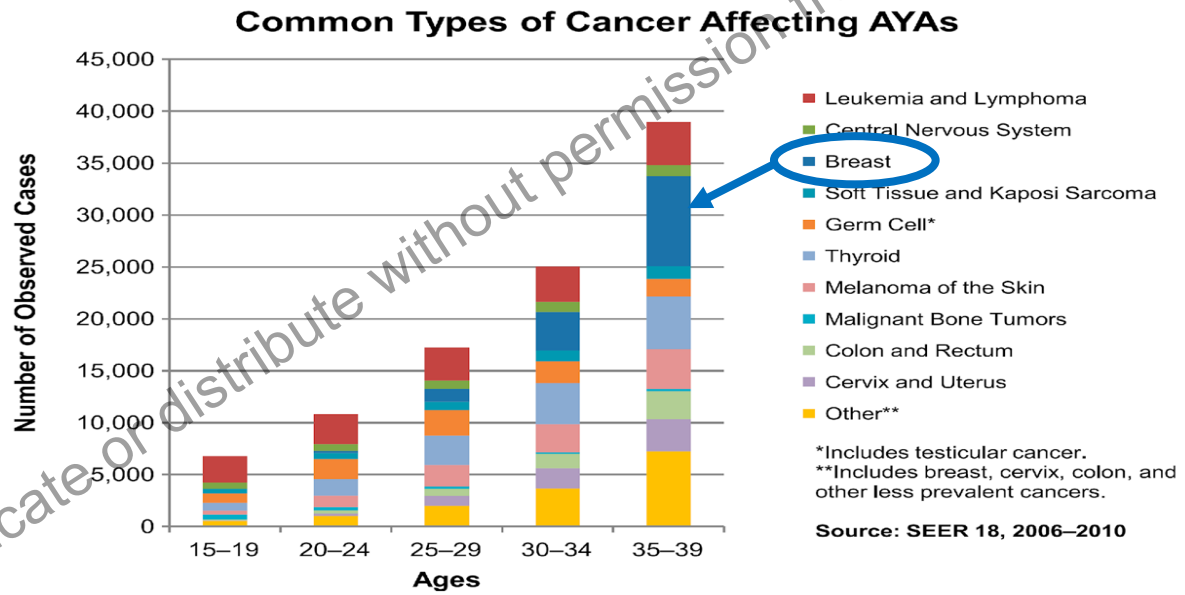


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Breast cancer

- a typical malignancy of *older* age
- happens to the young (AYA)
- search for **underlying conditions**
  - radiation field
  - tumor predisposition

syndromes
(BRACA, Li Fraumeni, …)

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Breast cancer

- *often treated by non-oncologists (gyn.)*
- prognosis ***younger < older*** women (more aggressive biology)

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Soft-tissue & Kaposi Sarcoma

Nass, Beaupin, Demark-Wahnefried et al.

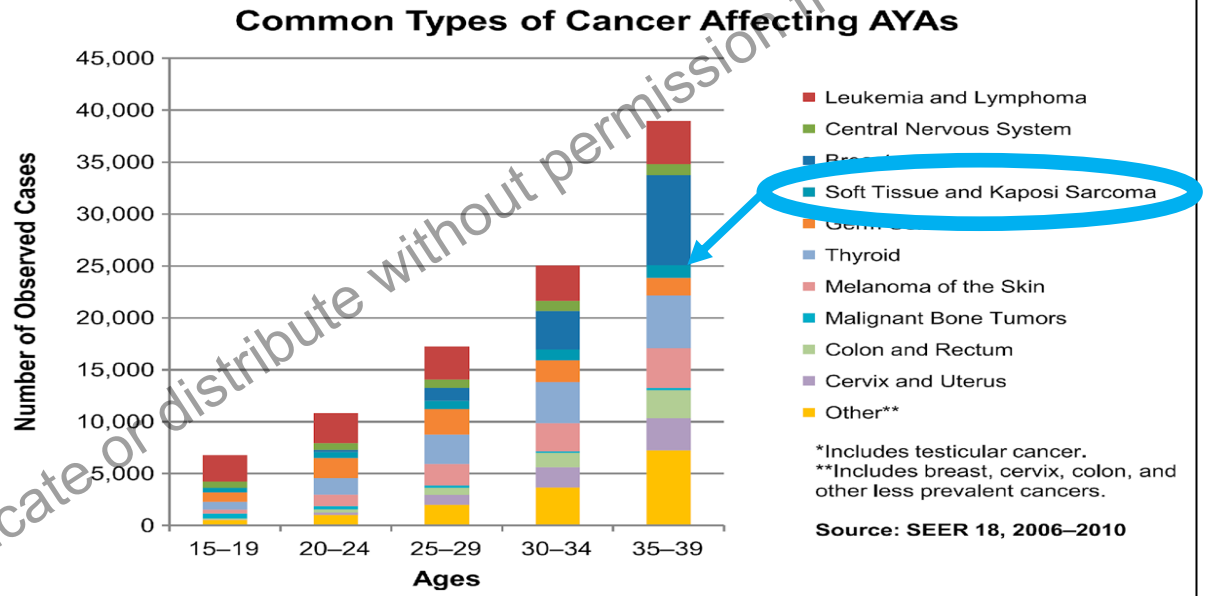


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Soft-tissue & Kaposi Sarcoma

- AYA oncology often dominated by STS-experts

- STS of **children** often ***exquisitely chemosensitive*** (>>>RMS)
- STS of **AYA** often ***„adult type“***, often ***not chemosensitive***

- treatment decisions may reflect *ped. vs. med. oncologist* rather than necessity

- recent years have witnessed closer ***interdisciplinary collaboration***

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Example:
Treatment of synovial sarcoma

Ped.

Med.

History for ***none***

chemo for ***all***

chemo

Modern ***need it***

chemo for those who really

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Soft-tissue & Kaposi Sarcoma

Pediatric and ***adult*** oncologists must learn from one another for the benefit of their AYA-patients

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Germ cell tumors

Nass, Beaupin, Demark-Wahnefried et al.

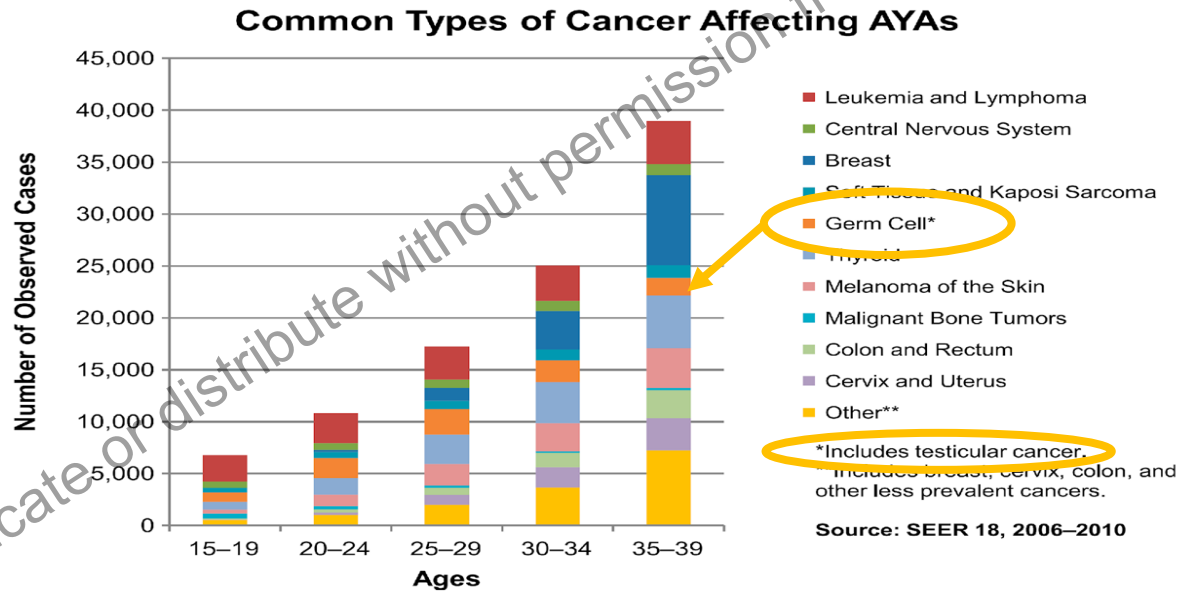


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AYA may be ashamed of their reproductive organs



diagnostic delays

⇒ tumor load ↑

sensitivity required

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Germ cell tumors

- particularly frequent in early adulthood
- exquisitely favorable prognosis
- ***detect the high-risk cases!!!***
- ped. & med.: convince / persuade other specialities to ***collaborate***

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Thyroid carcinoma

Nass, Beaupin, Demark-Wahnefried et al.

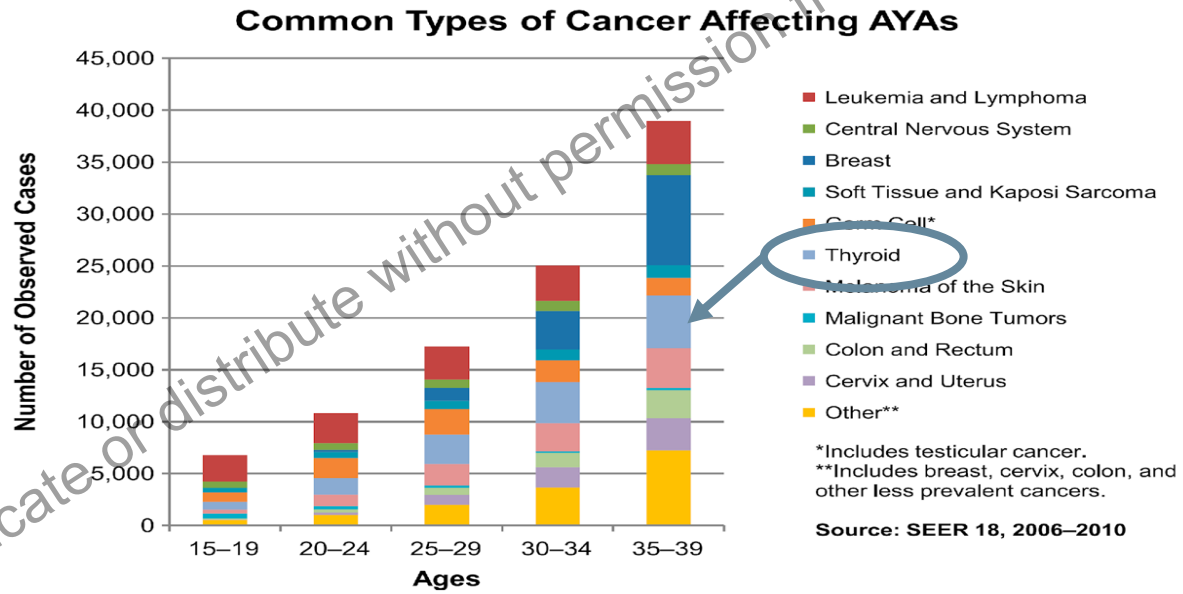


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Thyroid carcinoma

- **excellent prognosis**
- **radio-iodine treatment** often suffices
- => rarely seen in oncology units

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Thyroid carcinoma

- high-risk subtypes
- chemotherapy attempted
- prognosis remains dubious

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Melanoma

Nass, Beaupin, Demark-Wahnefried et al.

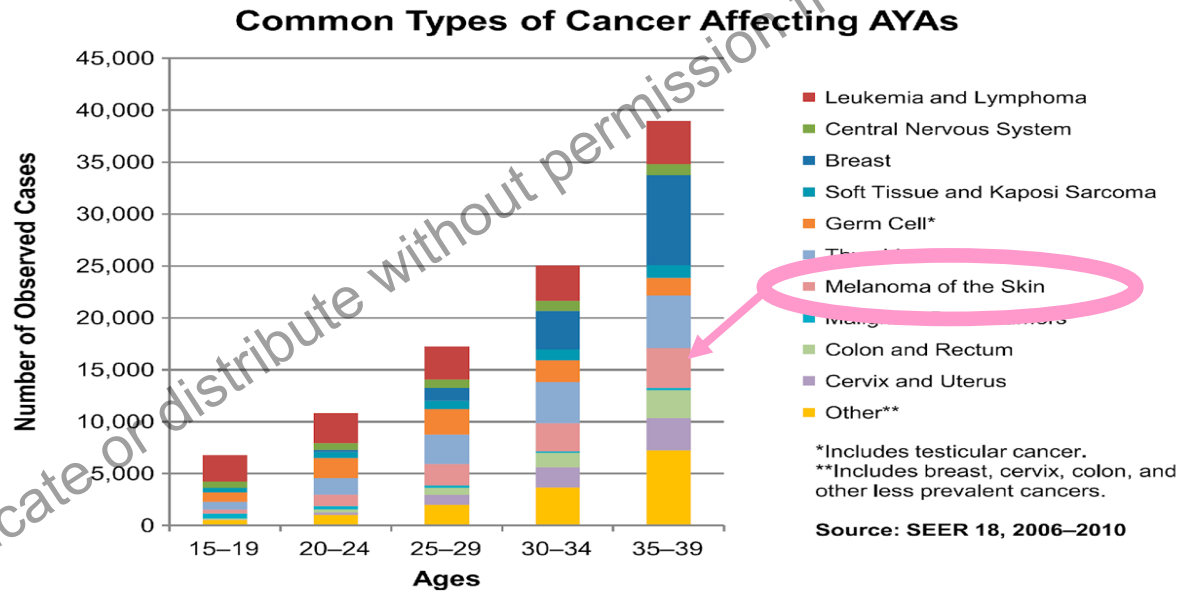


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Melanoma

- watch out for **DD Spitz naevus** in the young
- AYA ***incidence increasing*** (sunlight exposure)
- complete surgery essential at all ages
- systemic treatments insufficient at all ages
- ***another disease treated by others***

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Malignant bone tumors

Nass, Beaupin, Demark-Wahnefried et al.

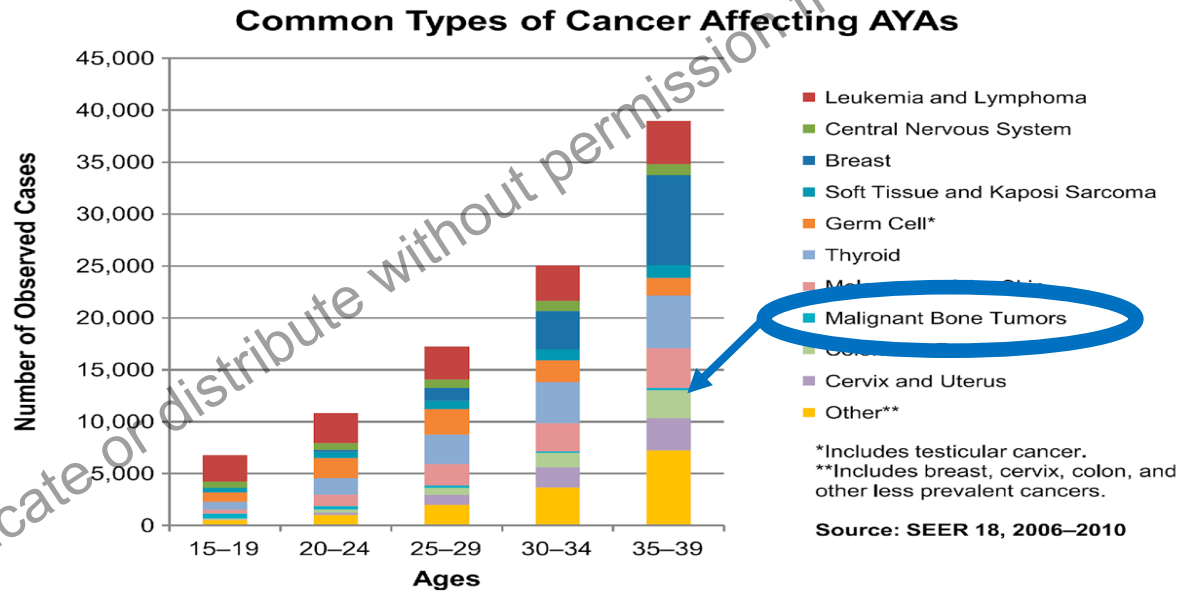


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Malignant Bone Tumors

Nass, Beaupin, Demark-Wahnefried et al.

typical tumors of younger AYAs

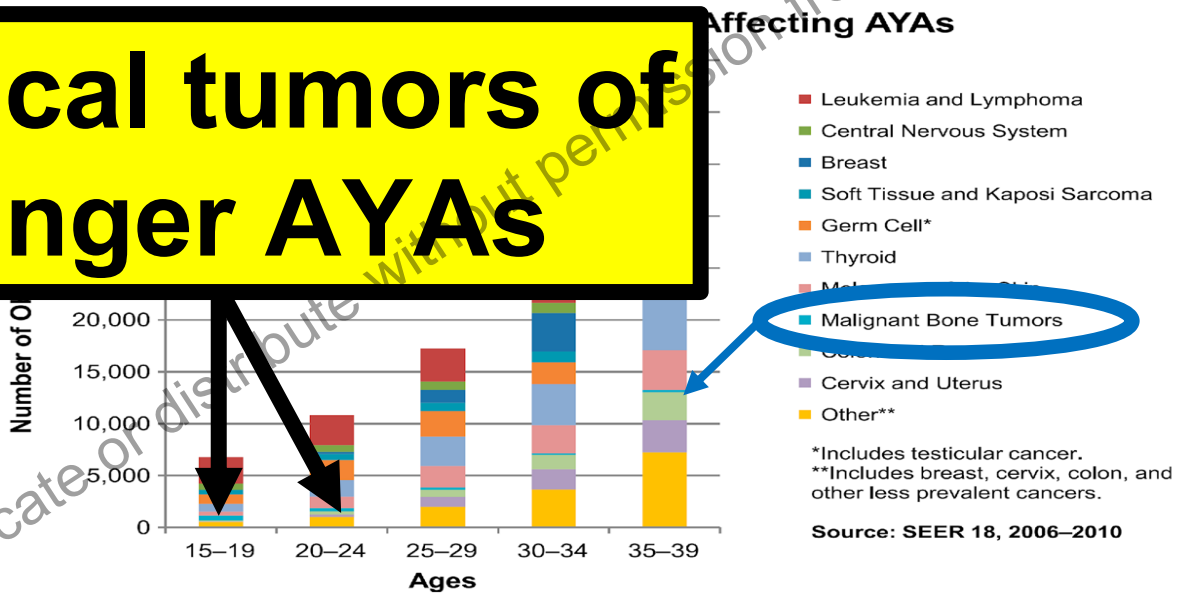


Figure 1. The prevalence of cancer histology by age, 15–39 years.
Abbreviation: AYAs, adolescents and young adults.

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Malignant Bone Tumors

- I am a bone tumor person!
- I believed bone tumor = AYA
- I was obviously (a little) wrong

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Malignant Bone Tumors - Types

Osteosarcoma

Ewing sarcoma

Ewing-like sarcomas

Chondrosarcoma

Others

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Osteosarcoma

- **young** an **extremity** disease
- **AYA** increasing proportion of **axial** **primaries** (local control!)

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Osteosarcoma

- **patients of all ages require complete tumor surgery for cure**

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Osteosarcoma

- patients of all ages require **multi-drug chemotherapy**
- AYA usually tolerate pediatric regimens

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Osteosarcoma

- studies usually open **0 – 40 years**
- ***recruitment of AYAs still insufficient***

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Ewing sarcoma

- **all** patients require
  - ***local therapy*** (OP, RX, both)
  - ***systemic therapy***
- ped. trials are open until 40-50 years
- are prognostic differences still seen?

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Ewing-like sarcomas

- look (somewhat) like Ewing
- various types (CIC-DUX, BCOR, …)
- often historically treated on Ewing protocols
- ***these are not Ewing sarcomas!***
- probably distinct prognosis by type

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Chondrosarcoma

- **a surgical disease regardless of age or tumor-stage**

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Other bone sarcomas

- there are quite a few
- most may (also) occur in AYAs
- prospective studies are characteristically lacking
- therapies required are quite distinct by type

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Colon and rectum

Nass, Beaupin, Demark-Wahnefried et al.

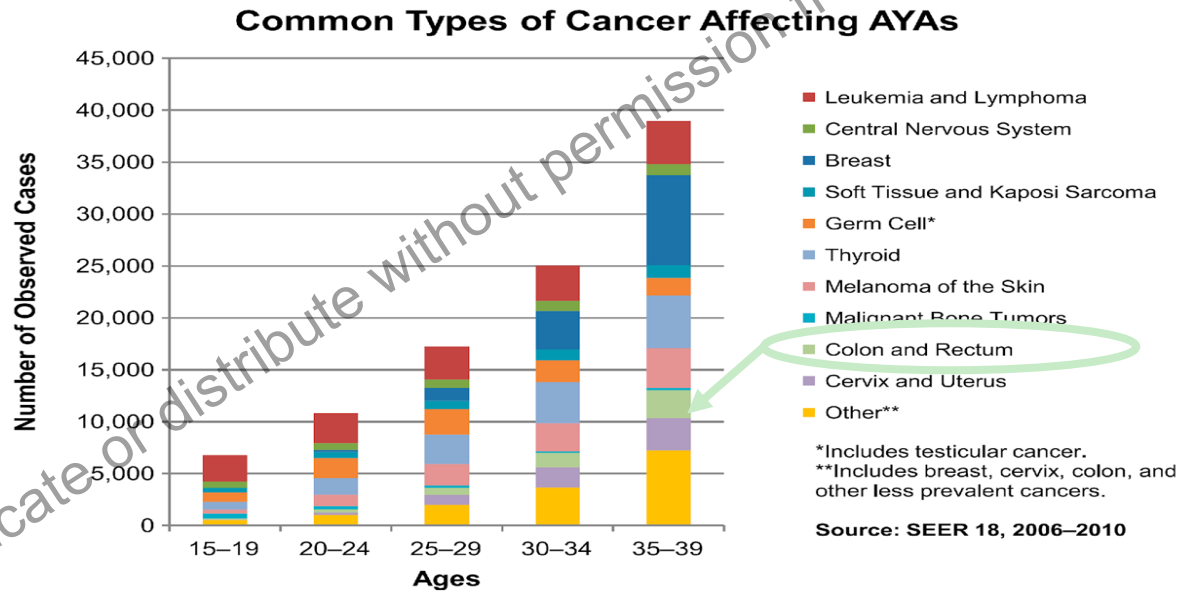


Figure 1. The prevalence of cancer histology by age, 15–39 years.
Abbreviation: AYAs, adolescents and young adults.

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Colon and rectum

- almost unheard of in the truly young
- one of the more frequent cancers of ***older AYAs***
- ***always search for genetic predispositions***
- ask your trusted med. oncologist how to treat

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Cervix and uterus

Nass, Beaupin, Demark-Wahnefried et al.

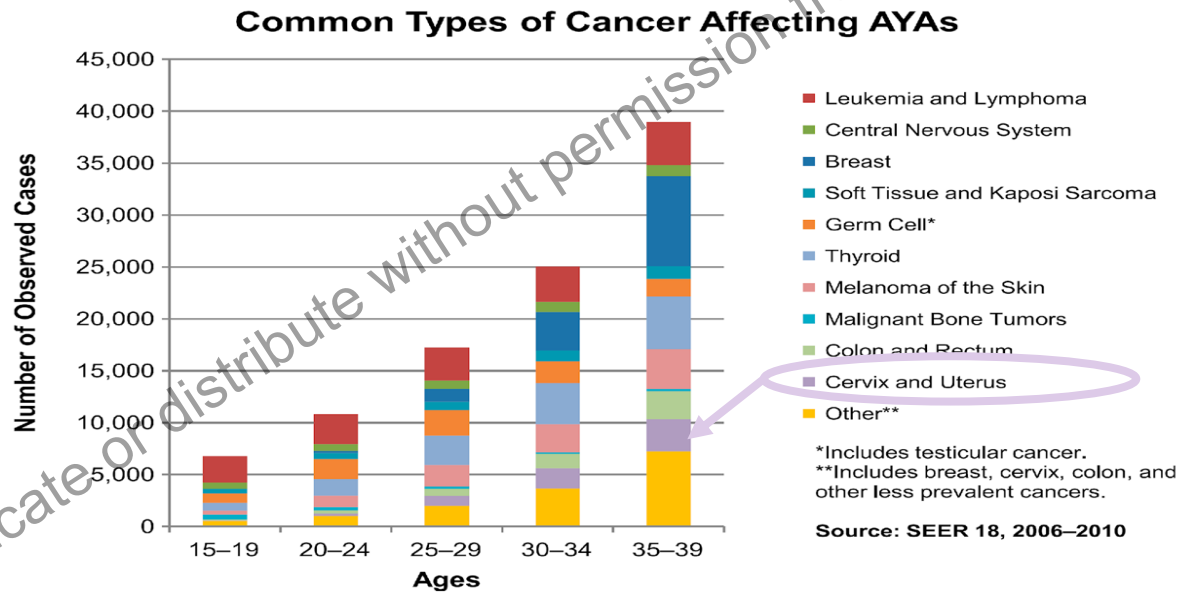


Figure 1. The prevalence of cancer histology by age, 15–39 years.
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Cervix and uterus

- alas! Another tumor often treated by non-oncologists
- (again) almost unheard of in the truly young
- (again) one of the more frequent cancers of **older AYAs**
- **prevent papilloma-virus *(pediatricians!)***
- (again) ask your trusted med. oncologist how to treat

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Other

Nass, Beaupin, Demark-Wahnefried et al.

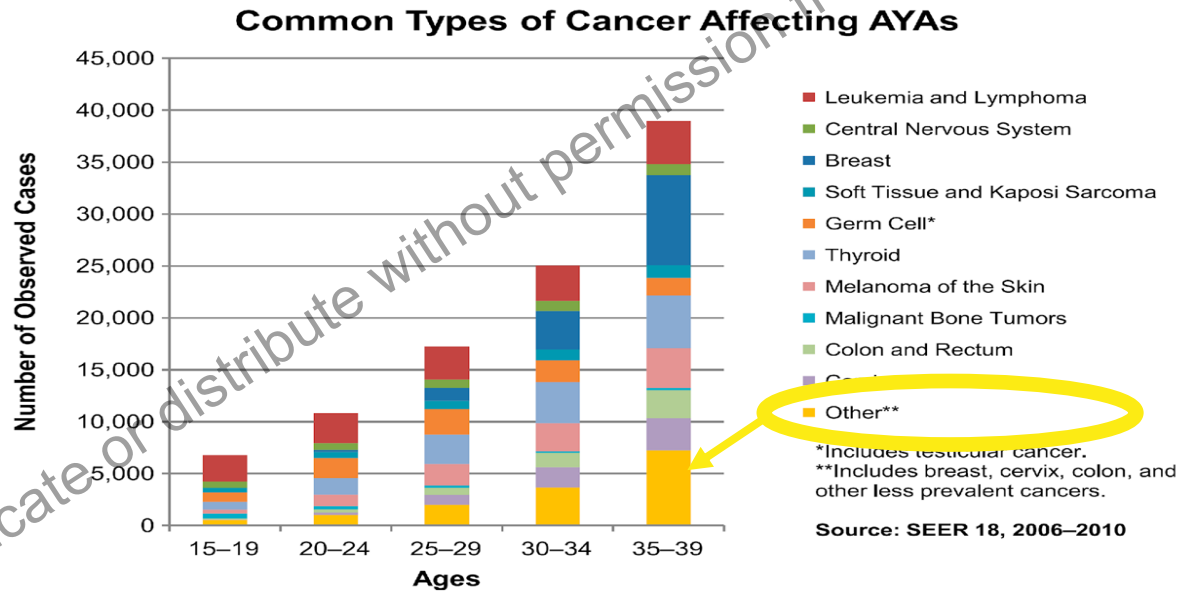


Figure 1. The prevalence of cancer histology by age, 15–39 years.
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Other

- a truly mixed bag
- all types of ***carcinoma***
- **increasing with age**

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Let’s not forget

- AYAs need age-appropriate surroundings
- AYAs have specific psychosocial needs
- AYs need ***professional support*** for their ***specific requirements***

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The message(s)

- **AYAs have age specific needs**
- AYAs may contract pediatric or adult cancers
- AYAs may have age-specific risk-factors
- **AYAs should be treated by experts**

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The message(s)

- learn from each other
- **cooperate**
- get the other disciplines to join

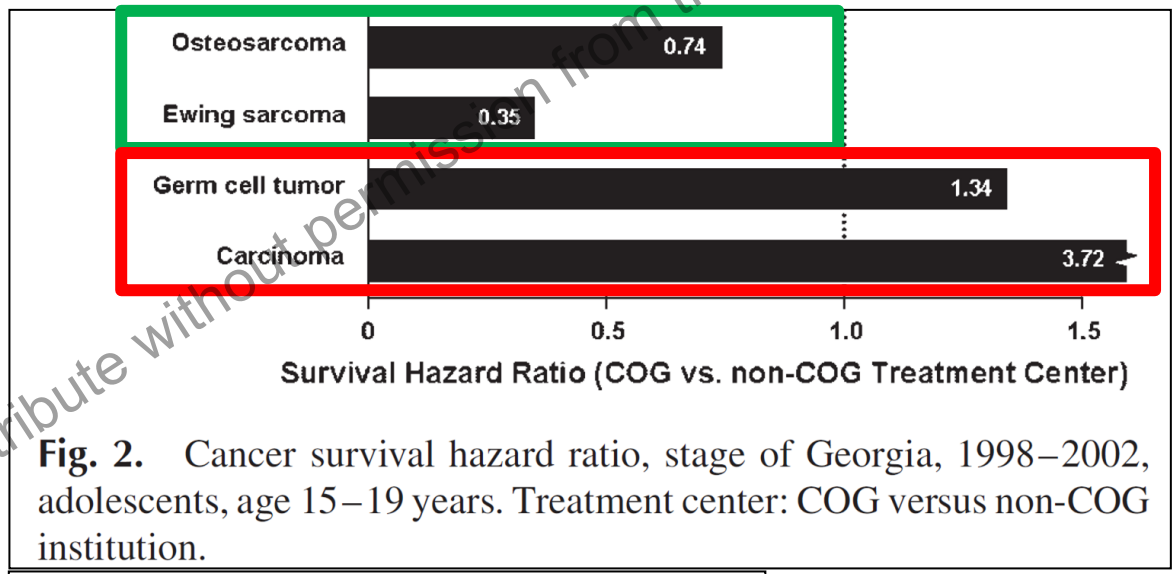


Fig. 2. Cancer survival hazard ratio, stage of Georgia, 1998–2002, adolescents, age 15–19 years. Treatment center: COG versus non-COG institution.

Pediatr Blood Cancer 2010;54:238–241

The Quid Pro Quo of Pediatric Versus Adult Services for Older Adolescent Cancer Patients

Archie Bleyer, MD[1,2,3,4*,†,‡,§,¶]

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Thank you!

Stefan Bielack
28.10.22

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