

Cancer in kidney transplant recipients: epidemiology and prevention

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Outline

1. The burden of cancer after kidney transplantation
2. Epidemiology of post-transplant cancer
 - The common cancers: incidence versus mortality
 - Who is at risk?
3. Can we prevent post-transplantation cancer?
 - Lifestyle modification
 - Screening programs
 - Modified immunosuppression
 - Personalised medicine
4. Expanding our evidence-base – the EpCOT project
5. Conclusions



The burden of cancer after kidney transplantation



UK Transplant data – long-term mortality

Table 11.2 Patient survival after first adult kidney only transplant from a DBD

Year of transplant	No. at risk on day 0	% Patient survival (95% confidence interval)			
		One year	Two year	Five year	Ten year

75 (73-77)

Table 11.4 Patient survival after first adult kidney only transplant from a DCD

Year of transplant	No. at risk on day 0	% Patient survival (95% confidence interval)			
		One year	Two year	Five year	Ten year

67 (57-75)

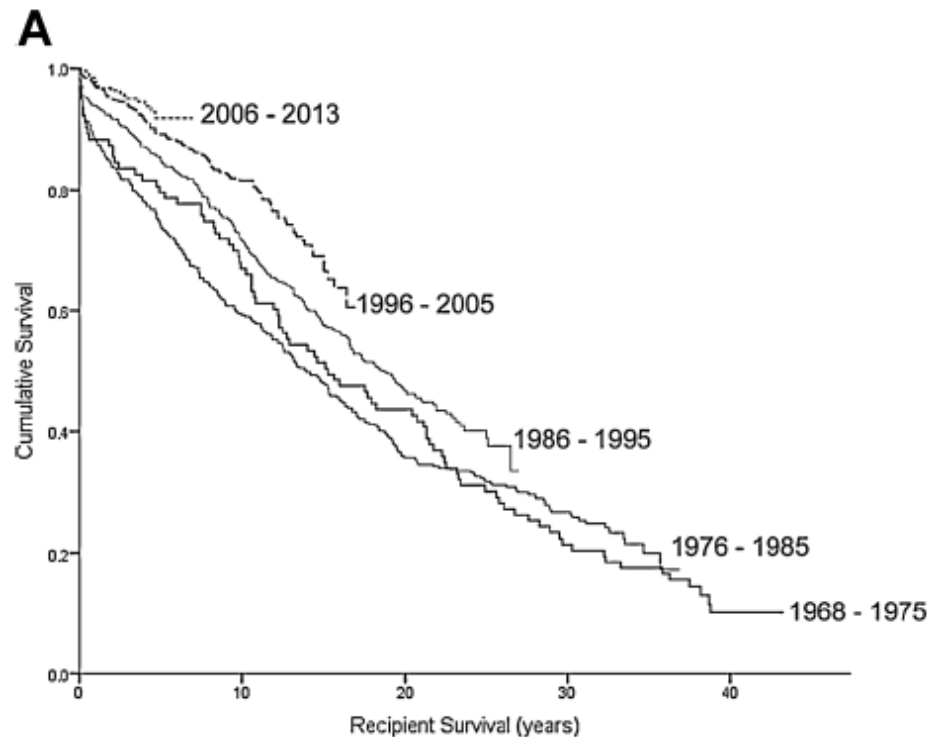
Table 11.6 Patient survival after first adult living donor kidney transplant

Year of transplant	No. at risk on day 0	% Patient survival (95% confidence interval)			
		One year	Two year	Five year	Ten year

1998-2000	655	98 (96-99)	98 (96-98)	95 (93-97)	90 (87-92)
2001-2003	916	98 (97-99)	97 (96-98)	95 (94-96)	
2004-2006	1317	99 (98-99)	98 (97-99)	96 (95-97)	
2007-2010	2860	99 (98-99)			



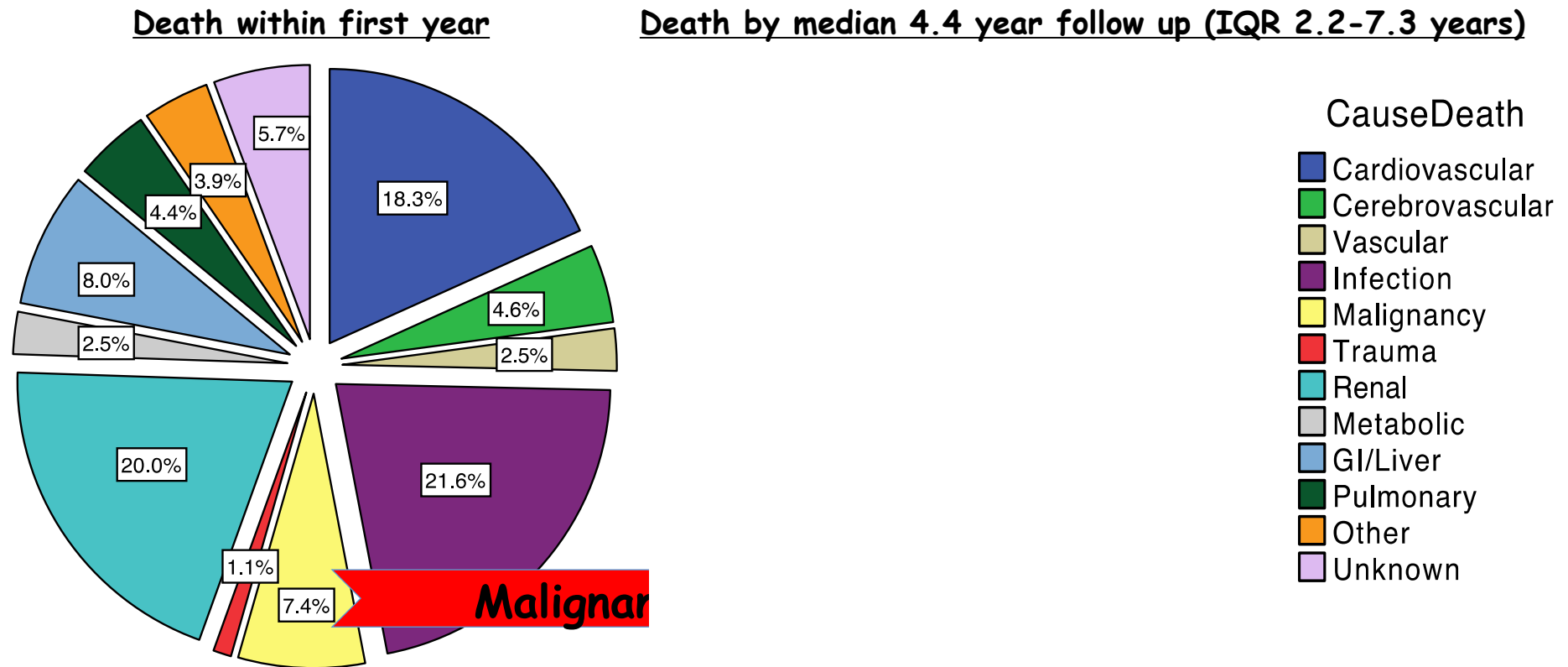
Risk for cancer increases with time post-transplant



Comorbidity	n
Hypertension ¹	62 (41%)
Cancer	58 (37%)
Nonmelanoma skin cancer	42
Squamous cell carcinoma of vulva	3
Squamous cell carcinoma of cervix	2
Squamous cell carcinoma of larynx	2
Squamous cell carcinoma of breast	1
Squamous cell carcinoma of lung	1
Adenocarcinoma of colon	8
Adenocarcinoma of lung	3
Adenocarcinoma of prostate	2
Adenocarcinoma of breast	1
Adenocarcinoma of thyroid	1
Posttransplant lymphoproliferative disorder	4
Transitional cell carcinoma of bladder	1
Malignant melanoma	1
Cardiovascular disease	42 (27%)
New onset diabetes after transplantation ¹	11 (8%)

¹Recipients who developed comorbidity after 20 years of graft function.

Cause of mortality after kidney transplantation (kidney-only transplants, England, 2001-2012)

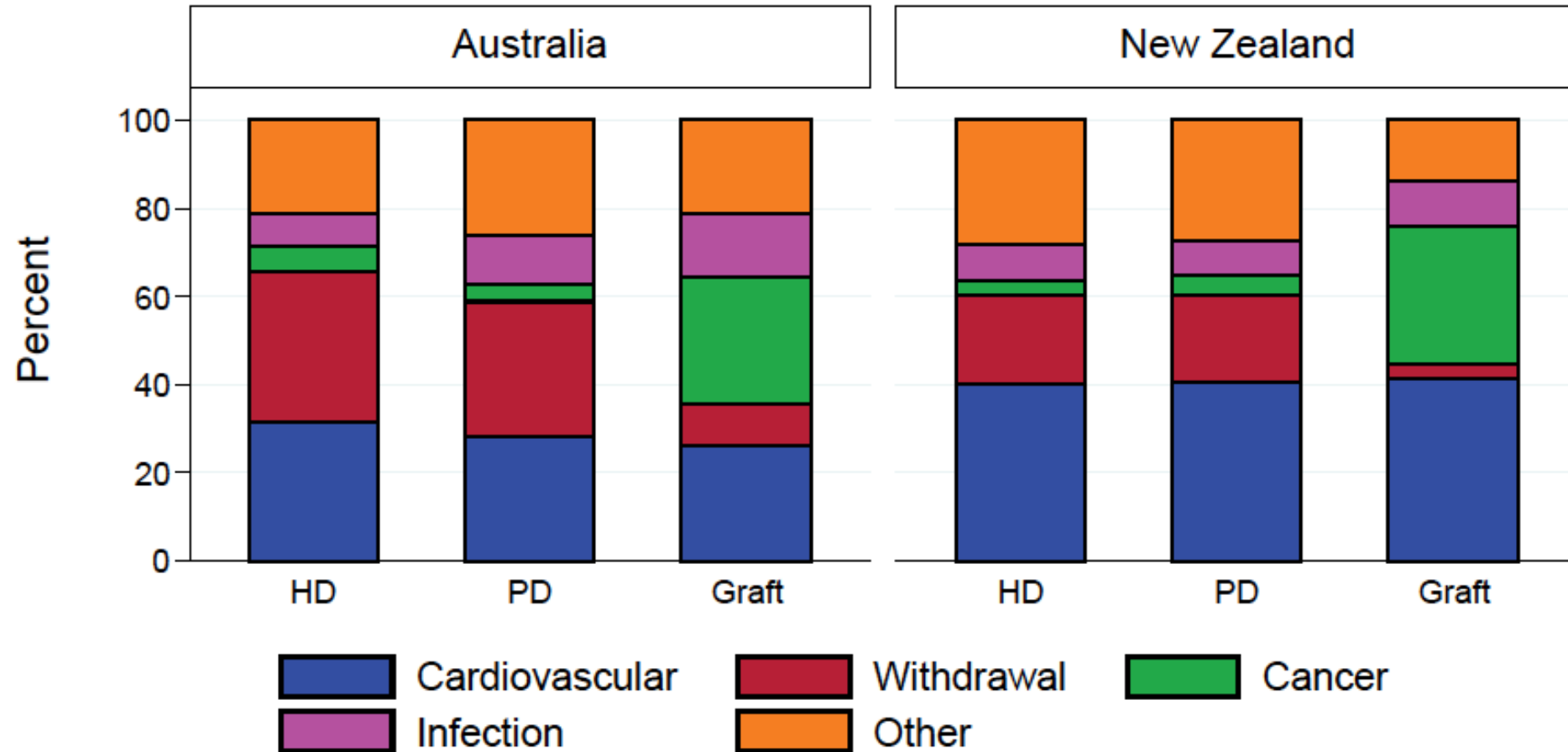


UK Renal Registry 19th Annual Report: Chapter 5 Survival and Causes of Death in UK Adult Patients on Renal Replacement Therapy in 2015

Causes of death	All modalities		Dialysis		Transplant	
	<i>N</i>	%	<i>N</i>	%	<i>N</i>	%
Cardiac disease	714	22	613	23	101	18
Cerebrovascular disease	138	4	114	4	24	4
Infection	688	21	554	21	134	24
Malignancy	327	10	201	7	126	22
Treatment withdrawal	581	18	566	21	15	3
Other	666	20	534	20	132	24
Uncertain	144	4	115	4	29	5
Total	3,258		2,697		561	
Missing data	1,747	35	1,439	35	308	35



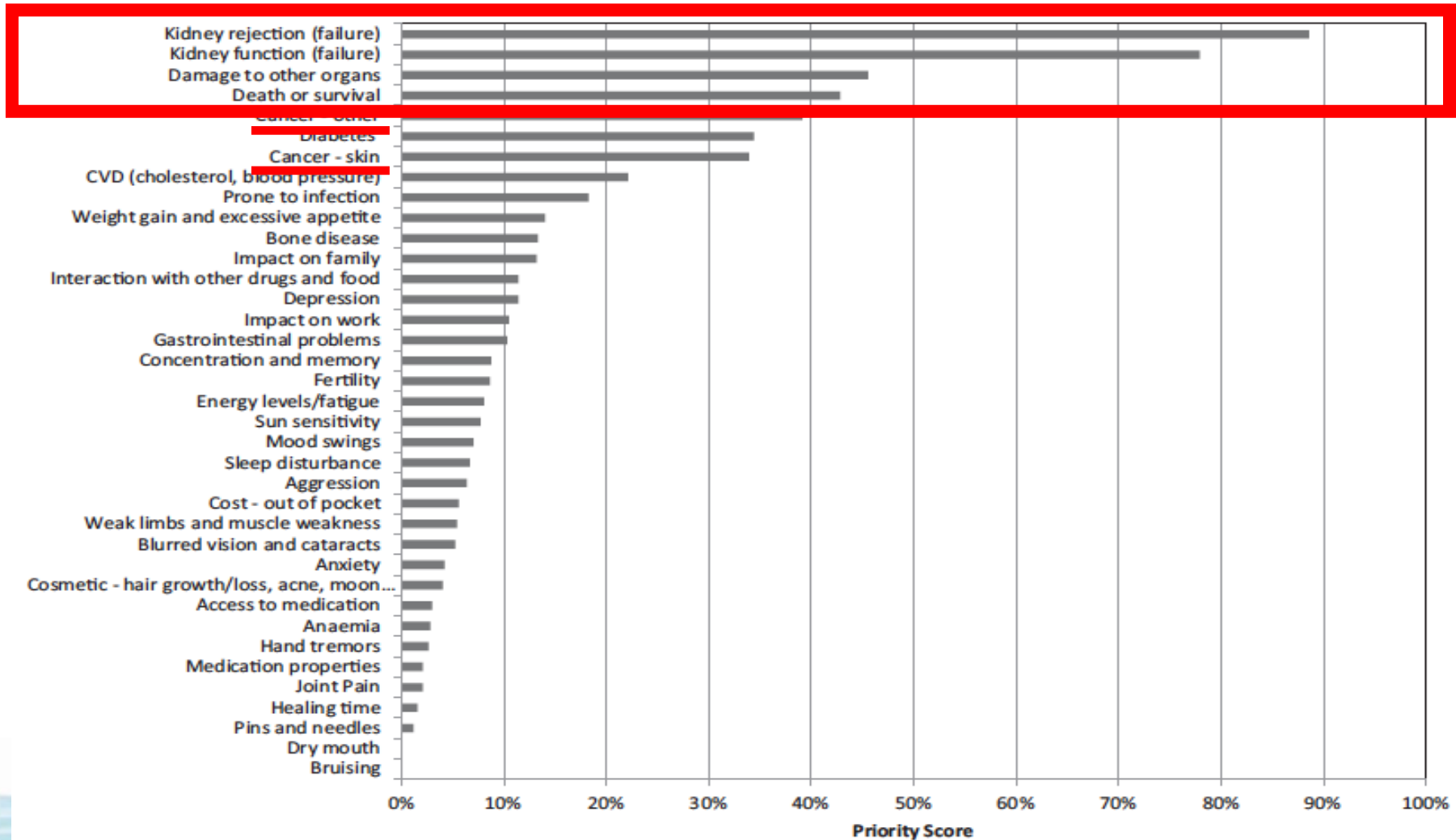
Deaths in Australia/NZ for 2016 for RRT patients



Outcomes in Australia/NZ for 1990-2012 after incident post-transplant cancer

	Overall graft loss Adjusted HR (95%CI)	Death censored graft loss Adjusted HR (95%CI)	Death with a functioning graft Adjusted HR (95%CI)
Incident cancer			
None	1.00	1.00	1.00
Yes	4.34 (3.90, 4.82)	1.43 (1.16, 1.77)	9.53 (8.30, 10.95)

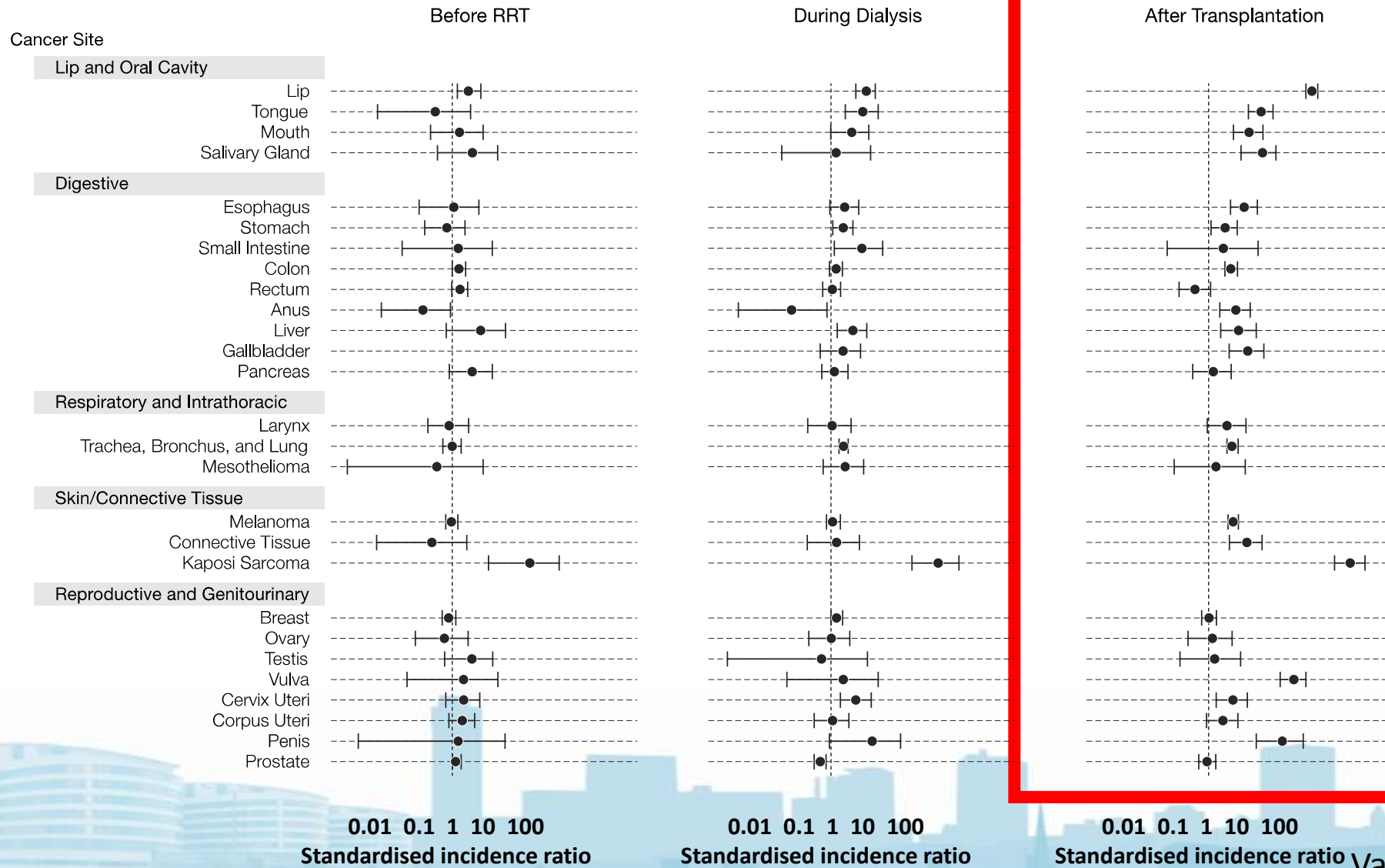
Patient perspectives after transplantation



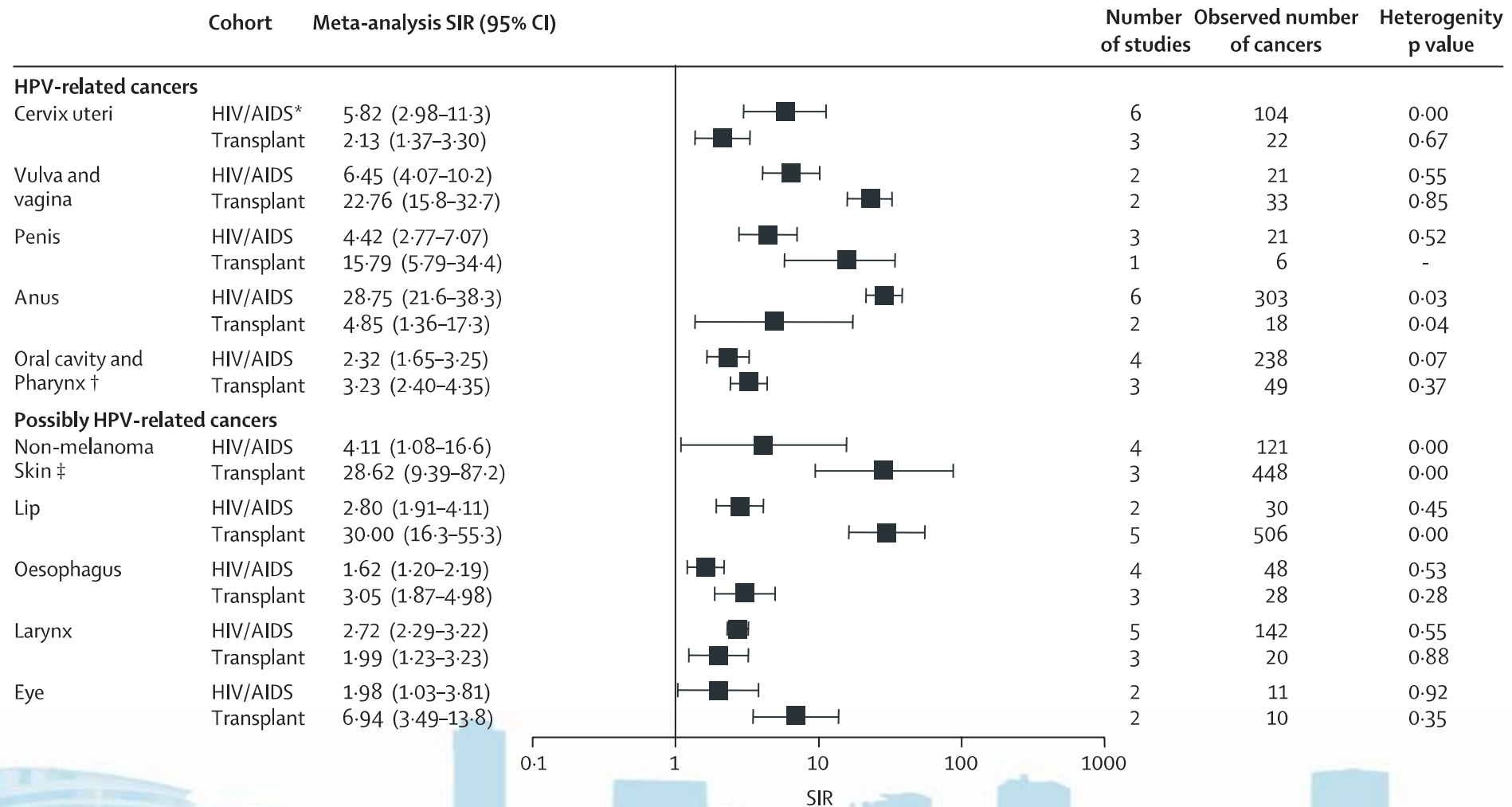
Epidemiology of post-transplant cancer



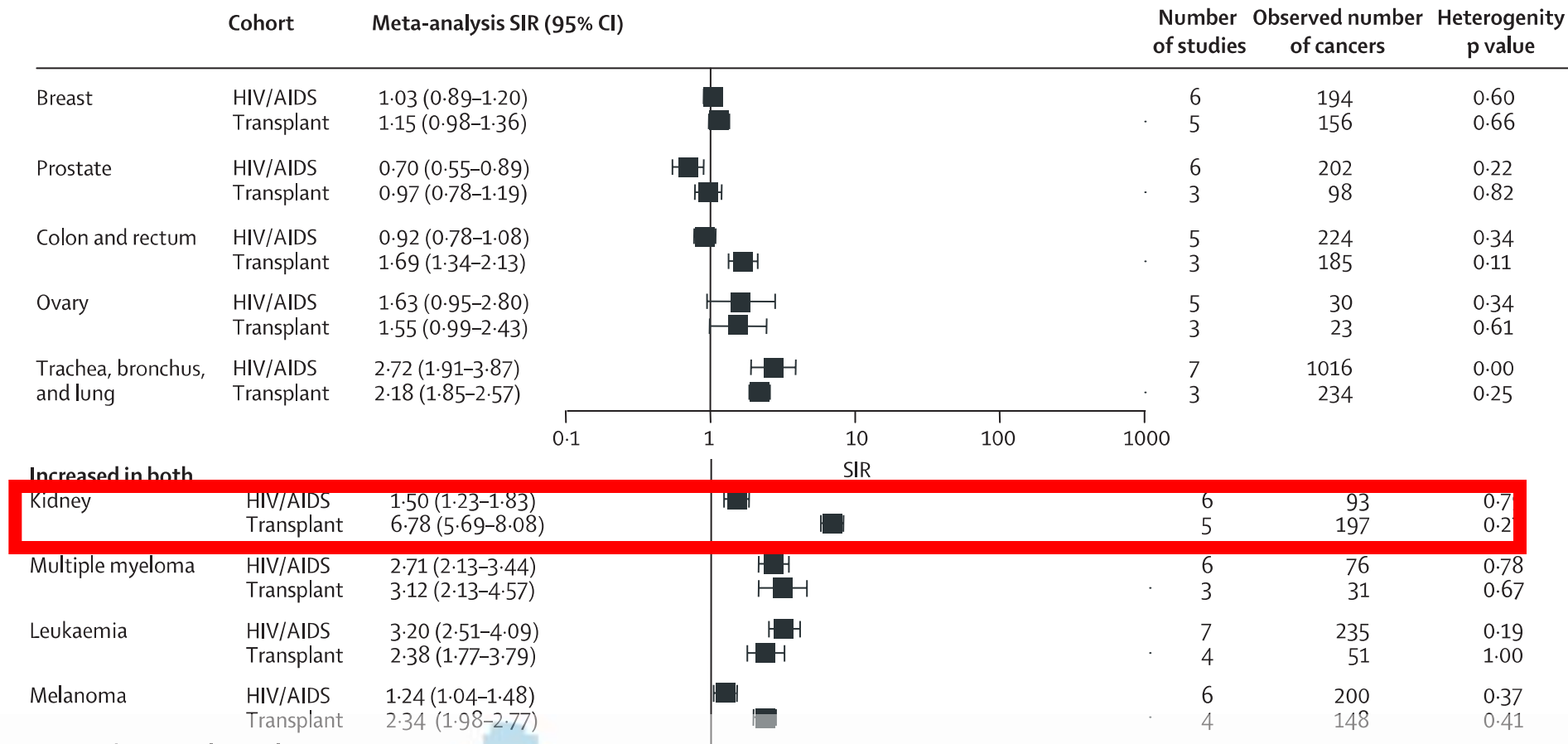
Cancer incidence before and after kidney transplantation



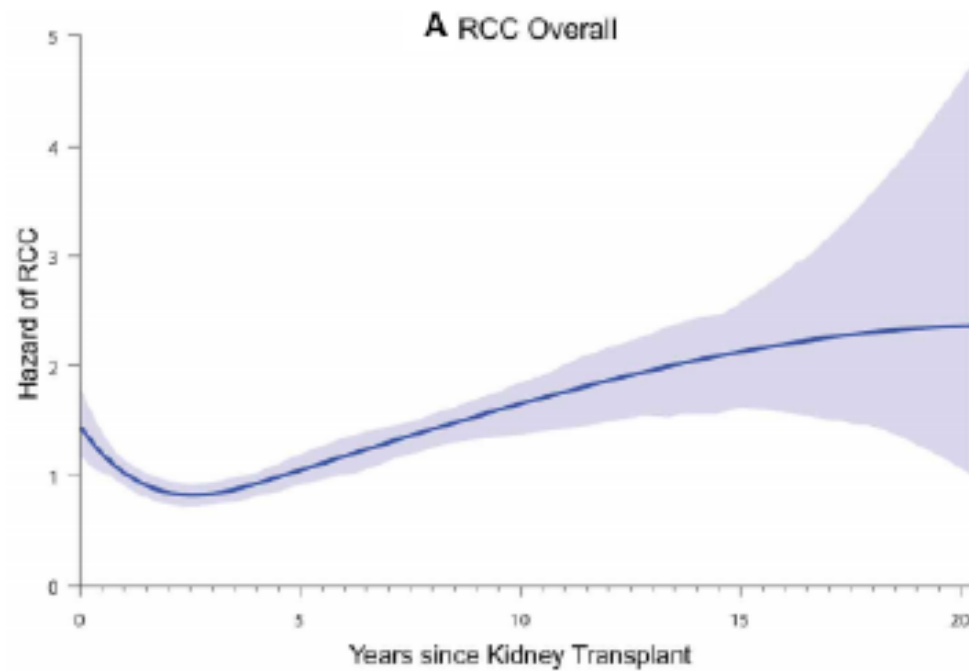
SIR for HPV-related cancers comparing HIV/AIDS versus transplant



SIR for selected cancers comparing HIV/AIDS versus transplant



Risk for renal cell cancer stratified by time on dialysis before kidney transplantation



Duration of dialysis (vintage), yrs					HR	95% CI	
No	40	5.9	12 264	10.6	1.00		
<1	114	16.7	23 658	20.5	1.26	0.87–1.81	
1–2	146	21.4	23 330	20.2	1.60	1.12–2.29	
2–3	79	11.6	16 788	14.5	1.23	0.84–1.81	
3+	301	44.1	38 401	33.2	2.23	1.58–3.13	
Missing/unknown	3	0.4	1084	0.5	0.51	0.16–1.64	<0.0001

Post-transplant cancer in the UK – incidence versus mortality

Site	Incidence ¹ (17.6%)	Mortality ² (18.0%)
Renal	3.5%	9.8%
Upper GI	2.0%	7.2%
Lower GI	4.7%	8.0%
Lung	4.0%	17.6%
Lymphoma	8.8%	18.4%
Breast	2.6%	3.2%
GU (not including renal)	1.7%	2.7%
Prostate	2.5%	1.6%
Haematological	0.4%	2.7%
Skin	55.9%	3.2%
Pancreas	0.6%	4.0%
Liver	0.4%	2.7%
Female	1.4%	2.4%

¹Incidence population (n=25,104, median follow up 16 years), Collett et al, AJT 2010

²Mortality population (n=19,103, median follow up 4.4 years), Farrugia et al, Kidney Int 2014

What general risk factors exist for developing cancer?

- Age
- Alcohol
- Cancer-causing substances
- **Chronic inflammation**
- Diet
- Genetic
- Hormones

- **Infectious agents**
- **Immunosuppression**
- **Obesity**
- Radiation
- Sun exposure
- Tobacco

Transplantation risk



The diagram features a central red text label 'Transplantation risk' at the bottom. Two red arrows originate from this label. One arrow points diagonally up and to the left towards the red-bordered box containing 'Chronic inflammation'. The other arrow points diagonally up and to the right towards a larger red-bordered box that encloses three items: 'Infectious agents', 'Immunosuppression', and 'Obesity'.



Post-transplant cancer as a complication of (over)immunosuppression

INCREASED CANCER RISK

- T-cell depletion treatment for rejection¹
- Increasing HLA-DR mismatches²
- Extended criteria kidneys³
- Kidney re-transplants (RCC only)⁴

NO INCREASED CANCER RISK

- Steroid treatment for rejection¹
- Kidney re-transplants (non-RCC cancers)⁴
- ABO-incompatible kidney transplantation⁵

¹Lim et al. Transplantation 2014

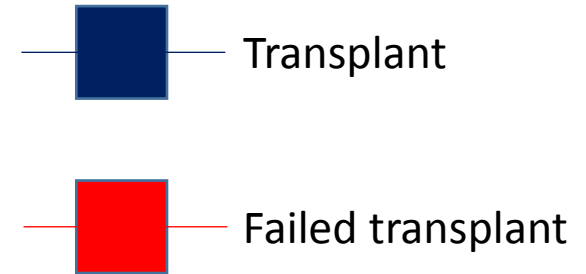
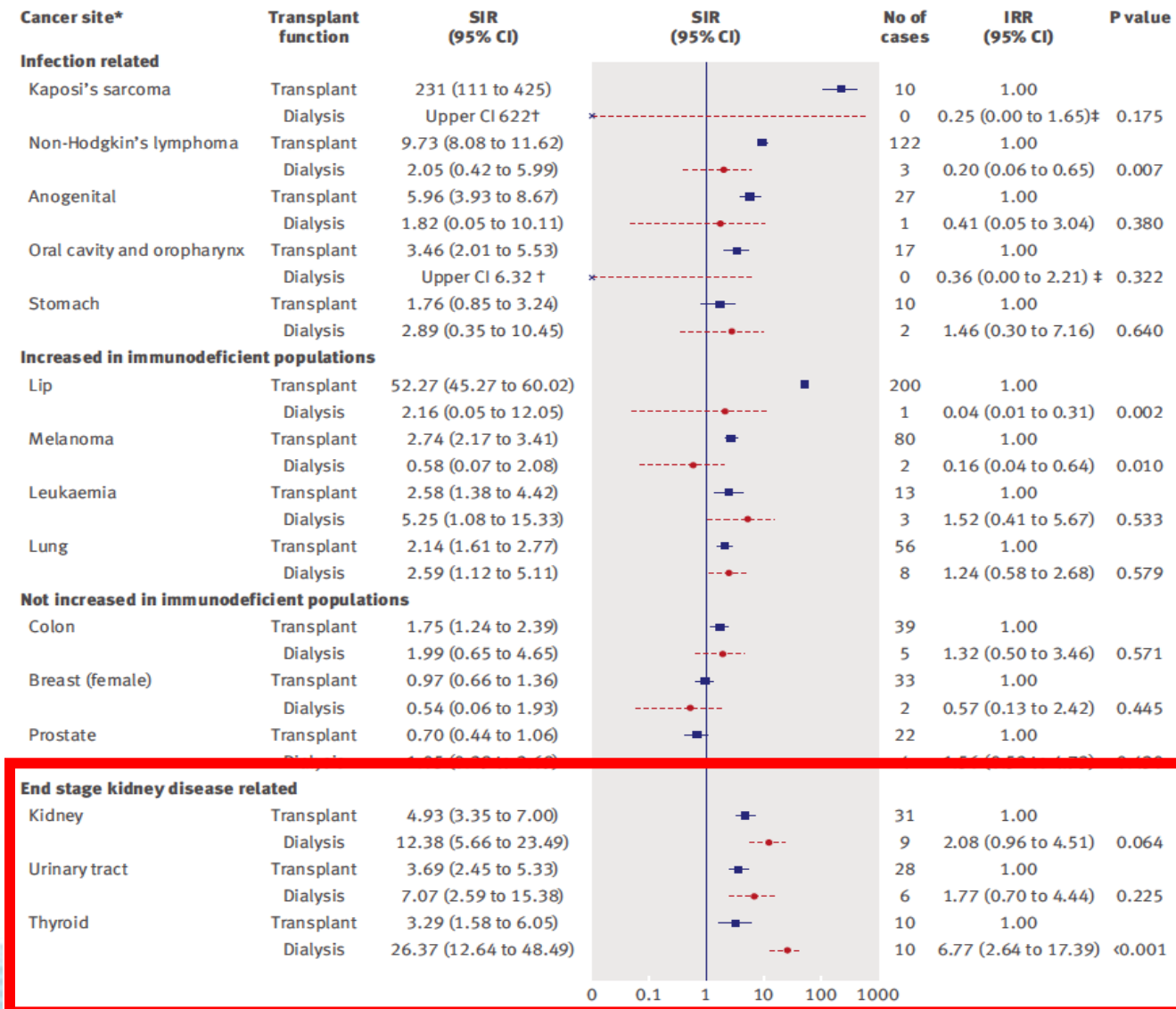
²Hussain et al. Transplantation 2016

³Kalil et al. Clin Transplant 2015

⁴Ma et al. Transplantation 2014

⁵Hall et al. Transplantation 2013

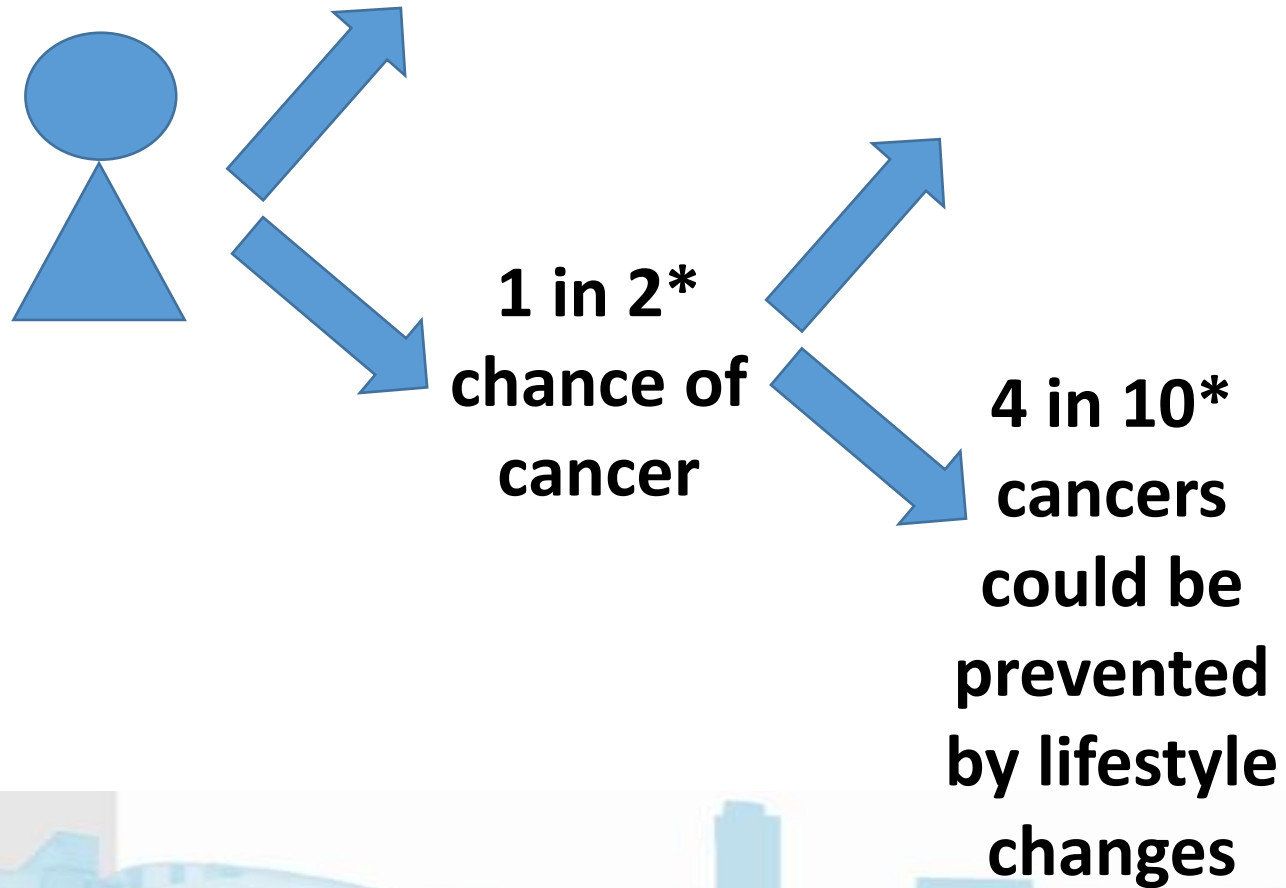
Risk for cancer comparing transplant versus failed transplant recipients



Can we prevent cancer post kidney transplantation?



(1) Encourage lifestyle modifications



- **Not smoking**
- **Keep a healthy body weight**
- **Eat a healthy, balanced diet**
- **Cut back on alcohol**
- **Enjoy the sun safely**
- **Keep active**

*General population data from Cancer Research UK

(2) Screening guidelines from the RA (endorsed by the BTS)

Pre-transplantation (2010)

- We recommend that renal transplantation should only be considered in potential recipients with previous malignancy (excluding NMSC) if there is no evidence of persistent cancer. It is recommended the waiting time between treatment/remission and transplantation be at least 2-years (and in some cases >5 years). The Israel Penn Transplant Tumour Registry should be consulted for specific advice (1A)

(2) Screening guidelines for minimum cancer-free time intervals for transplantation

Type	Stage	AST	CARI	B&D	CST	EBPG	MMOH
Renal cell carcinoma	Small or discovered incidentally	○	○	○			○
	Symptomatic	⊙	●	⊙		⊙	
	Large or invasive	●		⊙			▨
Bladder cancer	In situ or noninvasive papilloma	○	○	○	○	⊙	○
	Invasive	⊙	⊙	⊙	⊙		⊙
Breast cancer	Stage 0–2 (including early stage)	⊙	▨	▨	⊙	●	▨
	Stage 3–4 (advanced/invasive)	●	●	▨	●	●	▨
Colorectal cancer	Duke A or B1	⊙	⊙		▨	⊙	⊙
	Duke C		●			⊙	⊙
	Duke D		●			⊙	⊙
	Patients with a history of colorectal cancer	●			●		



0 years



Minimum 2 years



5 years



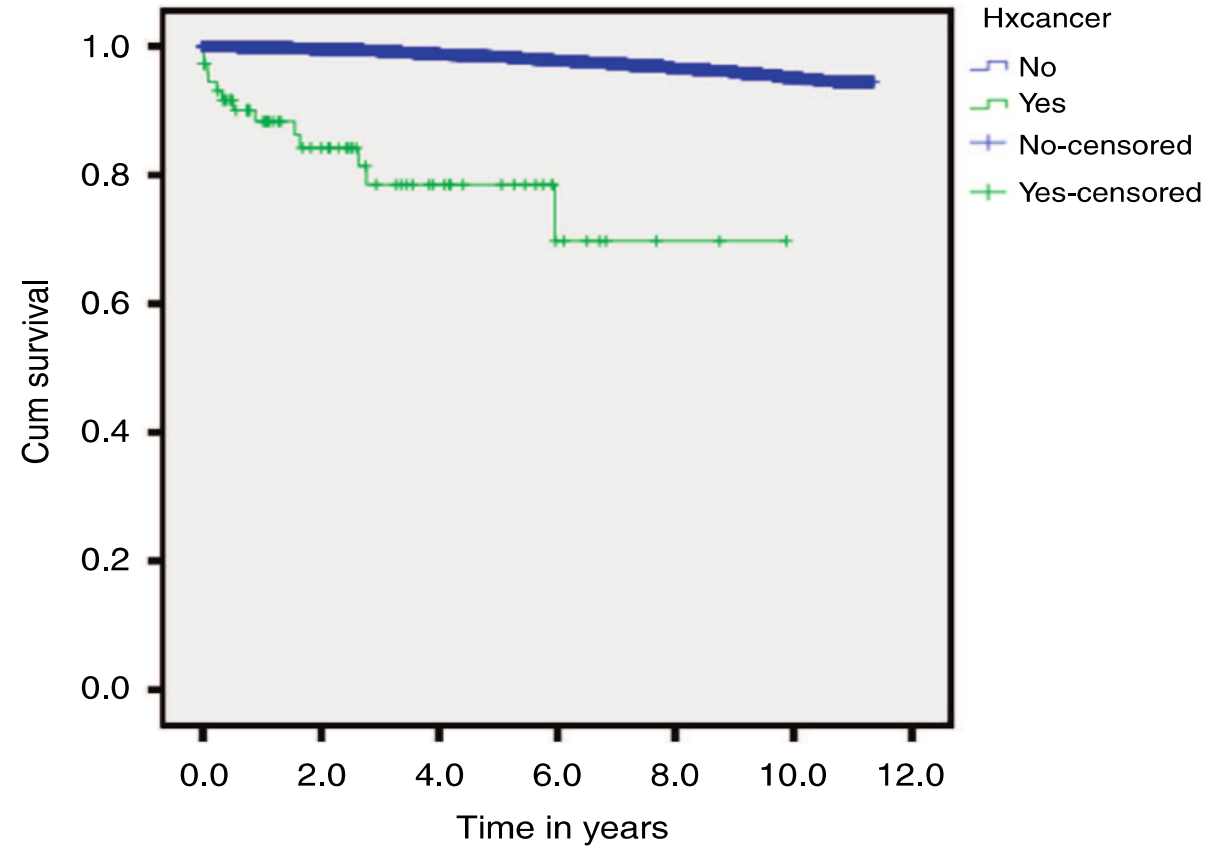
Minimum 5 years



Contraindicated

No guidance

(2) Pre-transplant cancer is a risk for post-transplant cancer mortality



Time (years)	0	1	2	3	4	5	6	7	8	9	10	11
No previous cancer	19,029	17,042	14,795	12,532	10,413	8557	6793	5268	3875	2572	1377	377
Previous cancer	74	51	39	26	20	16	7	3	2	1	0	0

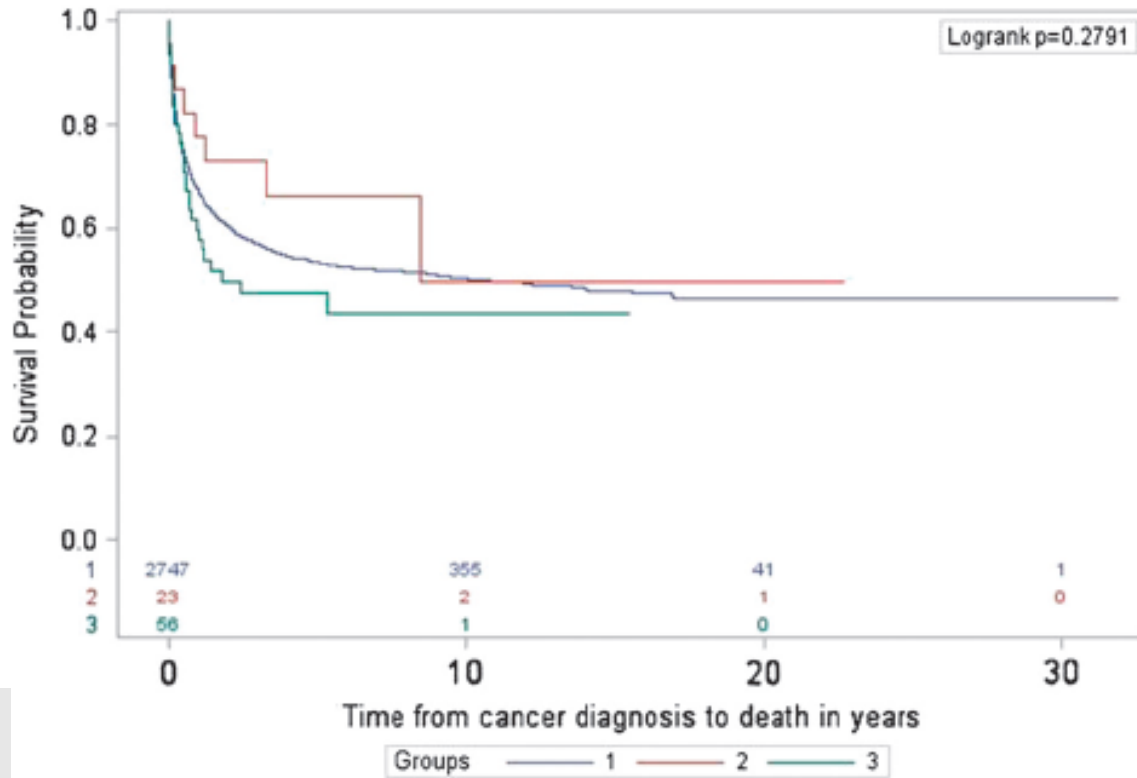
(2) Pre-transplant cancer is **NOT** a risk for post-transplant cancer mortality

A

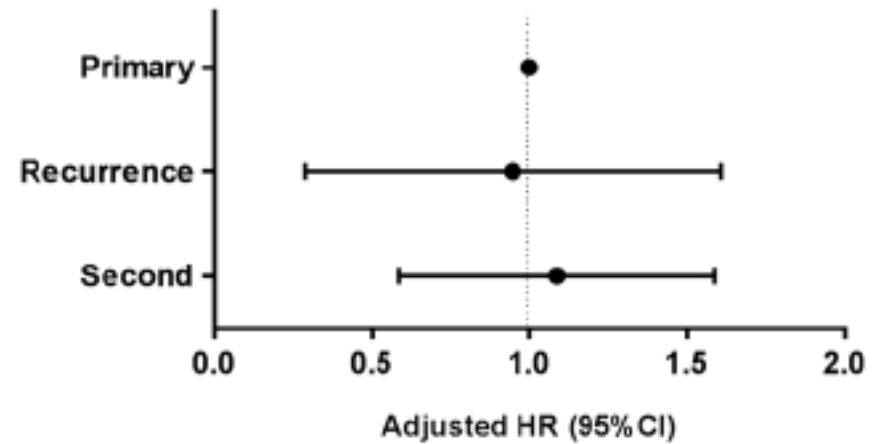
Cancer-specific survival

Product-Limit Survival Estimates

With Number of Subjects at Risk



Adjusted hazards for cancer-specific mortality



**adjusted for the effects of age, gender, BMI, smoking status, time on dialysis, era of transplantation, history of diabetes mellitus and COPD*

(2) Screening guidelines from the RA (endorsed by the BTS)

Pre-transplantation (2010)

- We recommend that renal transplantation should only be considered in potential recipients with previous malignancy (excluding NMSC) if there is no evidence of persistent cancer. It is recommended the waiting time between treatment/remission and transplantation be at least 2-years (and in some cases >5 years). The Israel Penn Transplant Tumour Registry should be consulted for specific advice (1A)

Post-transplantation (2017)

- Screening should be similar to the general population for cervical, breast, colon and prostate cancer (2C)
- Screening is not recommended for renal cell carcinoma (2C)

(2) Which cancers are we meant to screen?

Official UK screening programs

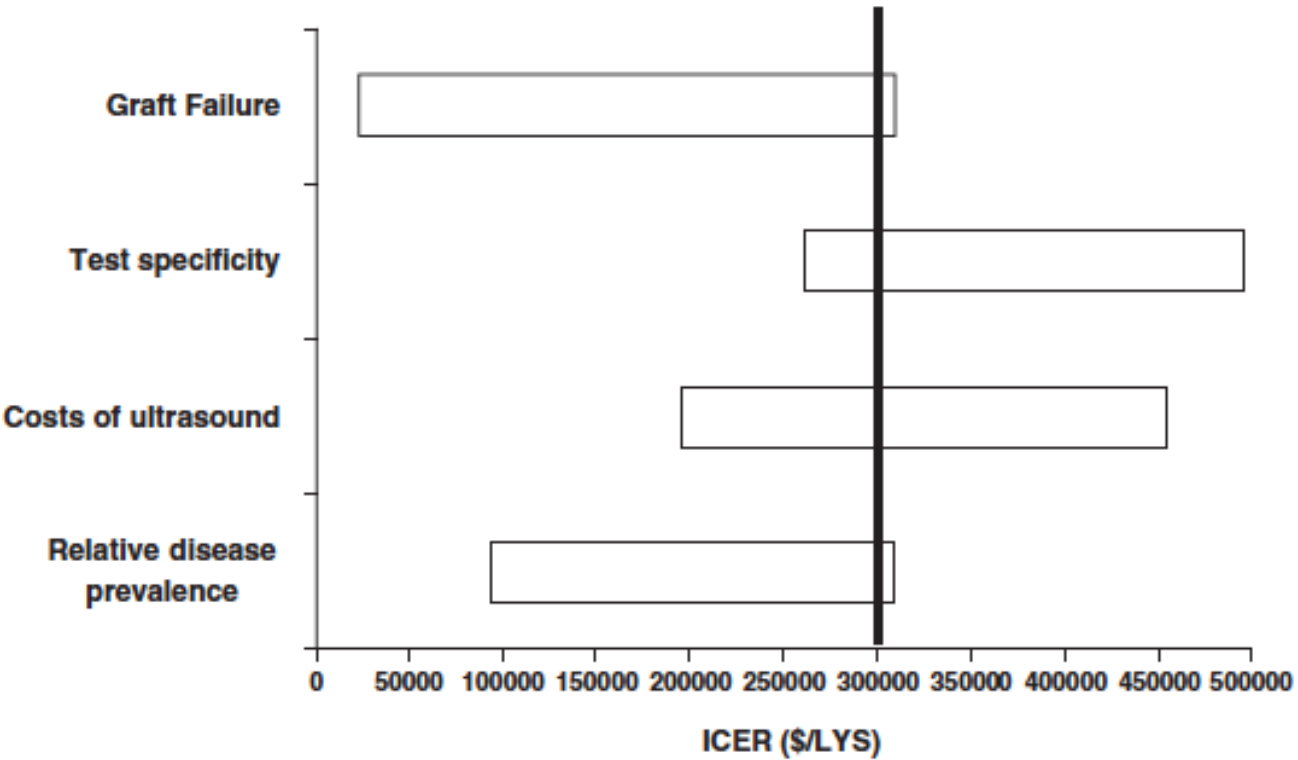
- **Bowel**
 - Two-yearly test kits for men and women aged 60-74 (50-74 in Scotland)
- **Breast**
 - All women aged 50-70 (every three-years)
- **Cervical**
 - All women aged 25-64 (every three-years)

Other screening available

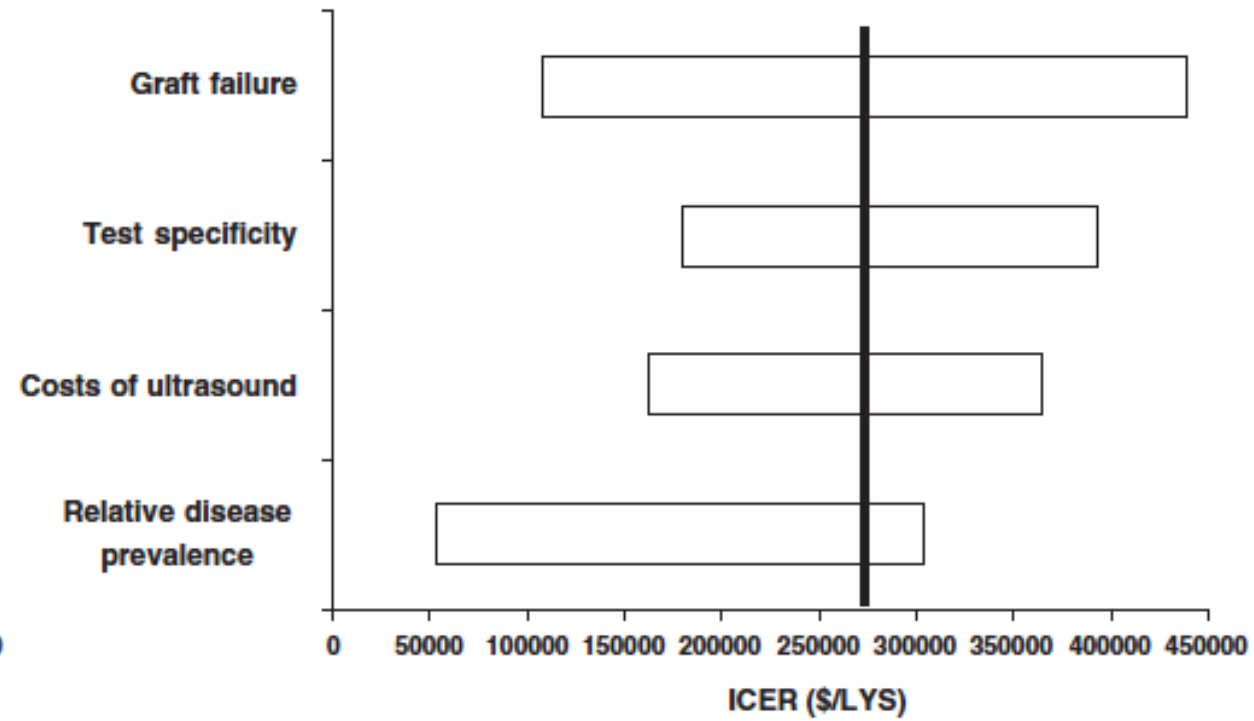
- **Prostate**
 - Men over 50 can request
- **Lung**
 - Trials in progress
- **Ovarian**
 - Trials in progress
- **PTLD**
 - EBV PCR in paediatric and stem cell transplant setting only
- **Renal**
 - No strong evidence base

(2) Screening for RCC post kidney transplantation

A) Comparing annual screening with no screening



B) Comparing biennial screening with no screening



(2) Cancer Screening Recommendations for Solid Organ Transplant Recipients: A Systematic Review of Clinical Practice Guidelines

Guideline	Domain (%)					
	Scope and purpose	Stakeholder involvement	Rigor of development	Clarity of presentation	Applicability	Editorial independence
KDIGO (23)	80	63	78	80	37	97
KHA-CARI (24)	91	42	66	94	50	100
AASLD-Adult (30)	91	56	38	69	0	50
AASLD-Pediatric (31)	89	61	71	56	21	42
AST-Kidney (25)	100	54	64	63	14	0
AST-Liver (32)	94	63	10	98	18	72
EBPG (26)	89	39	46	91	1	6
ISHLT (31)	100	63	62	74	1	100
RA (27)	93	48	33	61	0	28
SCPG (33)	96	57	20	72	28	25

Domain 1. Scope and Purpose

Domain 2. Stakeholder Involvement

Domain 3. Rigour of Development relates to the process used to gather and synthesize the evidence, the methods to formulate the recommendations, and to update them.

Domain 4. Clarity of Presentation

Domain 5. Applicability pertains to the likely barriers and facilitators to implementation, strategies to improve uptake, and resource implications of applying the guideline.

Domain 6. Editorial independence

(2) Aggressive cancer screening post kidney transplantation

ANNUAL

- Abdominal USS and CT
- Chest CT
- Neck USS
- Upper GI endoscopy
- Tumour markers
- Mammogram (women)
- Pap smears (women)
- PSA (men)
- Skin and lip exam

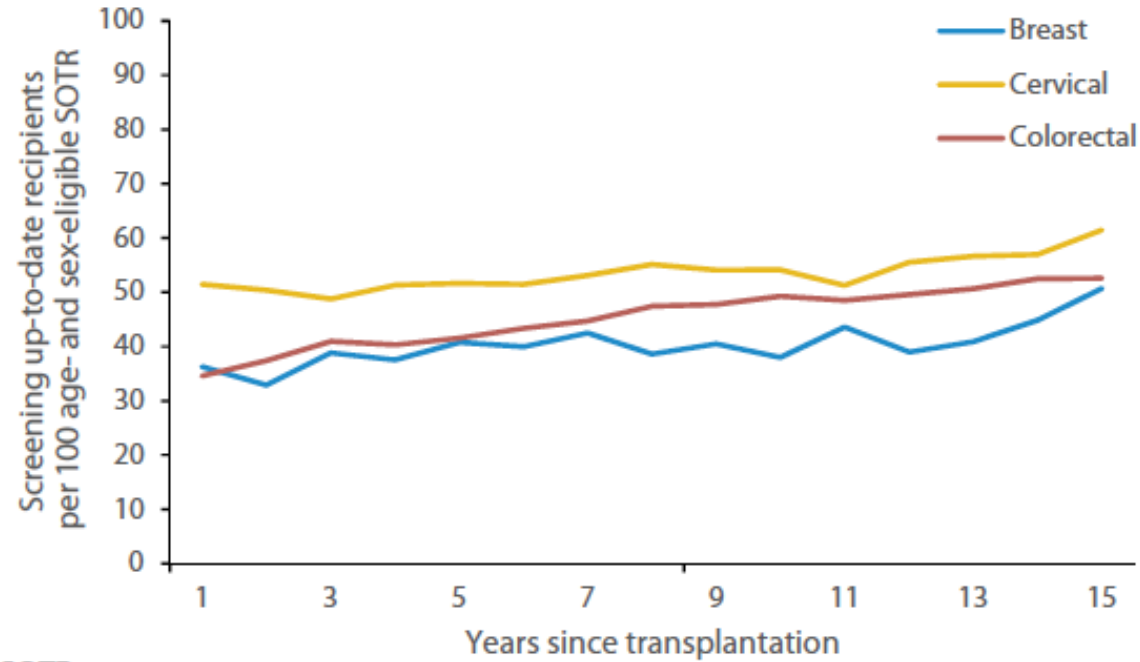
3-6 MONTHLY

- Faecal blood test (colonoscopy if +)
- Urine cytology

Table 2. Types of screening-detected and symptom-detected cancers after kidney transplantation.

	Screening-detected cancers		Symptom-detected cancers	
	Group A		Group B	Group C
			Screening (-)	Screening (+)
Lymphomas	3		2	10
Urinary tract				
Renal cell carcinoma of the native kidney	8		1	1
Renal cell carcinoma of the allograft kidney	0		1	1
Urothelial carcinoma	0		0	3
Gastrointestinal tract				
Gastric cancer	7		1	0
Colorectal cancer	1		1	3
Hepatocellular cell carcinoma	1		1	1
Genital tract				
Uterine cancer	2		1	0
Ovarian cancer	1		1	0
Breast cancer	8		1	0
Thyroid cancer	5		0	1
Others	0		11	0
Total	36		21	20

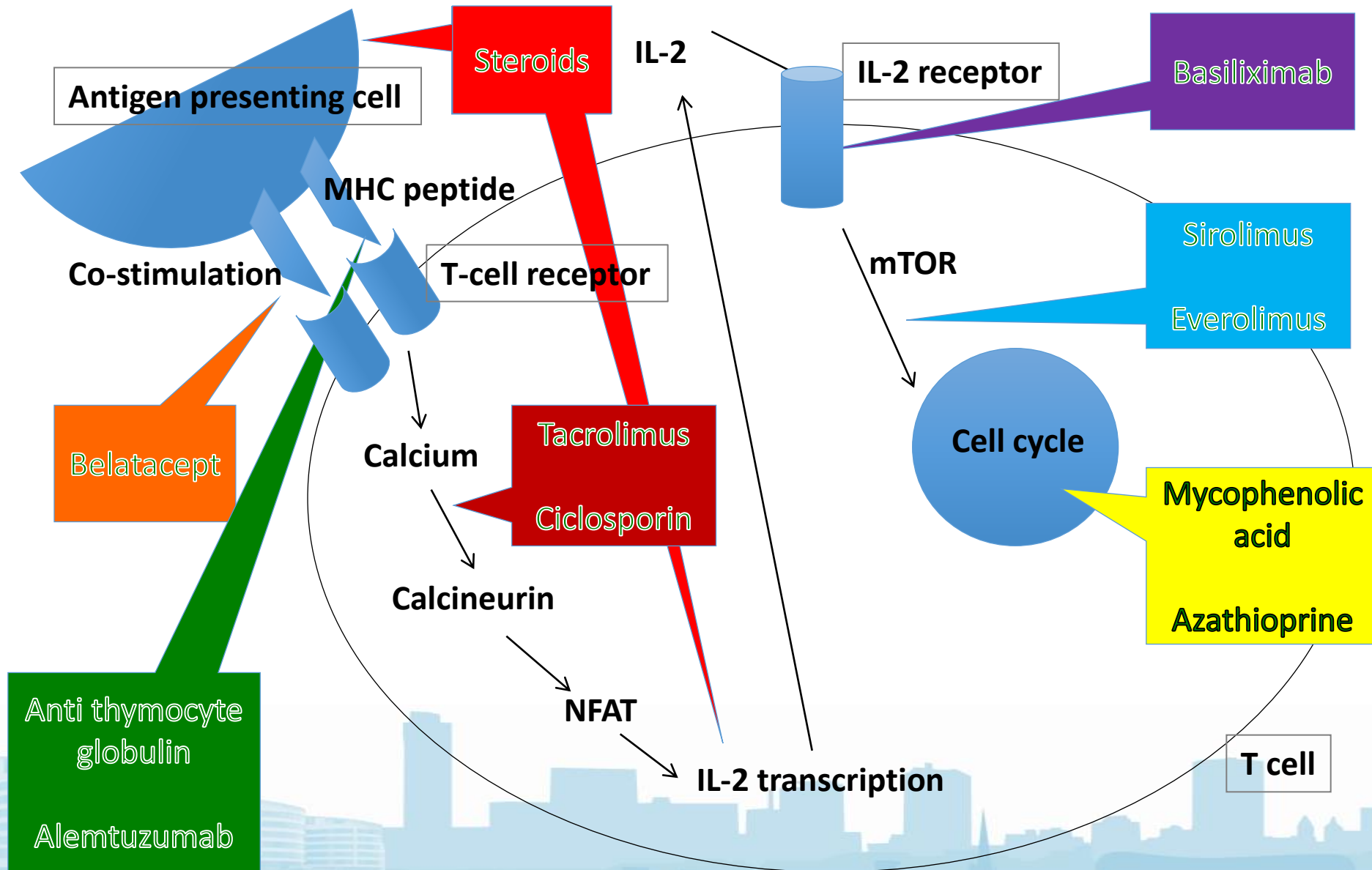
(2) Screening compliance is poor post-transplantation



EligibleSOTR

Breast	1,154	1,184	979	729	484	328	181	71
Cervical	2,225	2,030	1,545	1,079	719	476	256	96
Colorectal	3,459	3,505	2,806	2,041	1,353	909	561	253

(3) Can we pre-emptively modify immunosuppression?



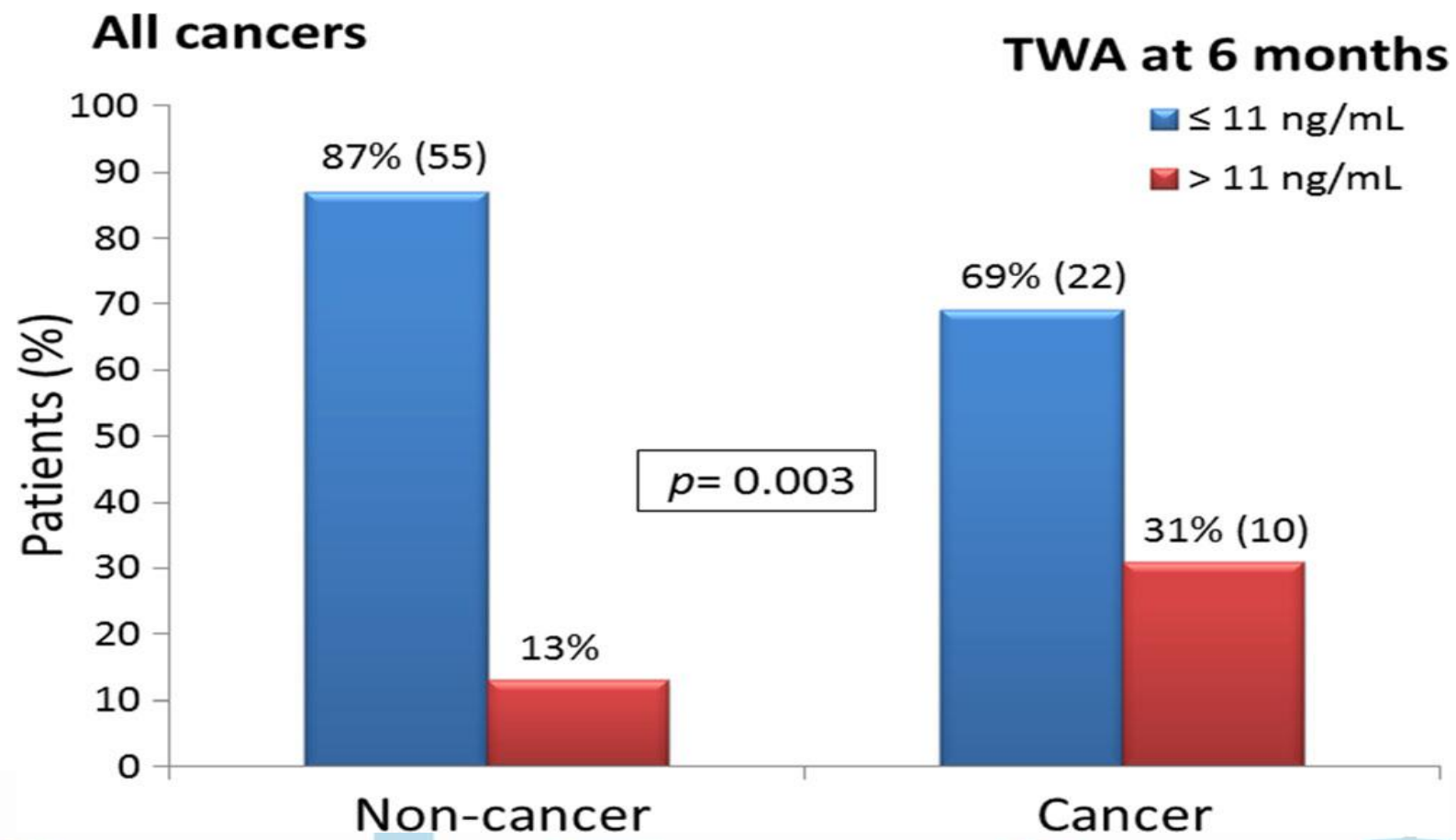
(3) Induction agents and risk for post-transplant cancer

TABLE 2. Association between induction therapy and incident virus-related cancers

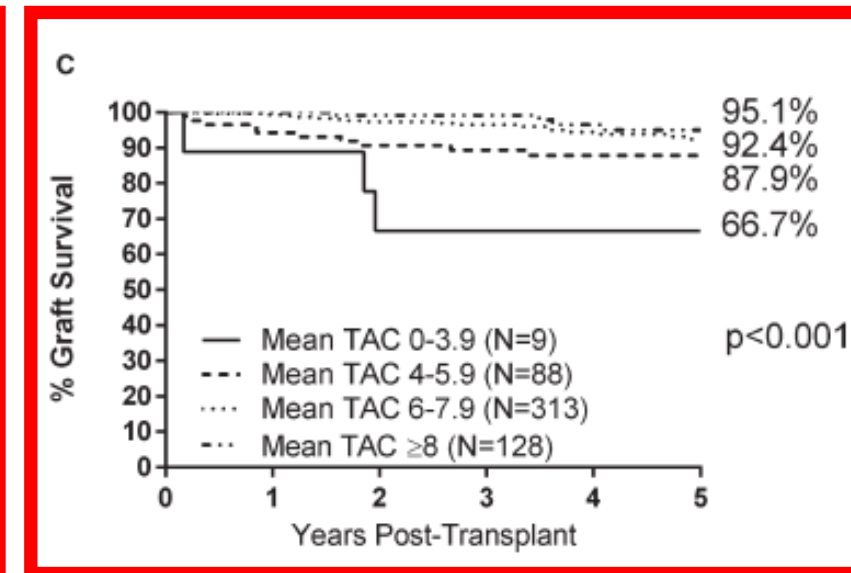
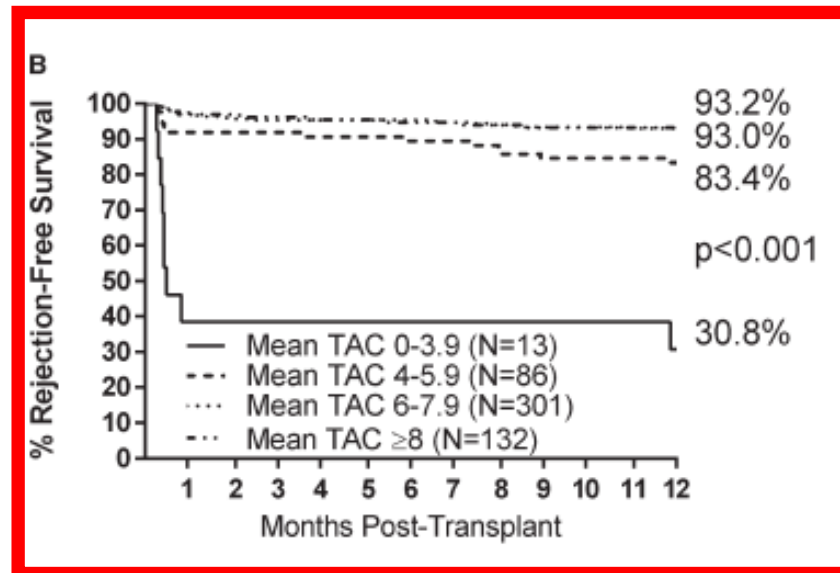
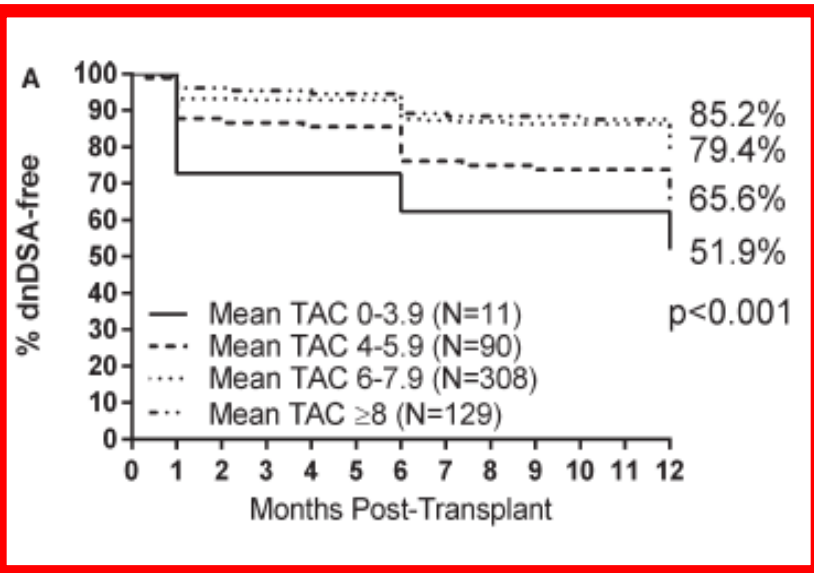
	Cancers, N	Incidence ^a	aIRR (95% CI)	P
NHL				
No induction	377	142.1	Reference	
Polyclonal	125	131.6	0.96 (0.77–1.20)	0.7
Muromonab-CD3	80	210.9	1.37 (1.06–1.76)	0.02
Alemtuzumab	15	216.2	1.79 (1.02–3.14)	0.04
Anti-IL2R	96	114.9	0.82 (0.65–1.05)	0.1
Non-NHL VRCs				
No induction	164	61.8	Reference	
Polyclonal	56	60.0	1.11 (0.82–1.53)	0.5
Muromonab-CD3	25	65.9	1.02 (0.65–1.58)	0.9
Alemtuzumab	4	57.6	2.05 (0.66–6.33)	0.2
Anti-IL2R	53	63.5	1.09 (0.78–1.51)	0.6
All VRCs				
No induction	541	203.9	Reference	
Polyclonal	181	190.6	1.01 (0.84–1.21)	0.9
Muromonab-CD3	104	276.8	1.26 (1.01–1.57)	0.04
Alemtuzumab	19	273.8	1.84 (1.11–3.03)	0.02
Anti-IL2R	149	178.4	0.90 (0.74–1.10)	0.3

^a Per 100,000 person-years.

(3) Risk of post-transplant cancer is related to time-weighted average tacrolimus exposure



(3) Low tacrolimus exposure is linked to poor graft-related outcomes



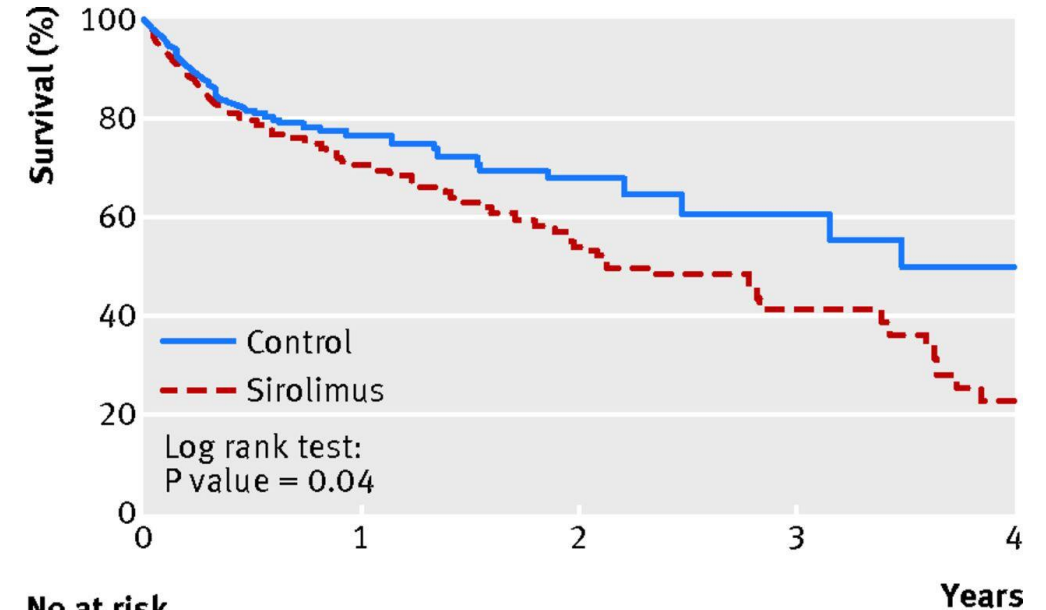
(3) MMF versus azathioprine for post-transplant cancer risk

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	AZA	MMF				
Death, all cause Follow-up: 0.5 to 5 years	49 per 1000	47 per 1000 (34 to 63)	RR 0.95 (0.7 to 1.29)	2987 (16)	⊕⊕⊕○ moderate ¹	No evidence for difference due to low precision
Graft loss, censored for death Follow-up: 0.5 to 6 years	11 per 100	9 per 100 (7 to 11)	RR 0.78 (0.61 to 0.98)	2540 (17)	⊕⊕⊕⊕ high ²	Statistically significant risk reduction of meaningful magnitude (~20%) with MMF treatment
Malignancy, any Follow-up: 1 to 6 years	10 per 100	8 per 100 (6 to 11)	RR 0.81 (0.6 to 1.09)	1735 (5)	⊕○○○ very low ^{3,4,5}	Statistically not significant favourable point estimate (~20%) with MMF treatment, but very low quality evidence
Acute rejection, steroid resistant/antibody treated As reported in the articles	11 per 100	5 per 100 (4 to 7)	RR 0.48 (0.36 to 0.65)	2914 (15)	⊕⊕⊕⊕ high	Statistically significant risk reduction of meaningful magnitude (~50%) with MMF treatment

(3) Effect of sirolimus on cancer and survival after kidney transplantation

	Trials	Events	Patients	Hazard ratio (95% CI)	Hazard ratio (95% CI)
Any cancer					
All trials	21	243	5876		0.60 (0.39 to 0.93)
De novo trials	15	109	4717		1.09 (0.74 to 1.61)
Conversion trials	6	134	1159		0.34 (0.28 to 0.41)
Low dose sirolimus trials	12	76	2384		0.65 (0.30 to 1.41)
High dose sirolimus trials	9	167	3492		0.57 (0.36 to 0.91)
Non-melanoma skin cancer					
All trials	21	150	5876		0.44 (0.30 to 0.63)
De novo trials	15	51	4717		0.65 (0.36 to 1.17)
Conversion trials	6	99	1159		0.32 (0.24 to 0.42)
Low dose sirolimus trials	12	54	2384		0.43 (0.24 to 0.78)
High dose sirolimus trials	9	96	3492		0.43 (0.26 to 0.70)
Other cancer					
All trials	21	106	5876		1.05 (0.57 to 1.94)
De novo trials	15	61	4717		1.70 (0.98 to 2.93)
Conversion trials	6	45	1159		0.52 (0.38 to 0.69)
Low dose sirolimus trials	12	24	2384		1.73 (0.55 to 5.46)
High dose sirolimus trials	9	82	3492		0.84 (0.52 to 1.36)

Favours Sirolimus : Favours Control

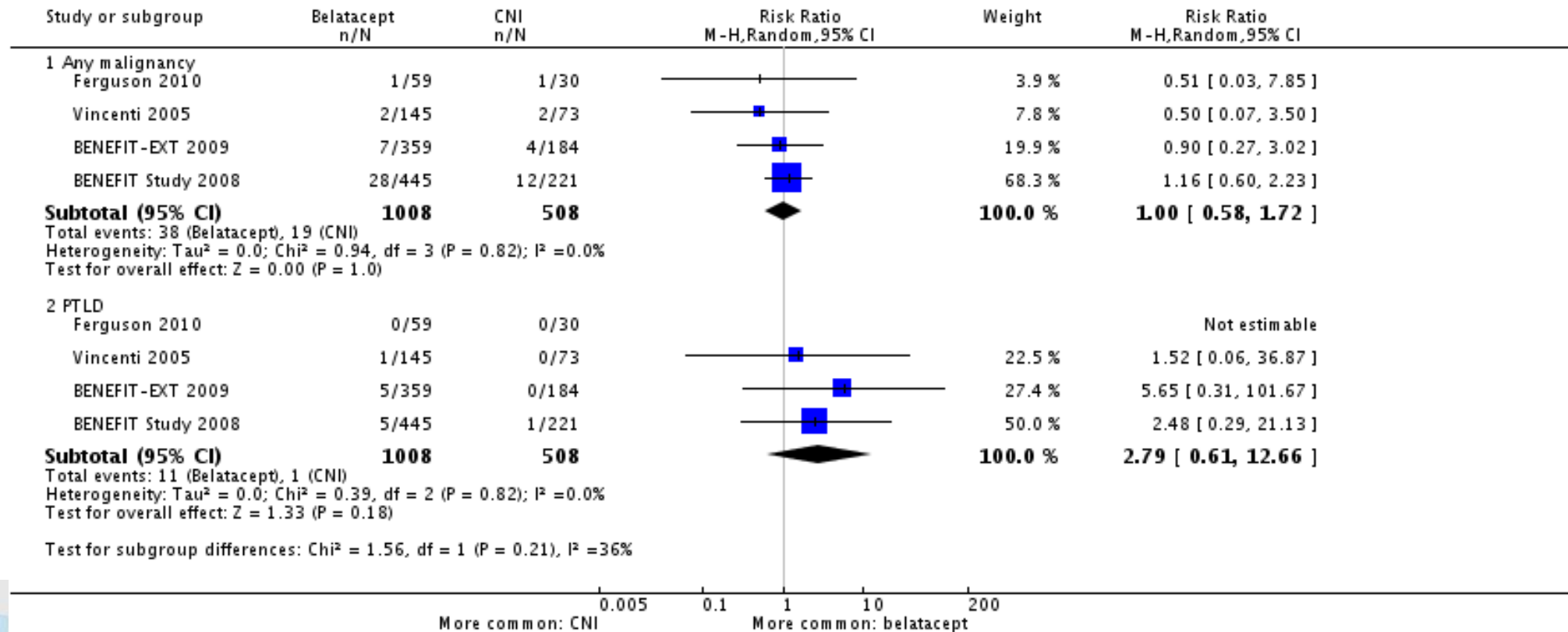


No at risk

	0	1	2	3	4
Control	2600	1809	613	184	
Sirolimus	3276	2375	1362	363	

(3) Cochrane review – belatacept v CNI (cancer data)

Review: Belatacept for kidney transplant recipients
 Comparison: 1 Any dosage belatacept versus calcineurin inhibitor (CNI)
 Outcome: 5 Malignancy



(4) Personalised cancer medicine

1. Find out the chances of a person developing cancer and selecting screening strategies to lower the risk
2. Match patients with treatments that are likely to be more effective and cause fewer side effects
3. Predict the rate of cancer recurrence



(4) Limitations of the data


- Transplantation practice has evolved over last decade
- US data cannot be translated to the UK for transplant recipients
- Lack of patient-level data on screening and management after post-transplantation cancer diagnosis
- Registry or administrative data in isolation is limited

Cancer Medicine

Open Access

ORIGINAL RESEARCH

Cancer-related outcomes in kidney allograft recipients in England versus New York State: a comparative population-cohort analysis between 2003 and 2013

Francesca Jackson-Spence¹, Holly Gillott¹, Sanna Tahir¹, Jay Nath^{1,2}, Jemma Mytton³, Felicity Evison³ & Adnan Sharif^{1,2} 

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Cancer Medicine

Open Access

ORIGINAL RESEARCH

Mortality risk after cancer diagnosis in kidney transplant recipients: the limitations of analyzing hospital administration data alone

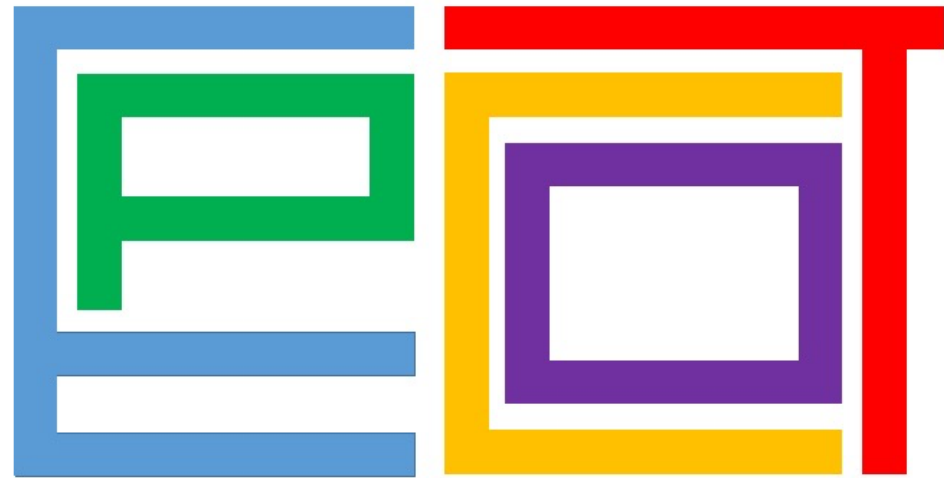
Francesca Jackson-Spence¹, Holly Gillott¹, Sanna Tahir¹, Jay Nath^{1,2}, Jemma Mytton³, Felicity Evison³ & Adnan Sharif^{1,2} 

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Improving our understanding of cancer epidemiology after solid organ transplantation



Epidemiology of Cancer after solid Organ Transplantation

EpCOT research questions

1. Compare observed and expected risks of specific causes of deaths after transplantation
2. Investigate survival and causes of death after cancer in post-transplant patients
3. Compare observed and expected risks of specific cancer types after transplantation
4. Estimate risk of morbidity requiring hospitalisation post-transplantation
5. Post-transplant cancer risk prediction using machine learning

National
record
linkage

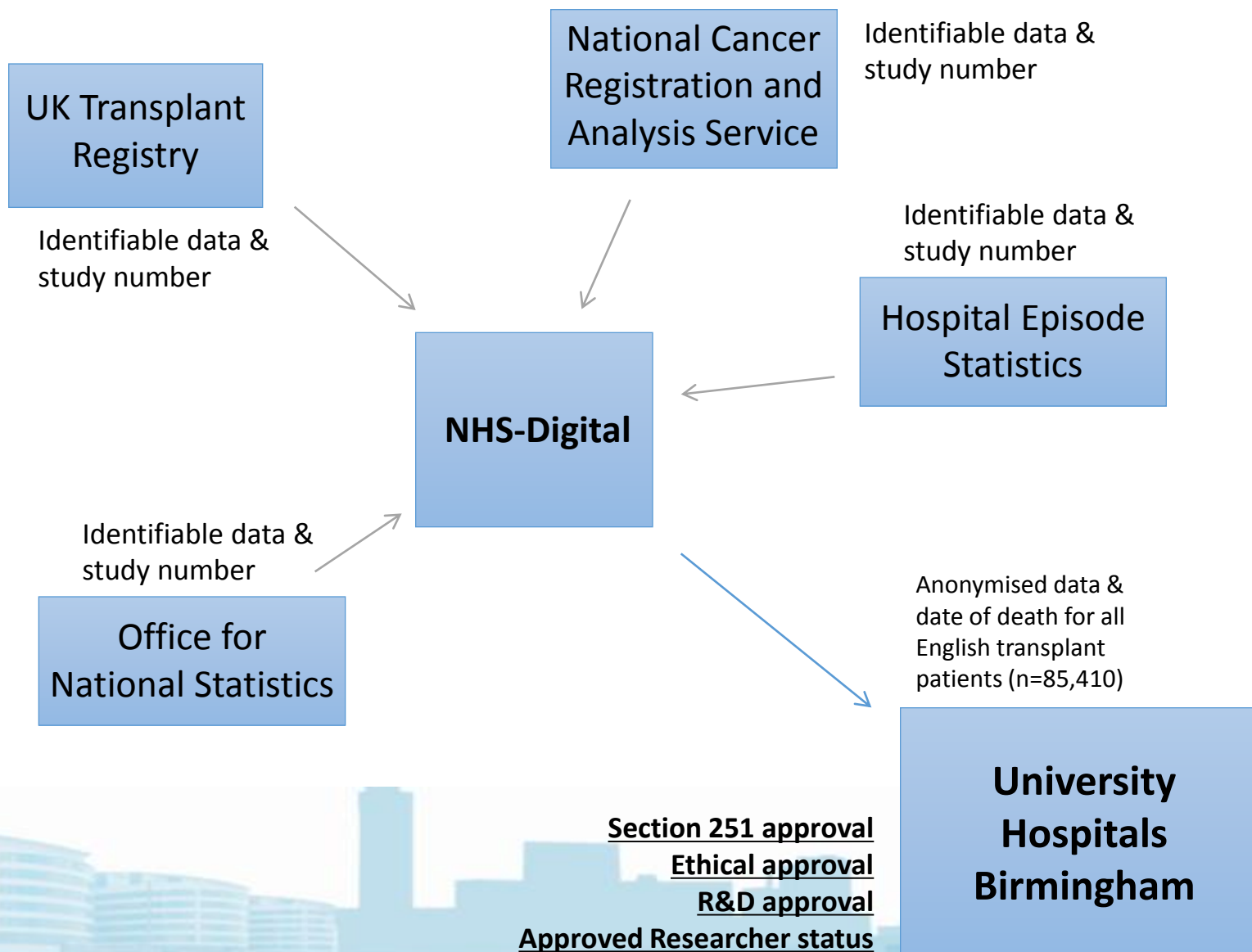
6. Evaluate up-take of existing general population cancer screening among solid organ transplant recipients
7. Investigate management of cancer after solid organ transplantation

UHB
recruitment

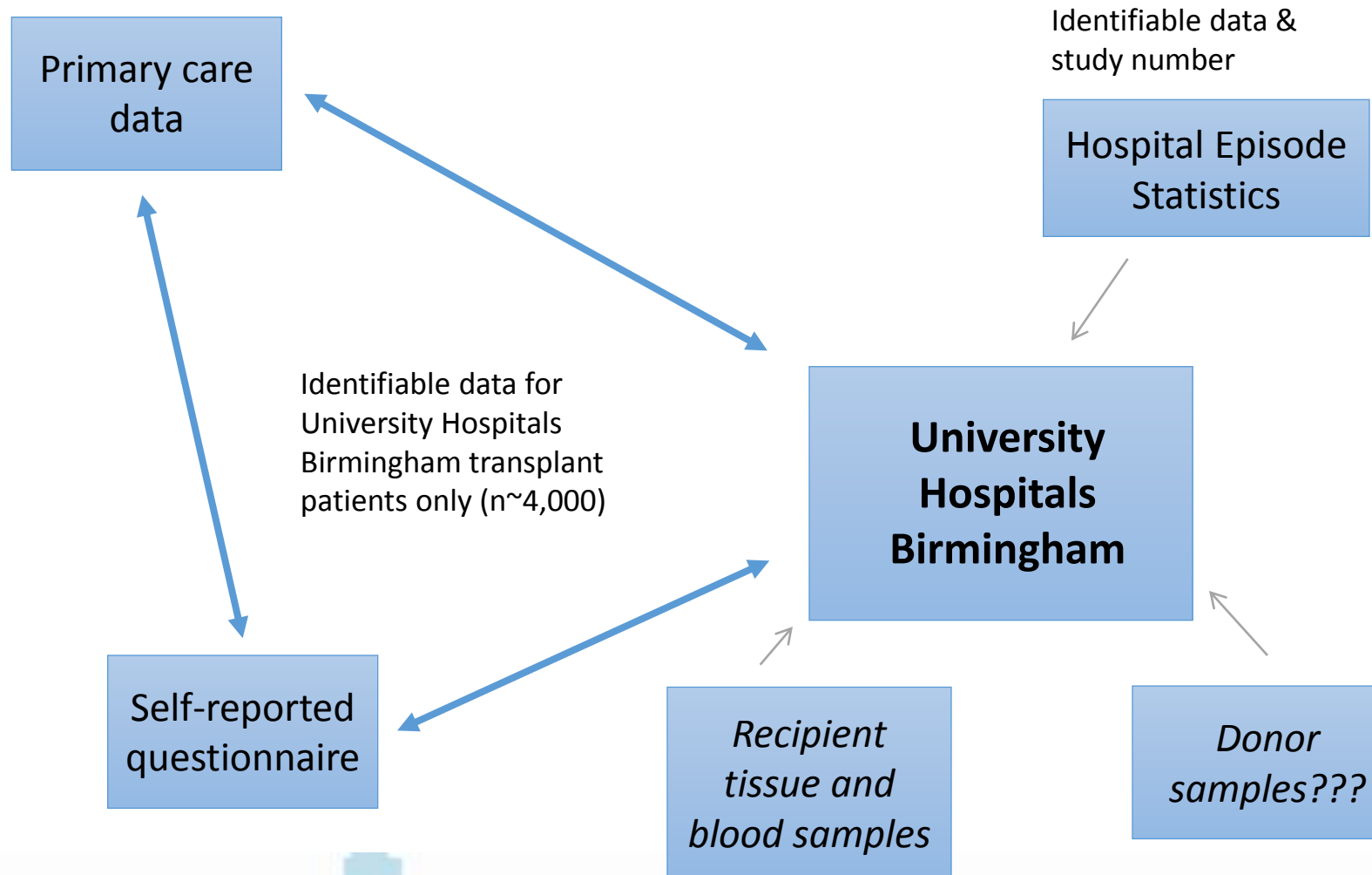
8. Develop standardised clinical follow-up guidelines for solid organ transplant recipients

British
Transplantation
Society

National record linkage



UHB recruitment



Conclusions

- Mortality from cancer is increasing with time post-transplantation and becoming the leading cause of death
- Particular groups are at high risk for developing cancer
- Lifestyle modification must be strongly encouraged
- Screening strategies should follow national guidelines but also may require tailoring for transplant-specific risk:
 - Routine native kidney USS if high dialysis vintage?
- Attenuation/modification of immunosuppression must balance risk-versus-benefit stratification on patient-by-patient basis
- Population-based health data may provide answers and updates to un-answered questions – the EpCOT study is designed to address this evidence-base gap



Thank you
for you
attention

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