Health issues for adult survivors of childhood malignancy – unmet needs

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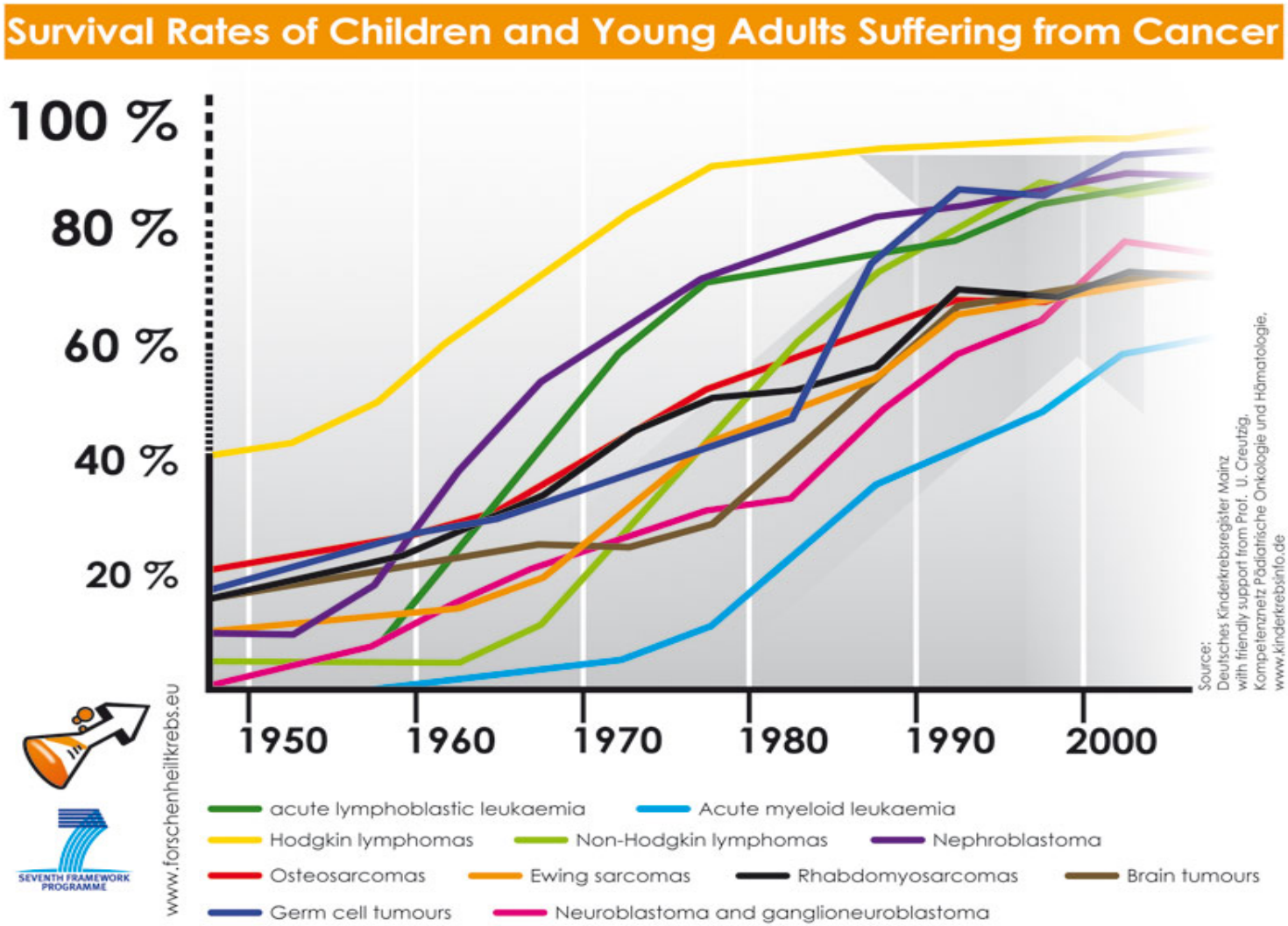
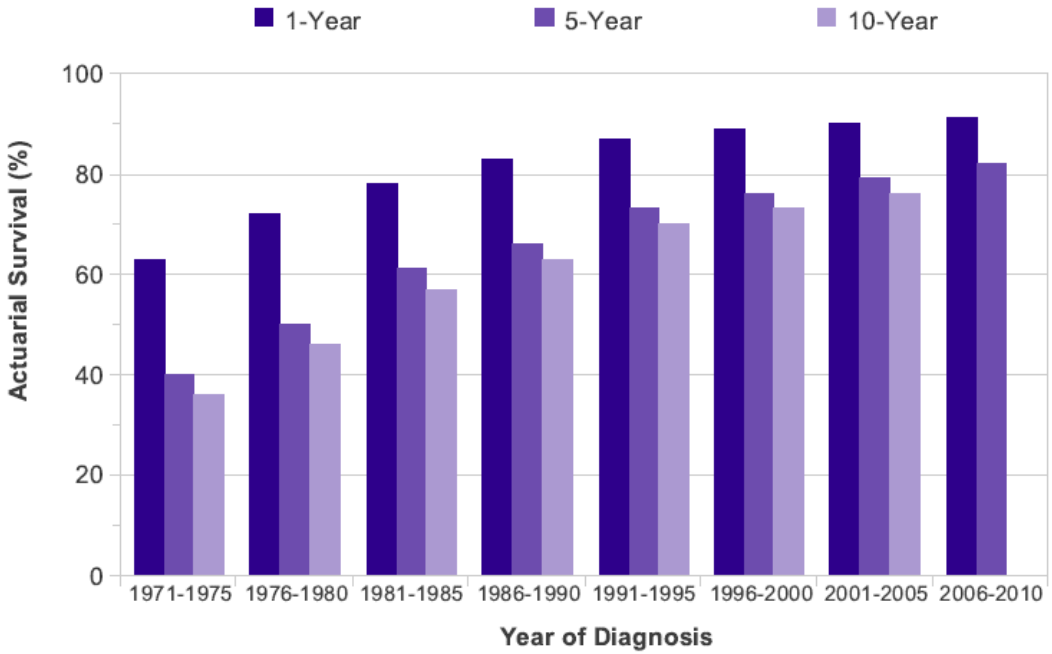
Progress over time



Childhood Cancer, 1971-2010

One-, Five- and Ten-Year Actuarial Survival (%), Children (Aged 0-14), Great Britain

Year of Diagnosis	1-Year	5-Year	10-Year
1971-1975	63	40	36
1976-1980	72	50	46
1981-1985	78	61	57
1986-1990	83	66	63
1991-1995	87	73	70
1996-2000	89	76	73
2001-2005	90	79	76
2006-2010	91	82	



All childhood cancers includes all malignant tumours (ICD-10 codes: C00-C97), and all benign, uncertain or unknown behaviour brain, other central nervous system (CNS) and intracranial tumours (ICD-10 codes: D32-D33, D35.2-D35.4, D42-D43 and D44.3-D44.5).

Please include the citation provided in our Frequently Asked Questions when reproducing this chart: http://info.cancerresearchuk.org/cancerstats/faqs/#How

Prepared by Cancer Research UK

Original data sources:

1. National Cancer Intelligence Network. National Registry of Childhood Tumours Progress Report, 2012. Oxford: NRCT; 2013.
2. Ten-year actuarial survival, children aged 0-14 years, Great Britain, 1971-2005 data were provided by Charles Stiller at the National Registry of Childhood Tumours on request in 2013.

Scope of issue

Improved prognosis has been accompanied by the occurrence of late, treatment-related complications which may emerge many years, even decades, after completion of treatment.

By 2000 one in 640 adults between the ages of 20 and 39 was a survivor of childhood cancer. Now one in 680 between the ages of 20 and 50.

The major childhood cancer survivor study has been tracking patients diagnosed with childhood cancer between 1970 and 1986.

These survivors are now entering their fourth and fifth decades.

What are the long term consequences of treatment of childhood cancer?

Is screening for and managing late effects cost effective?

Who provides care to these survivors and how informed is it?

Proviso that information about late effects is based on treatment modalities that are now out of date eg. mantle radiation for Hodgkin lymphoma

Challenges of life after cancer

- Physical
- Social
- Psychological
- Financial and legal

Physical challenges

- Affected by disease process
  - Location
  - Type of cancer
- Affected by treatment exposures
  - Chemo/surgery/radiation/HSCT
- Affected by complications of therapy
  - Infections, toxicities etc
- Affected by host factors **including age at treatment** and health behaviour

Health issues

The most frequent occurring late effects affecting quality of life include

- second malignancies
- organ dysfunction
- endocrine and metabolic disorders
- cognitive and psychosocial problems

The Childhood cancer survivor study results

CCSS compared the results of 10397 survivors with 3034 siblings (self reported questionnaire)

At a mean age of 26 years 62.3% of survivors had at least one chronic condition

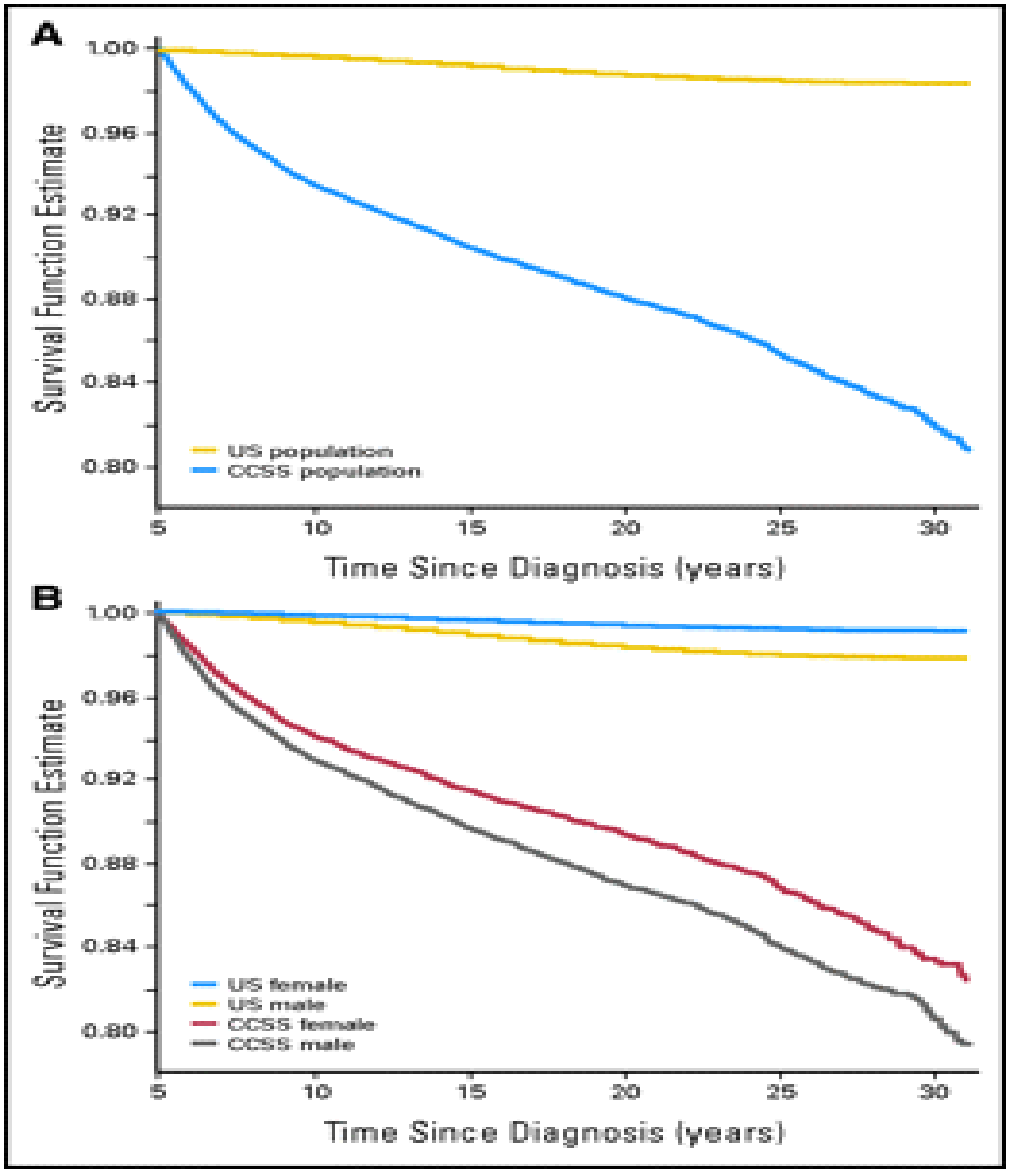
27.5% had a severe or life threatening condition

Relative risk of a chronic condition 3.3 and a severe/life threatening condition 8.2 compared to siblings

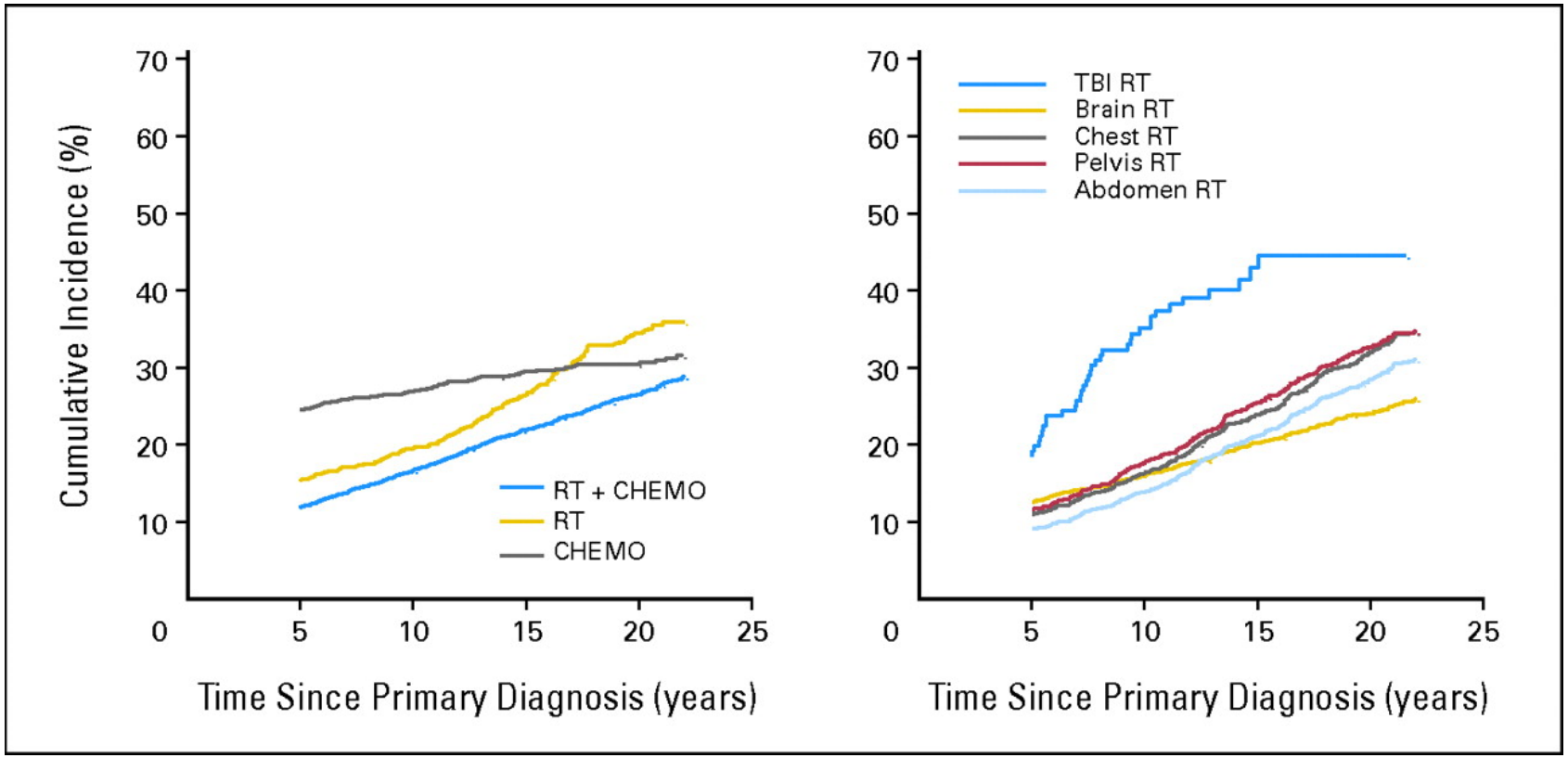
Highest risk seen in those with a diagnosis of bone sarcoma, CNS tumour and Hodgkins disease

Initial study report in 2006 – but 4 additional follow up surveys have been performed

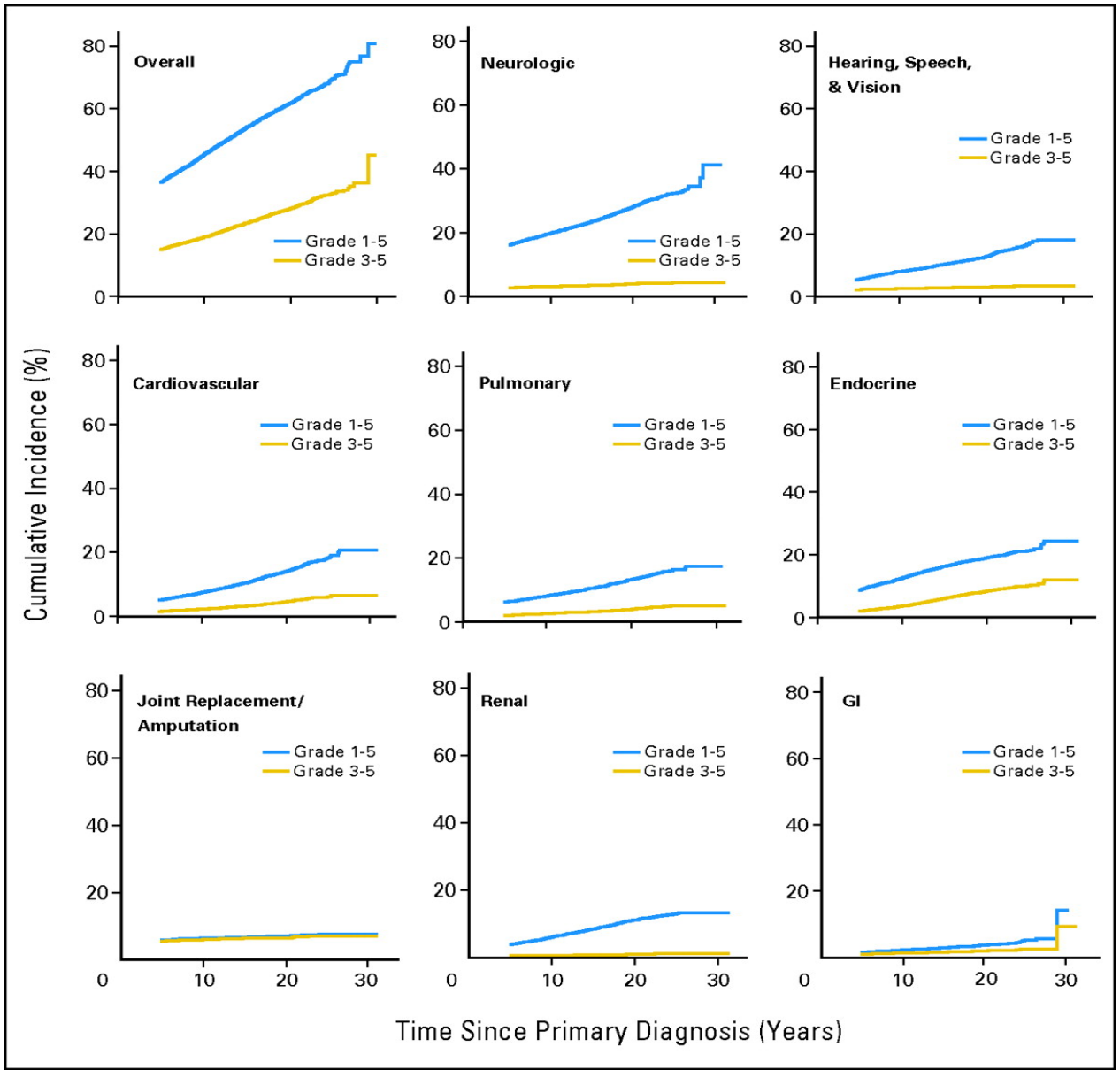
Late mortality among survivors



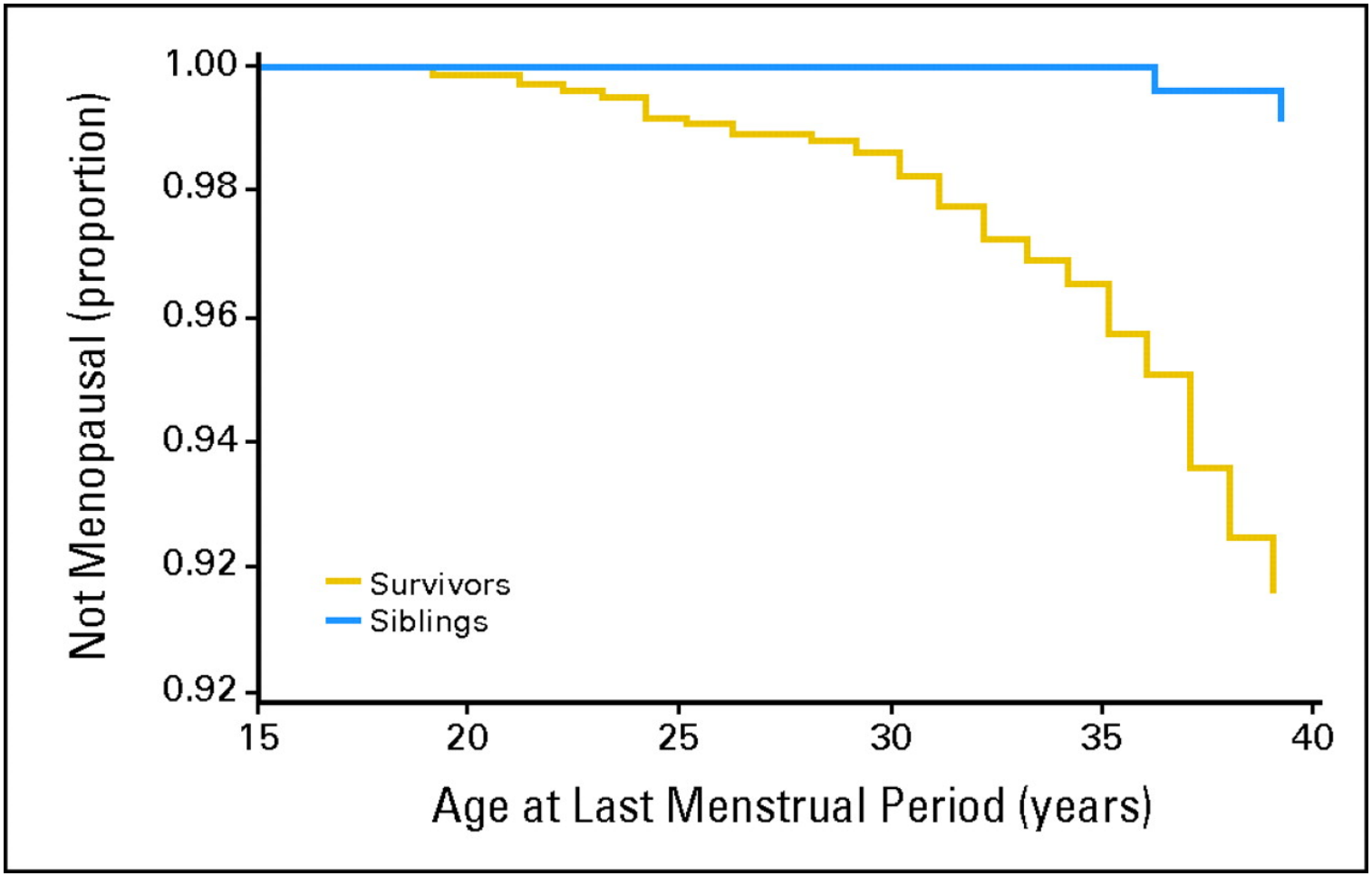
Chronic medical conditions in survivors



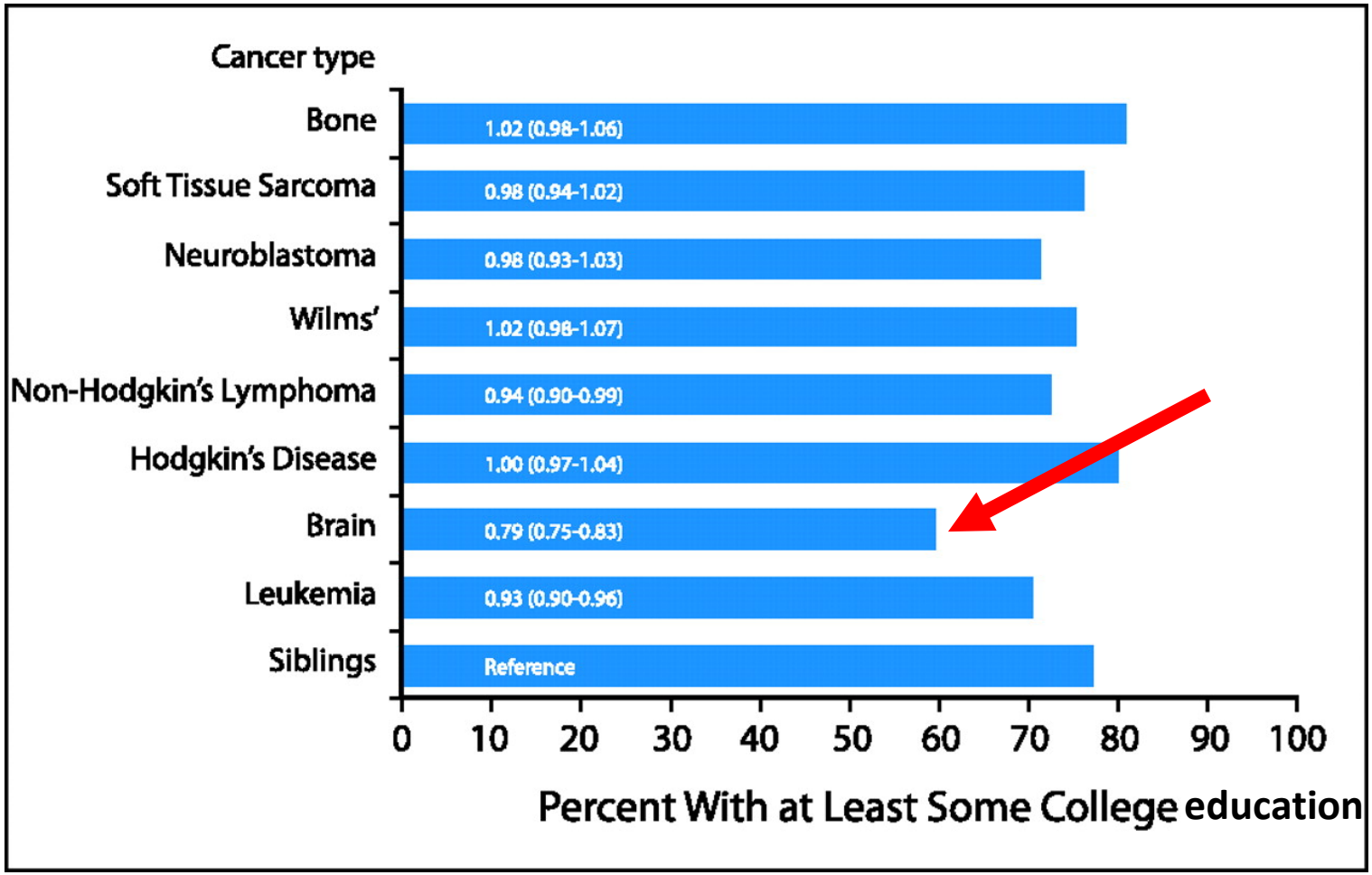
Chronic medical conditions



Fertility in females



Social outcomes



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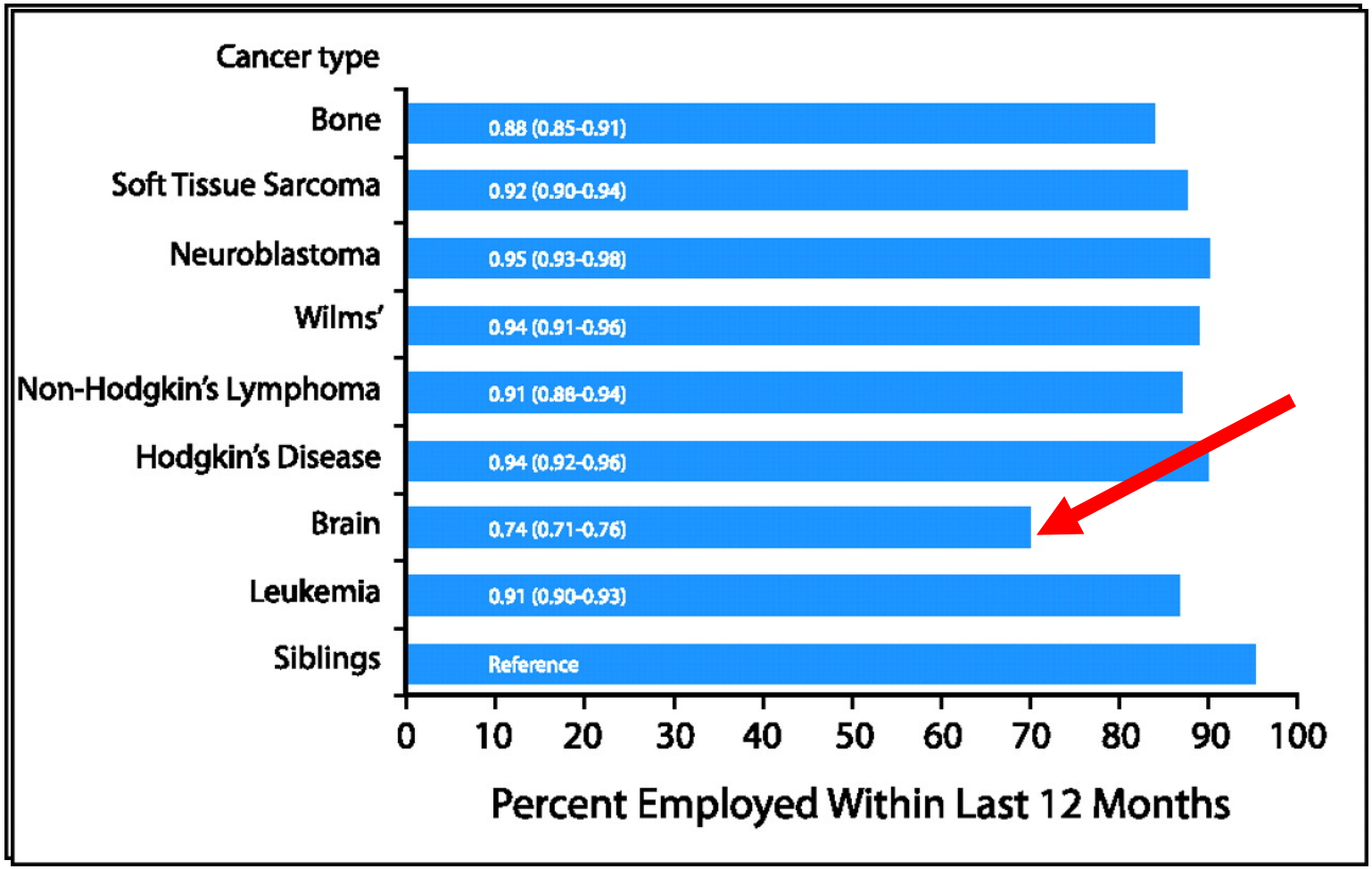
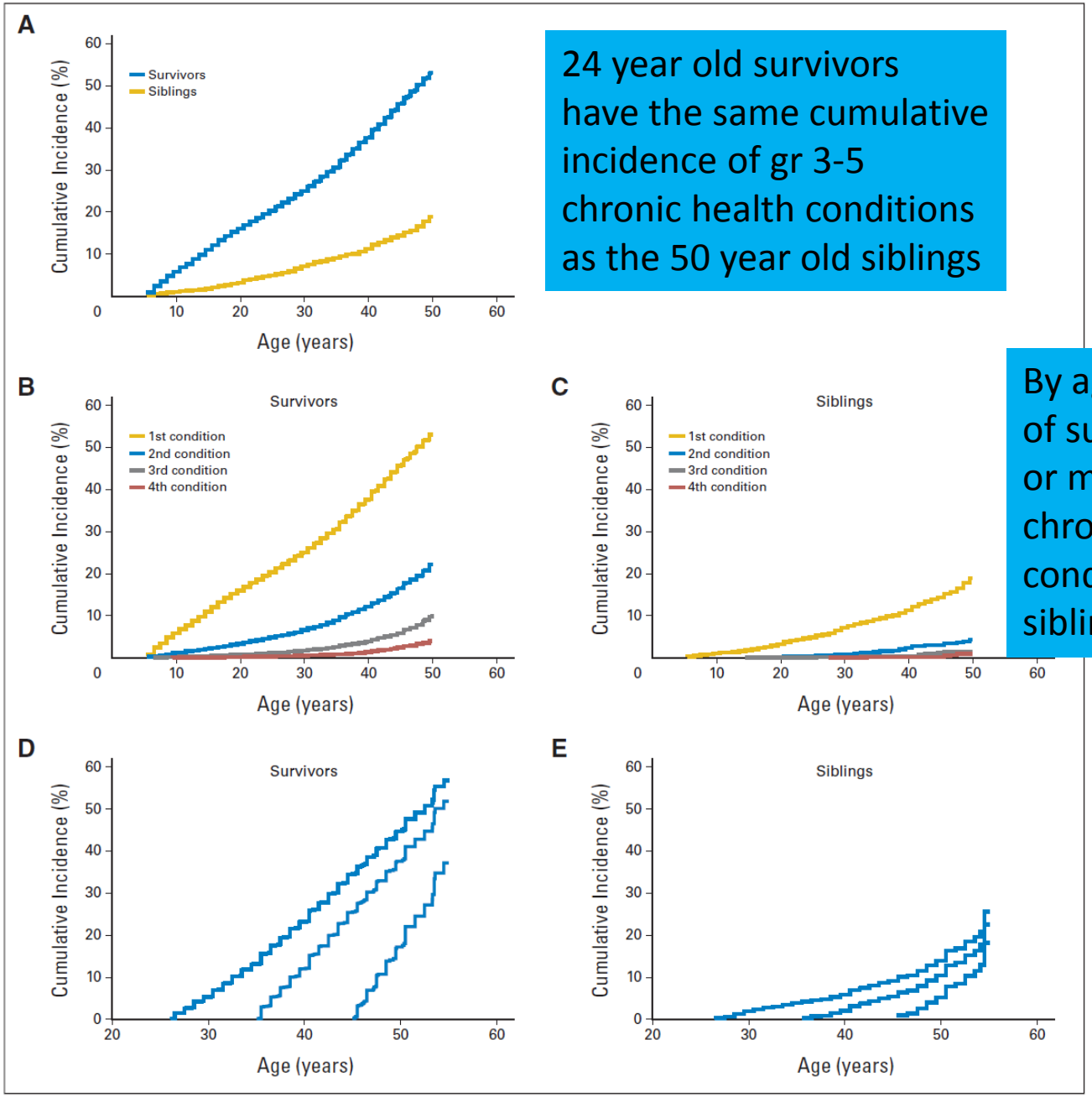


Results from most recent follow up

Armstrong et al (JCO March 17 2014) identifies that the elevated risk for severe, disabling, life threatening or fatal health conditions increases significantly beyond age 35 years in comparison to the sibling cohort.

By age 50 years 50% of survivors of childhood cancer will have experienced severe, disabling or life threatening morbidity or death – most commonly as a result of **cardiovascular, second malignancies**, pulmonary, hepatic, renal and gonadal dysfunction.

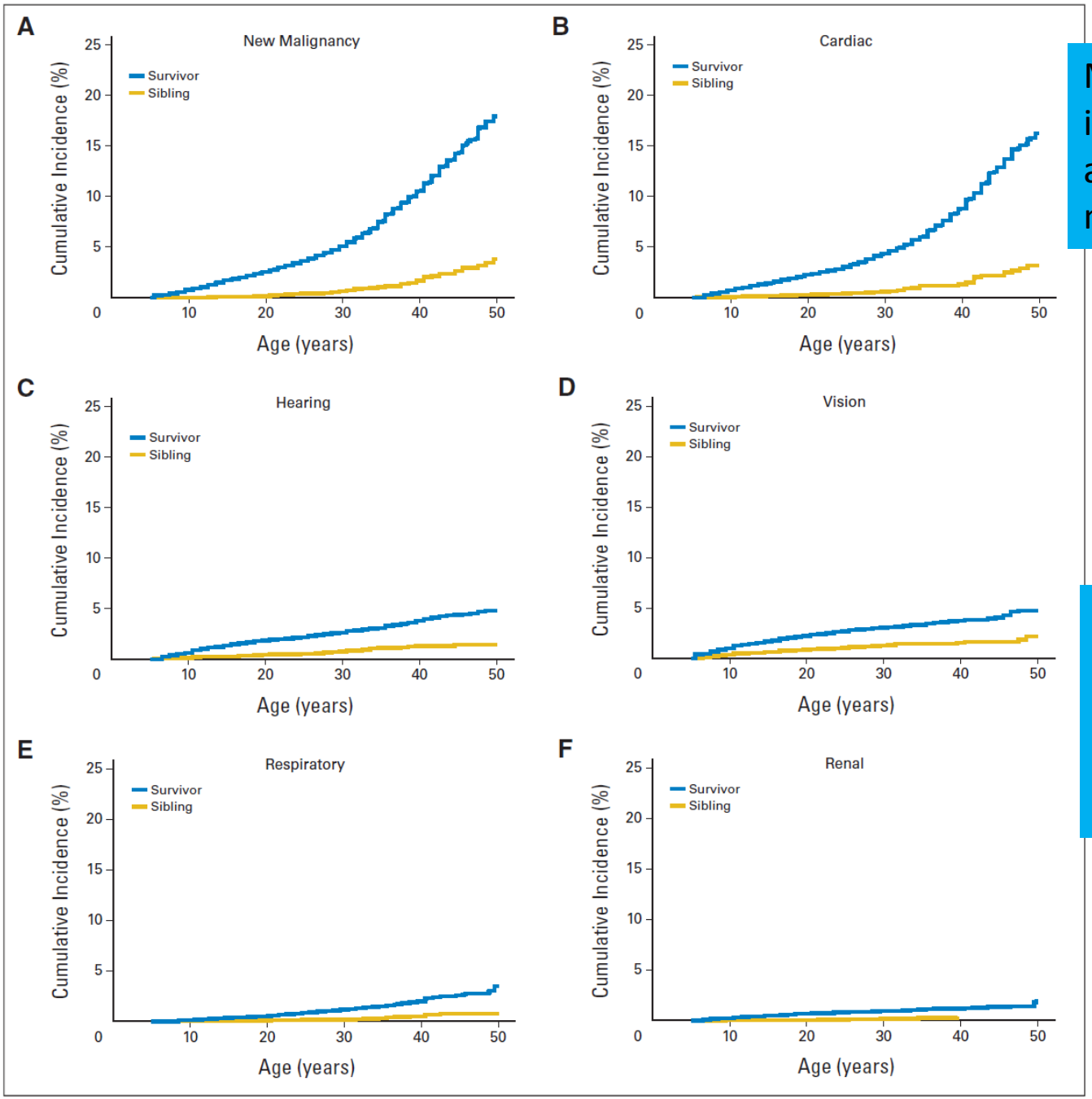
24 year old survivors of childhood cancer have the same cumulative incidence of grade 3-5 health conditions as the 50 year old siblings



24 year old survivors have the same cumulative incidence of gr 3-5 chronic health conditions as the 50 year old siblings

By age 50 yrs 22.5% of survivors have 2 or more gr 3-5 chronic health conditions cf 4.3% of siblings

Fig 1. Cumulative incidence of chronic health conditions for (A) grades 3 to 5 chronic health conditions, (B) multiple grade 3 to 5 conditions in survivors, (C) multiple grade 3 to 5 conditions in siblings, (D) conditioned based on no previous grade 3 to 5 conditions among survivors by ages 25, 35, or 45, and (E) conditioned based on no previous grade 3 to 5 conditions among siblings by ages 25, 35, or 45.



Marked increase in cardiac events and new malignancy

Relatively low cumulative incidence in certain organ systems

Fig 2. Cumulative incidence of selected grade 3 to 5 conditions by organ system. (A) New malignancy, (B) cardiac, (C) hearing, (D) vision, (E) respiratory, and (F) renal.

Aging survivors of childhood cancer

Of note the increase in second malignancies occurs before the age threshold when general population screening guidelines recommend screenings commence

Can early detection of cardiomyopathy and medical intervention mitigate progression to CHF in those with exposures to anthracyclines or radiation???

Does exposure to therapy for childhood cancer accelerate the aging process? What is the mechanism for this?

Table A2. Grade 3-5 Conditions

Category	Grade	Condition	Occurring More Than 5 Years After Diagnosis				Occurring at or After Age 35 Years			
			Survivors (n = 14,359)		Siblings (n = 4,031)		Survivors (n = 5,604)		Siblings (n = 1,969)	
			No. of Participants	%	No. of Participants	%	No. of Participants	%	No. of Participants	%
Subsequent neoplasms	3	Benign meningioma with surgery, thyroid cancer	153	1.1	10	0.2	29	0.5	4	0.2
	4	Breast carcinoma-in-situ	63	0.4	3	0.1	51	0.9	3	0.2
		Malignancy other than non-melanoma skin cancer or thyroid cancer	657	4.6	35	0.9	229	4.1	15	0.8
	5	Malignancy, death	360	2.5	5	0.1	139	2.5	2	0.1
		Total	1,233	8.6	53	1.3	448	8.0	24	1.2
Cardiac	3	Arrhythmia, requiring pacemaker	83	0.6	11	0.3	41	0.7	3	0.2
		Cerebral embolism	5	0.0	0	0.0	1	0.0	0	0.0
		Congestive heart failure requiring medication	302	2.1	11	0.3	120	2.1	5	0.3
		Heart attack, angina or coronary heart disease not requiring a cardiac catheterization	184	1.3	16	0.4	103	1.8	13	0.7
		Hypertension, severe	8	0.1	2	0.0	0	0.0	0	0.0
		Hypotension	18	0.1	3	0.1	3	0.1	0	0.0
		Pericardial disease requiring surgical intervention	22	0.2	0	0.0	13	0.2	0	0.0
	4	Endocarditis	14	0.1	1	0.0	5	0.1	0	0.0
		Heart attack requiring cardiac catheterization or angioplasty or CABG	169	1.2	20	0.5	101	1.8	12	0.6
		Heart transplantation	30	0.2	0	0.0	3	0.1	0	0.0
		Heart valve replacement	59	0.4	3	0.1	48	0.9	0	0.0
		Stroke/CVA	302	2.1	18	0.4	89	1.6	7	0.4
		Ventricular fibrillation/flutter	1	0.0	1	0.0	1	0.0	1	0.1
	5	Cardiovascular death	156	1.1	2	0.0	73	1.3	2	0.1
		Total	1,353	9.4	88	2.2	601	10.7	43	2.2

Risk factors

Table A6. HRs and 95% CIs for Development of Grade 3-5 Health Conditions at or After Age 35 Years, After Specific Therapy for Primary Cancer, Versus Siblings Both With and Without Weighting for Nonparticipation

	With Weights		Without Weights	
Therapy for Treatment of Primary Cancer	HR	95% CI	HR	95% CI
Surgery				
Any surgery	5.1	4.2 to 6.2	5.0	4.1 to 6.1
Surgery only	1.8	1.2 to 2.7	1.8	1.2 to 2.7
Nephrectomy	3.3	2.0 to 5.3	3.1	1.9 to 5.1
Splenectomy	7.5	6.1 to 9.3	7.4	6.0 to 9.1
Radiation				
Any radiation	5.8	4.7 to 7.0	5.7	4.6 to 7.0
Chest RT	7.1	5.8 to 8.7	7.0	5.7 to 8.6
CNS RT	5.0	3.9 to 6.4	4.9	3.8 to 6.3
Abdominal RT	7.1	5.7 to 8.8	7.1	5.7 to 8.7
Pelvic RT	6.6	5.3 to 8.2	6.6	5.3 to 8.2
No radiation	2.6	2.0 to 3.3	2.6	2.0 to 3.3
Chemotherapy				
Any chemotherapy	4.9	4.0 to 6.1	4.9	4.0 to 6.0
Cisplatin	4.8	3.1 to 7.5	4.5	2.9 to 6.9
Alkylator	5.5	4.5 to 6.8	5.5	4.4 to 6.7
Anthracycline	4.7	3.7 to 5.9	4.6	3.7 to 5.8
Methotrexate	3.7	2.9 to 4.7	3.6	2.9 to 4.6
Bleomycin	7.0	5.3 to 9.4	6.9	5.1 to 9.2
Combinations				
Chest RT + bleomycin	9.3	6.7 to 13.0	9.1	6.5 to 12.7
Chest RT + abdominal or pelvic RT	7.8	6.3 to 9.6	7.7	6.2 to 9.5
Abdominal or pelvic RT + alkylator	6.9	5.5 to 8.7	6.9	5.5 to 8.6
Chest RT + anthracyclines	7.4	5.6 to 9.9	7.3	5.5 to 9.7
Anthracyclines + an alkylator	4.7	3.7 to 5.9	4.6	3.7 to 5.8

NOTE. Each row represents a separate multivariable model adjusted for sex and race, with age as the time scale. Models allow for multiple events and participants may have had a grade 3-4 event before age 35 years.
Abbreviations: HR, hazard ratio; RT, radiation therapy.

Resources available to inform care

Currently, clinical practice guidelines addressing the surveillance for late effects in long-term survivors of childhood and young adult cancer have been published by the

- US based Children's Oncology Group (COG)
  - www.survivorshipguidelines.org
- Dutch Childhood Oncology Group (DCOG)
- United Kingdom Children's Cancer and Leukaemia Group (CCLG)
  - www.ukccsg.org
- Scottish Intercollegiate Guidelines Network (SIGN)
  - www.sign.ac.uk

Comprehensive and exposure based

Systems based – less daunting

Non integrated approach with varying recommendations

Harmonisation of guidelines

- International project to harmonise clinical practice guidelines for surveillance of survivors
- Aim to increase QOL, decrease complication related healthcare costs, promote healthy lifestyles, facilitate early detection of late effects and advise about timely intervention strategies to preserve health

Questions to be addressed by the harmonisation guideline

- Who needs surveillance
- When should surveillance be commenced (at what age or time from exposure)
- How frequently should surveillance be performed
- What surveillance modality
- What effective treatments are available if health problems are identified

TABLE I. Criteria for Grading the Levels of Evidence and Strength of Recommendations*

Grade of Recommendation / Conclusions of evidence (based on GRADE)	I Strong recommendation to do Benefits >>> risk & burdens	IIa Moderate recommendation to do Benefits >> risk & burdens	IIb Weak recommendation to do Benefits >= risks & burdens	III Recommendation not to do No benefit / Potentially harm
A High level of evidence Consistent evidence from well performed and high quality studies or systematic reviews (low risk of bias, direct, consistent, precise).	Strong recommendation based on high level of evidence	Moderate recommendation based on high level of evidence	Weak recommendation based on high level of evidence	Recommendation based on high level of evidence
B Moderate /Low level of evidence Evidence from studies or systematic reviews with few important limitations.	Strong recommendation based on moderate/ low level of evidence	Moderate recommendation based on moderate/ low level of evidence	Weak recommendation based on moderate/ low level of evidence	Recommendation based on moderate/ low level of evidence
C Very low level of evidence Evidence from studies with serious flaws. Only expert opinion, or standards of care.	Strong recommendation based on expert opinion	Moderate recommendation based on very low level of evidence Diverging expert opinions	Weak recommendation based on very low level of evidence Diverging expert opinions	Recommendation based on very low level of evidence Expert opinion
Wording in recommendations:	We recommend We should Is recommended Is indicated Is useful Is beneficial Is effective	We suggest Is reasonable Is probably recommended Can be useful Can be beneficial Can be effective	We might suggest Might be reasonable Might be considered Usefulness is unknown	We do not recommend Should not be performed Is not useful Is not beneficial Is not effective Is potentially harmful

TABLE II. Results Delphi Round One Questionnaire

Late effect	Mean score[a]			
	High prevalence such that screening warranted	Severe such that screening warranted	Accurate screening tests to detect early	Early effective treatment options
Secondary malignant neoplasms				
Acute myeloid leukemia	2.27	4.34	2.79	2.44
Bladder cancer	3.57	2.24	4.14	4.21
Cervical cancer	2.24	4.14	4.21	4.14
CNS benign tumors	3.47	3.31	3.86	3.14
CNS malignant tumors	2.62	4.38	3.54	2.75
Colorectal cancer	2.48	4.45	4.21	4.34
Endometrial cancer	1.52	4.07	2.89	3.61
Kidney cancer	1.62	4.14	2.70	3.36
Lung cancer	2.10	4.31	2.89	3.04
Melanoma	2.53	4.40	3.64	4.11
Non-melanoma skin cancer	3.50	3.00	3.57	4.29
Oral cancer	1.96	4.31	3.04	3.46
Prostate cancer	1.83	3.83	3.59	3.93
Testicular cancer	1.38	3.79	3.07	4.14
Thyroid cancer	3.23	3.67	3.43	4.18
Cardiovascular disease				
Arrhythmias	2.00	3.39	3.43	3.37
Cardiac valvular abnormalities	2.18	3.32	4.11	2.79
Carotid artery disease	2.17	3.89	3.68	3.37
Coronary artery disease	2.83	4.24	3.61	3.64
Pericardial disease	1.64	2.89	3.25	2.52
Bone abnormalities				
Osteonecrosis	2.57	3.61	3.11	2.68
Osteoporosis	3.52	4.34	4.14	3.71
Endocrine abnormalities				
Adrenal dysfunction	1.86	4.04	3.61	4.07
Gonadal ovarian dysfunction	3.79	4.07	3.96	3.89
Gonadal testicular dysfunction	3.72	4.04	4.18	3.79
Growth hormone deficiency	3.50	4.14	3.97	4.34
Insulin resistance	3.36	3.82	3.82	3.64
Thyroid dysfunction	2.93	3.48	4.03	3.00
Pulmonary toxicity				
Diffusion capacity impairment	2.75	3.39	4.11	2.21
Obstructive lung disease	2.39	3.68	4.07	2.93
Restrictive lung disease	2.93	3.72	4.07	2.18
Renal toxicity				
Glomerular injury	2.61	3.54	3.96	2.57
Tubular injury	2.93	3.48	4.03	3.00
Hepatic toxicity				
Biliary tract disease	1.57	2.89	3.11	2.61
Cellular liver injury	2.14	3.04	3.43	2.46
Ocular toxicity				
Cataract	3.24	3.32	2.29	3.33
Retinopathy	1.75	3.54	3.78	2.70
Psychosocial problems				
Behavioral disorders	3.30	3.67	3.15	3.04
Fatigue	3.43	3.35	2.85	2.42
Other				
Dental abnormalities	3.31	3.18	3.88	3.62
Hearing disabilities	3.52	3.89	4.44	3.57
Mental health disorders	2.96	3.74	3.19	2.85
Neurocognitive deficits	3.62	4.25	3.93	3.04

Current and proposed guidelines

International harmonized recommendations for

- Breast cancer surveillance among female survivors given chest radiation before 30 yrs (Lancet Oncology 2015)
- Cardiomyopathy surveillance in those receiving anthracyclines or chest radiation (Lancet Oncology 2015)

Further guidelines in development

1. Gonadal ovarian and testicular dysfunction
2. Coronary artery disease
3. CNS malignancy
4. GH deficiency
5. Neurocognitive deficits

What are the unmet needs

- Access to informed, well educated and interested health providers
  - GP's , general physicians and specialties
- Equitable access to services eg rehabilitation
- Appropriate transition models with adequate infrastructure to support transfer of care
  - See "Got transition" (American College of Physicians) and "Key Principles for Transition of Young People from Paediatric to Adult Health Care" (NSW)
  - Patient education and engagement are big factors (phone apps in development)

What are the unmet needs

- Health Service structures that recognise the complexity of these patients
  - Reimbursement for long reviews and multidisciplinary assessment
- Appropriate access to and funding of screening (not age dependent)
- Validated risk stratification models based on evidence
  - Not only medical but psychosocial
- Research into the cost effectiveness of screening, monitoring and intervention strategies