Childhood, Adolescent, and Young Adult Cancer Survivorship

John van Doorninck, MD

May 30, 2018

Rocky Mountain Hospital for Children
A new generation of care.

WYCC Wyoming Cancer Coalition
www.rockymountainhospitalforchildren.com

Health ONE Presbyterian/St. Luke's Medical Center

Objectives

- Discuss improvement in cure rates of childhood cancer
- Discuss health problems associated with survivorship of childhood and adolescent/young adult (AYA) cancer survival
- Describe strategies used to improve health problems associated with cancer survivorship
- Describe how these interventions have improved the health of childhood/AYA cancer survivors
- Discuss two specific issues of childhood/AYA cancer survival
  - Fertility
  - Psychosocial

Objectives

- **Discuss improvement in cure rates of childhood cancer**
- Discuss health problems associated with survivorship of childhood and adolescent/young adult (AYA) cancer survival
- Describe strategies used to improve health problems associated with cancer survivorship
- Describe how some of these interventions have improved the health of childhood/AYA cancer survivors
- Discuss two specific issues of childhood/AYA cancer survival
  - Fertility
  - Psychosocial

www.rockymountainhospitalforchildren.com

Childhood Cancer: Improved Outcomes

- 1960s: <50% overall survival
- 1975: 60% overall survival
- 2010: 80-90% overall survival

Armstrong, GT, et al. NEJM. 2016

Childhood Cancer: Epidemiology

- >83% of children and adolescents who are diagnosed with cancer will become long term survivors
- By 2020, an estimated 500,000 survivors of childhood cancer in the United States

Armstrong, GT, et al. NEJM. 2016

Objectives

- Discuss improvement in cure rates of childhood cancer
- **Discuss health problems associated with survivorship of childhood and adolescent/young adult (AYA) cancer survival**
- Describe strategies used to improve health problems associated with cancer survivorship
- Describe how some of these interventions have improved the health of childhood/AYA cancer survivors
- Discuss two specific issues of childhood/AYA cancer survival
  - Fertility
  - Psychosocial

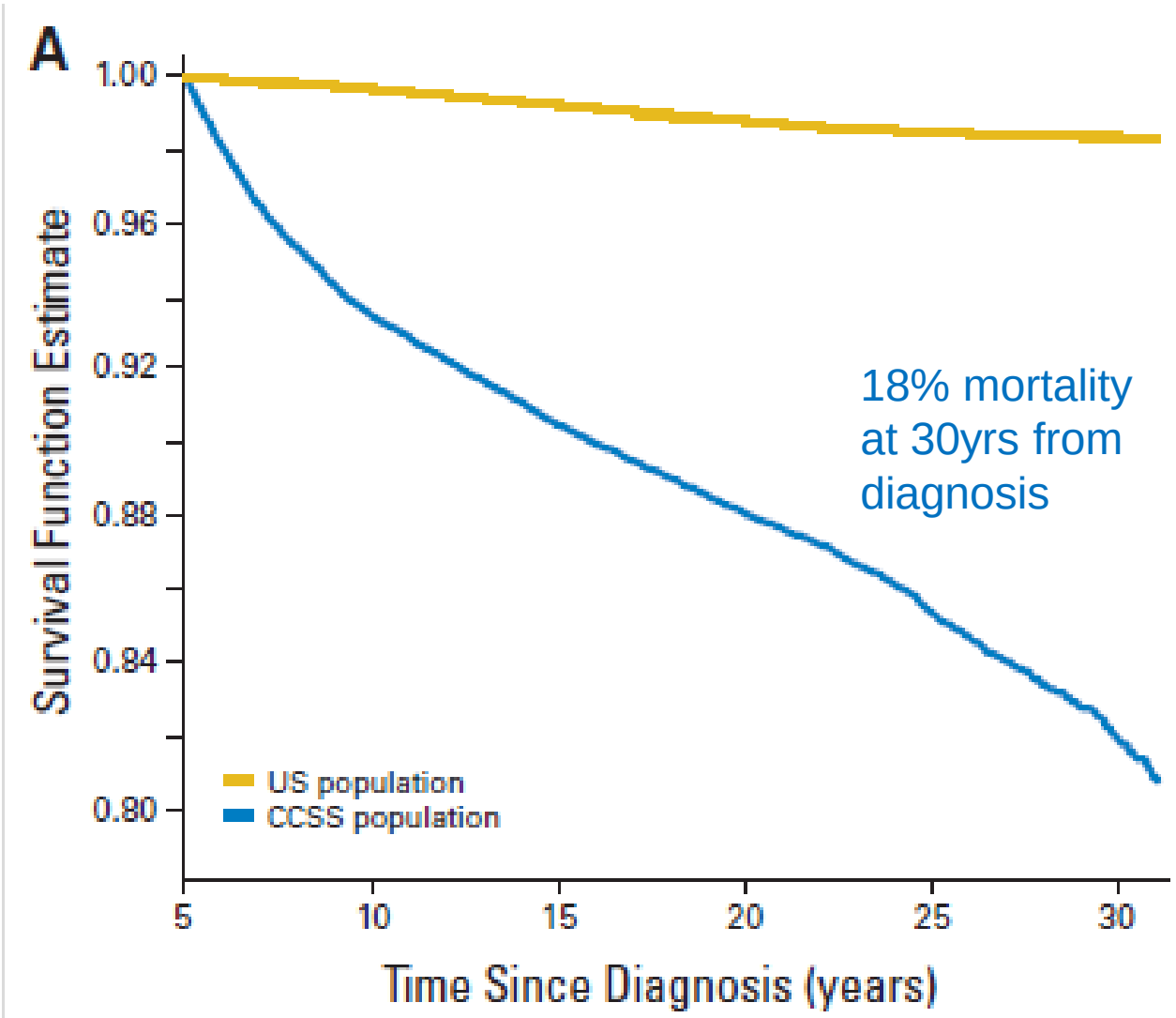
Challenges facing Childhood/Young Adult Cancer Survivor

- Childhood Cancer Survivor Study (CCSS)
  - Initial cohort: Patients diagnosed with childhood cancer between 1970-1986 and alive at least 5yrs from diagnosis
  - Described morbidity and mortality associated with childhood cancer treatment
    - Late effects experienced by patients treated in later eras could be compared to this cohort

Mortality after treatment for childhood cancer: The Childhood Cancer Survivor Study (CCSS):

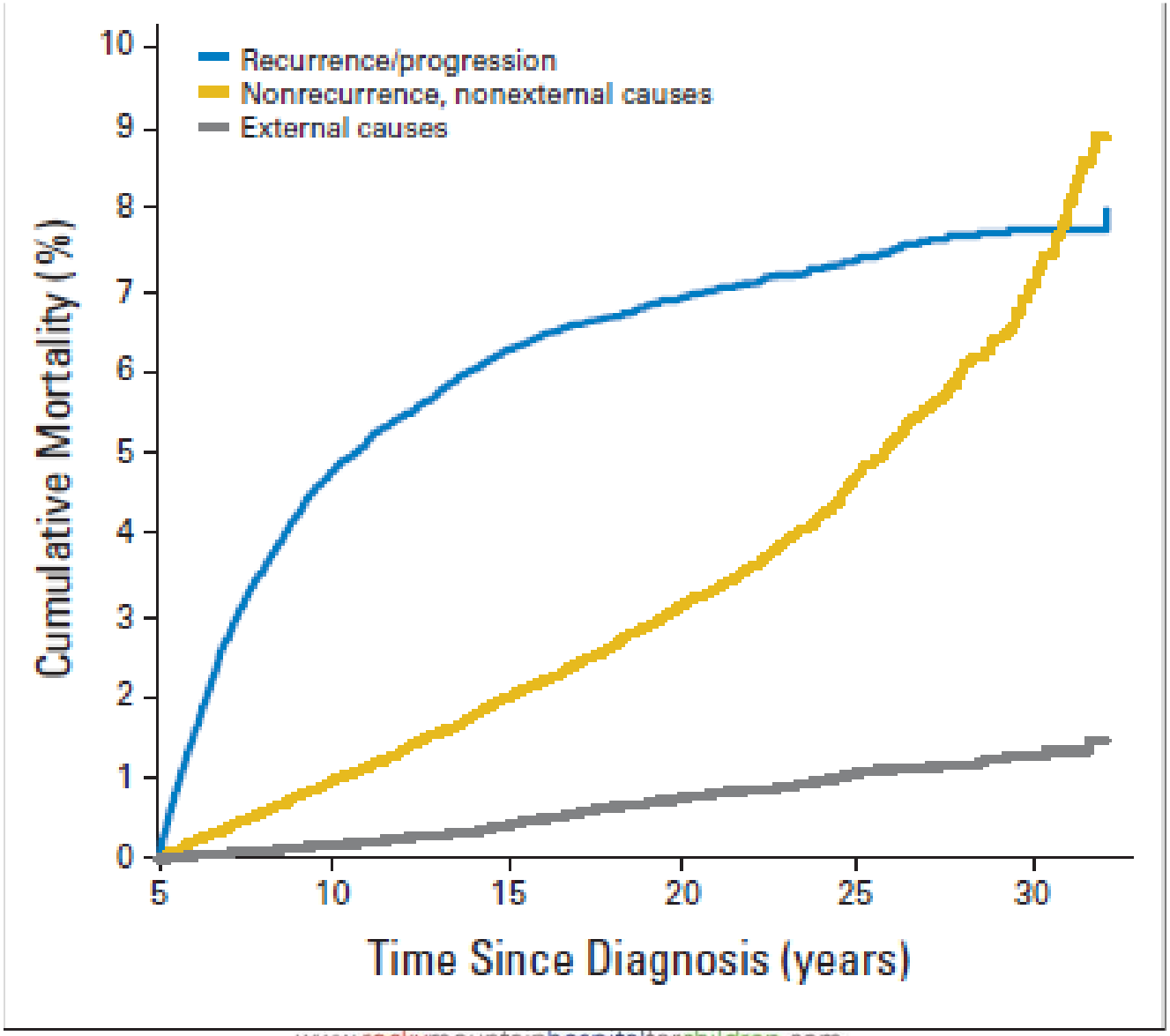
- Study population: 20,227 five-year survivors of childhood cancer diagnosed between 1970-1986
- Key finding: 11-fold excess in mortality than expected versus population controls

Mertens AC, et al. J Clin Oncol. 2001;19:3163-3172



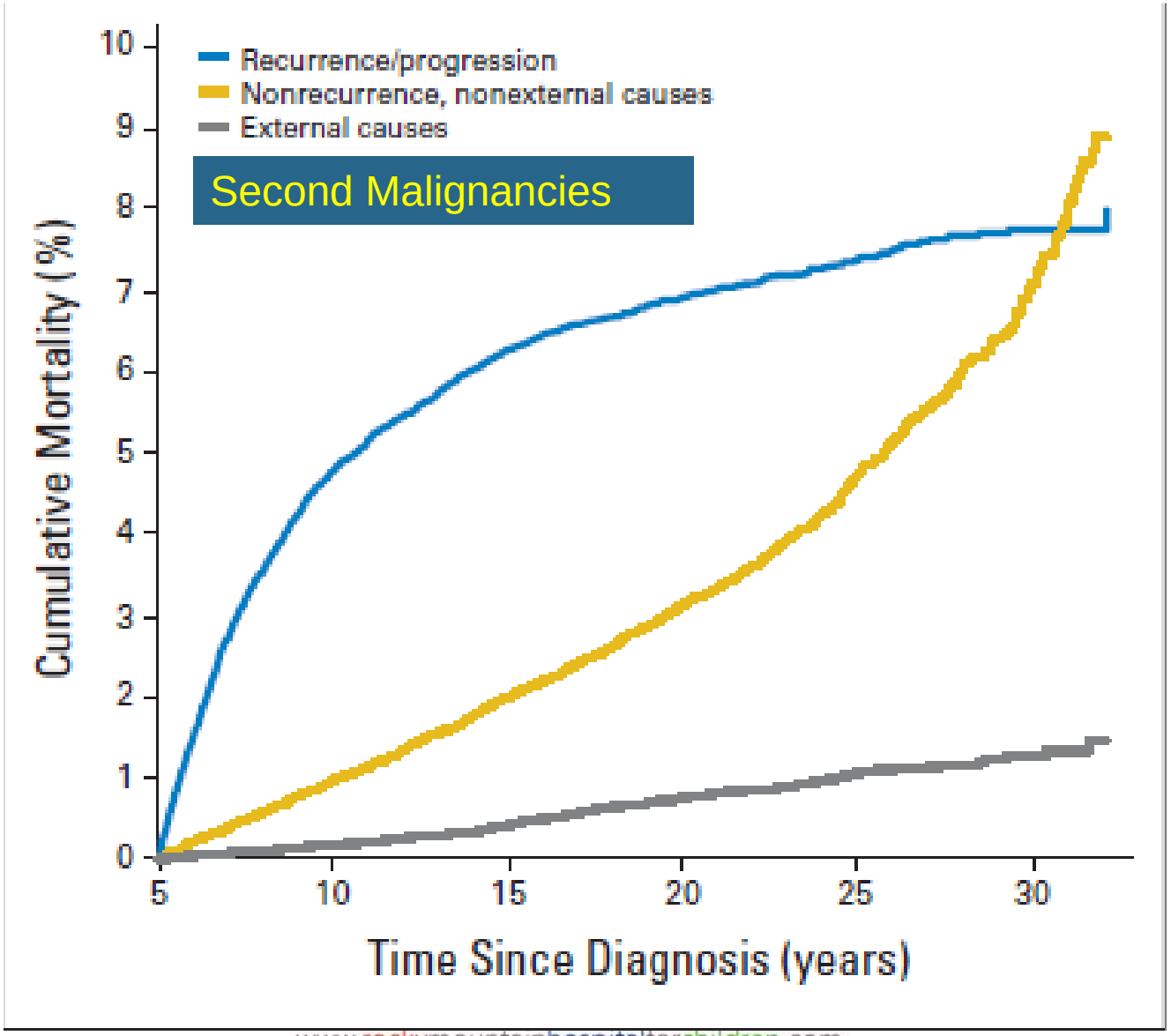
All-cause mortality--sex-specific survival.
(Compared with age-adjusted expected survival in U.S.)

Armstrong GT, et al. JCO. 2009

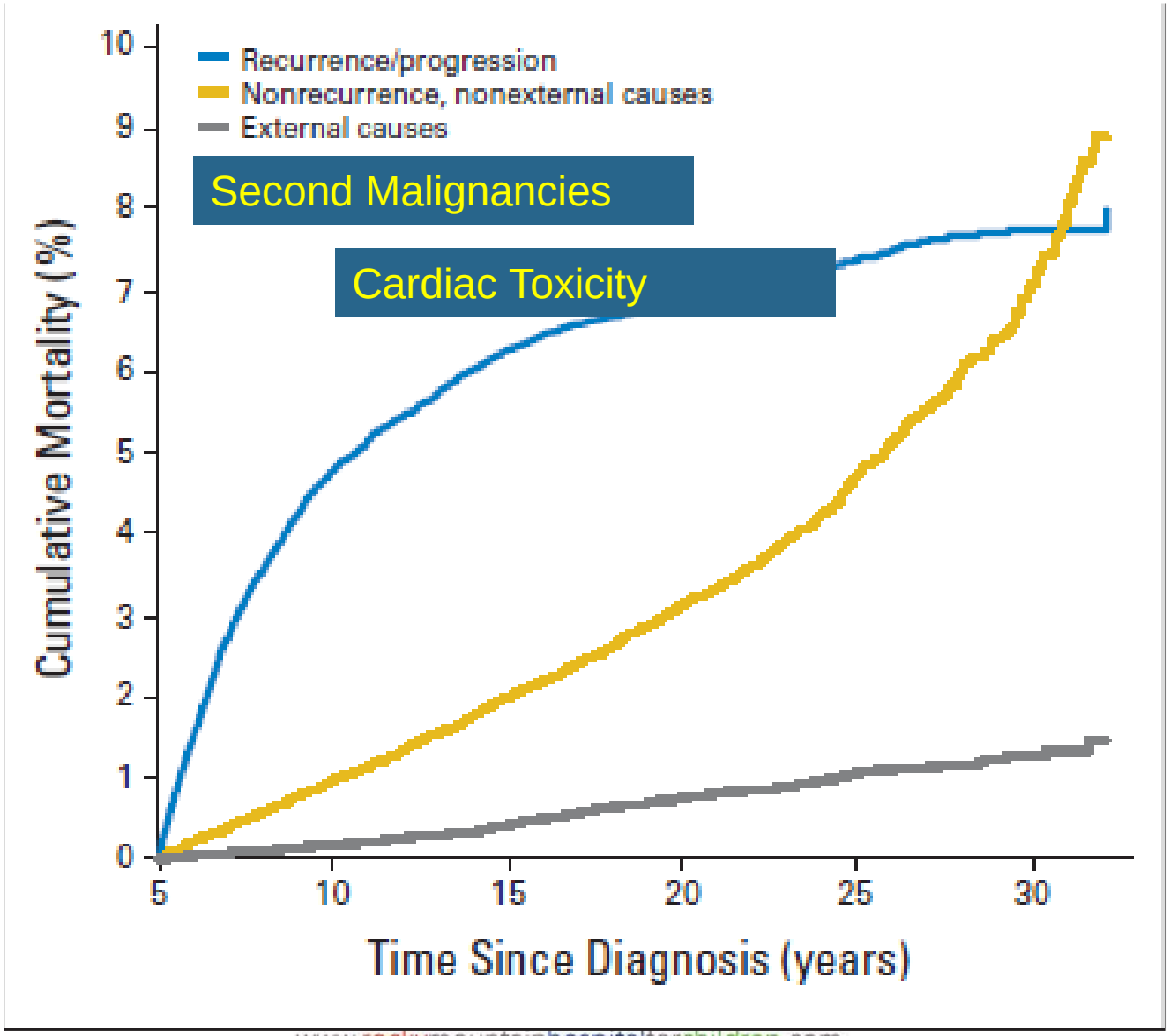


www.rockymountainhospitalforchildren.com

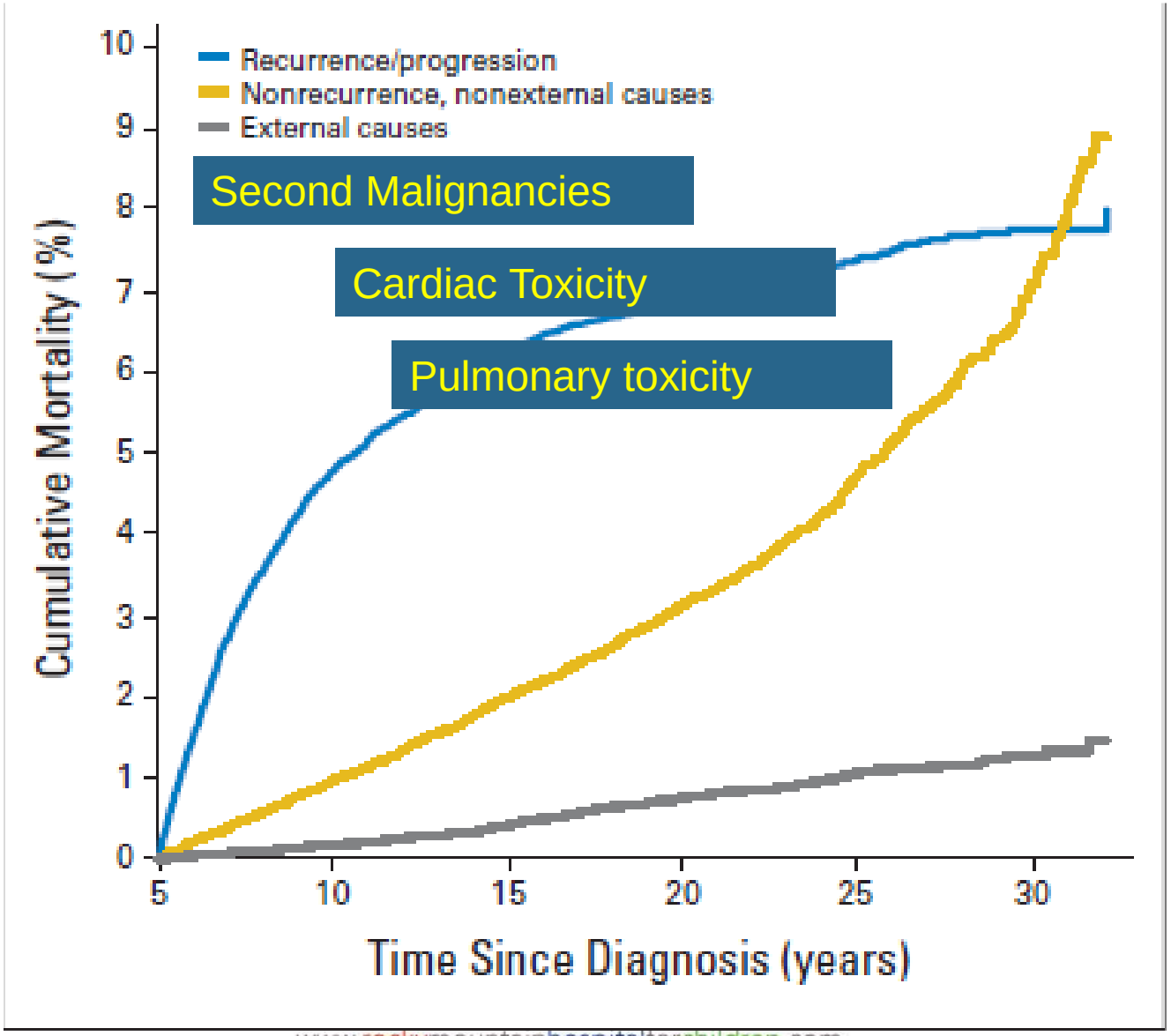
Armstrong GT, et al. JCO. 2009



Armstrong GT, et al. JCO. 2009



Armstrong GT, et al. JCO. 2009



Armstrong GT, et al. JCO. 2009

Morbidity after treatment for childhood cancer: The Chronic Health Conditions in Adult Survivors of Childhood Cancer Study[1]

- Study population: 10,397 survivors of childhood cancer diagnosed between 1970-1986
- Key findings:
  - 62.3% had at least one chronic condition (RR 3.3)
  - 27.5% had a severe or life-threatening chronic illness (RR 8.2)

Oeffinger, K. NEJM 2006;355:1572-82

Table 2. Cancer Survivors and Siblings with a Chronic Health Condition, According to the Severity Score.*

Health Condition	Survivors (N=10,397)	Siblings (N=3034)
	no. (%)	
No condition	3887 (37.4)	1917 (63.2)
Grade 1 (mild)	1931 (18.6)	610 (20.1)
Grade 2 (moderate)	1635 (15.7)	349 (11.5)
Grade 3 (severe)	2128 (20.5)	128 (4.2)
Grade 4 (life-threatening or disabling)	653 (6.3)	30 (1.0)
Grade 5 (fatal)	163 (1.6)	NA†
Any condition‡		
Grades 1–4	6482 (62.3)	1117 (36.8)
Grade 3 or 4	2858 (27.5)	158 (5.2)
Multiple health conditions		
≥2	3905 (37.6)	397 (13.1)
≥3	2470 (23.8)	163 (5.4)

* The severity of health conditions was scored according to the Common Terminology Criteria for Adverse Events (version 3). Health conditions of survivors did not include conditions the patients had before their cancer diagnosis or acute conditions they had within 5 years after the diagnosis. NA denotes not applicable.

† All siblings were alive at the time of enrollment. Survivors may have died in the interval between 5 years after their cancer diagnosis and the time of the study. The composite percentage for survivors with grade 3 or 4 conditions includes conditions that were reported before the time of death in the 163 survivors who died.

‡ The number of patients in each subgroup may not reflect the sum of the grades of conditions, since grades 1 through 5 were calculated by taking the maximum grade per subject. A subject with grade 5 may have had other lower grades.

The NEW ENGLAND JOURNAL of MEDICINE

Oeffinger K, et al, 2006

Table 3. Relative Risk of Selected Severe (Grade 3) or Life-Threatening or Disabling (Grade 4) Health Conditions among Cancer Survivors, as Compared with Siblings.

Condition	Survivors (N = 10,397)	Siblings (N = 3034)	Relative Risk (95% CI)
	percent		
Major joint replacement*	1.61	0.03	54.0 (7.6–386.3)
Congestive heart failure	1.24	0.10	15.1 (4.8–47.9)
Second malignant neoplasm†	2.38	0.33	14.8 (7.2–30.4)
Cognitive dysfunction, severe	0.65	0.10	10.5 (2.6–43.0)
Coronary artery disease	1.11	0.20	10.4 (4.1–25.9)
Cerebrovascular accident	1.56	0.20	9.3 (4.1–21.2)
Renal failure or dialysis	0.52	0.07	8.9 (2.2–36.6)
Hearing loss not corrected by aid	1.96	0.36	6.3 (3.3–11.8)
Legally blind or loss of an eye	2.92	0.69	5.8 (3.5–9.5)
Ovarian failure‡	2.79	0.99	3.5 (2.7–5.2)

* For survivors, major joint replacement was not included if it was part of cancer therapy.
† For both groups, this category excludes basal-cell and squamous-cell carcinoma (grade 2). For siblings, this category includes a first cancer.
‡ Values are for women only.

Oeffinger K, et al, 2006

The NEW ENGLAND JOURNAL of MEDICINE

Objectives

- Discuss improvement in cure rates of childhood cancer
- Discuss health problems associated with survivorship of childhood and adolescent/young adult (AYA) cancer survival
- **Describe strategies used to improve health problems associated with cancer survivorship**
- Describe how some of these interventions have improved the health of childhood/AYA cancer survivors
- Discuss two specific issues of childhood/AYA cancer survival
  - Fertility
  - Psychosocial

Strategies to Improve Long Term Side Effects:

- Primary Prevention:
  - Reduce exposure to and/or risk from agents cause late side effects
- Secondary prevention:
  - Reduce risk of complications of agents already received

Strategies to Improve Long Term Side Effects:

- Primary Prevention:
  - Reduce exposure to and/or risk from agents cause late side effects
- Secondary prevention:
  - Reduce risk of complications of agents already received

Strategies to Improve Long Term Side Effects

- Primary Prevention:
  - Changes in chemotherapy
    - Less reliance on traditional agents
    - Targeted therapy
      - Imatinib (CML, Ph +ALL). Can eliminate BMT
      - Immunotherapy
  - Co-administration of medicines to reduce toxicity from chemotherapy agents being received
    - Dexrazoxane (reduce cardiac toxicity)
    - Sodium thiosulfate (reduce ototoxicity)

Chow, E. ASPHO. 2018

Strategies to Improve Long Term Side Effects

- Primary Prevention:
  - Decrease radiotherapy
    - ALL:
      - 1970's: 80% received radiation
      - 1990's: 19% received radiation
    - Wilms tumor
      - 1970's: 78% received radiation
      - 1990's: 43% received radiation
    - Hodgkin lymphoma:
      - 1970's: 87% patients received radiation
      - 1990's: 61% patients received radiation
  - Changing form of radiation (from photons to protons)

Chow, E. ASPHO. 2018
Armstrong GT, et al. NEJM. 2016.

Strategies to Improve Long Term Side Effects:

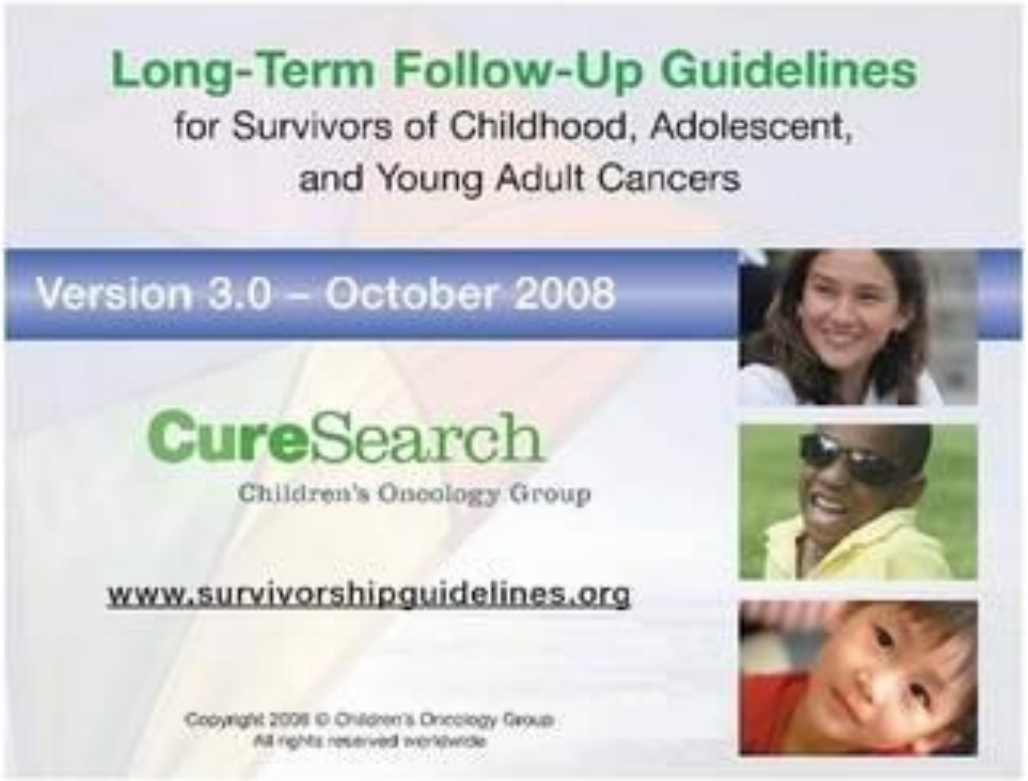
- Primary Prevention:
  - Reduce exposure to and/or risk from agents cause late side effects
- Secondary prevention:
  - Reduce risk of complications of agents already received

Strategies to Improve Long Term Side Effects

- Secondary prevention:
  - Improving adherence of recommended screening

Strategies to Improve Long Term Side Effects

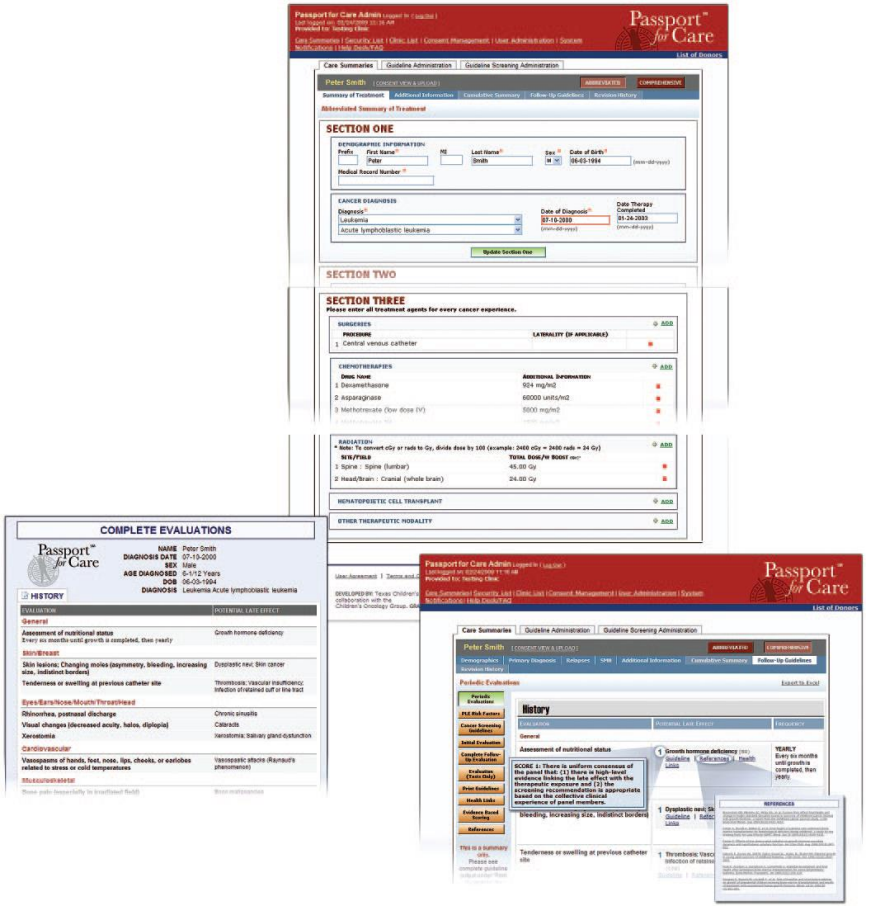
- Secondary prevention:
  - Improving adherence of recommended screening



Passport for Care: Implementing the Survivorship Care Plan

By Marc E. Horowitz, MD, Michael Fordis, MD, Susan Krause, Julie McKellar, and David G. Poplack, MD

Texas Children's Cancer Center; and Center for Collaborative and Interactive Technologies, Baylor College of Medicine, Houston, TX



www.rockymountainhospitalforchildren.com

Strategies to Improve Long Term Side Effects

- Secondary prevention:
  - Medications to reduce long term risk of agents received (clinical trials)
    - Reduce breast cancer (i.e. women receiving radiation therapy)
      - Tamoxifen prophylaxis x2 years
    - Reduce cardiac toxicity
      - Carvedilol x2 years

Objectives

- Discuss improvement in cure rates of childhood cancer
- Discuss health problems associated with survivorship of childhood and adolescent/young adult (AYA) cancer survival
- Describe strategies used to improve health problems associated with cancer survivorship
- **Describe how some of these interventions have improved the health of childhood/AYA cancer survivors**
- Discuss two specific issues of childhood cancer/AYA survival
  - Fertility
  - Psychosocial

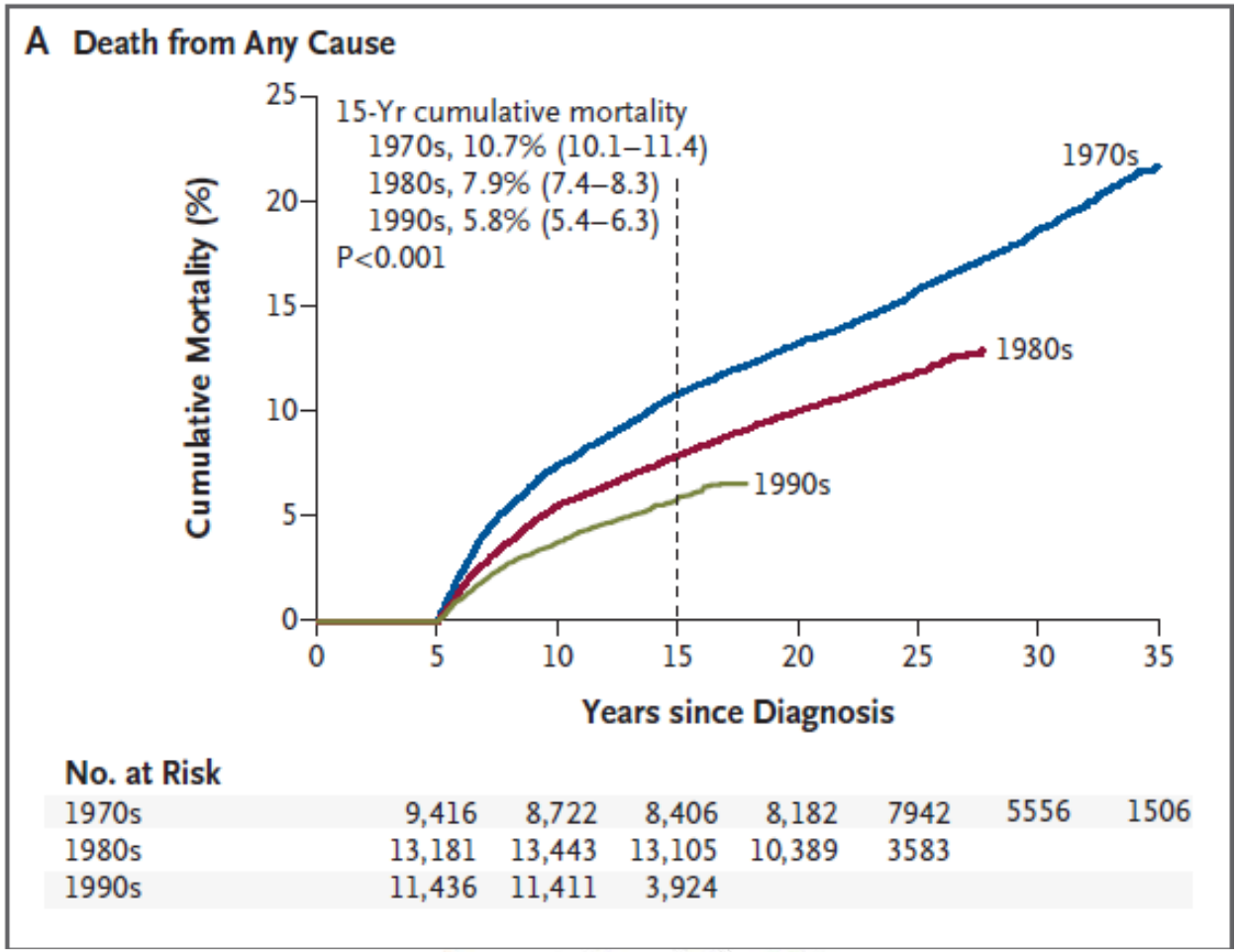
www.rockymountainhospitalforchildren.com

Primary and Secondary Prevention Strategies have reduced late mortality

- CCSS:
  - Initial cohort: Patients diagnosed with childhood cancer between 1970-1986 and alive at least 5yrs from diagnosis
  - New expanded cohort to include patients diagnosed between 1987-1999
    - 10,004 patients

Armstrong GT, et al. NEJM. 2016.

Primary and Secondary Prevention Strategies have reduced late mortality



Armstrong GT, et al. NEJM. 2016.

Good News!

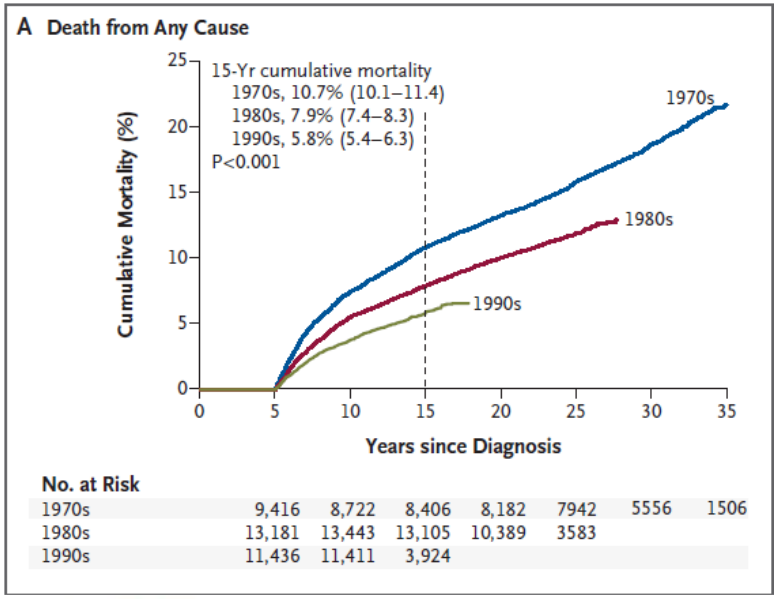
Good News!

- Improved Outcomes
  - 1960s: <50% overall survival
  - 1975: 60% overall survival
  - 2010: 80-90% overall survival

Good News!

- Improved Outcomes
  - 1960s: <50% overall survival
  - 1975: 60% overall survival
  - 2010: 80-90% overall survival

Decreased Treatment Related Mortality



Objectives

- Discuss improvement in cure rates of childhood cancer
- Discuss health problems associated with survivorship of childhood and adolescent/young adult (AYA) cancer survival
- Describe strategies used to improve health problems associated with cancer survivorship
- Describe how these interventions have improved the health of childhood/AYA cancer survivors
- **Discuss two specific issues of childhood/AYA cancer survival**
  - **Fertility**
  - **Psychosocial**

Challenges facing Childhood/Young Adult Cancer Survivor

- Three quarters of young cancer survivors hope to have children in the future
- Risk of infertility depends on the specific cancer diagnosis and treatments provided:
  - Certain chemotherapy agents
  - Radiation
    - Gonads
    - Cranial irradiation (pituitary)

Best Risk Assessment of Subfertility after Current Treatment for Childhood/AYA Cancer

Low risk (<20%)
Acute lymphoblastic leukaemia
Wilms' tumour
Soft-tissue sarcoma: stage I
Germ-cell tumours (with gonadal preservation and no radiotherapy)
Retinoblastoma
Brain tumour: surgery only, cranial irradiation <24 Gy

Medium risk
Acute myeloblastic leukaemia (difficult to quantify)
Hepatoblastoma
Osteosarcoma
Ewing's sarcoma: non-metastatic
Soft-tissue sarcoma: stage II or III
Neuroblastoma
Non-Hodgkin lymphoma
Hodgkin's disease: alternating treatment
Brain tumour: craniospinal radiotherapy, cranial irradiation >24 Gy

High risk (>80%)
Whole-body irradiation
Localised radiotherapy: pelvic or testicular
Chemotherapy conditioning for bone-marrow transplantation
Hodgkin's disease: treatment with alkylating-drugs
Soft-tissue sarcoma: stage IV (metastatic)
Ewing's sarcoma: metastatic

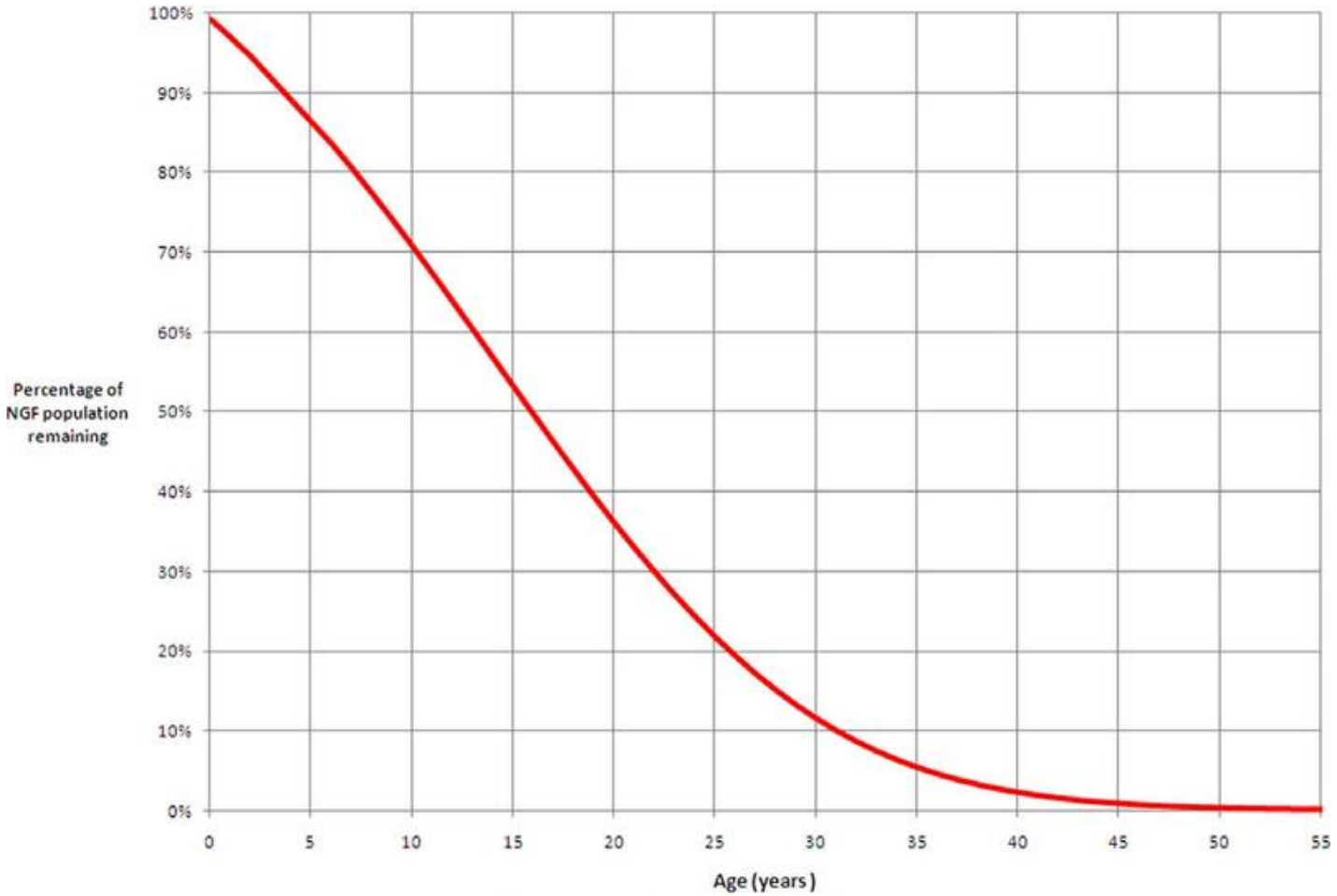
Wallace et al. 2005

www.rockymountainhospitalforchildren.com

Females

- Brief review of physiology:
  - Females have a finite number of eggs (“oocytes”), most of which naturally die off
    - Fetus: about 5 million
    - Birth: 600,000-800,000
    - Puberty: about 180,000
  - Only about 400 oocytes mature and are ovulated in the typical female lifespan

Oocyte Depletion



www.rockymountainhospitalforchildren.com

Fertility: Females

- Effects of treatment are therefore dependent upon the age at which therapy is given
- Early menopause an issue:
  - 42% of female patients treated with chemotherapy and radiation before age 20 had reached menopause by age 31 years[1]

[1]Byrne et al. 1992.

Fertility Preservation Options: Females

- Embryo cryopreservation
- Oocyte cryopreservation
- Surgically displace ovaries outside of the radiation field
- Hormonal suppression of ovulation
- Ovarian tissue cryopreservation

Fertility Preservation Options: Females

- Embryo cryopreservation
  - Ovarian stimulation, egg retrieval, fertilization, storage (freezing), and transfer of embryo into the uterus
  - Requires a male partner or sperm donor at time of procedure
  - Requirement for hormonal stimulation and time may preclude use due to need to embark on therapy

Fertility Preservation Options: Females

- Oocyte cryopreservation
  - Ovarian stimulation, egg retrieval, storage, then fertilization and transfer of embryo into the uterus
  - Requirement for hormonal stimulation and time may preclude use due to need to embark on therapy

Fertility Preservation Options: Females

- Mitigating effects of radiation:
  - Surgically displace ovaries outside of the radiation field
  - Shielding ovaries from radiation
- Preserving Oocytes: Hormonal suppression of ovulation

Fertility Preservation Options: Females

- Ovarian tissue cryopreservation
  - Surgery to remove part or all of an ovary
  - Tissue frozen
  - After treatment, surgically re-implanted with hopes of regaining ovarian function
  - Still experimental: 130 live births as of June 2017
  - Advantage: immediacy of procedure, little delay in treatment
  - Limited availability: About 100 centers worldwide
    - Children's Hospital Orange County; Texas Children's, Houston; Children's Memorial Hospital in Chicago; University of Pittsburgh

Fertility Effects: Males

- Risks:
  - Irradiation
  - Chemotherapy
  - Disease itself may effect sperm count (Hodgkin lymphoma)

Challenges of a Young Adult Cancer Survivor: Fertility

- Fertility preservation options: Males:
  - Sperm banking
    - Viability for decades
    - Adolescents less successful

Challenges of a Childhood/AYA Cancer Survivor: Psychosocial

Erik Erickson: 1902-1994

Erik Erikson's Stage of Psychosocial Development

- Adolescence (age 13-19yrs): Identity
- Young Adulthood (20-39yrs): Intimacy
- Middle Adulthood: (25-64yrs): Generativity

Challenges of a Young Adult Cancer Survivor: Psychological

- Prevalence of symptoms among adult survivors of childhood cancers:
  - Learning/memory problems: 26.9%
  - Anxiety: 13.1%
  - Depression: 15.8%
  - Somatization: 19.3%

Huang et al. 2013.

Summary

- Primary and Secondary Prevention Strategies have reduced late mortality from childhood cancers
- Still much work to be done
- Specific issues of emotional importance
  - Fertility
  - Psychosocial

WYCC
WYOMING CANCER COALITION

ROCKY MOUNTAIN HOSPITAL *for* CHILDREN

Health ONE®

www.rockymountainhospitalforchildren.com