



Looking beyond 5-year survival: What metrics should we consider in long-term childhood cancer survivorship?

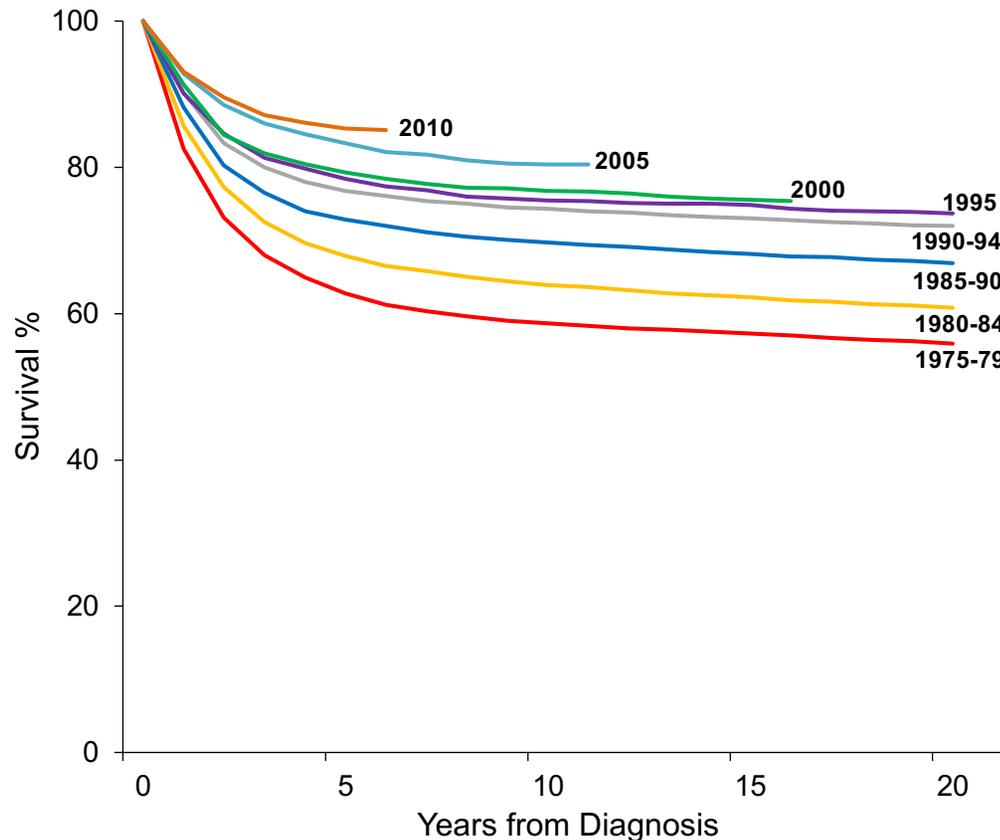
Stephanie Dixon, MD, MPH
Cancer Survivorship Division, St. Jude Children's Research Hospital

Outline

- Define five-year survival, late-mortality and excess deaths due to childhood cancer
- Acknowledge success through a disease specific example
- Demonstrate that chronic conditions and lifestyle factors impact late-mortality risk
- Identify opportunities to gain understanding and improve outcomes

Improvements in five-year survival over time

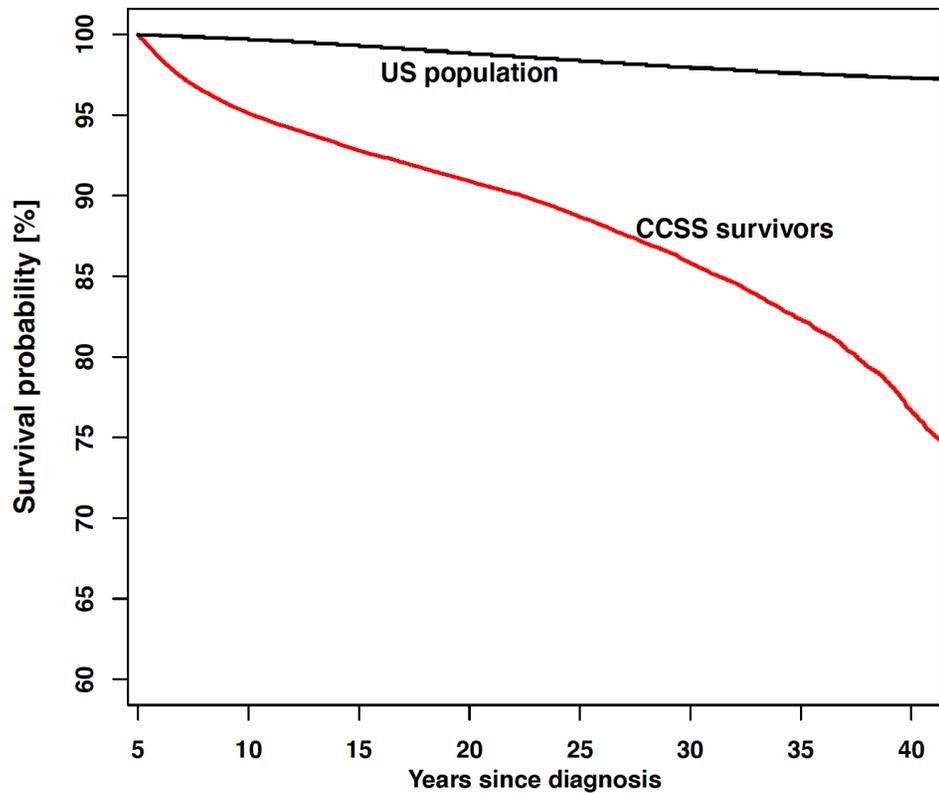
SEER Survival by Year of Diagnosis, 0-19 yr



Survivorship Statistics

- >85% of children with a malignancy will achieve five-year survival
- In 2013, estimated 420,000 survivors of childhood cancer in the U.S.
- Now estimated to be over 500,000 survivors
- Approximately 1 in 750 in US is a childhood cancer survivor

Late-mortality among five-year survivors



Number at risk

34,230 32,450 31,596 28,369 21,730 16,139 9,924 4,550

Cumulative mortality among survivors

20-year:

9.1% (8.8-9.4)

30-year:

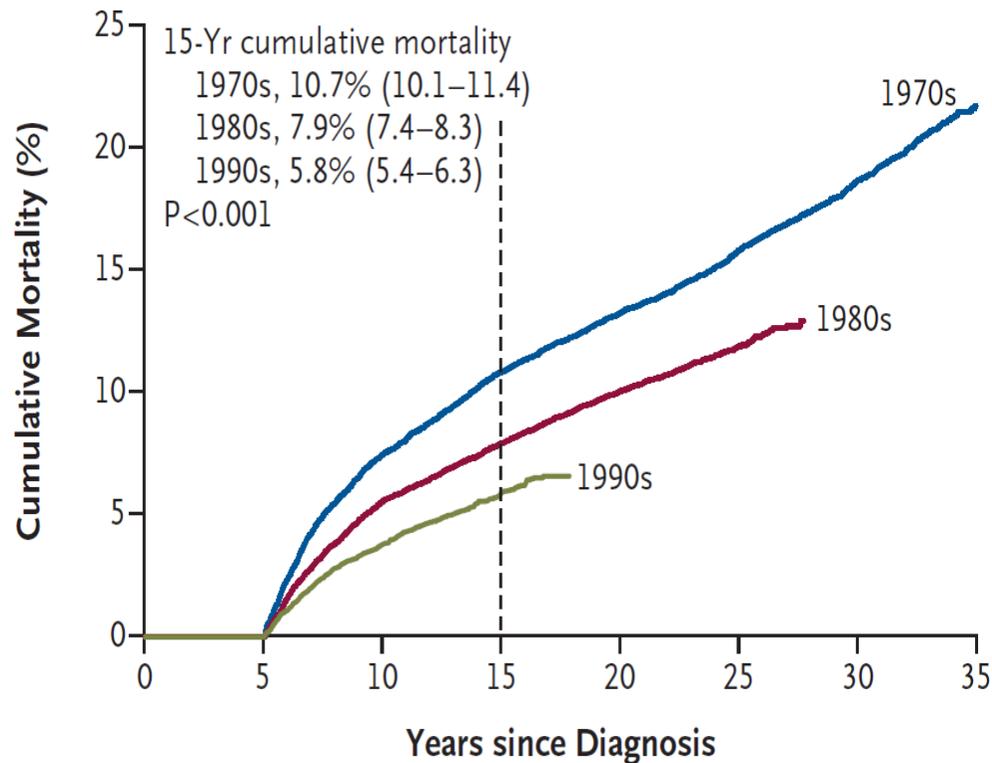
14.2% (13.8-14.6)

40-year:

23.3% (22.7-24.0)

Temporal Trends in Late-Mortality

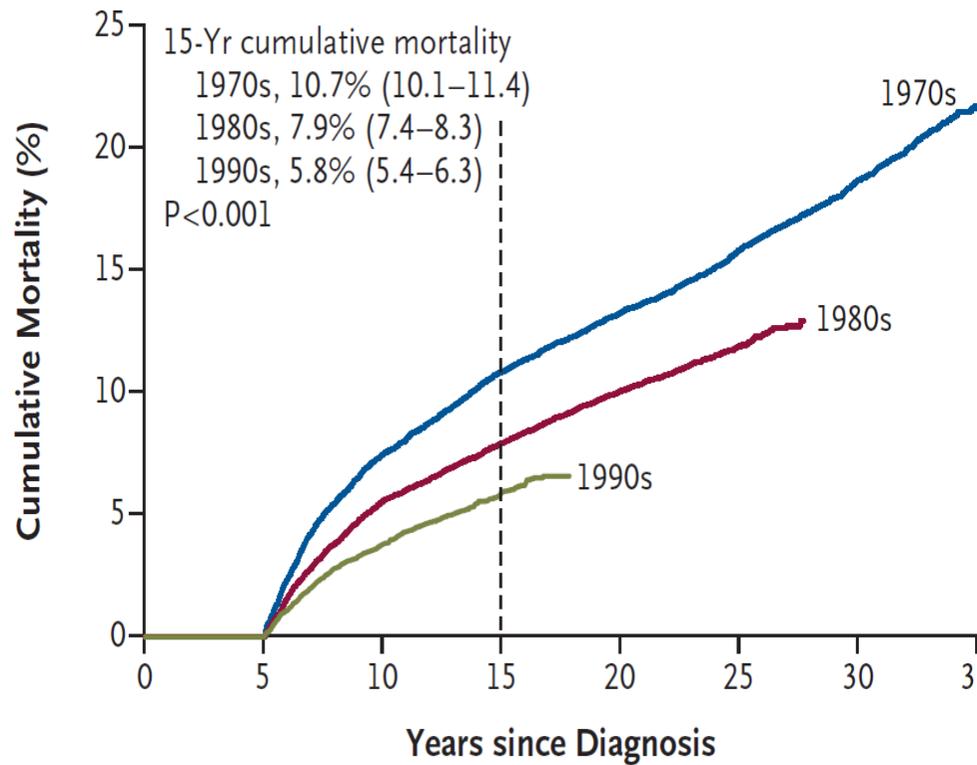
Death from Any Cause



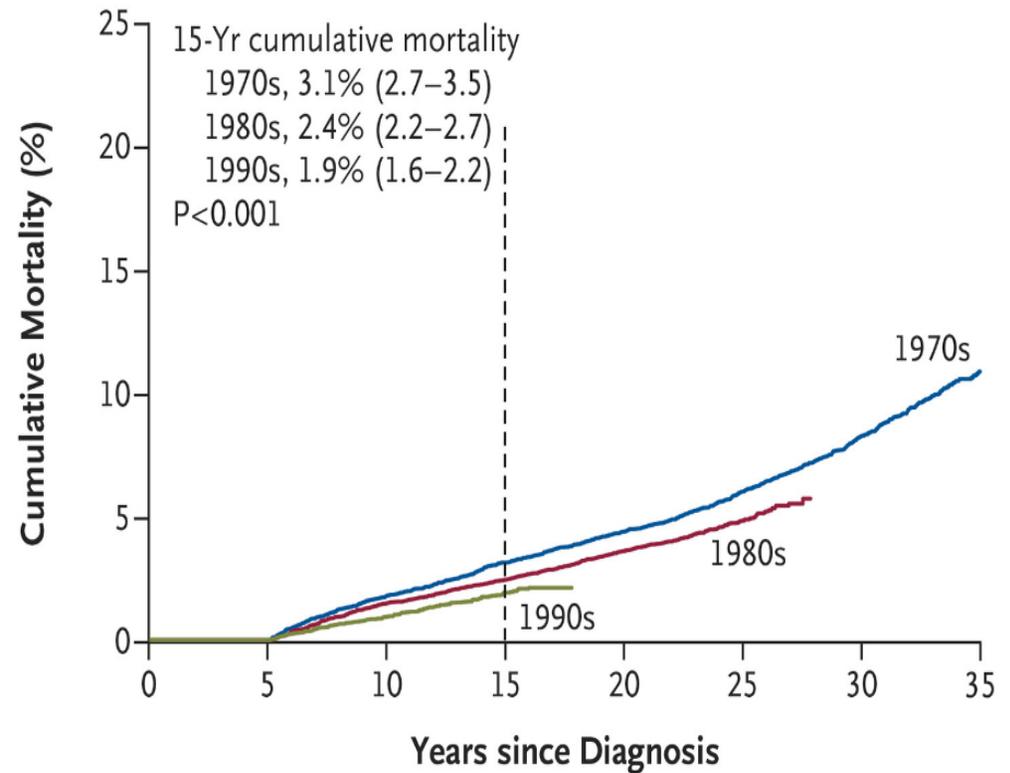
- Strategies of lowering treatment exposures have led to reductions in survivor **mortality** over time.

Temporal Trends in Late-Mortality

Death from Any Cause



Death from Health-Related Cause

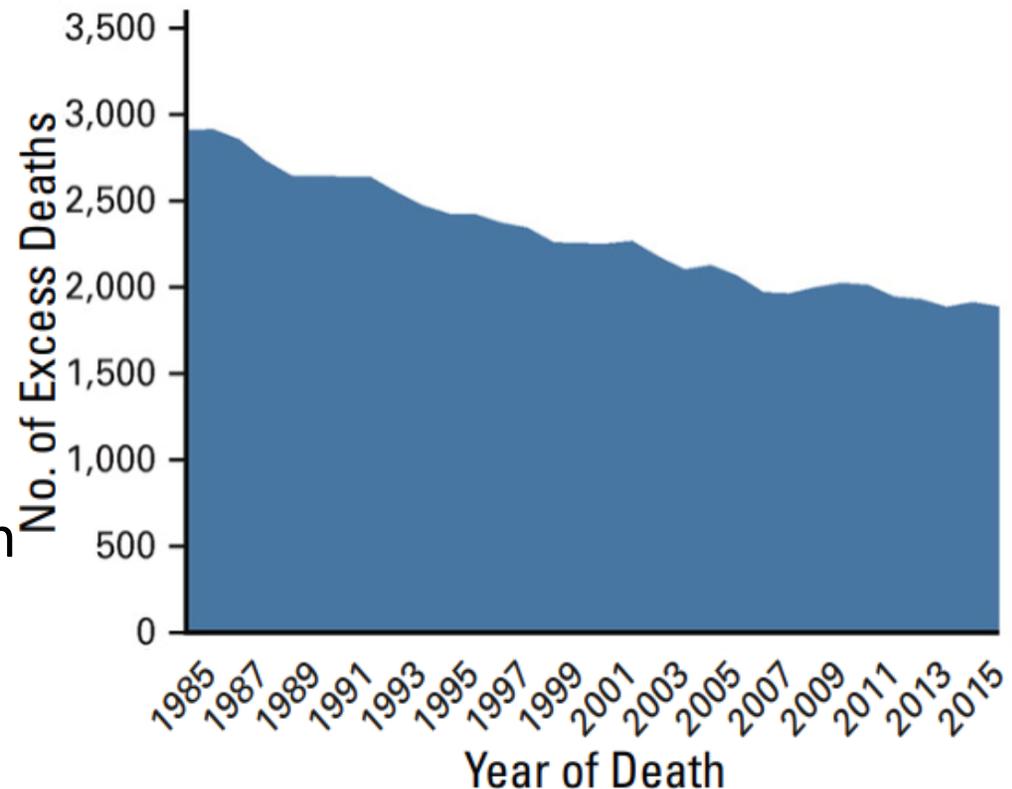


Excess Deaths Due to Childhood Cancer

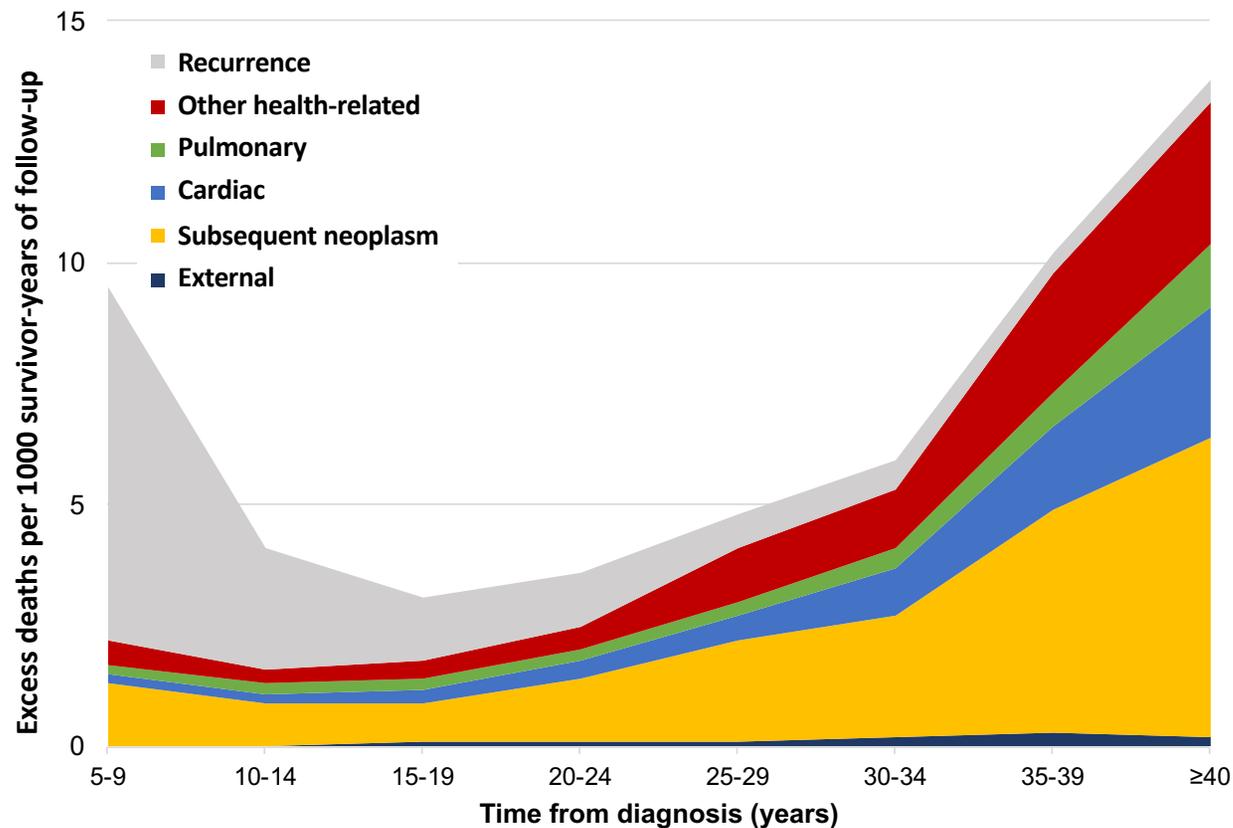
Excess deaths in the first five years from diagnosis have decreased.

Excess deaths in survivors 5-9 years from diagnosis have remained relatively stable.

Excess deaths in survivors more than 10 years from diagnosis has increased.



Excess Risk of Death Compared to US Population



**Excess deaths per
1000 person years
(95% CI)**

5-9 years

All-cause:

9.5 (9.1-10.0)

Health-related:

2.1 (1.9-2.3)

≥40 years

All-cause:

13.8 (11.7-16.1)

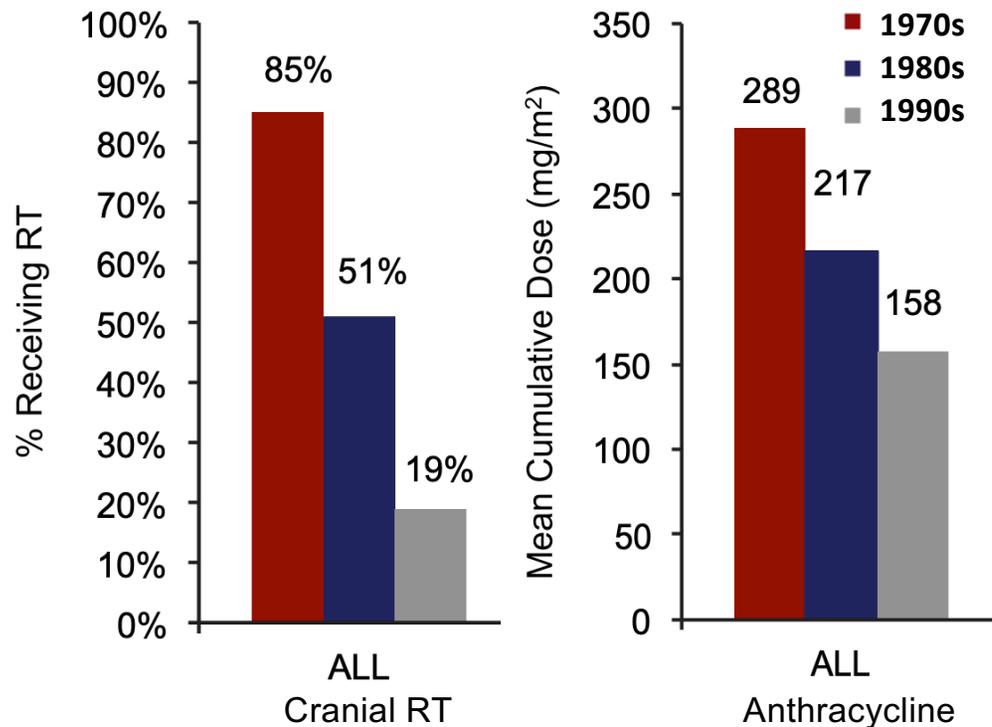
Health-related:

13.1 (11.1 – 15.3)

Interval Summary

- Five-year survival from childhood cancer continues to improve.
- Late-mortality, beyond five years, has also improved with reductions in treatment exposures.
- Health-related deaths in survivors of childhood cancer occur in excess of what we would expect in the general population and increase with increasing survival.

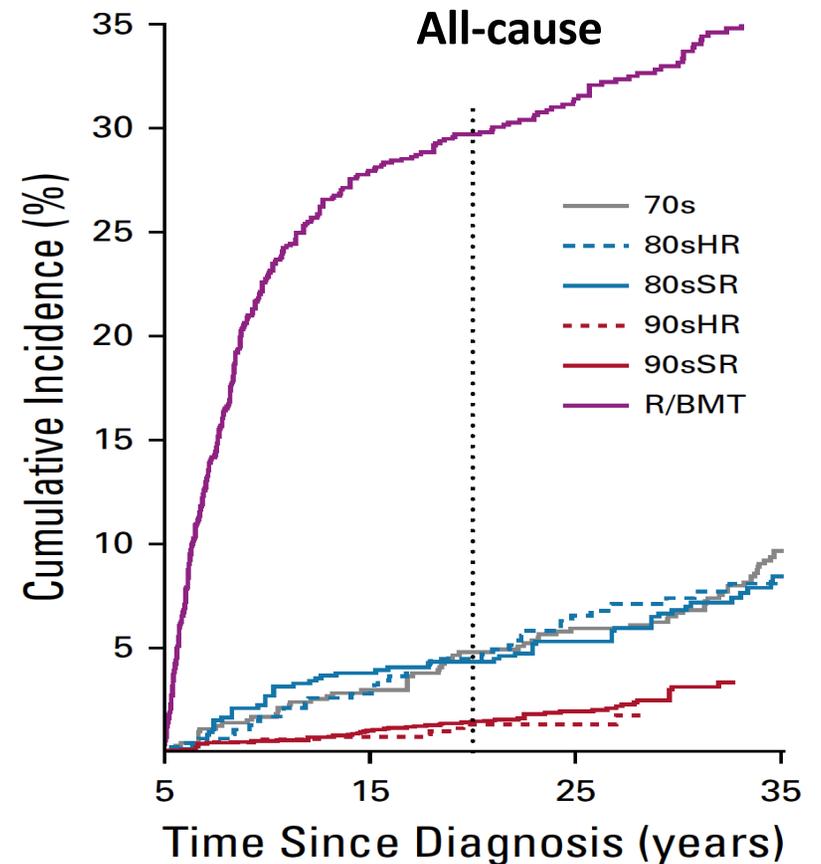
Therapy exposures among ALL survivors by era



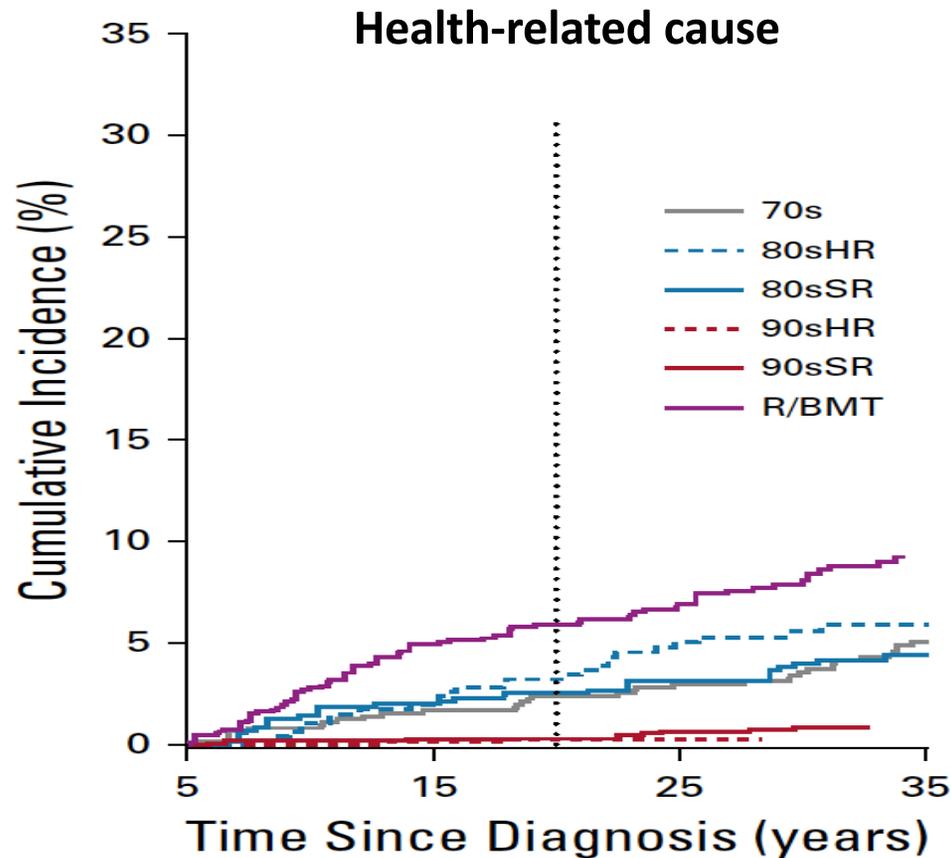
- Reduction in use and dose of prophylactic cranial radiation
- Reduction in cumulative dose of anthracycline chemotherapy
- Concurrent increase in use of asparaginase, dexamethasone and high-dose methotrexate

Late Mortality Among ALL Survivors by Era

- Over 6000 survivors categorized by treatment groups representing risk-stratified therapy changes over time.
- Survivors in 90sSR were treated without cranial radiation, using low cumulative doses of anthracycline and cyclophosphamide.
- Survivors treated with 1990s standard- and high-risk therapy experienced reduced late-mortality.



Late Mortality Among ALL Survivors by Era



20-Year Cumulative Mortality

70s: 2.4%

80sHR: 3.2%

80sSR: 2.5%

90sHR: 0.6%

90sSR: 0.3%

R/BMT: 5.6%

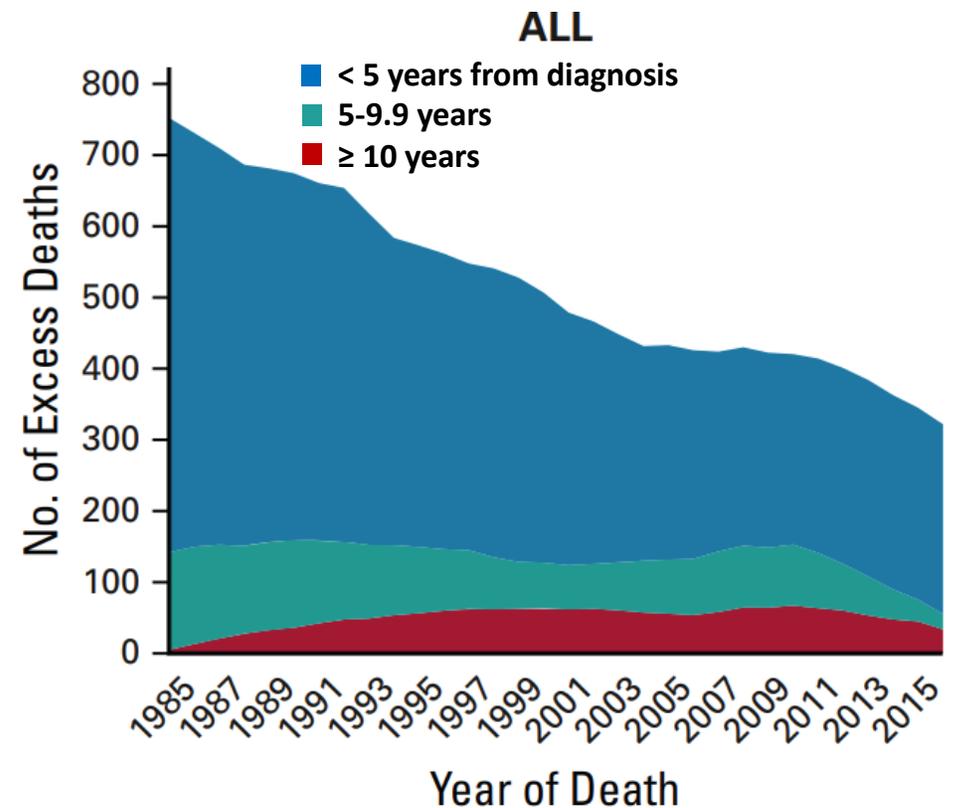
*p-value compared to 70s <0.01

Excess Deaths Due to Childhood ALL

Excess deaths in the first five years from diagnosis have decreased.

Excess deaths in survivors 5-9 years from diagnosis have **decreased**.

Excess deaths in survivors more than 10 years from diagnosis have **remained low**.

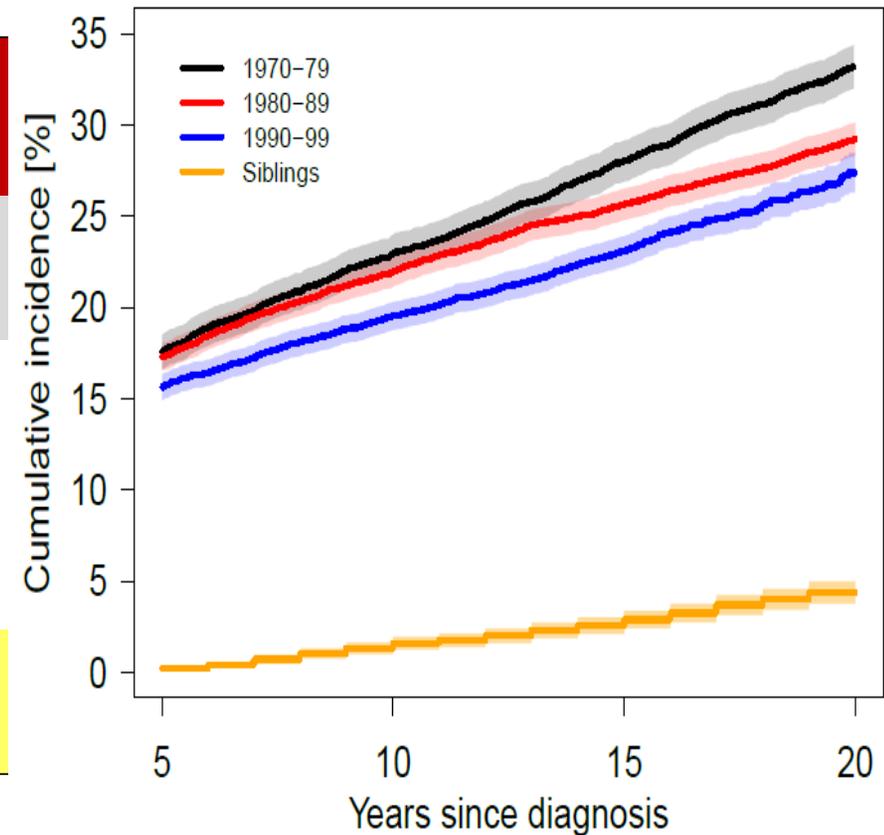


Factors impacting late morbidity and mortality

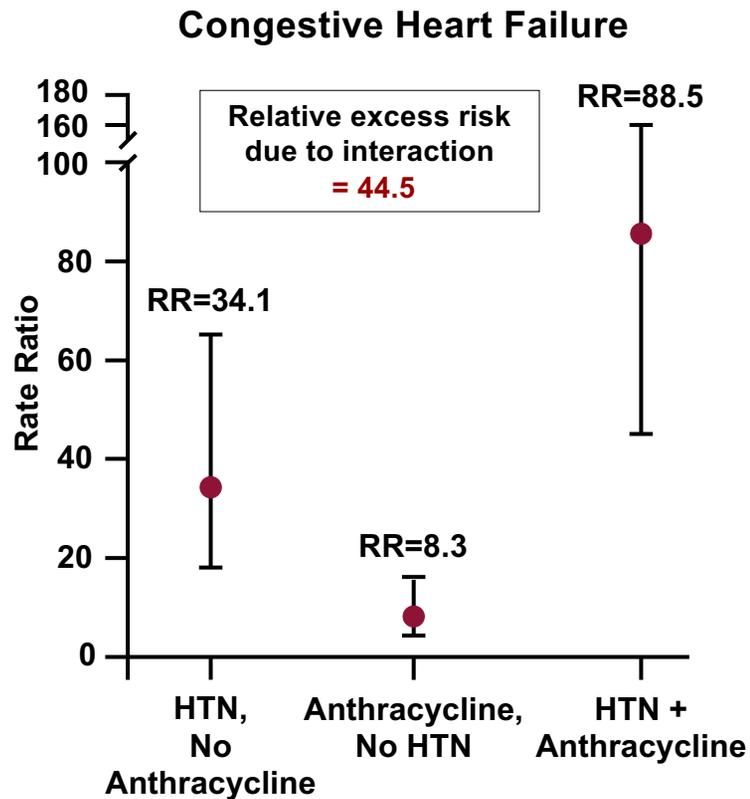


Late Chronic Health Conditions associated with Cancer Treatment

Cohort Size <i>Citation</i>	≥ 1 Chronic Condition	≥ 1 Severe Condition
290 <i>Eur J Cancer 1998;34:694-8</i>	58%	—
288 <i>(A)JPHO 1994;16:143-52</i>	69%	21%
10,397 <i>NEJM 2006;355:1572-82</i>	67%	33%
1,713 <i>JAMA 2013;309:2371-2381</i>	95.5%	80.5%

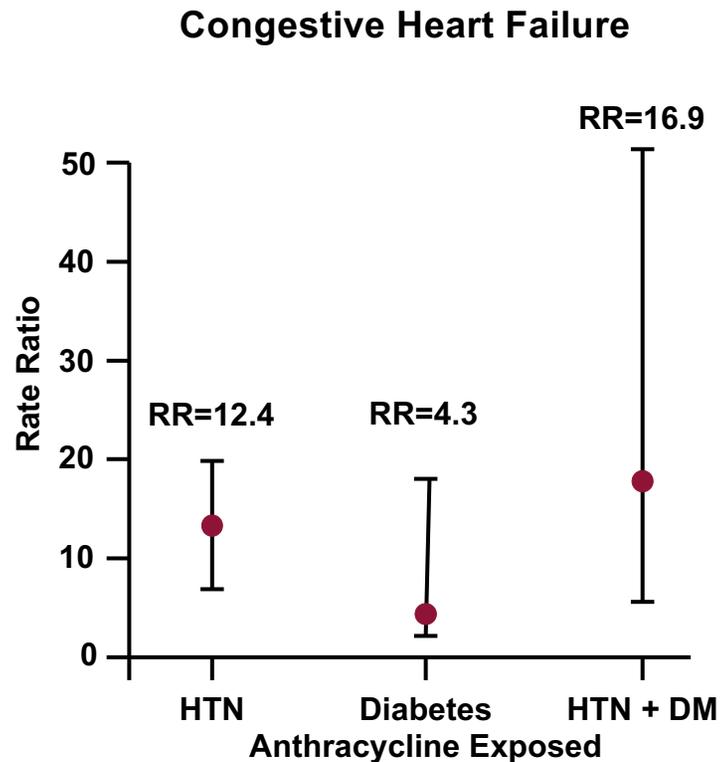


Modifiable Chronic Conditions Influence Risk



- Modifiable cardiovascular risk factors **increase** risk of future cardiac events, including anthracycline-associated cardiomyopathy.

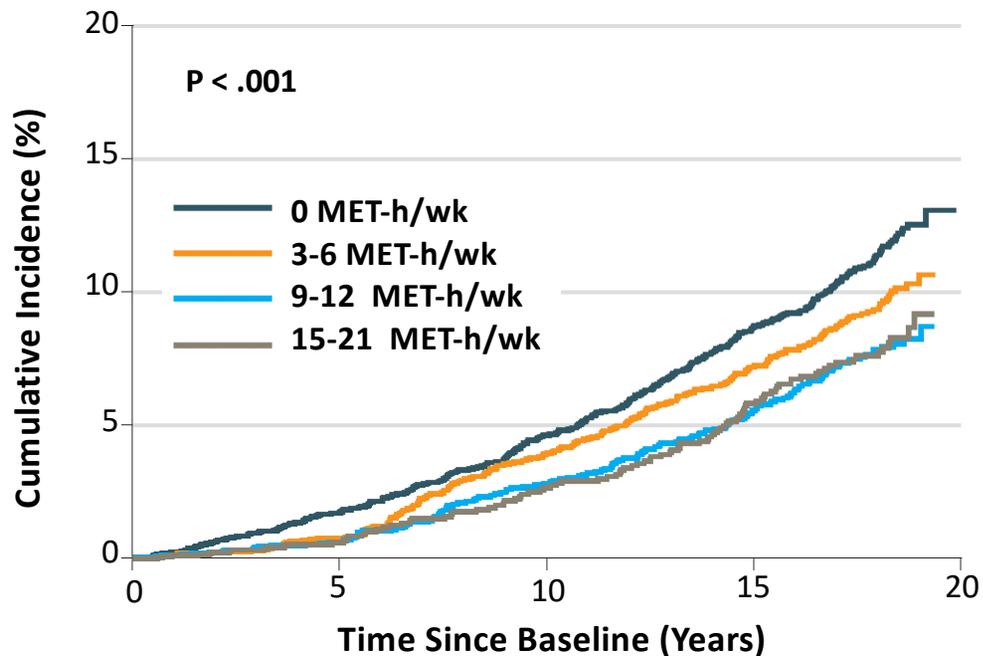
Modifiable Chronic Conditions Influence Risk



- Modifiable cardiovascular risk factors *increase* risk of future cardiac events.
- Multiple risk factors further increased risk.
- Modifiable cardiovascular risk factors were associated with increased risk of cardiac death.

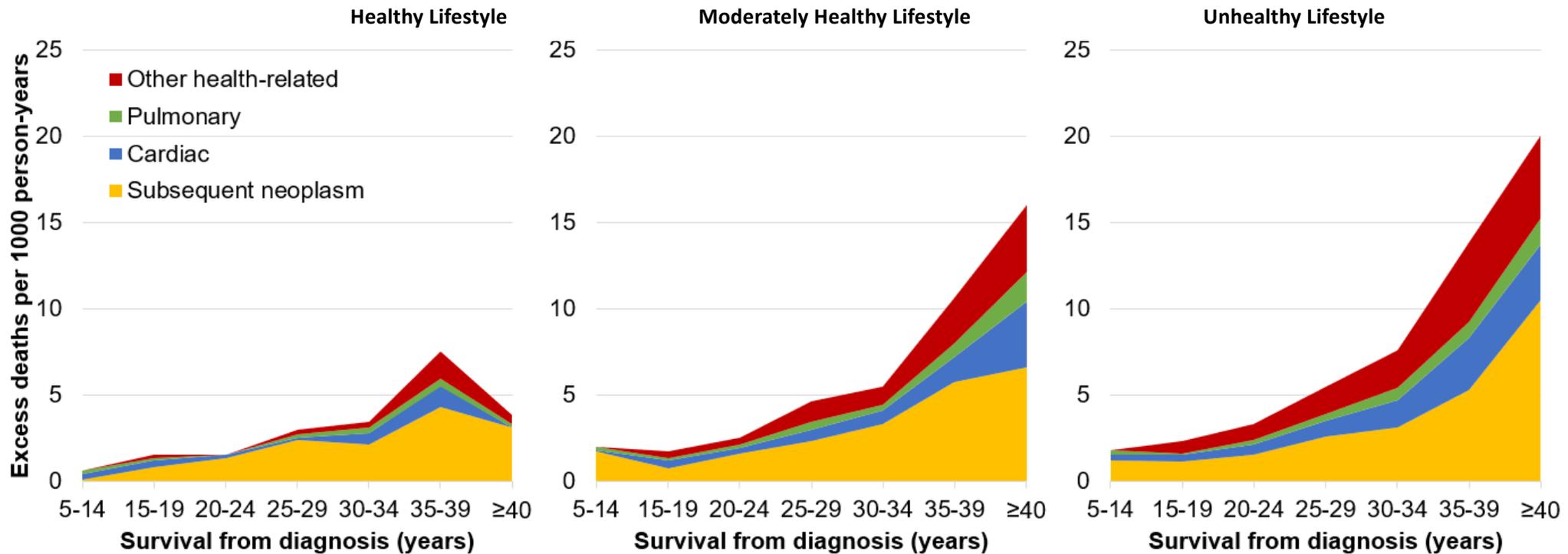
Modifiable Lifestyle Factors Influence Risk

Health-Related Mortality



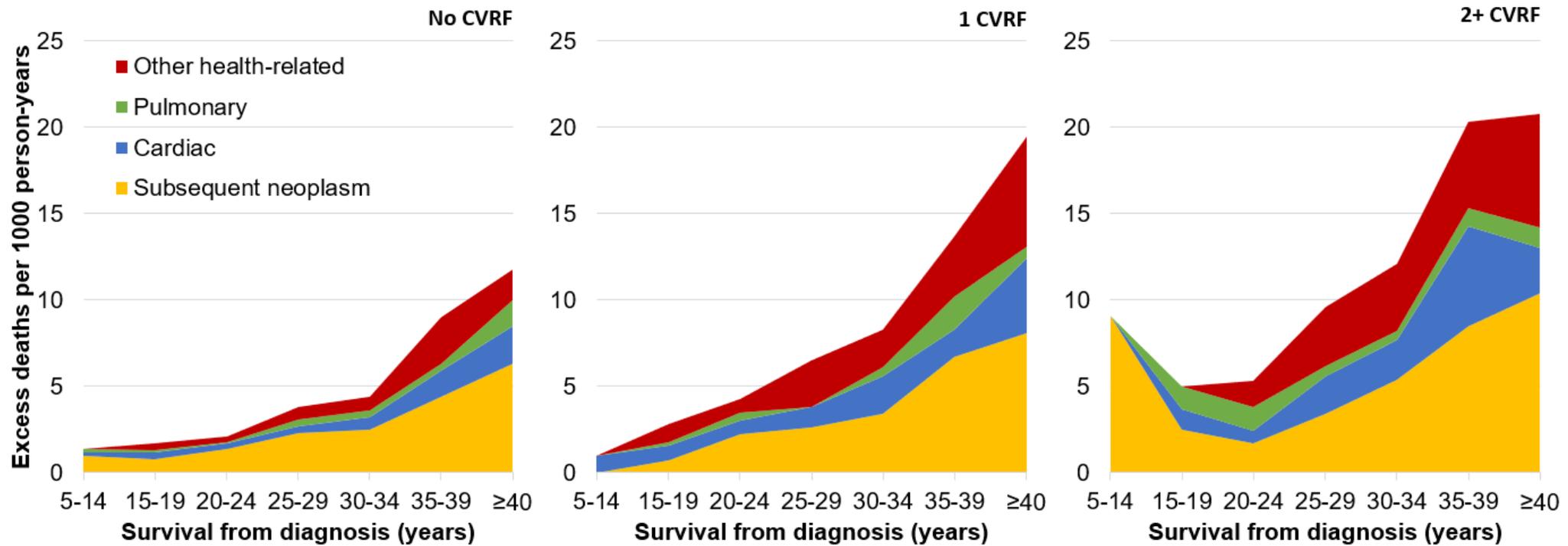
- Vigorous exercise is associated with a **lower** risk of death in adult survivors of childhood cancer.
- Increased exercise exposure over follow-up was associated with a **lower** risk of health-related death.

Modifiable Risk Factors Influence Late-Mortality



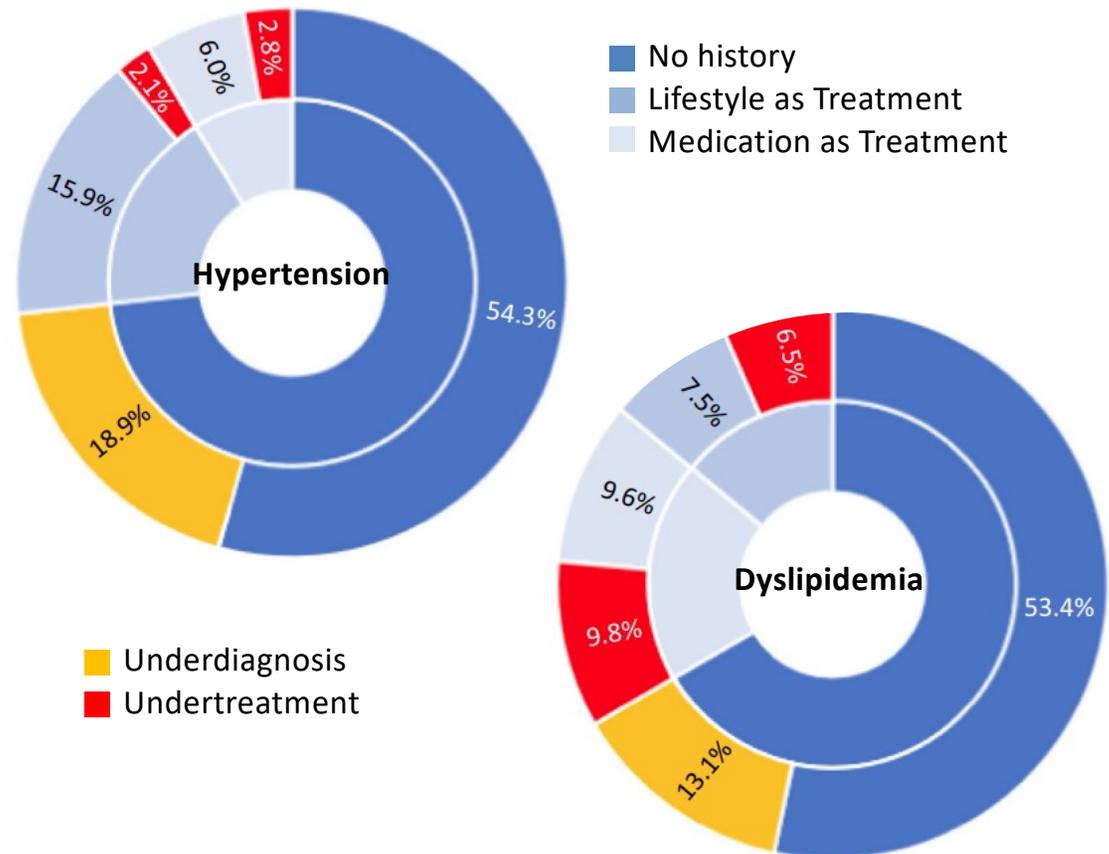
Lifestyle factors included smoking, alcohol use, unhealthy weight and physical activity.

Modifiable Risk Factors Influence Late-Mortality



Cardiovascular Risk Factors in Survivors may be Underdiagnosed and Undertreated

- Over 500 survivors evaluated for hypertension, dyslipidemia and diabetes or prediabetes.
- 1 in 4 survivors had an undiagnosed condition.
- 1 in 5 survivors had a known condition that was undertreated.

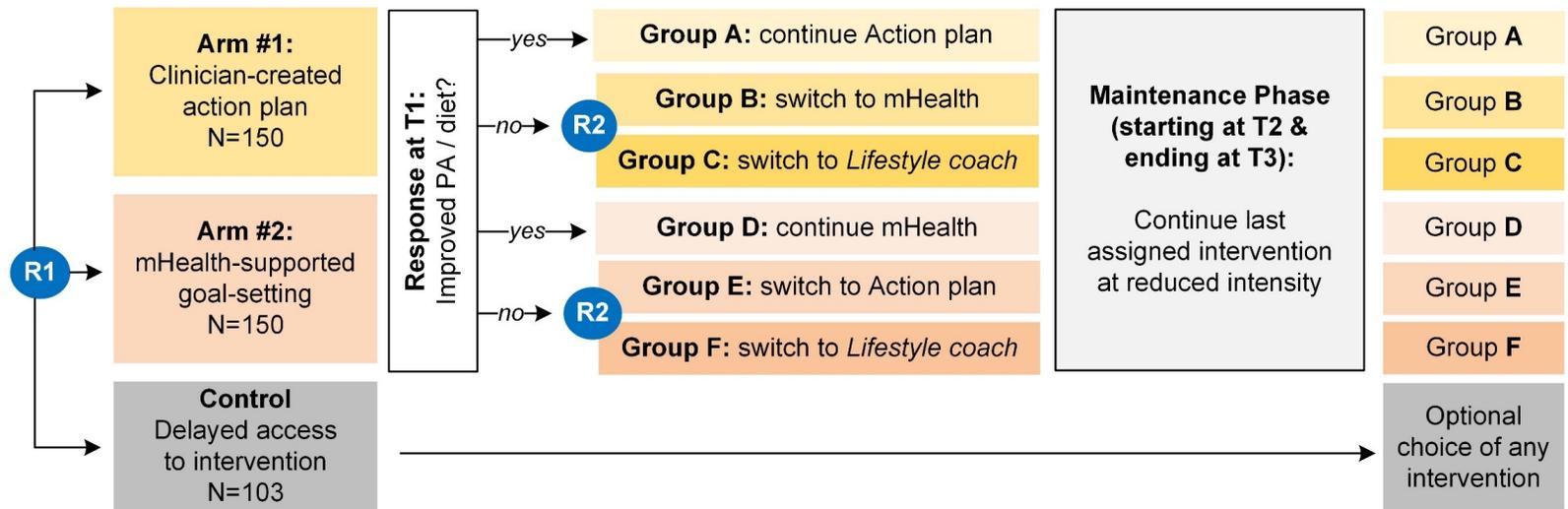


Intervention to Reduce Cardiovascular Risk



Childhood cancer survivor

- At increased CV risk per CCSS risk models
- Sedentary / Low diet quality / BMI ≥ 25 kg/m²
- N~550 screened (estimate ~75% will meet eligibility)



Eligibility screening

- Godin PA screener
- FFQ
- Self reported BMI

Baseline (T0)

- Actigraph
- (FFQ from eligibility)
- PROs
- Physiologic measures

3 months (T1)

- Actigraph
- FFQ

6 months (T2)

- Godin
- FFQ
- Physiologic (limited)

12 months (T3)

- Godin & Actigraph
- FFQ
- PROs
- Physiologic measures

Summary

- Improvements in five-year survival have been excellent but do not completely describe the increased risk of death due to childhood cancer.
- Reductions in therapy exposures have decreased late mortality and excess deaths for some groups of survivors.
- Chronic conditions and unhealthy lifestyle factors are prevalent, potentially modifiable, and associated with risk of late mortality.

Future Directions

- Impact of continued therapy modifications including novel and targeted treatments on risk for late morbidity and mortality.
- Implementation of recommended screening for early identification of conditions.
- Intervention to prevent, or optimally manage, conditions known to increase risk for late-mortality among survivors.

Improve the ***duration*** and ***quality*** of life for survivors of childhood cancer.

Questions?





Available Resources

CHILDREN'S ONCOLOGY GROUP *Foundation*

<http://www-survivorshipguidelines.org/>

“Health Links” addressing survivor specific concerns;
access to the COG Long-Term Follow-up Guidelines



<https://together.stjude.org/en-us/>

A resource for anyone affected by childhood and adolescent cancer, includes many resources for “Life After Cancer”

CCSS Childhood Cancer Survivor Study

<https://ccss.stjude.org/>

Information about this NCI-funded survivor cohort