

بِسْمِ اللَّهِ الرَّحْمَنِ الرَّحِيمِ



Post Kidney Transplant Malignancies

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Tabriz; Iran 2019***

Disclosures

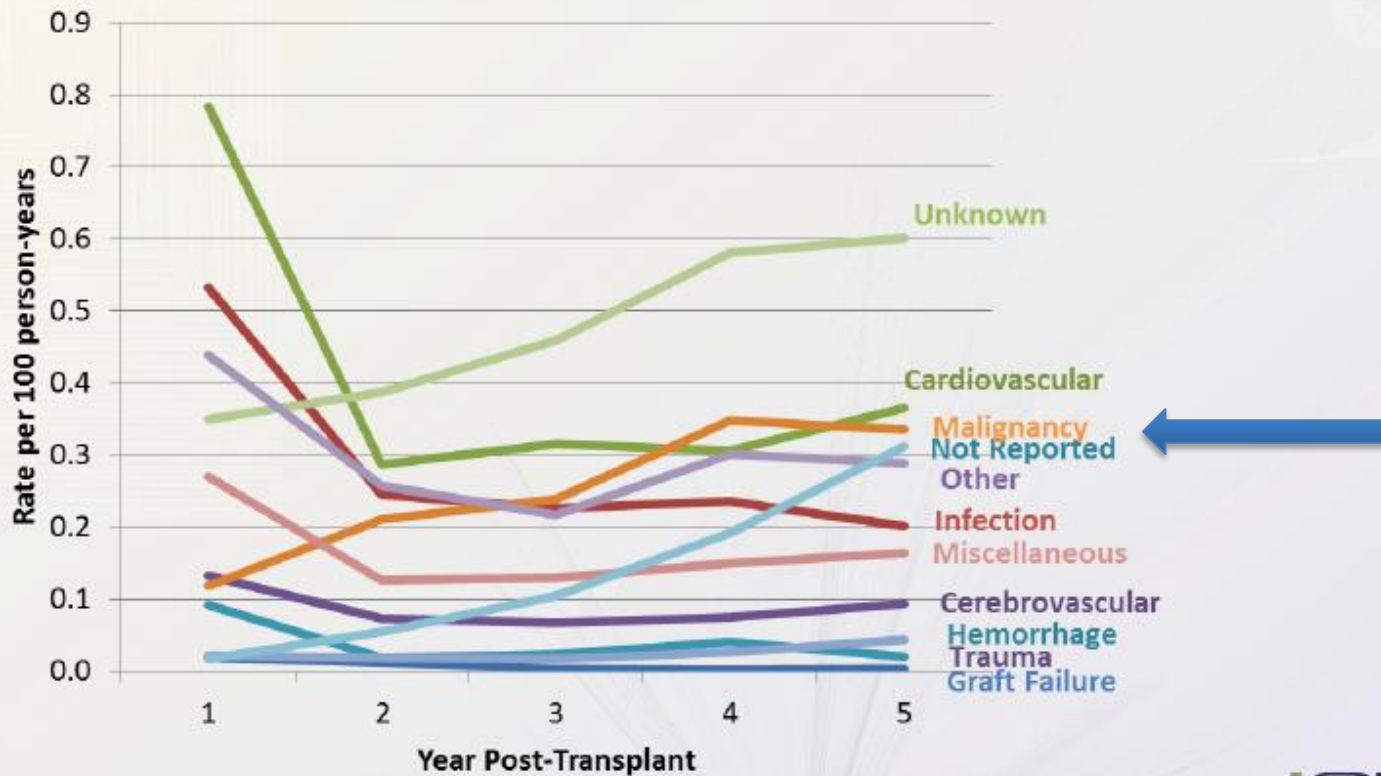
- **No financial conflicts to disclose that pertain to this presentation**
- **Discussion of off label use of medications: None**
- **Editorial board conflict disclosure: Chief Editor of NU-Monthly J**
- **I am a Nephrologist**

Are transplant patients at increased risk for malignancy?

Malignancy

- **Cancer after transplantation is 3x more likely than general population.**
- **These cancers have 5 fold or > increase in transplant patients**
 - Kaposi Sarcoma
 - Skin Cancer
 - Non-Hodgkin Lymphoma
 - Liver
 - Anus/Lip/Vulva
- **Malignancy represents the 3rd most common cause of death in renal transplant recipients.**

Cause-Specific Rates of Death with Function 2005-2010



14

SCTR
SCIENTIFIC REGISTRY OF
TRANSPLANT RECIPIENTS

Myth:

*All cancers are
increased by
immunosuppression.*

Standard Incidence Ratio (SIR) of cancer after kidney Tx, compared general population

Cancer rates vs. general population

Moderate Risk	Colon, lung, prostate, gastric, esophagus, pancreas, ovary and breast	2
	Testes and urinary, bladder	3
	Cutaneous melanoma, leukemia, liver and gynecological tumors	5
High risk	Kidney	15
	Kaposi sarcoma, PTLD, skin cancer	>20

Cancer		Overall Incidence %	Frequency and cumulative incidence					Total frequency			
			Freq1	Inc1%	Freq2	Inc2%	Freq3	Inc3%	frequency	percent	total
GI	Colon	0.04			2	0.75			6	2.4	17
	Gastric	0.03			1	0.4			4	1.6	
	Rectum	0.01	1	0.4					2	0.8	
	pancreases	0.007					1	0.4	1	0.4	
	hepatoma	0.02					2	0.75	3	1.2	
	esophagus	0.007	1	0.4					1	0.4	
skin	SCC	0.3	5	1.9	4	3.3	1	3.7	40	13.5	141
	BCC	0.1	3	1.1	2	1.9	2	2.6	15	6.1	
	Melanoma	0.01					1	0.4	2	0.8	
	KS	0.6	40	14.3	15	16.9	8	20	84	31	
	SCC+BCC	0.007							1	0.4	
GU & RS	Brest	0.02			1	0.4			3	1.2	25
	Uterin	0.01					1	0.4	2	0.8	
	Ovary	0.02							3	1.2	
	Prostat	0.007			1	0.4			1	0.4	
	Seminoma	0.01			1	0.4			2	0.8	
	RCC	0.04	1	0.4	1	0.75			6	2.4	
	TCC	0.06	1	0.4					8	3.3	
Pulmonary	Mesothelioma	0.007	1	0.4					1	0.4	3
	lung	0.02	1	0.4			1	0.75	3	1.2	
PTLD		0.5	17	6.4	7	3.8	7	11.6	72	27.3	72
Thyroid		0.01			1	0.4			2	0.8	2
Parathyroid		0.007							1	0.4	1
Chondrosarcoma		0.007							1	0.4	1
Pelvic sarcoma		0.007			1	0.4			1	0.4	1
Brain		0.02			1	0.4			3	1.2	3

Freq1: frequency 1st year, Freq2: frequency 2nd year, Freq3: frequency 3rd year

Inc1: incidence 1st year, Inc 2: incidence 2nd year, Inc 3: incidence 3rd year

GI: gastrointestinal, GU & RS: genitourinary and reproductive system, PTLD: post transplantation lymphoproliferative disorder, KS: Kaposi's sarcoma, SCC: squamous cell carcinoma, BCC: basal cell carcinoma, RCC: renal cell carcinoma, TCC: transitional cell carcinoma

12525 RTRs, accounting for up to 59% of all kidney transplantation in Iran

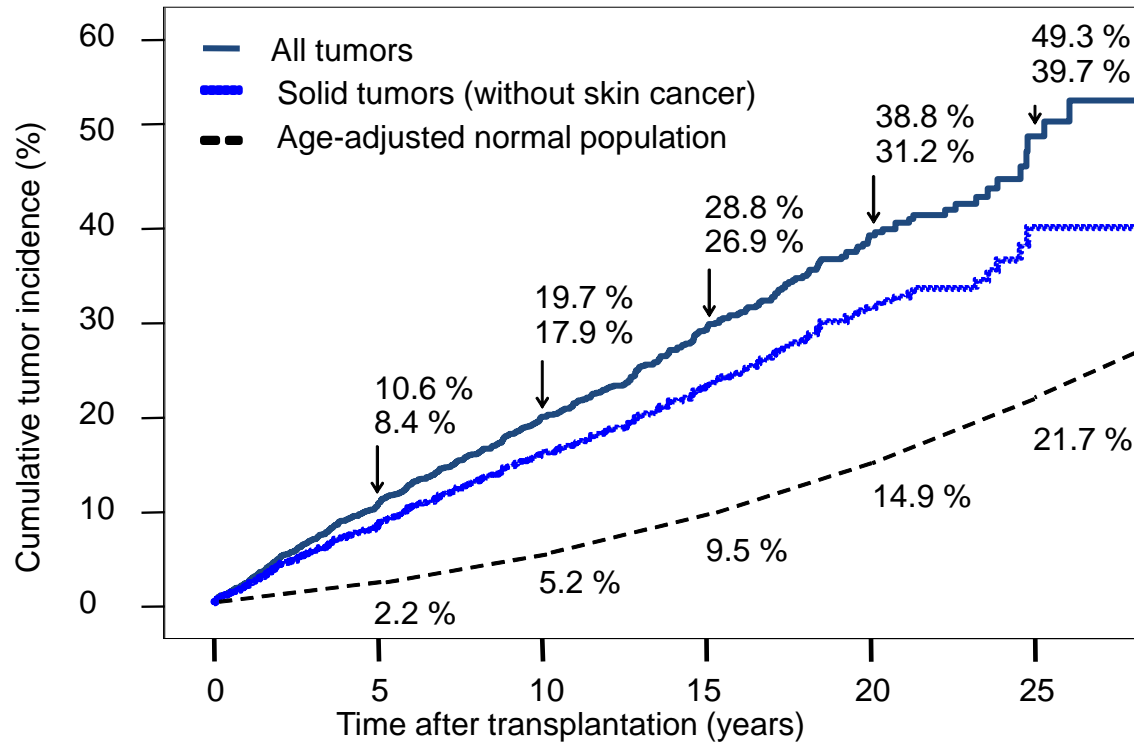
Einollahi B, et al. *Journal of Cancer* 2012

Common malignancies after KT

Cancer type	Incidence/10,000 person-years	SIR (95% CI)
Skin cancer	23.7	13.85 (11.92–16.00)
Kaposi sarcoma	15.5	61.46 (50.95–73.49)
PTLD	194.0	7.54 (7.17–7.93)
Lung	173.4	1.97 (1.86–2.08)
Liver	120	11.56 (10.83–12.33)
Kidney	97	4.65 (4.32–4.99)

Engels EA, et al. JAMA 306: 1891–1901, 2011

Risk for cancer increases with time post-transplant

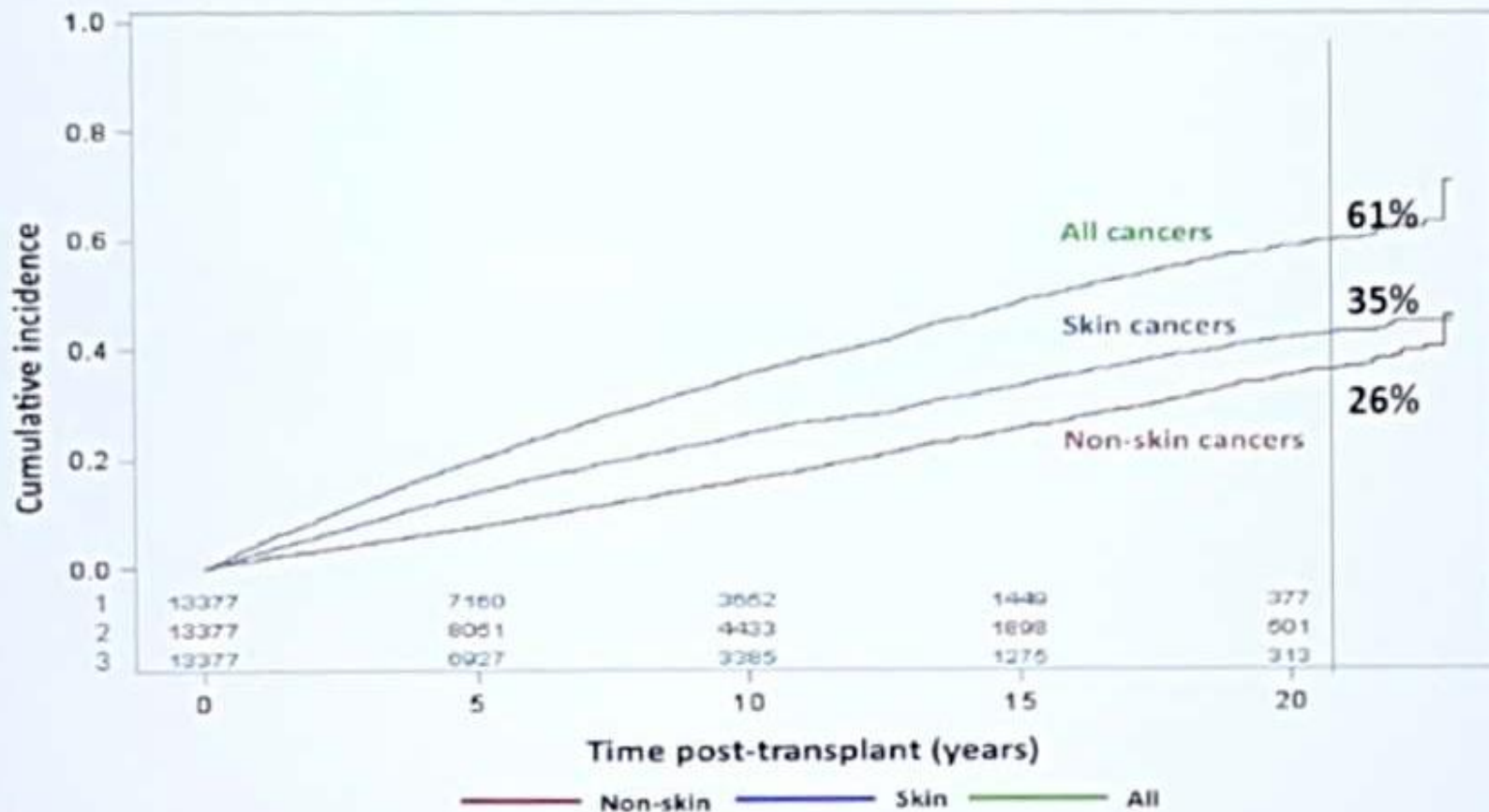


Based on 2419 renal transplant recipients from the Munich Großhadern transplantation center

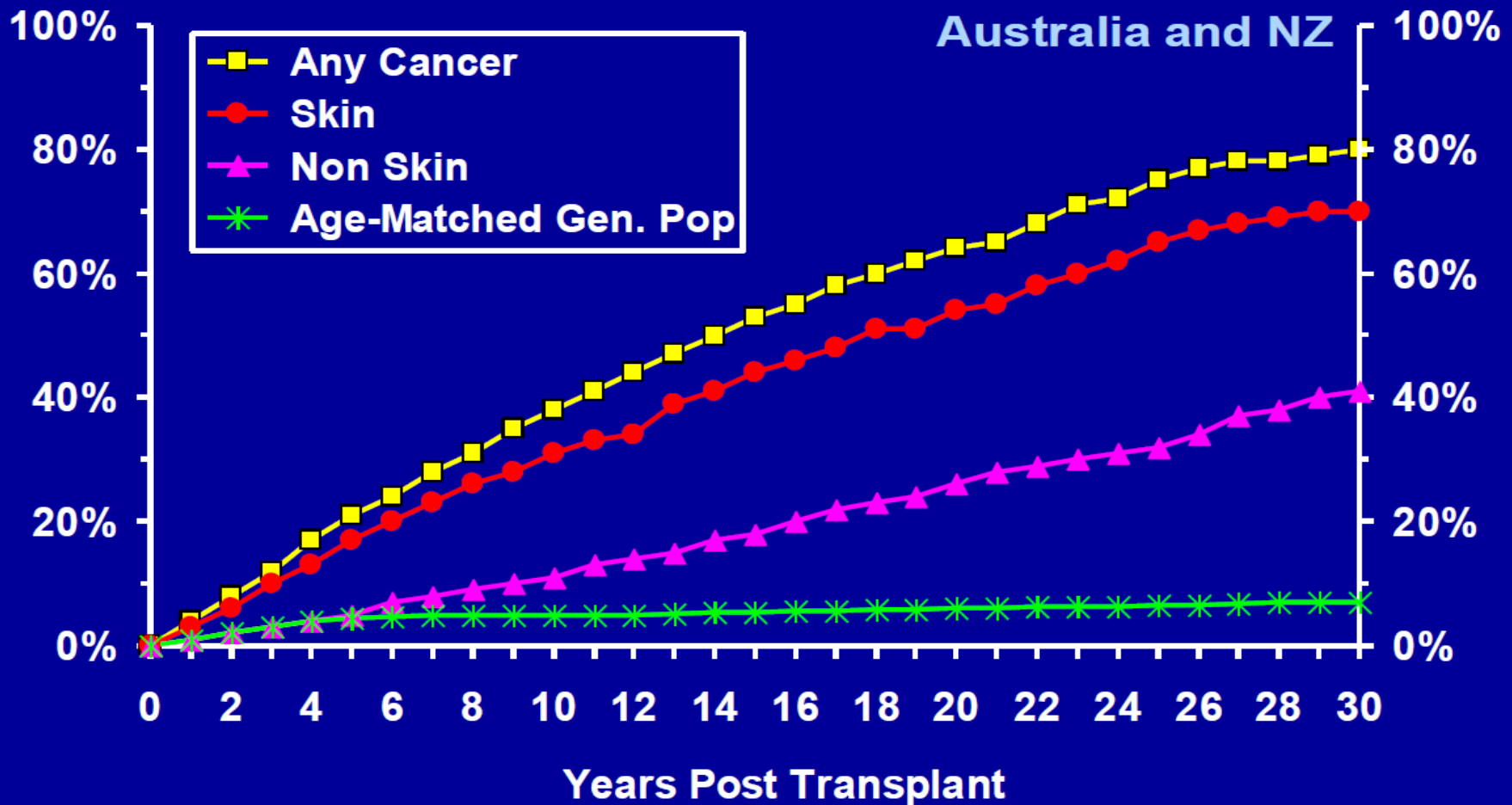
Wimmer CD, et al. Kidney Int. 2007;71:1271-1278.

Cancer is common after kidney transplantation

Cancer Incidence 1990-2012
Primary kidney transplant recipients in Australia and New Zealand



Cancer occurs in 80% of kidney transplanted patients by 30 years



No increased risk shown

- Breast
- Prostate
- Rectum
- Ovary/Uterus
- Brain
- Pancreas

Myth:

All cancers are increased by immunosuppression

Reality:

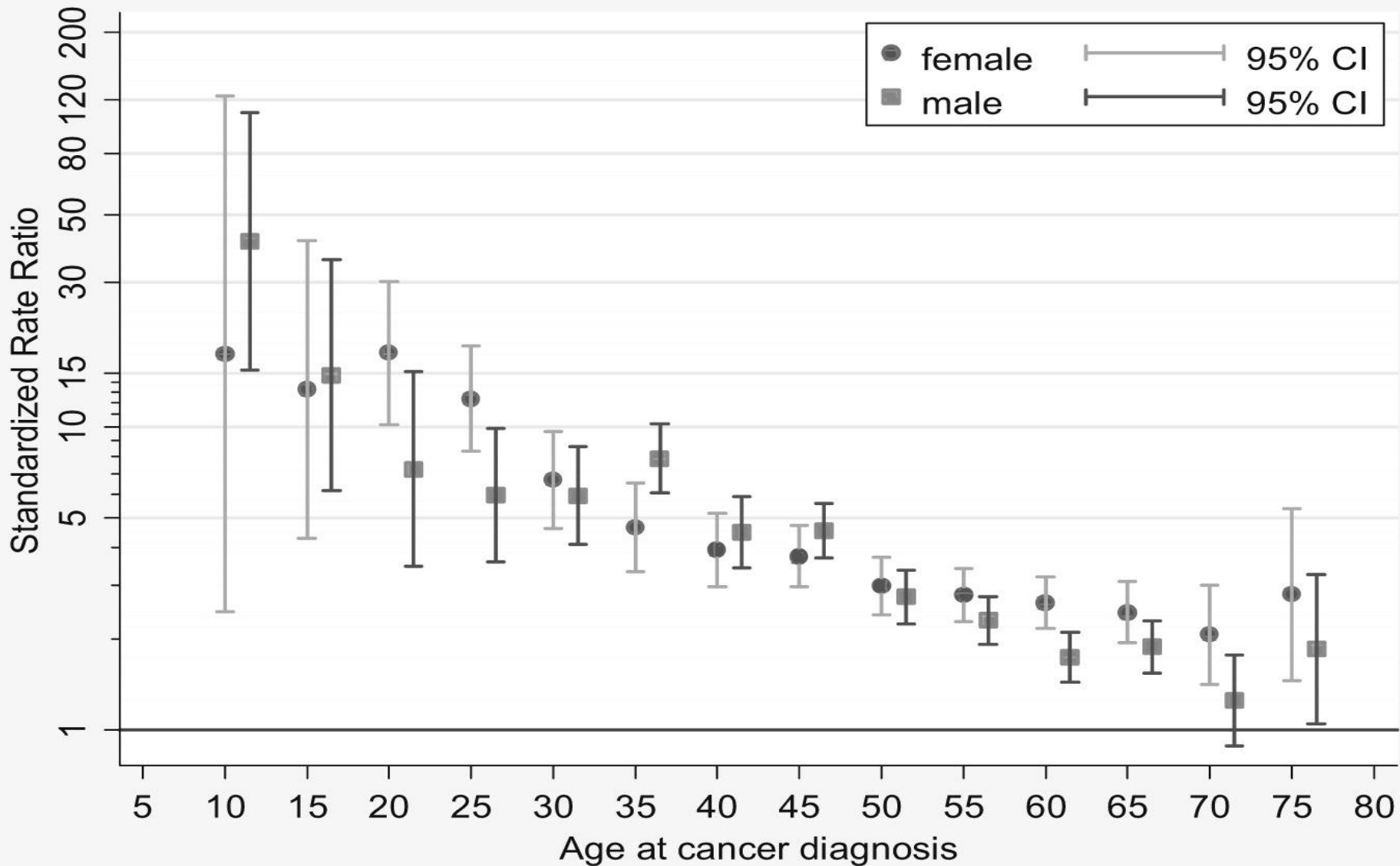
Some cancers are not increased

Myth:

Cancer is a disease of old people

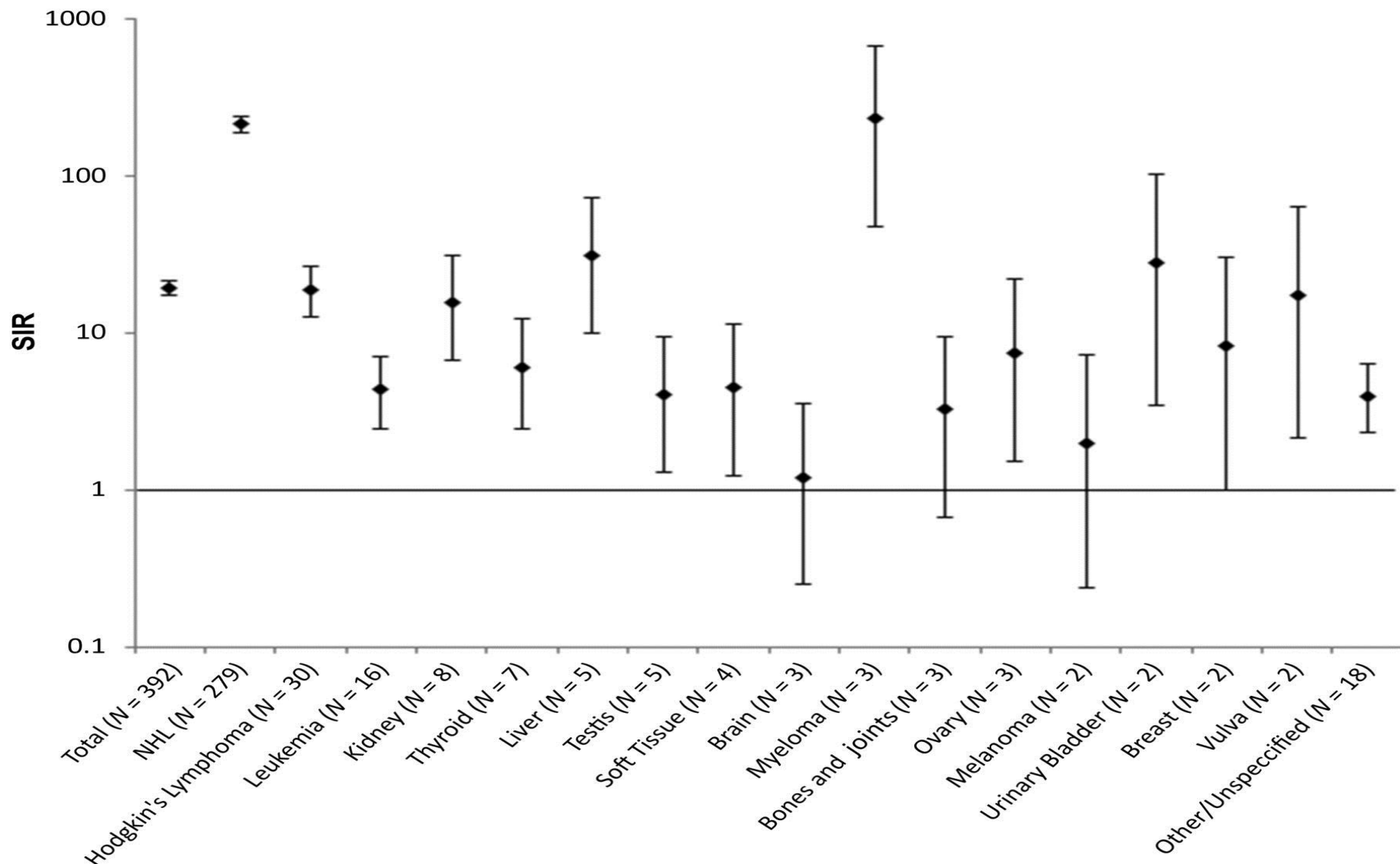
Reality:

More common in the old, but relatively much higher risk in young transplant patients



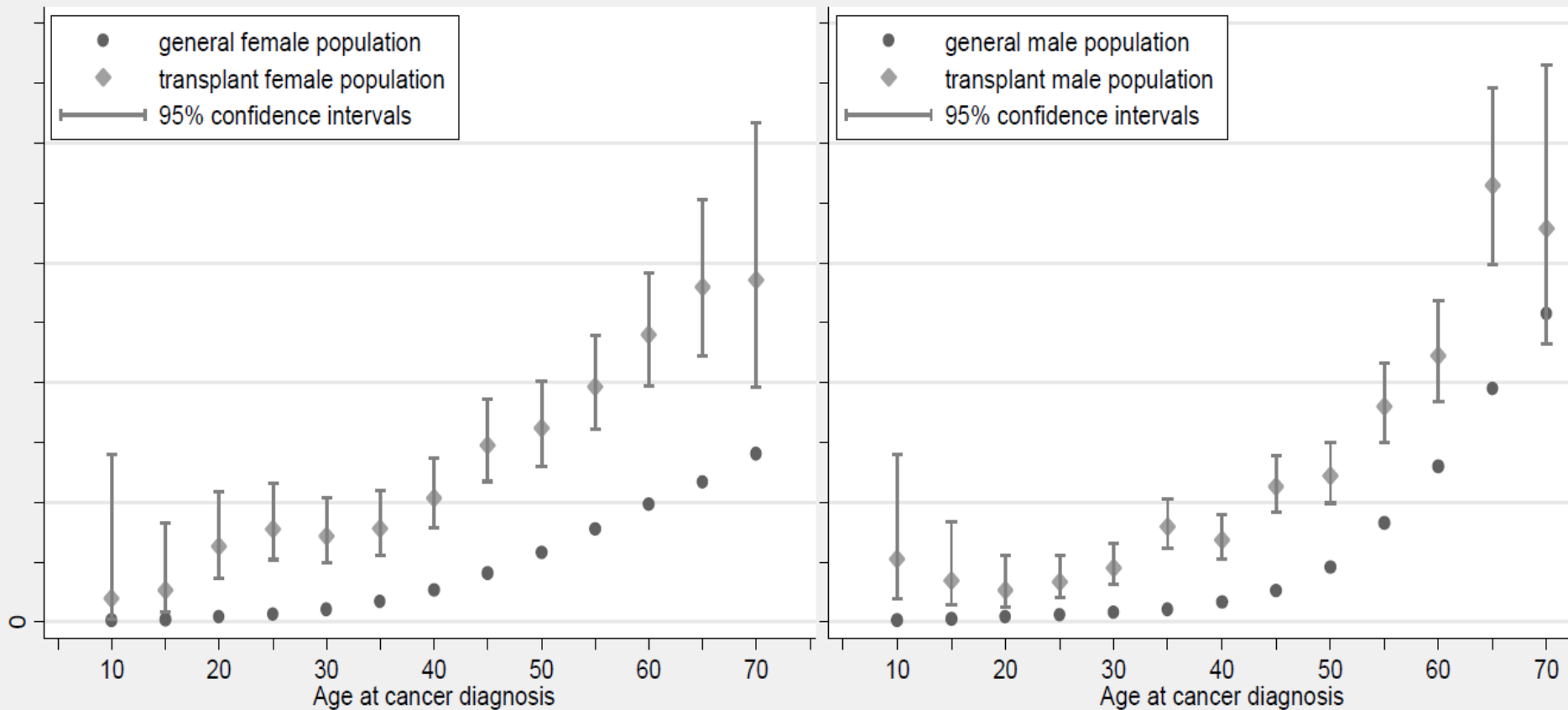
***Advances in Chronic Kidney Disease* 2014 21, 106-113 DOI: (10.1053/j.ackd.2013.07.003)**

SIRs for cancer among US pediatric transplant recipients.



Elizabeth L. Yanik et al. *Pediatrics* 2017;139:e20163893

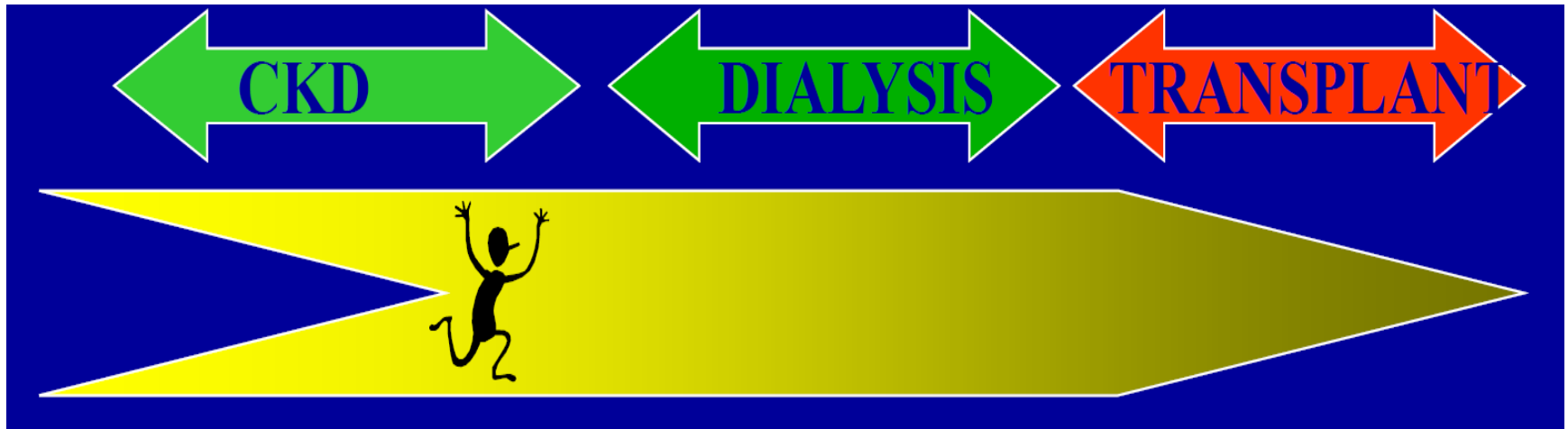
Incident cancer rates after kidney transplantation are similar to people 20+ years older in the gen pop



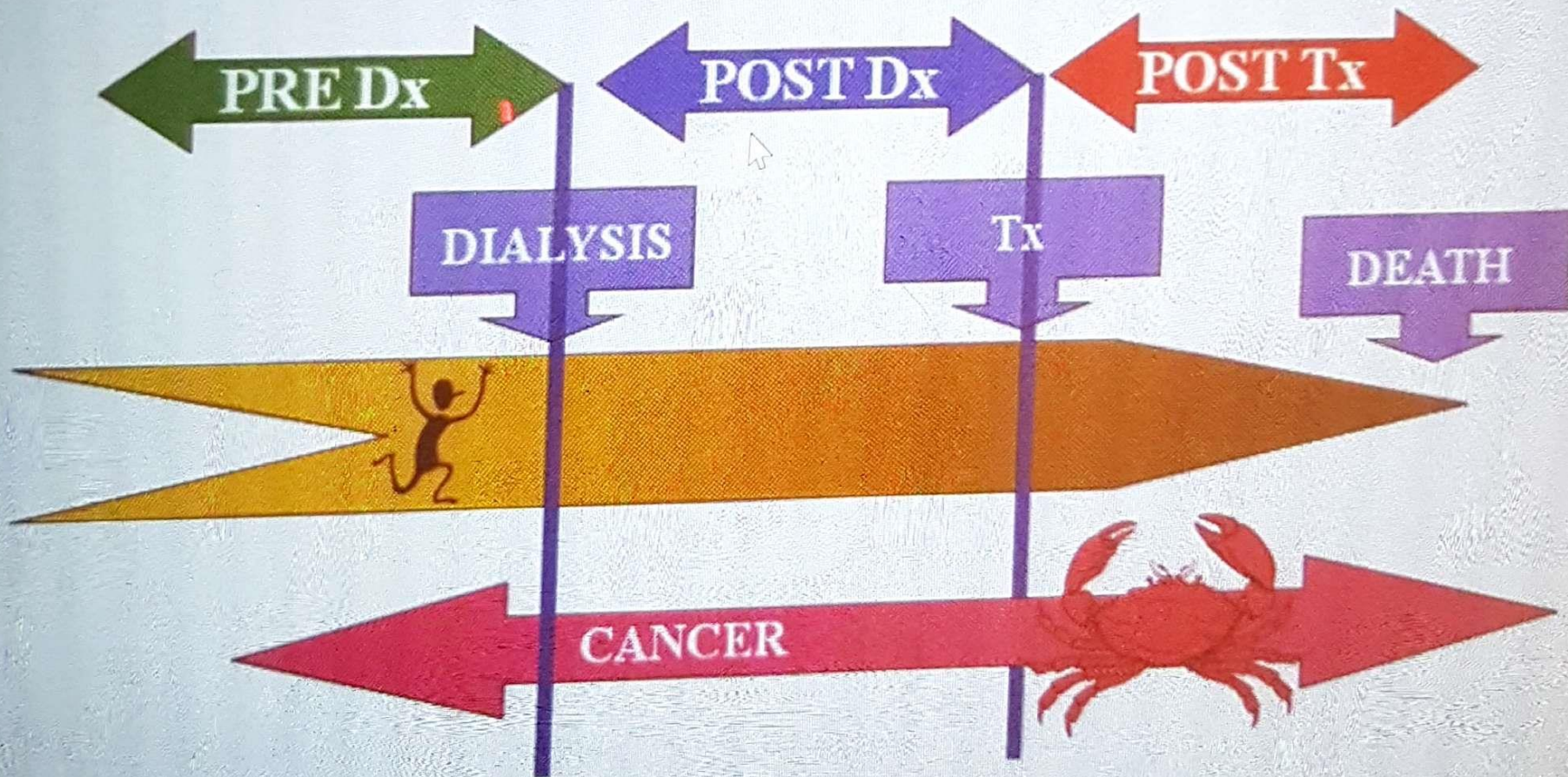
Myth:

***Cancer is only increased
after transplantation***

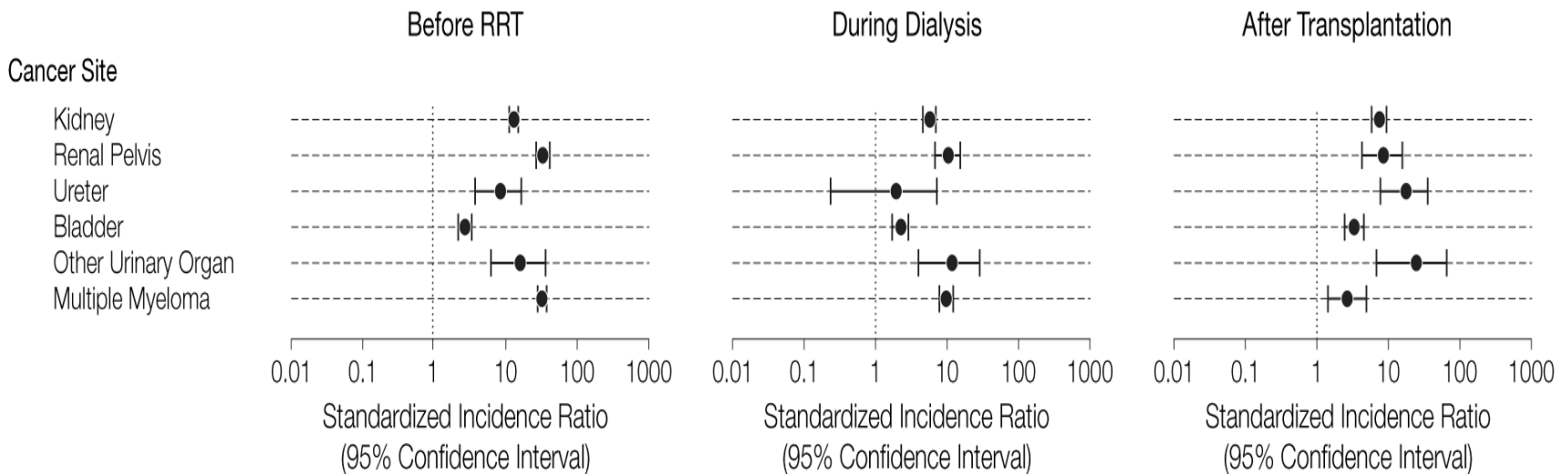
Timing of Cancer Diagnosis



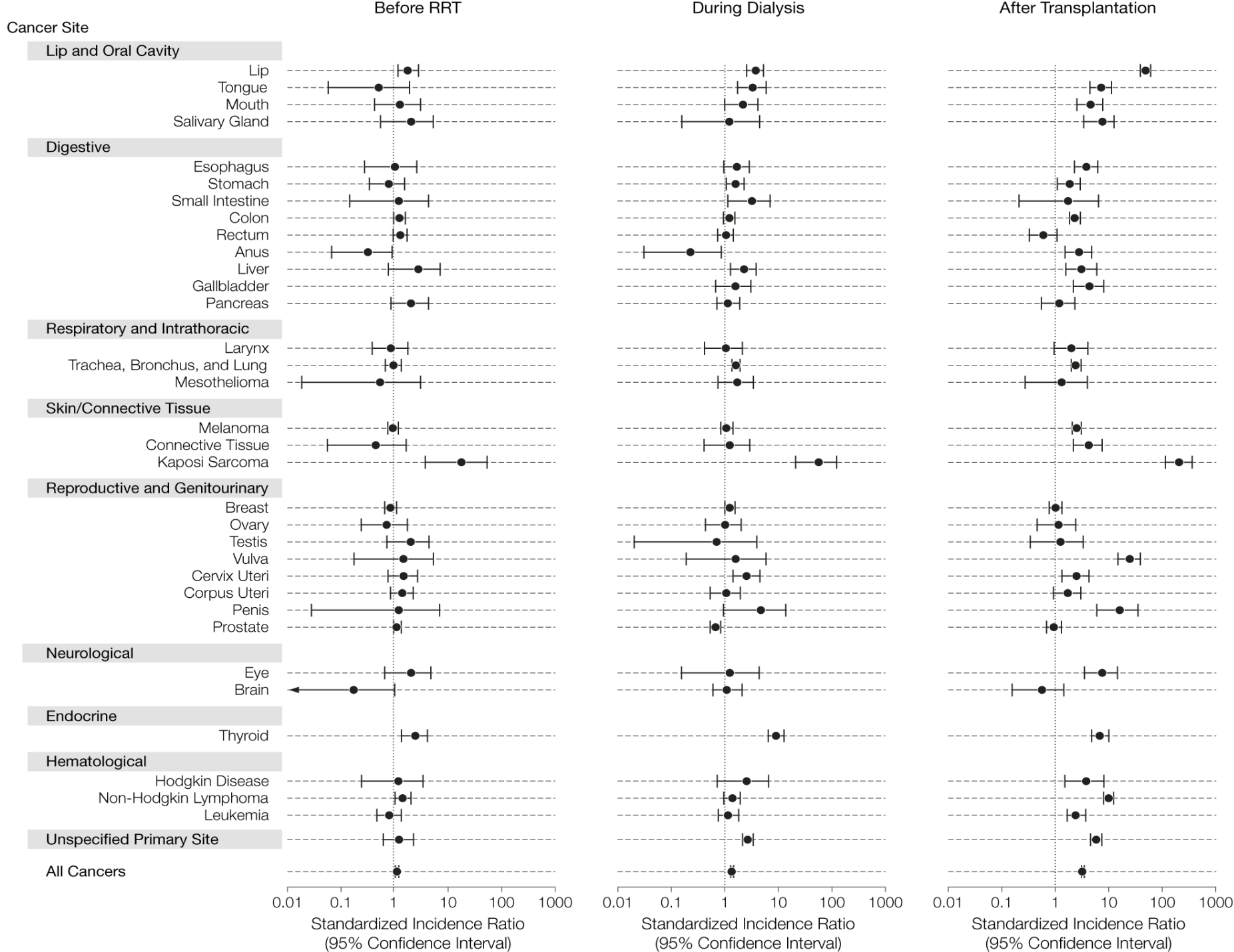
Timing of Cancer Diagnosis



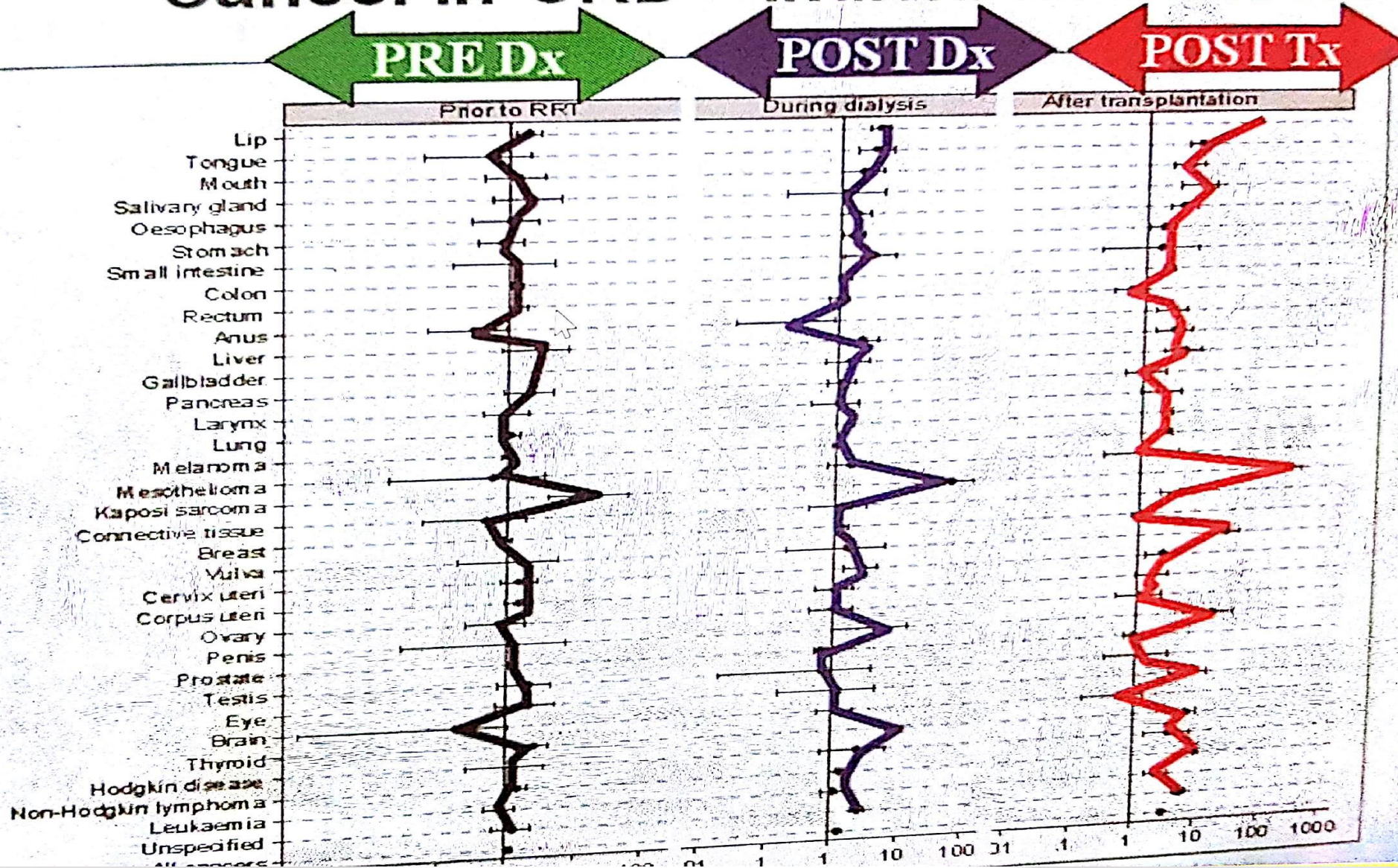
Risk of Cancers Frequently Known to Cause ESKD in Australian Patients With ESKD



Claire M. Vajdic, et al, JAMA. 2006;296(23):2823-2831.



Cancer in CKD – Individual Cancers



Myth:

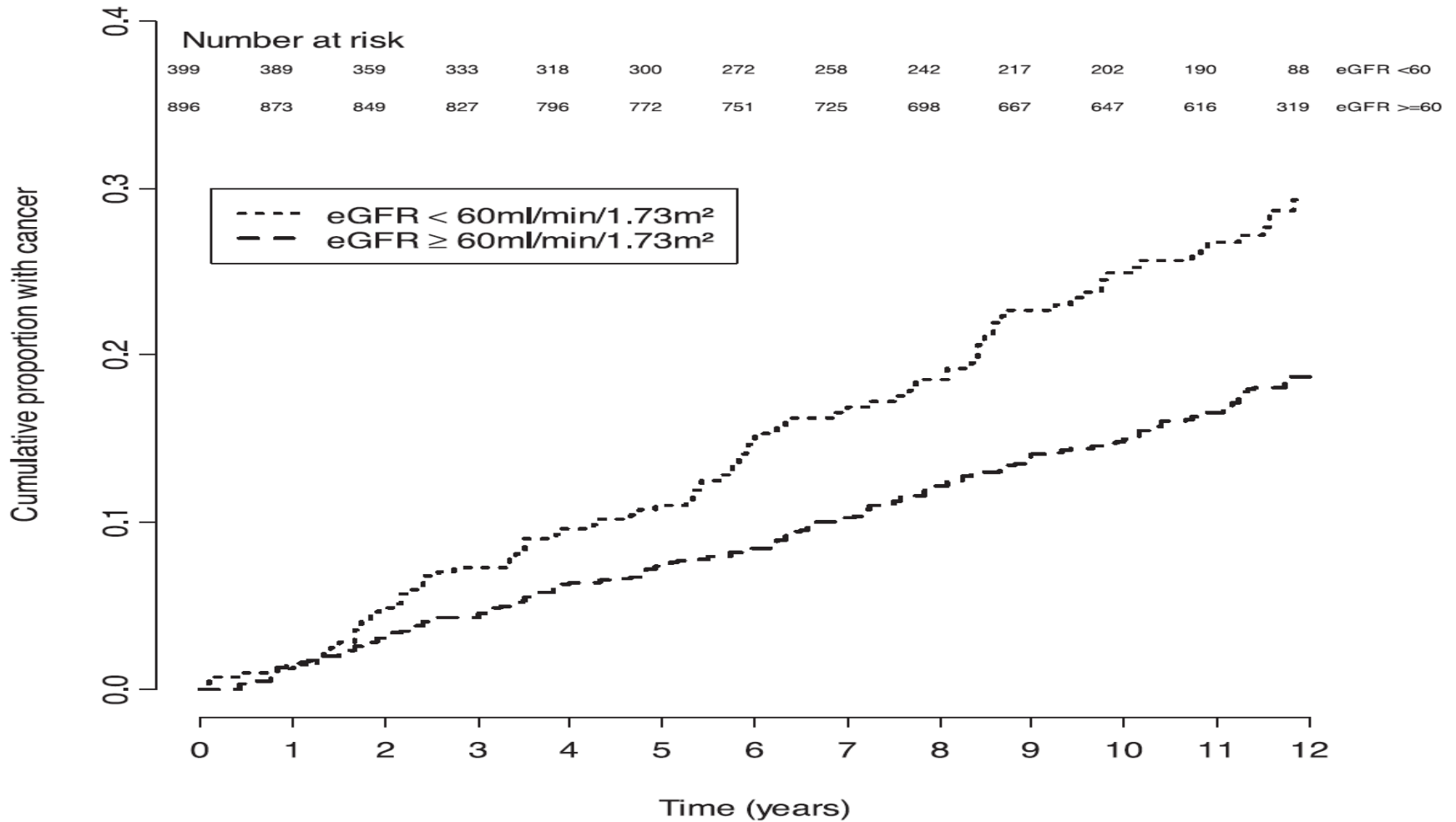
All cancer is increased by immunosuppression

Reality:

It starts at least 5 years before dialysis

Cancer Risk in CKD 1-3

Blue Mountains Eye Study



Cancer Risk in CKD 1-3

Blue Mountains Eye Study

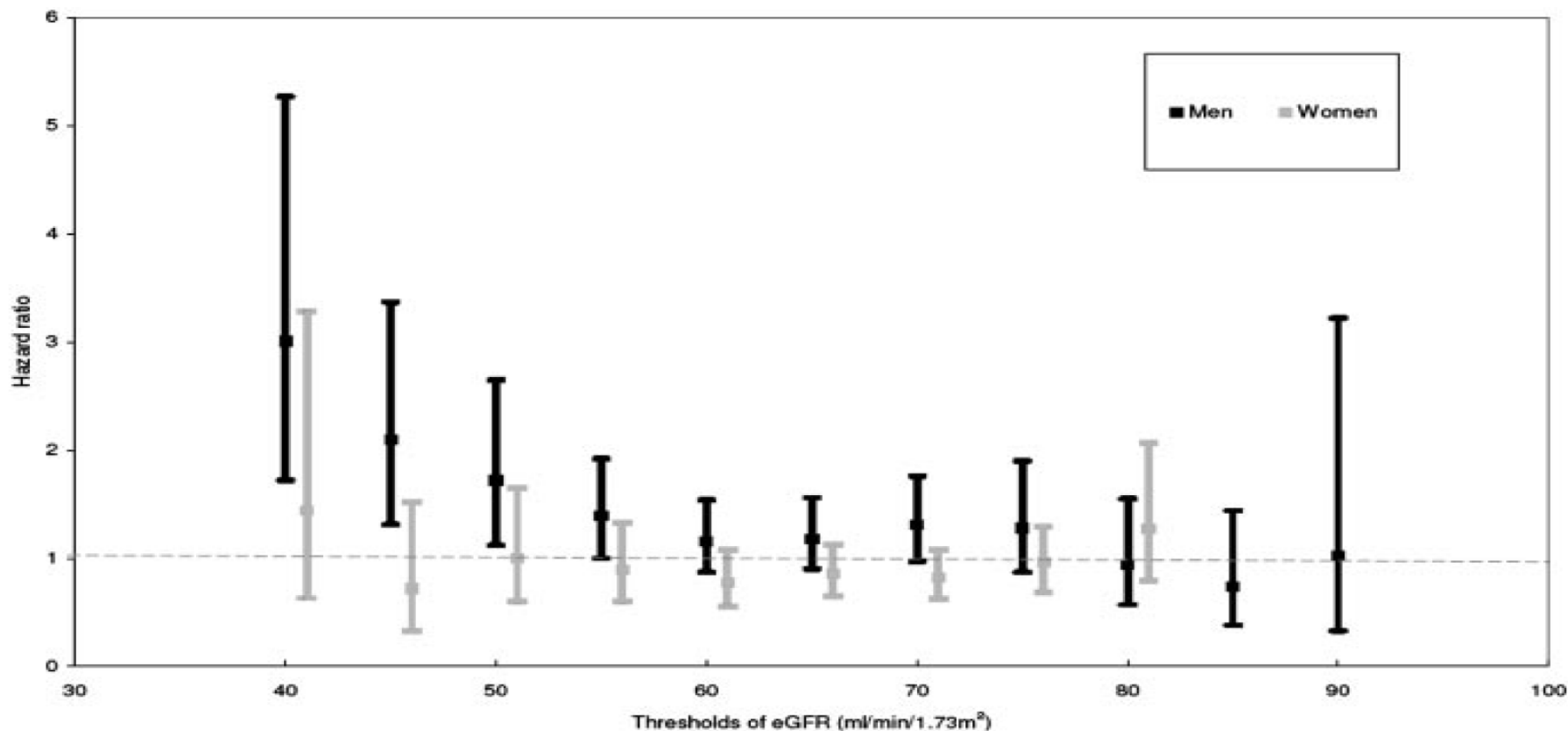


Figure 4. Adjusted HRs for incident cancers across various thresholds of eGFR in both men and women.

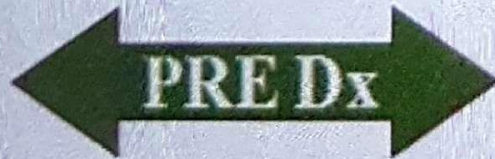
Myth:

All cancer is increased by immunosuppression

Reality:

It starts more than 5 years before dialysis

CKD



*Is increased cancer
risk reversed upon
cessation of
immunosuppression?*

Effect of reduced immunosuppression after kidney transplant failure on risk of cancer: population based retrospective cohort study

Marina T van Leeuwen, lecturer, epidemiologist,^{1,2} Angela C Webster, senior lecturer, medical epidemiologist, and nephrologist,^{3,4,5} Margaret R E McCredie, associate professor, epidemiologist,⁶ John H Stewart, nephrologist,⁶ Stephen P McDonald, associate professor, nephrologist,^{3,7} Janaki Amin, senior lecturer, statistician,¹ John M Kaldor, professor, epidemiologist,¹ Jeremy R Chapman, professor, nephrologist,⁵ Claire M Vajdic, senior lecturer, epidemiologist,⁸ Andrew E Grulich, professor, medical epidemiologist¹

Infection related

Kaposi's sarcoma	Transplant	231 (111 to 425)		10	1.00	
	Dialysis	Upper CI 622†	x	0	0.25 (0.00 to 1.65)‡	0.175
Non-Hodgkin's lymphoma	Transplant	9.73 (8.08 to 11.62)		122	1.00	
	Dialysis	2.05 (0.42 to 5.99)		3	0.20 (0.06 to 0.65)	0.007
Anogenital	Transplant	5.96 (3.93 to 8.67)		27	1.00	
	Dialysis	1.82 (0.05 to 10.11)		1	0.41 (0.05 to 3.04)	0.380
Oral cavity and oropharynx	Transplant	3.46 (2.01 to 5.53)		17	1.00	
	Dialysis	Upper CI 6.32 †	x	0	0.36 (0.00 to 2.21) ‡	0.322
Stomach	Transplant	1.76 (0.85 to 3.24)		10	1.00	
	Dialysis	2.89 (0.35 to 10.45)		2	1.46 (0.30 to 7.16)	0.640

Increased in immunodeficient populations

Lip	Transplant	52.27 (45.27 to 60.02)		200	1.00	
	Dialysis	2.16 (0.05 to 12.05)		1	0.04 (0.01 to 0.31)	0.002
Melanoma	Transplant	2.74 (2.17 to 3.41)		80	1.00	
	Dialysis	0.58 (0.07 to 2.08)		2	0.16 (0.04 to 0.64)	0.010
Leukaemia	Transplant	2.58 (1.38 to 4.42)		13	1.00	
	Dialysis	5.25 (1.08 to 15.33)		3	1.52 (0.41 to 5.67)	0.533
Lung	Transplant	2.14 (1.61 to 2.77)		56	1.00	
	Dialysis	2.59 (1.12 to 5.11)		8	1.24 (0.58 to 2.68)	0.579

Effect of reduced immunosuppression after kidney transplant failure on risk of cancer: population based retrospective cohort study

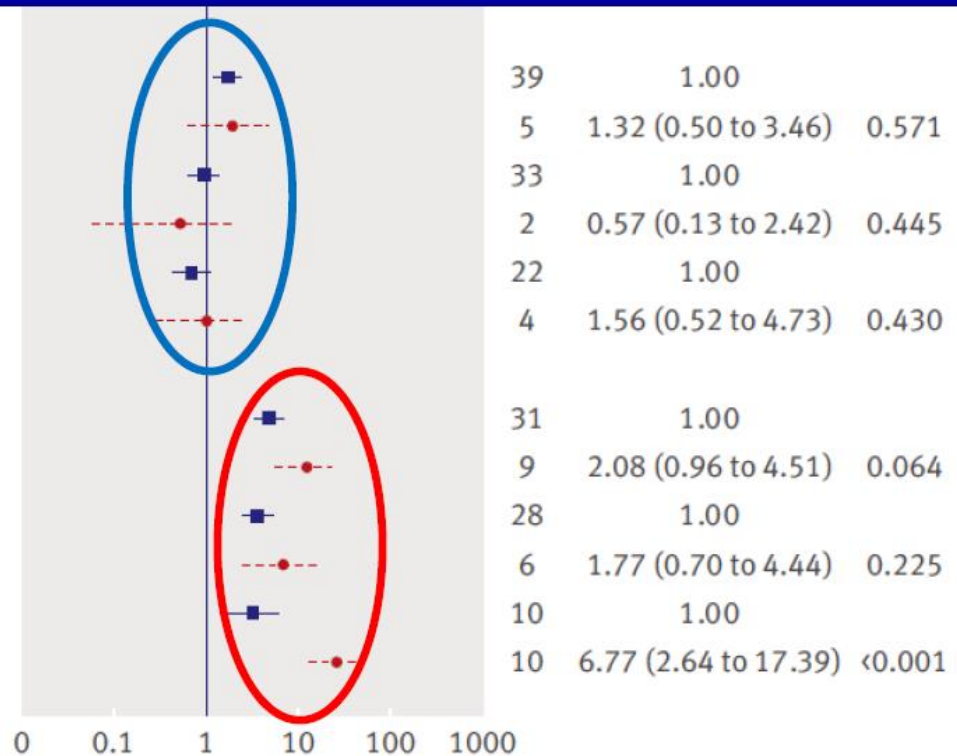
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Not increased in immunodeficient populations

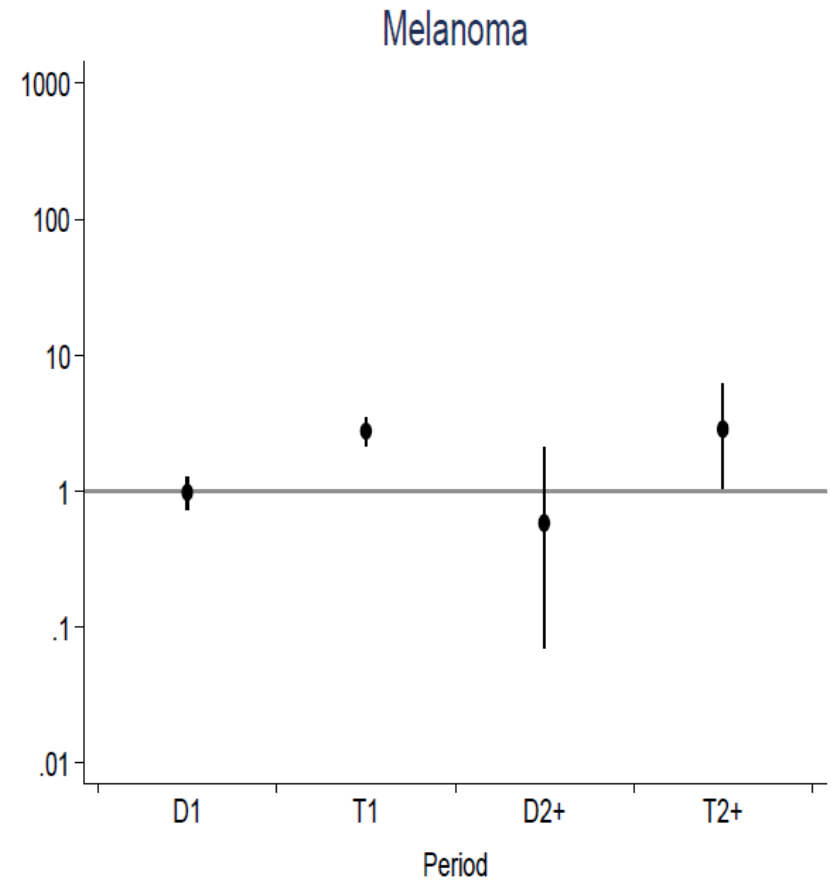
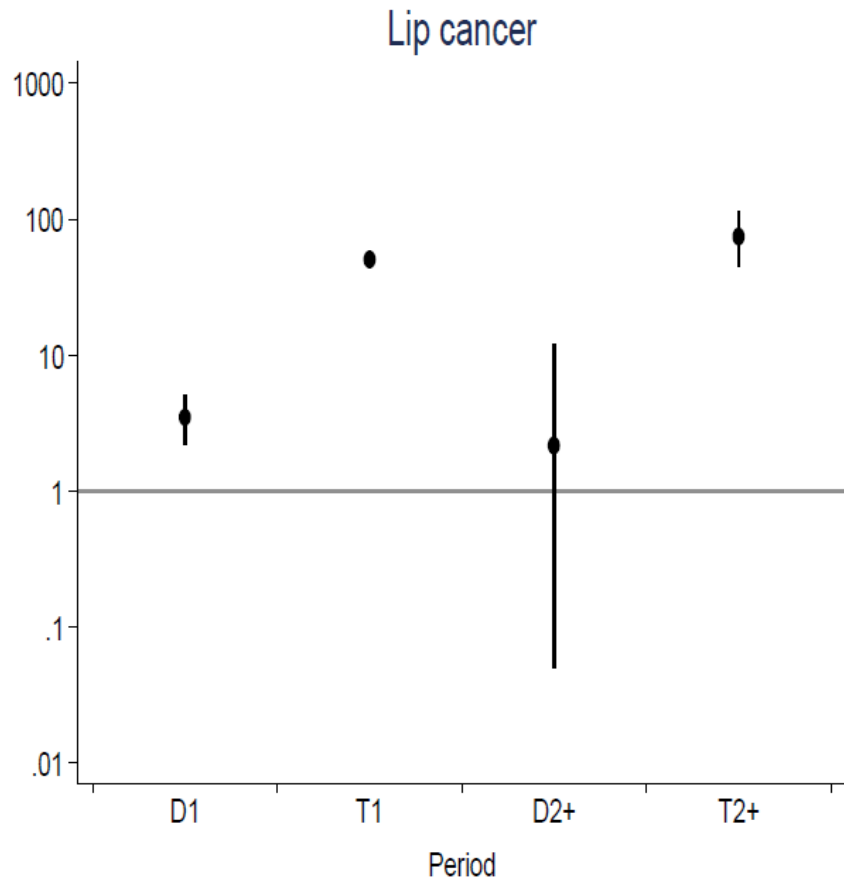
Colon	Transplant	1.75 (1.24 to 2.39)
	Dialysis	1.99 (0.65 to 4.65)
Breast (female)	Transplant	0.97 (0.66 to 1.36)
	Dialysis	0.54 (0.06 to 1.93)
Prostate	Transplant	0.70 (0.44 to 1.06)
	Dialysis	1.05 (0.29 to 2.69)

End stage kidney disease related

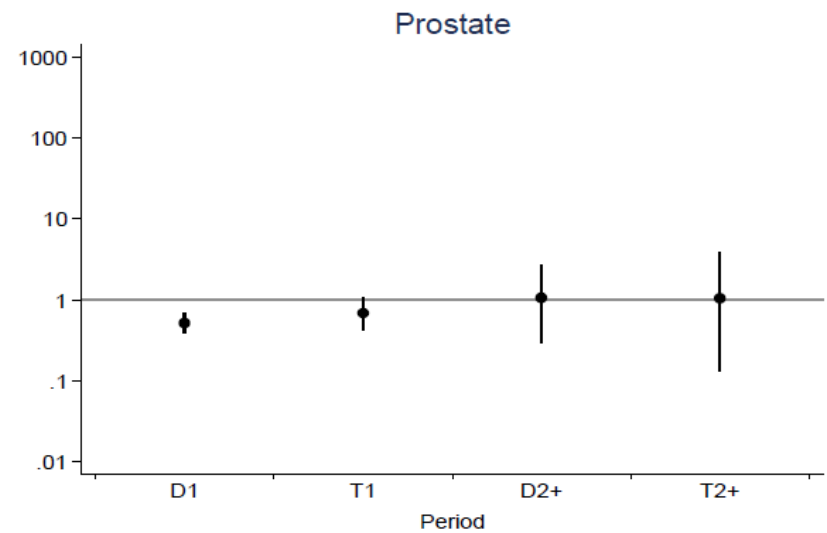
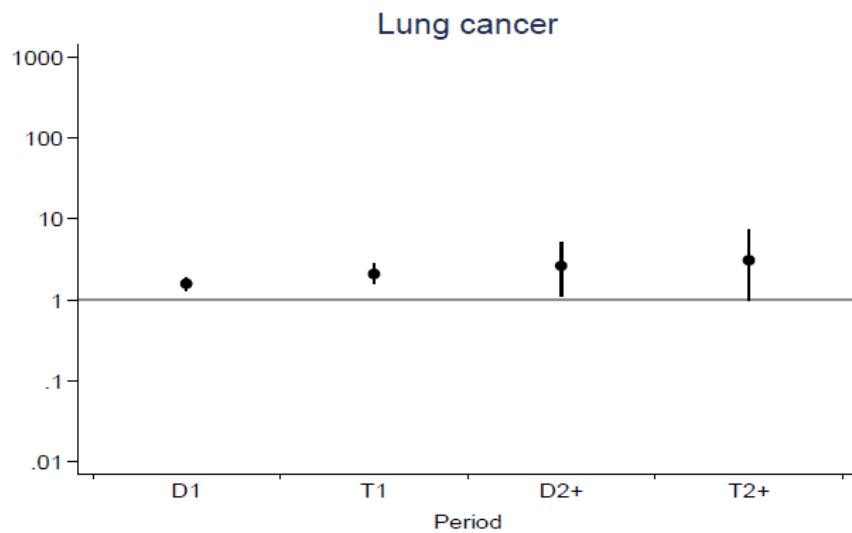
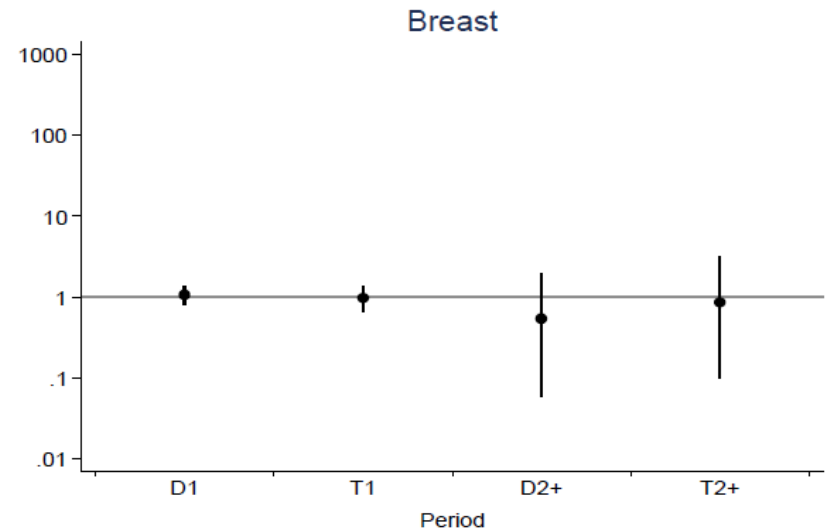
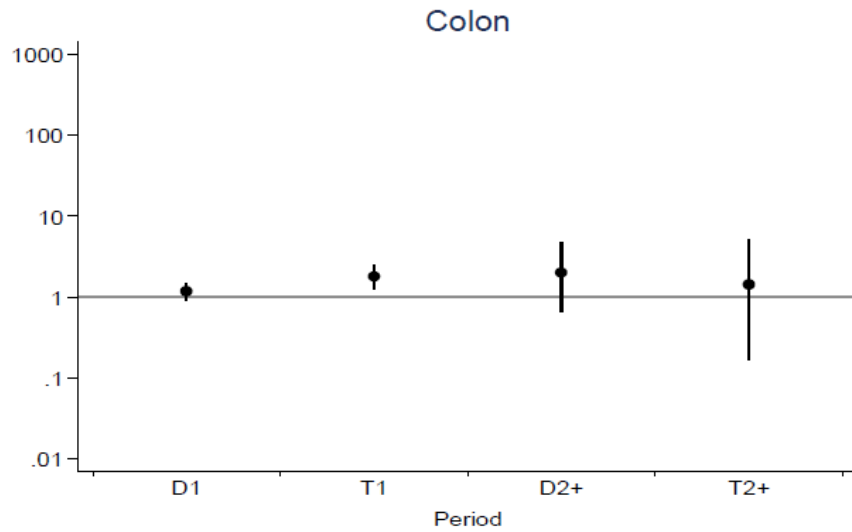
Kidney	Transplant	4.93 (3.35 to 7.00)
	Dialysis	12.38 (5.66 to 23.49)
Urinary tract	Transplant	3.69 (2.45 to 5.33)
	Dialysis	7.07 (2.59 to 15.38)
Thyroid	Transplant	3.29 (1.58 to 6.05)
	Dialysis	26.37 (12.64 to 48.49)



Intriguing cancers showing reversibility of risk



Cancers showing no change in risk



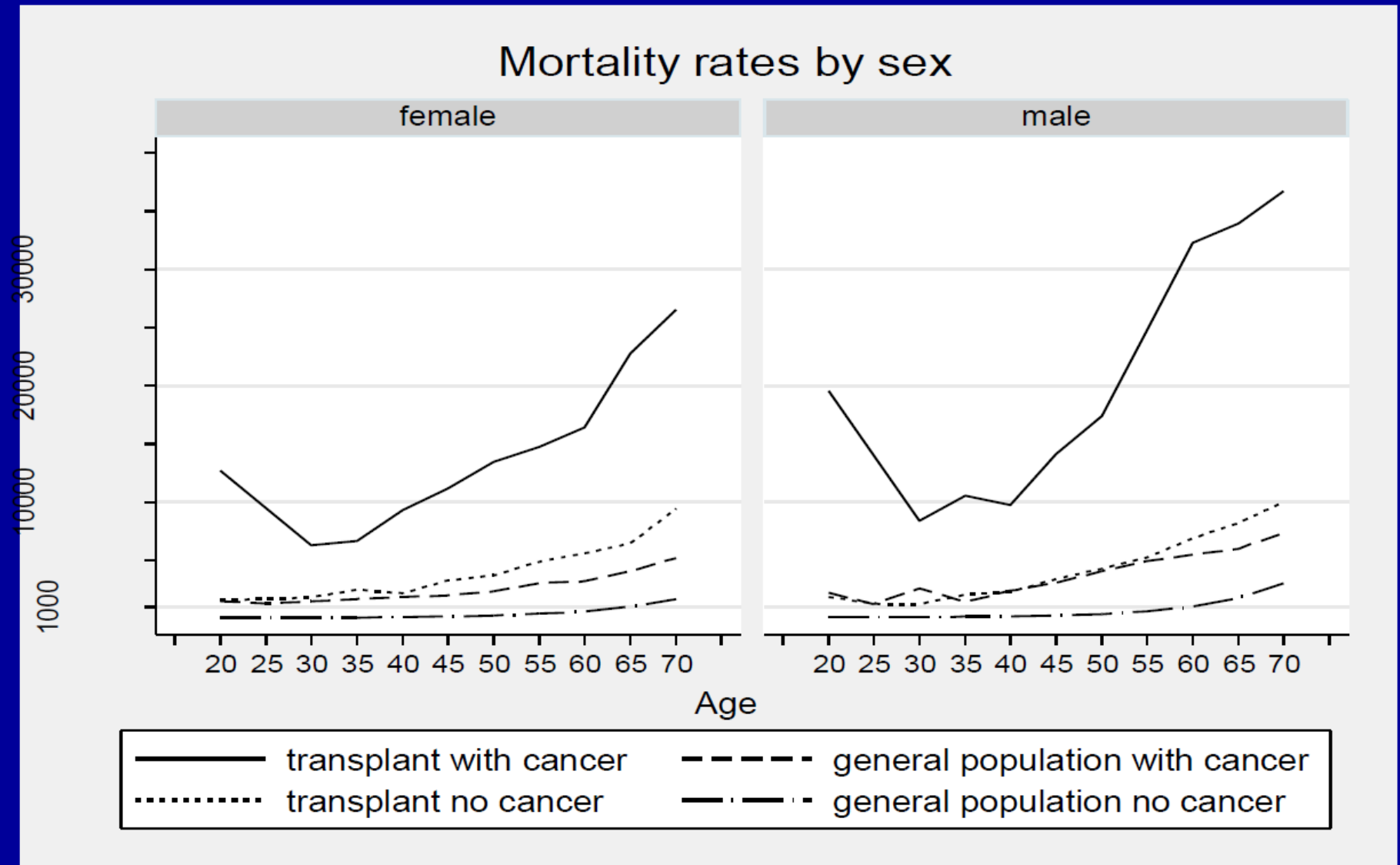
Immunosuppression currency and risk

- The effect of immunosuppression on cancer risk is rapidly reversible for some, but not all, cancer types
- Risk reversal was mostly, although not exclusively, observed for cancers with a confirmed infectious cause
- Risk of other cancers, especially those related to ESKD, remains significantly elevated after reduction of immunosuppression
- This finding offers insight into the role of current functional immunity in cancer prevention and may help inform the management of cancer risk in other immunosuppressed populations

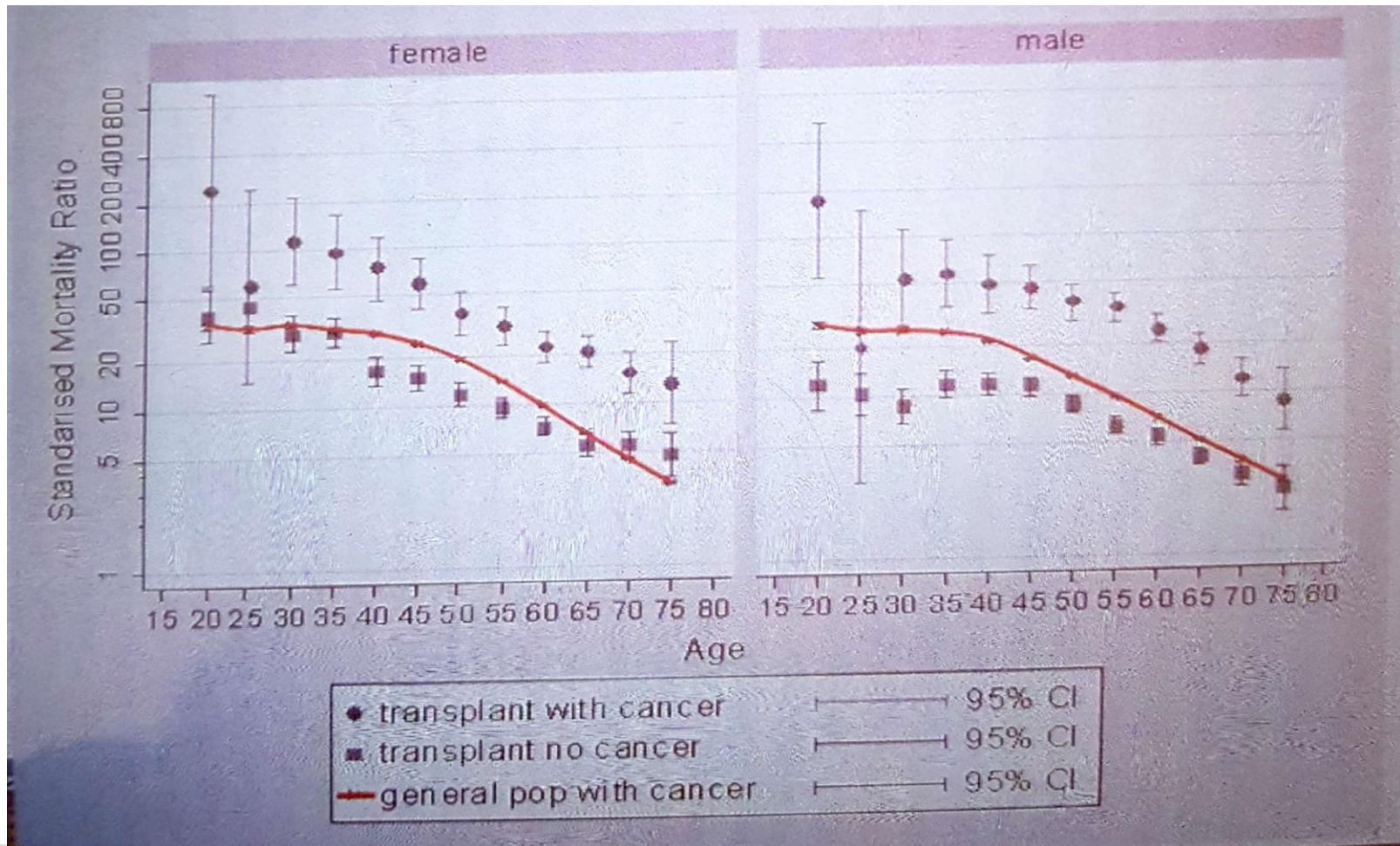
Myth

Cancer mortality is the same as in the general population

Impact of cancer: death rate comparisons



Mortality by age and sex



Impact of cancer on survival within transplant population

	Risk of death
Age 35-44	1.9
45-54	3.1
≥ 55	4.5
Men	1.1
DM ESKD	1.8
White race	0.8
Graft failure	3.8
Cancer	4.1

ANZDATA

15, 183 recipients

Mean follow up 9 years

Cox model with time dependent covariates

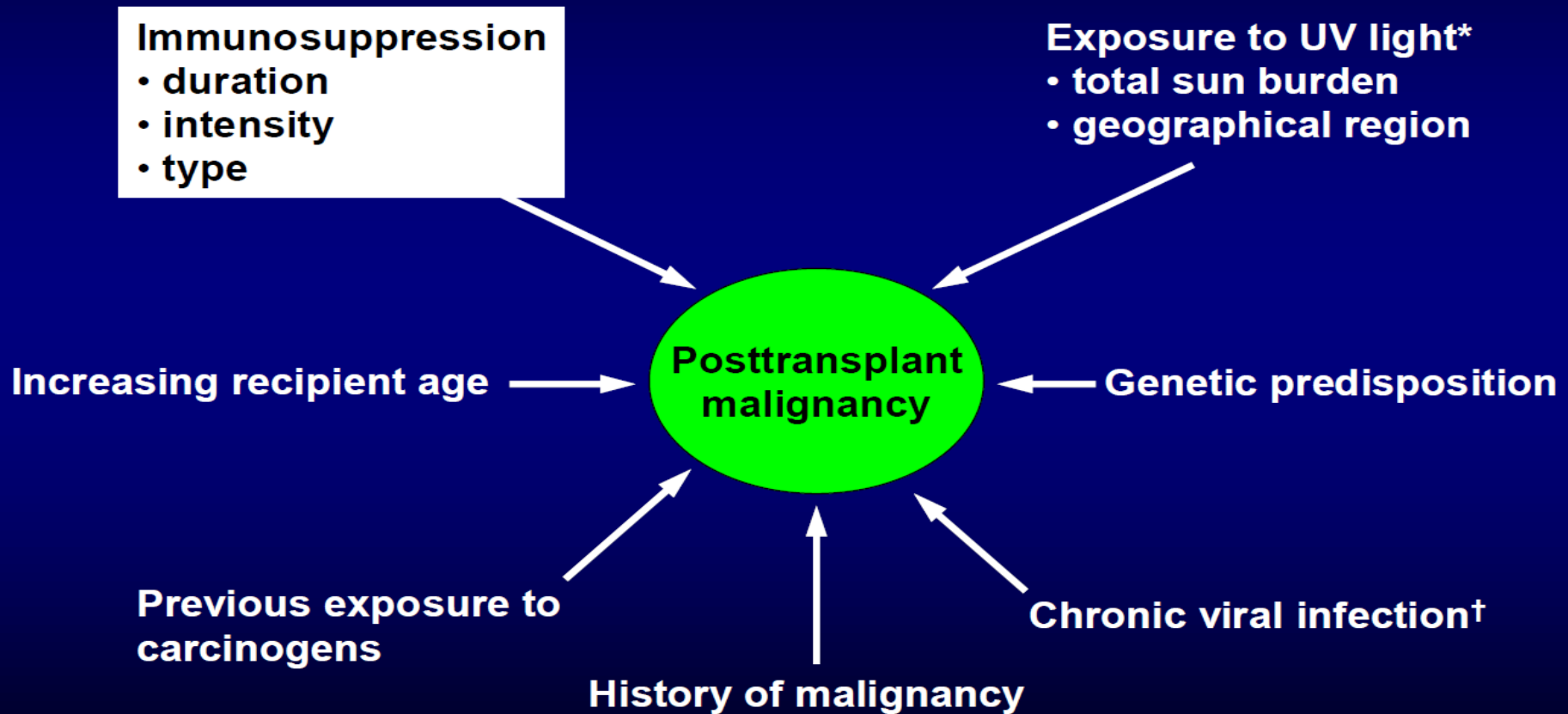
Myth:

Cancer mortality is the same as in the general population

Reality:

Mortality is far worse with both a transplant and cancer

Proposed Risk Factors for Posttransplant Malignancy



*NMSC; †predominantly PTLD and Kaposi's sarcoma

Adapted from Valentine H. *J Heart Lung Transplant.* 2007;26:557-64.

Mechanisms of developing malignancy

- Develop in three different ways:
 - Transmission of malignancy from donor
 - *De novo* occurrence in recipient
 - Recurrent malignancy in recipient

Peter J.Morris, Stuart, Kidney transplantation: principles and practice 6th edition

Very Low Incidence of Donor Transmission Cancers

UK Transplant Registry

- 2001-10: Tumor transmission with an incidence of 0.06%

Desai et al. Transplantation 2012,94(12): 1200-7

- 1985-2001: 177 Donors with CNS Neoplasms – no transmission even by high grade tumors

Watson et al. Am J Transplant 2010, 10(6): 1437-44

Transmission of Cancer from the Donor

- Melanoma : most common transferred from a donor to recipient
- Post-transplant lymphoproliferative disorder (PTLD) in a recipient may be a direct result of viral transmission from the donor.

Peter J.Morris, Stuart, Kidney transplantation: principles and practice 6th edition

Molecular Cytogenetic Tests

- **FISH – Fluorescence in situ hybridization**
Indicates only XX vs XY chromosomes
- **MAA – micro-satellite allelic analysis**
Distinction between individuals based on genetic polymorphism
- **CGH – comparative genomic hybridization**
Comparison of the chromosomes in the genome

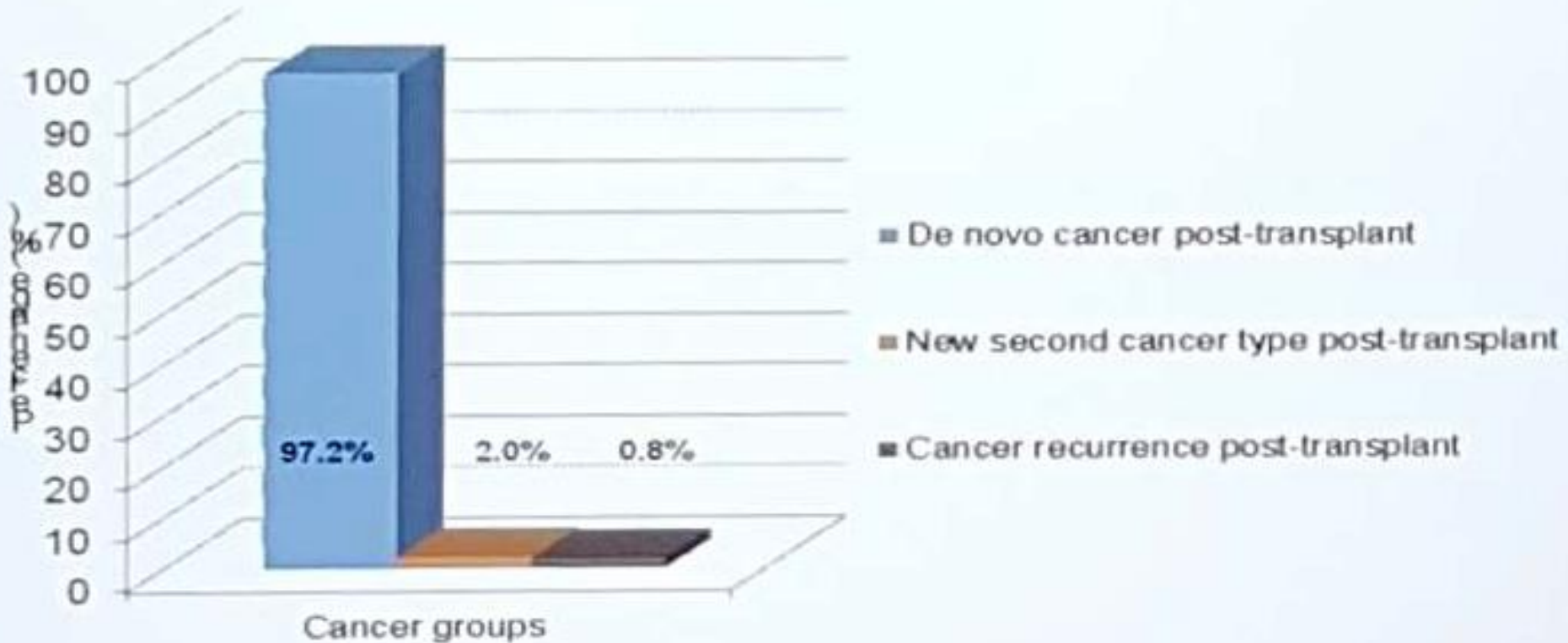
Myth

Is Cancer Recurrence after Kidney Transplantation Common?

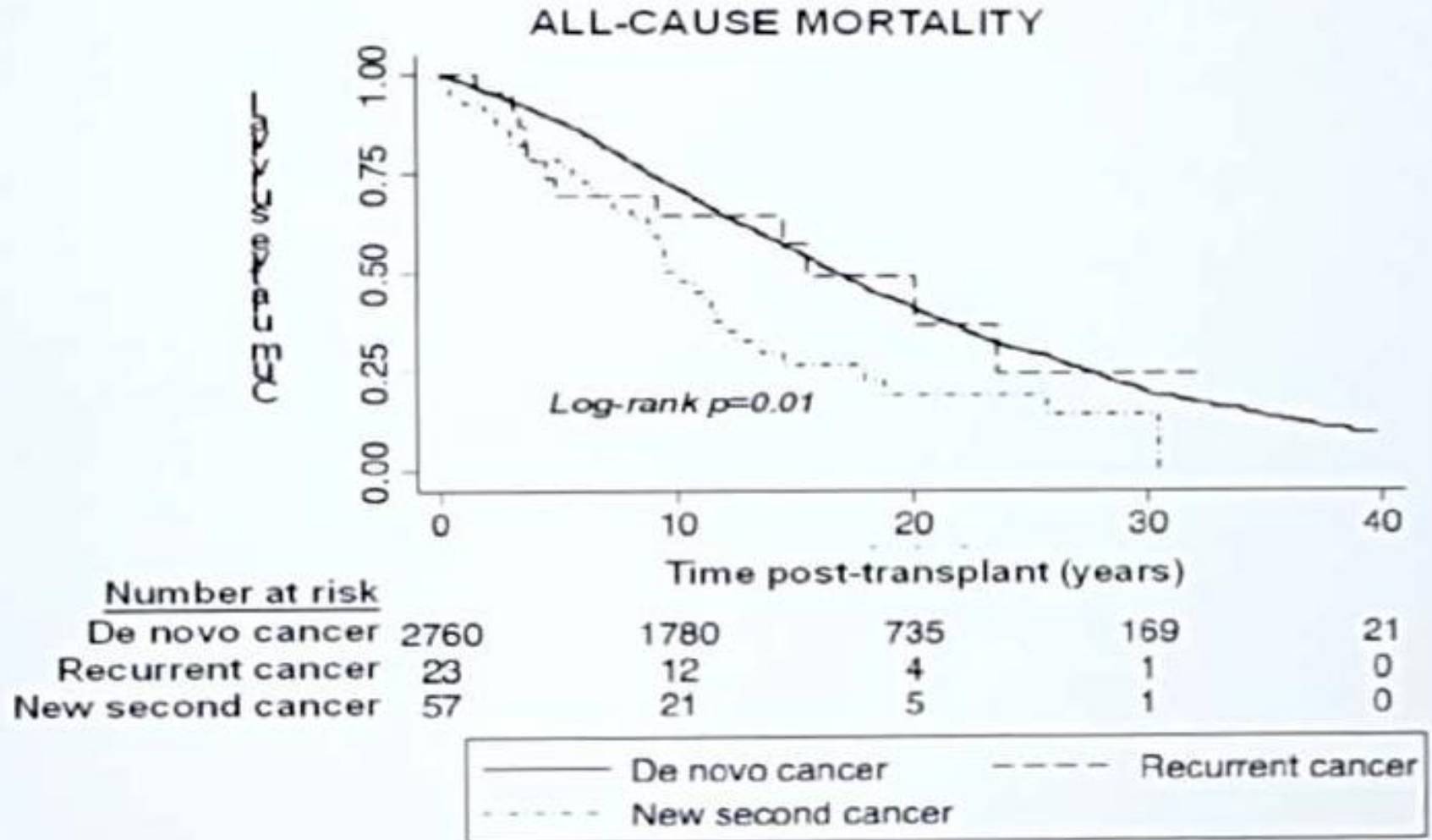
Cancer Recurrence Post-Transplant

Cumulative incidence of cancer post-transplant in recipients with and without prior cancer

Incident RTR with cancer after transplantation 1965-2012 (n=2840)



Cancer Recurrence Post-Transplant



Viecelli A et al Transplantation 2014, ANZDATA registry

Myth

- *m-TOR inhibitors could be reduced incidence of cancer after kidney Tx.*
- *Does it lead to the better outcomes?*

A2309: CNI + everolimus: any cancers

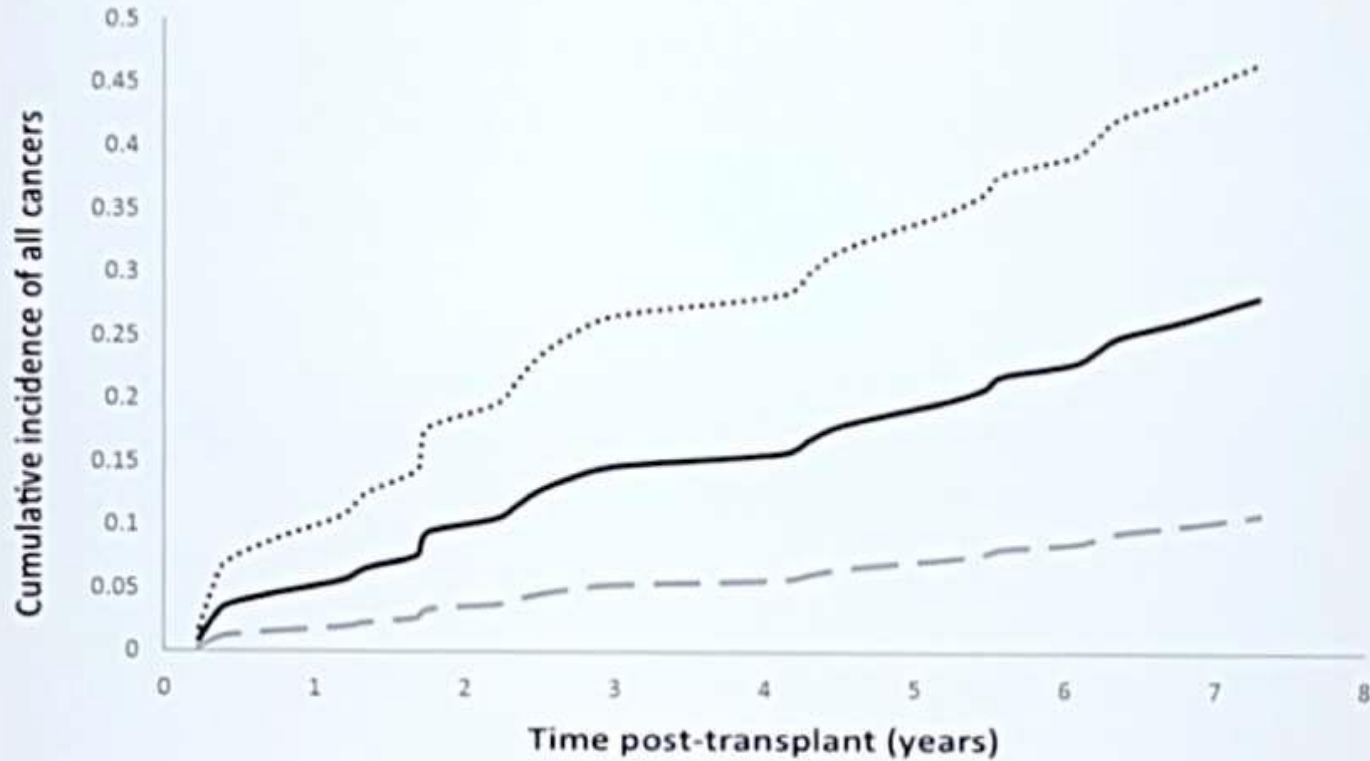


Figure 5

..... Myfortic — Everolimus 1.5mg - - Everolimus 3mg

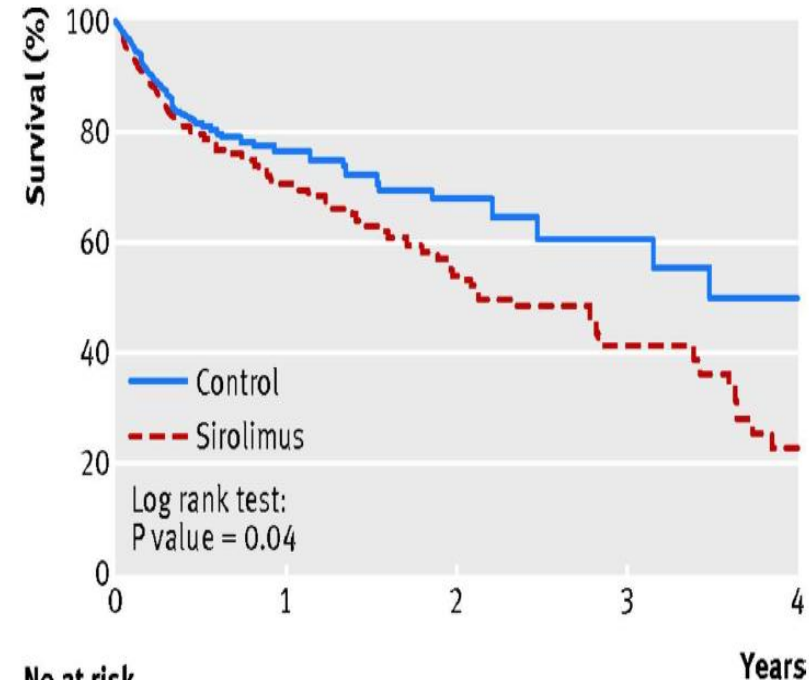
Lim WH et al *Kidney Int* 2017

Effect of sirolimus on cancer and survival after kidney transplantation

Knoll et al. BMJ 2014

	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	

So, final words.....

- Cancer after Tx is a real problem (higher incidence and higher mortality)
- Risk for cancer increases with time post-transplant
- Higher SIR of viral related and immune related cancer > ESRD-Cancer
- Cessation of immunosuppression decreases risk for cancers with known or suspected viral cause
- mTORI may be beneficial for those at risk of NMSC
- mTORI is not the definitive treatment and may incur harms

So, final words.....

- Post-transplant cancers are more common in the old recipients, but relatively much higher risk in young transplant patients
- Cancer recurrence is rare, but once recure, outcomes are poor



***Thank you
all for your
attention***