POST-TRANSPLANT MALIGNANCIES

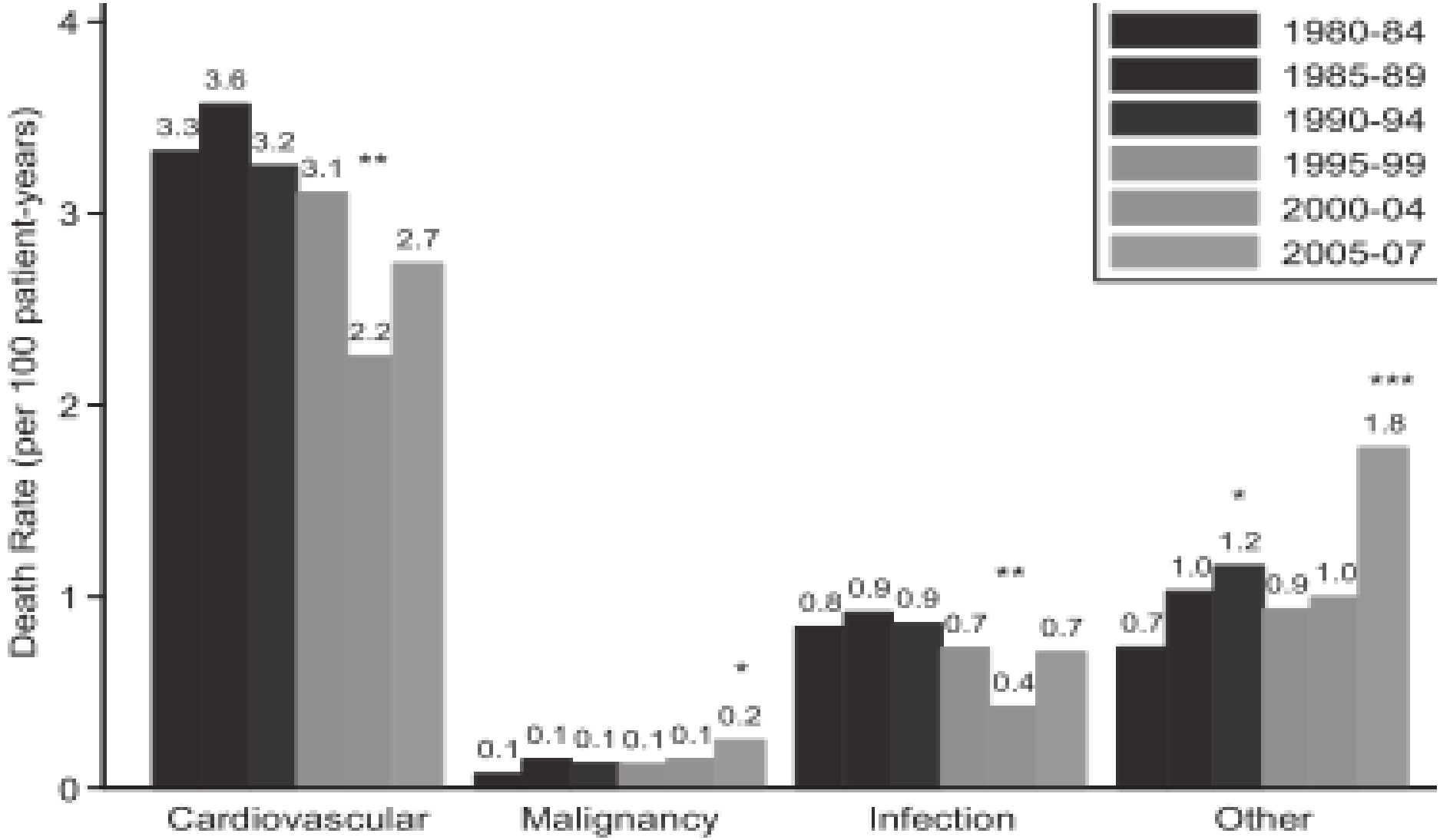
Post-transplant malignancies

- Malignancies are one of the three major causes of death after organ transplantation
- Mean age of organ recipients has risen by 10 years over the last decade
- Better patient and graft survival have lengthened the observation period

Post-transplant malignancies

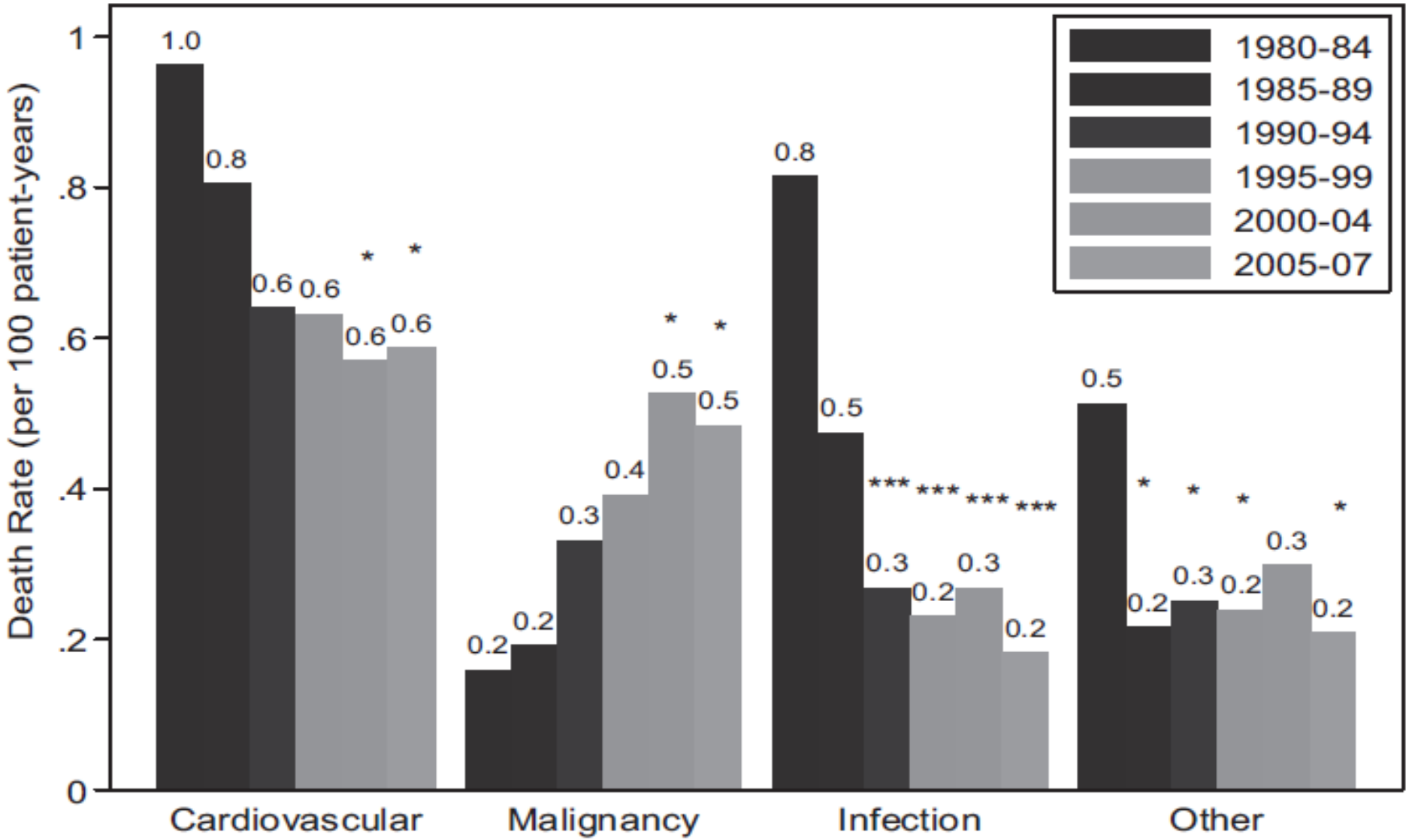
- Malignancies *de novo* *70-80%*
- Recurrent malignancies ok.20%
- Donor – transmitted malignancies occasionally

dialysis patients - causes of death



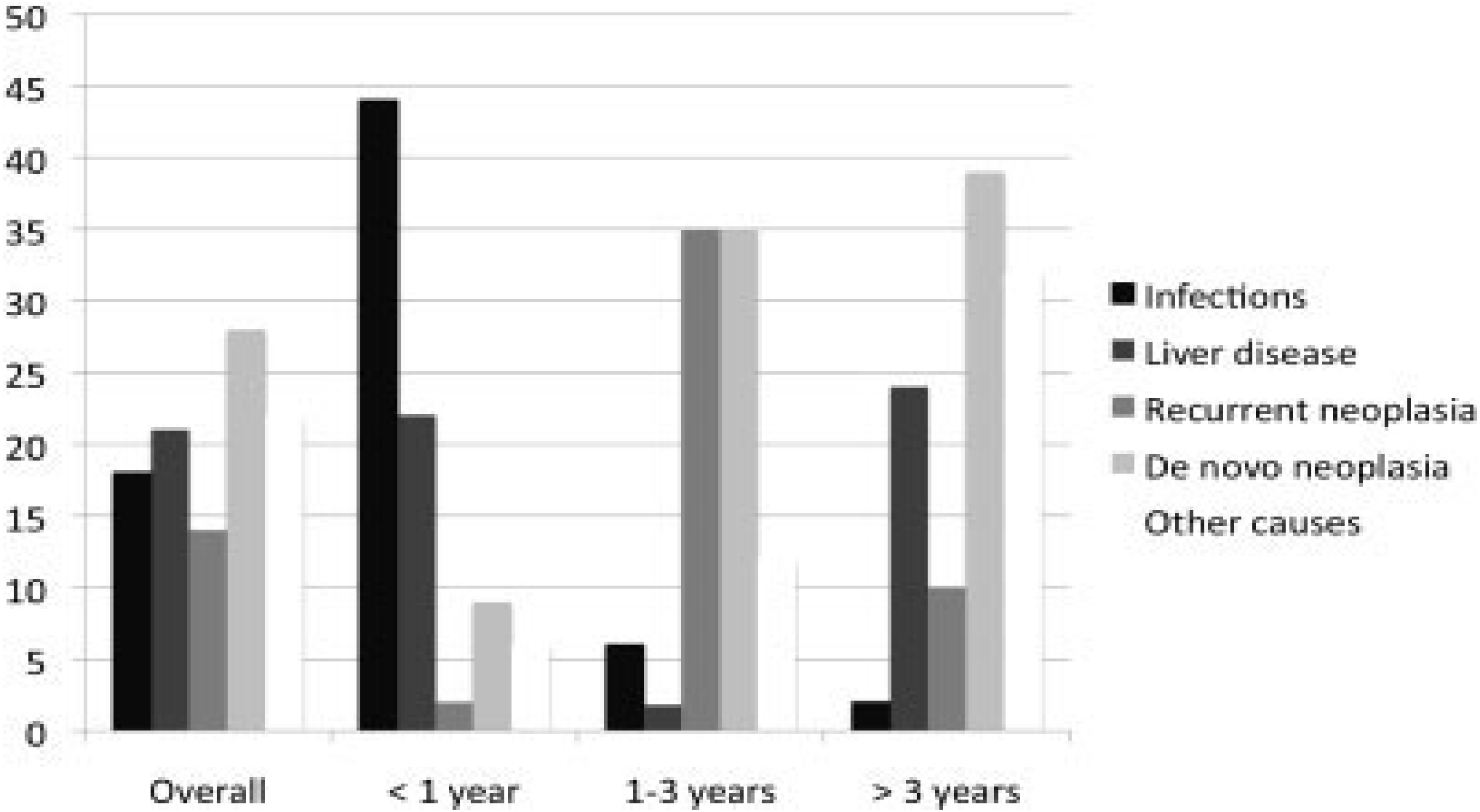
Pilmore H et al.: Transplantation 2010

kidney transplant recipients - causes of death

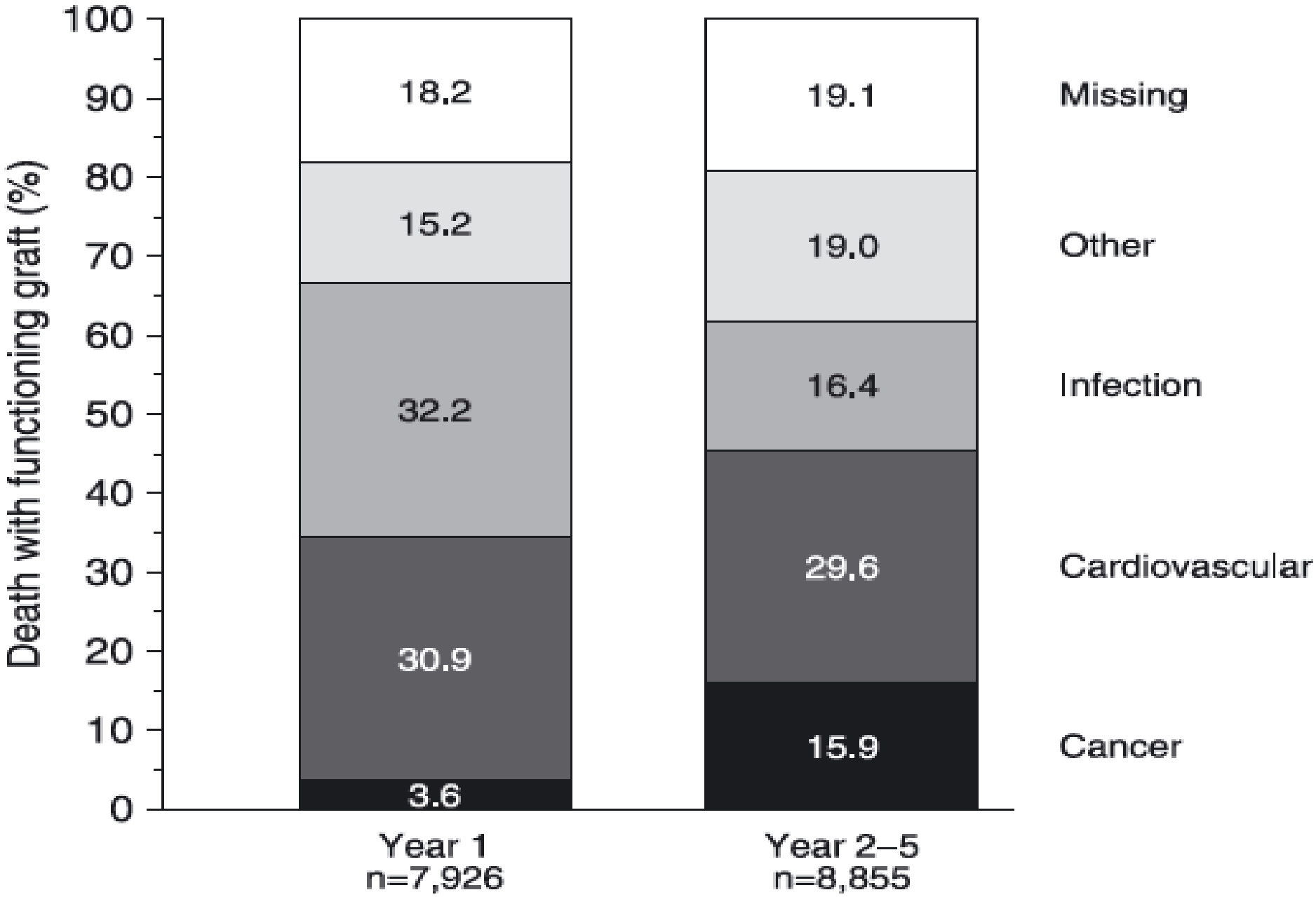


Pilmore H et al.: Transplantation 2010

liver transplant recipients - causes of death



Herrero J.I. Liver Transplantation 2009


Death with functioning graft (%)
100
90
80
70
60
50
40
30
20
10
0
18.2
15.2
32.2
30.9
3.6
19.1
19.0
16.4
29.6
15.9
Missing
Other
Infection
Cardiovascular
Cancer
Year 1
n=7,926
Year 2–5
n=8,855

Post-transplant malignancies

- Malignancies *de novo*
- Recurrent malignancies
- Donor – transmitted malignancies

Risk?

Risk of cancer by organ, expressed as standardized incidence ratios (SIRs) relative to the general population

Site and comparator national population	SIRs with 95% confidence intervals for different organ transplant recipients			
	Kidney	Liver	Heart	Lung
All site				
Australia	3.3 (3.1–3.7)	2.3 (1.9–2.7)	2.7 (2.4–3.0)	4.3 (3.5–5.2)
Canada	2.5 (2.3–2.7)		2.7 (2.3–3.2)	
Finland	3.3 (2.9–3.8)			
Sweden	3.9 (3.6–4.2)	4.9 (3.7–6.4)		
United Kingdom	2.4 (2.3–2.5)	2.2 (2.0–2.4)	2.5 (2.2–2.7)	3.6 (3.0–4.4)
United States	2.10 (2.06–2.14)			

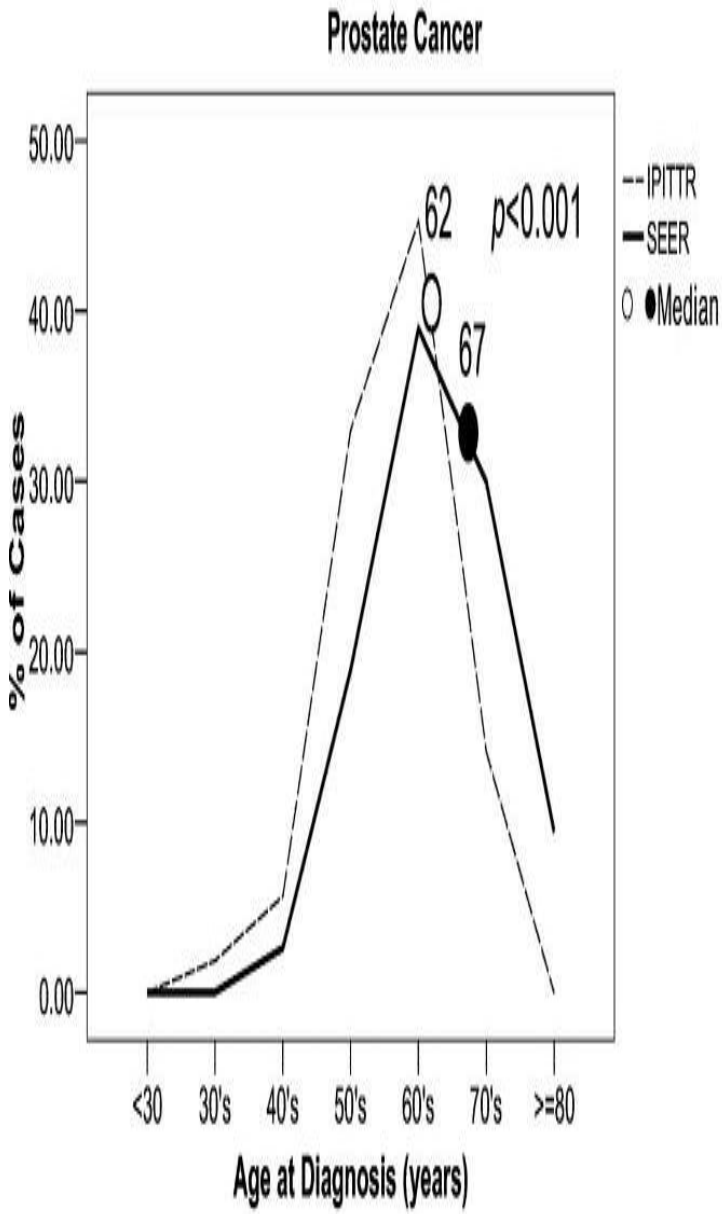
Chapman JR et al.: CSHPM2013

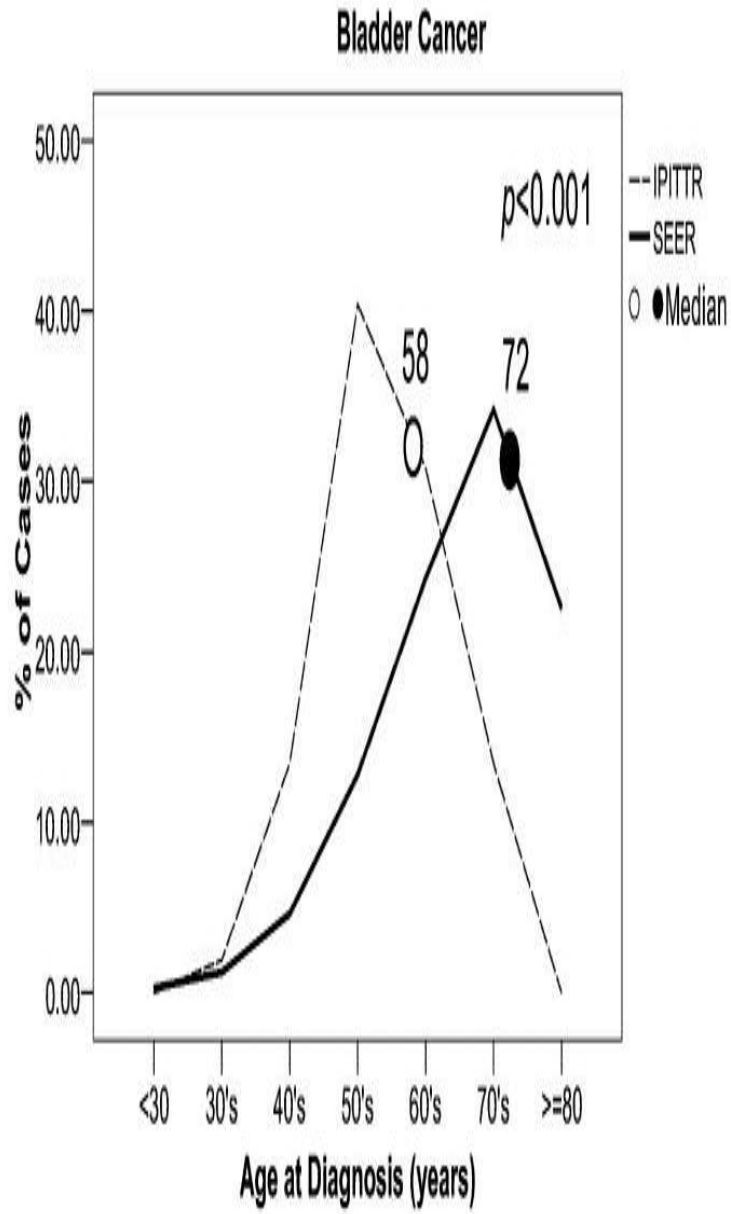
ANZDATA

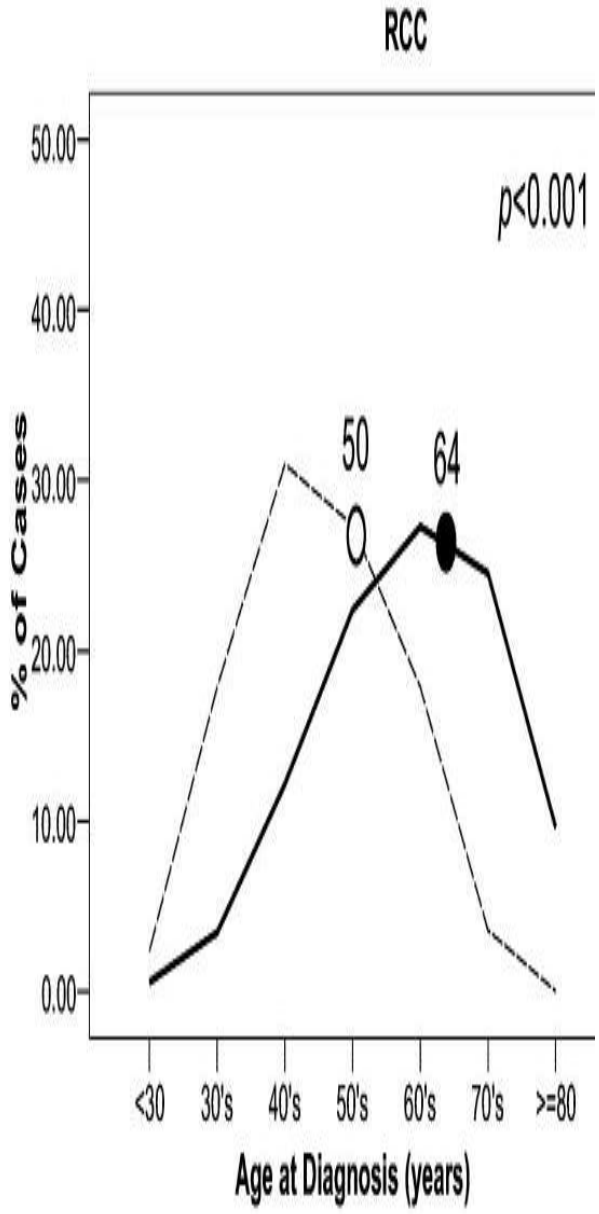
PChN5	dializa	transplantacja
n=689	n=870	n-= 1236
SIR 1.16	SIR 1.35	SIR 3.27

Vajdic CM et al.: JAMA 2006

Age at dignosis



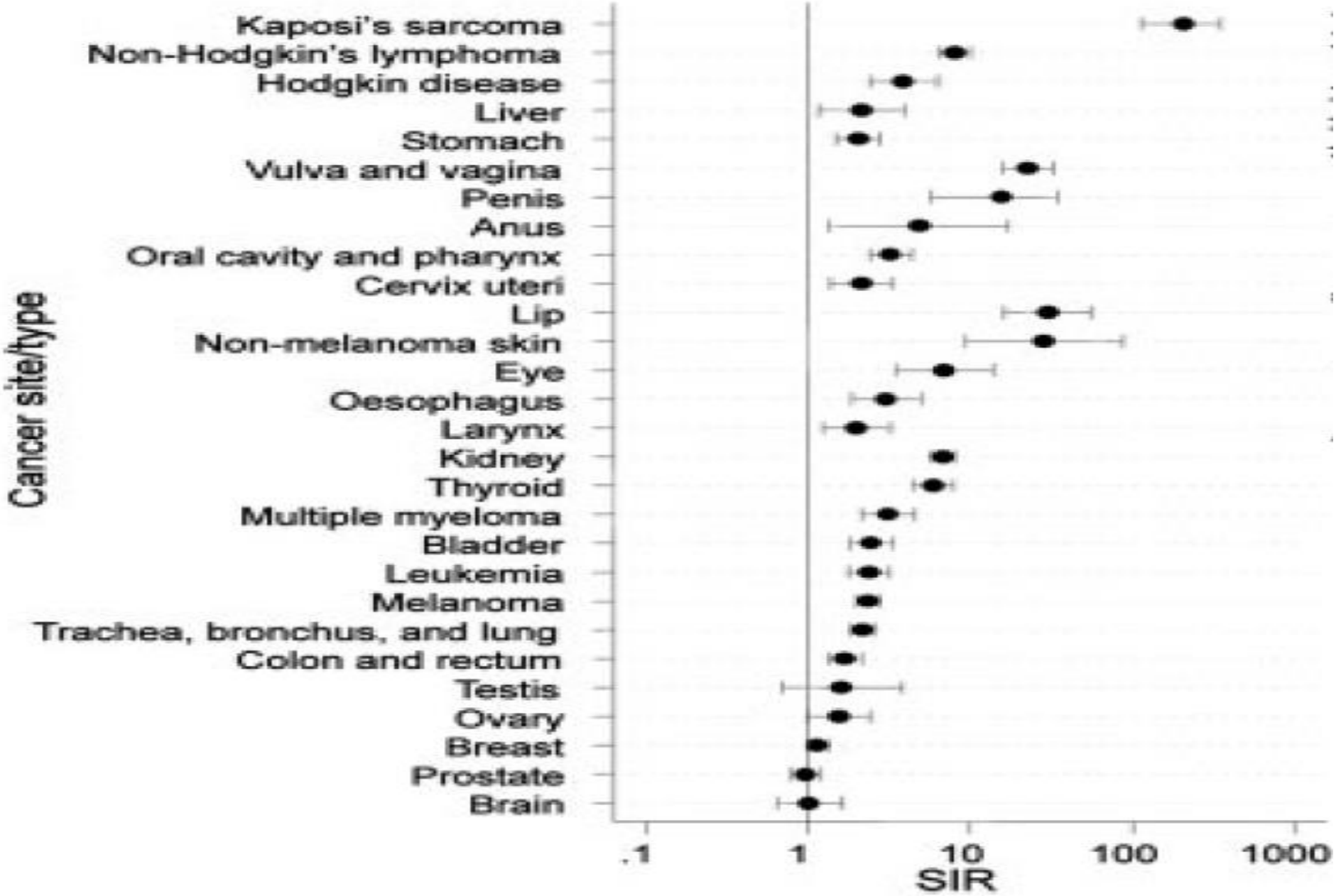




Israel Penn International Transplant Tumor Registry [IPITTR])

Miao Y. et al.: Transplantation 2009

Types of malignancy



Vajdic CM, Int J Cancer, 2009

	NHL observed/expected	Lung cancer	HCC	RCC
Kidney	635/105	517/354	48/44,5	565/84,9
Liver	365/47	300/153,7	831/19	67/37,2
Heart	267/34,3	364/136,5	13/12,8	85/29,3
Lung	125/6,7	147/24	4/2	8/5,4

Engels EA JAMA 2011

Risk of post-transplant malignancies

	incidence /100000 person-years observed/expected	**SIR**
• Lip	16.8/1.0	16.78
• Skin (nonmelanoma)	23.7/1.7	13.85
• NHL	194/25.7	7.54
• Kaposi sarcoma	15.5/0.3	61.46
• Liver	120/10.4	11.56
• Kidney	97/20.9	4.65

Engels EA JAMA 2011

Risk of post-transplant malignancies

	incidence /100000 person-years observed/expected	**SIR**
• Brain	5.8/7.7	0.76
• Ovary	7/7 .3	0.95
• Prostate	134/145.4	0.92
• Uterine corpus	12.1/14.1	0.86
• ALL	2.2/1.1	2.0
• Bones/joints	1.9/0.9	1.98

Engels EA JAMA 2011

Post-transplant malignancies

- Worse outcomes
- The average age at diagnosis is approximately 40 years, and the average latency is approximately three to five years after transplantation
- Tumors are more aggressive biologically at the time of diagnosis

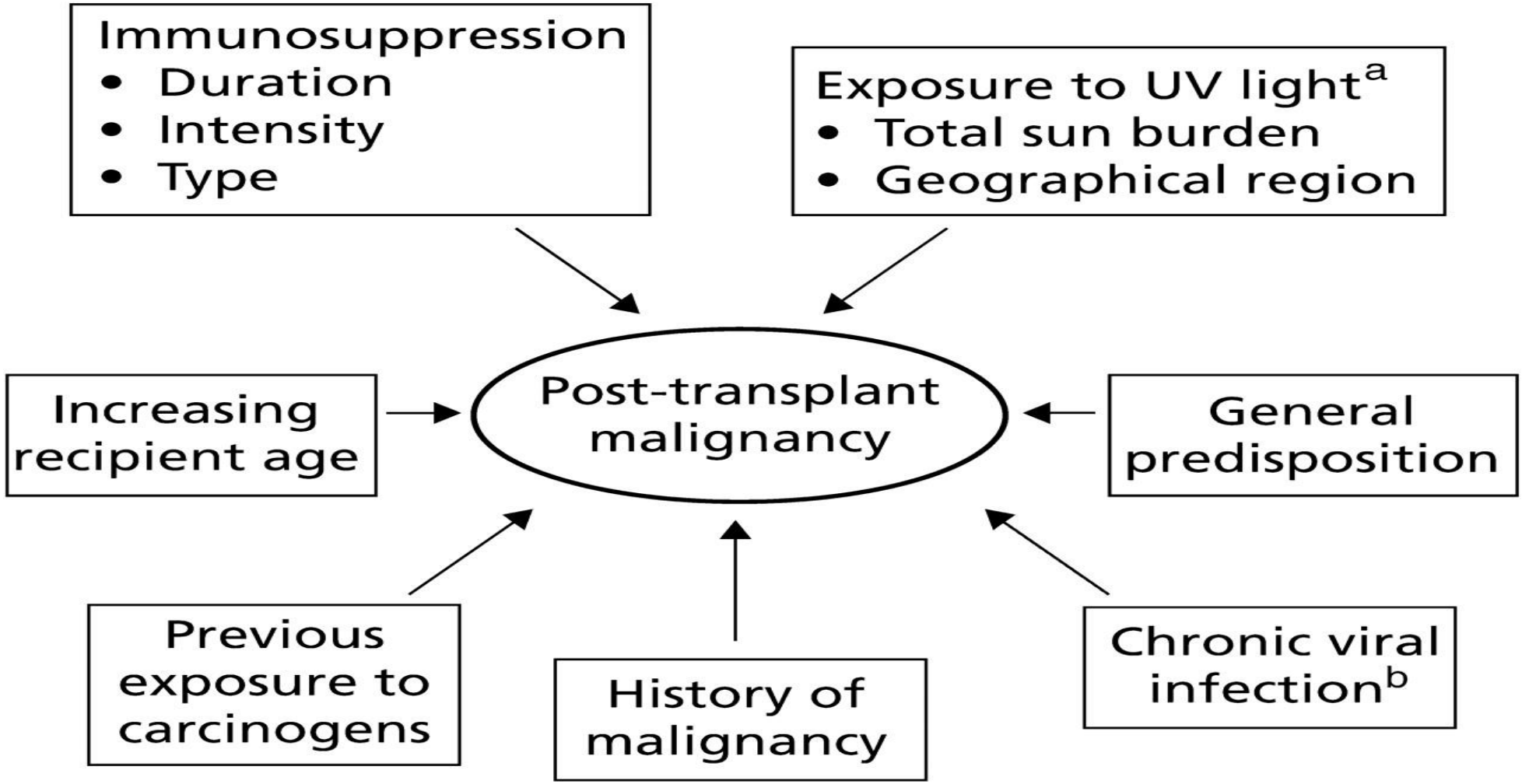
Risk factors for solid organ malignancy

Risk factor	HR (95% CI)	*P* value
Age by decade	1.33 (1.05–1.66)	.014
Smoking history	1.72 (1.06–2.79)	.029
ALD	2.14 (1.22–3.73)	.007
PSC	2.62 (1.50–4.56)	.001

ALD, alcohol-related liver disease; CI, confidence interval; HR, hazard ratio; PSC, primary sclerosing cholangitis.

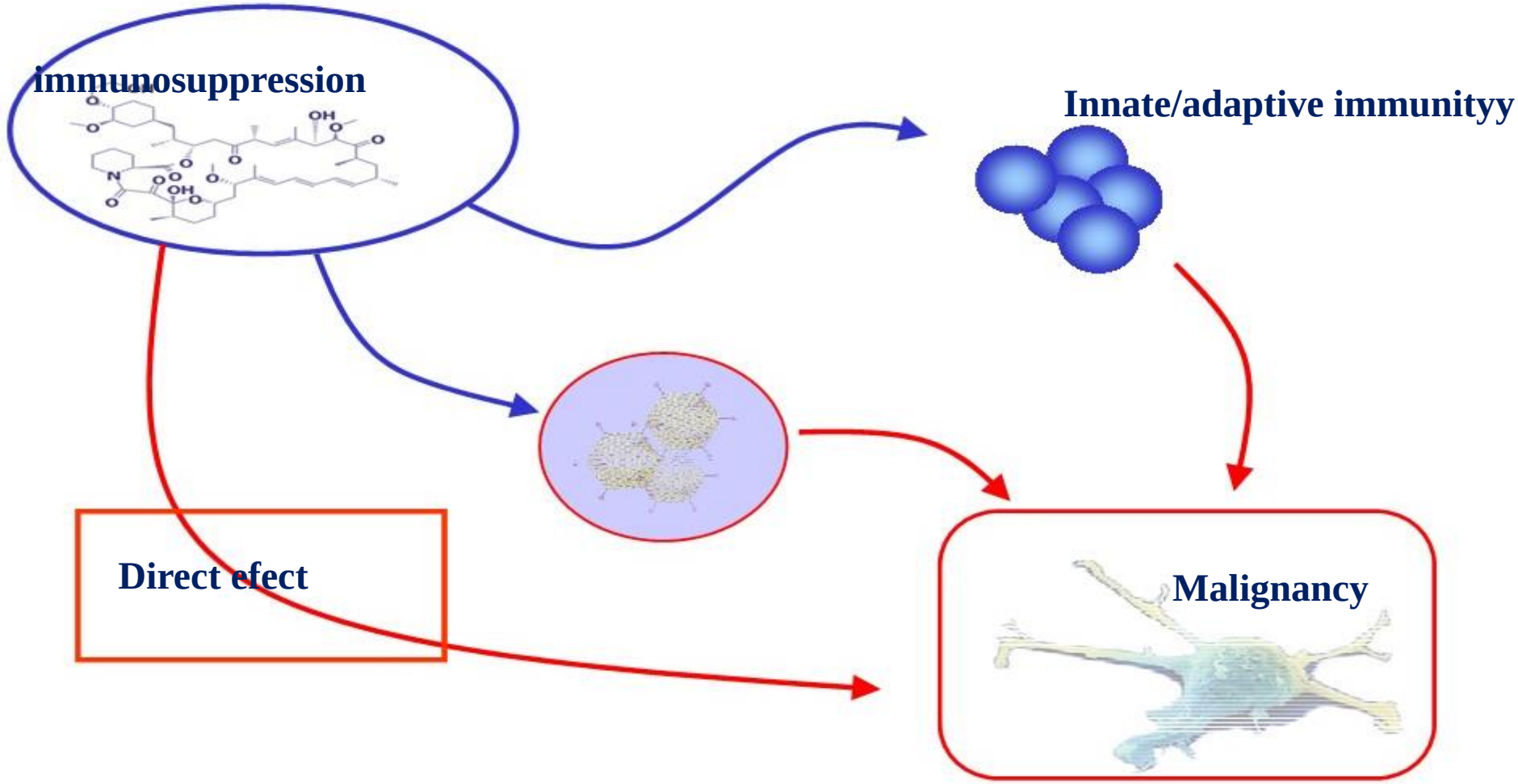
Watt KDS et al. Gastroenterology. 2009

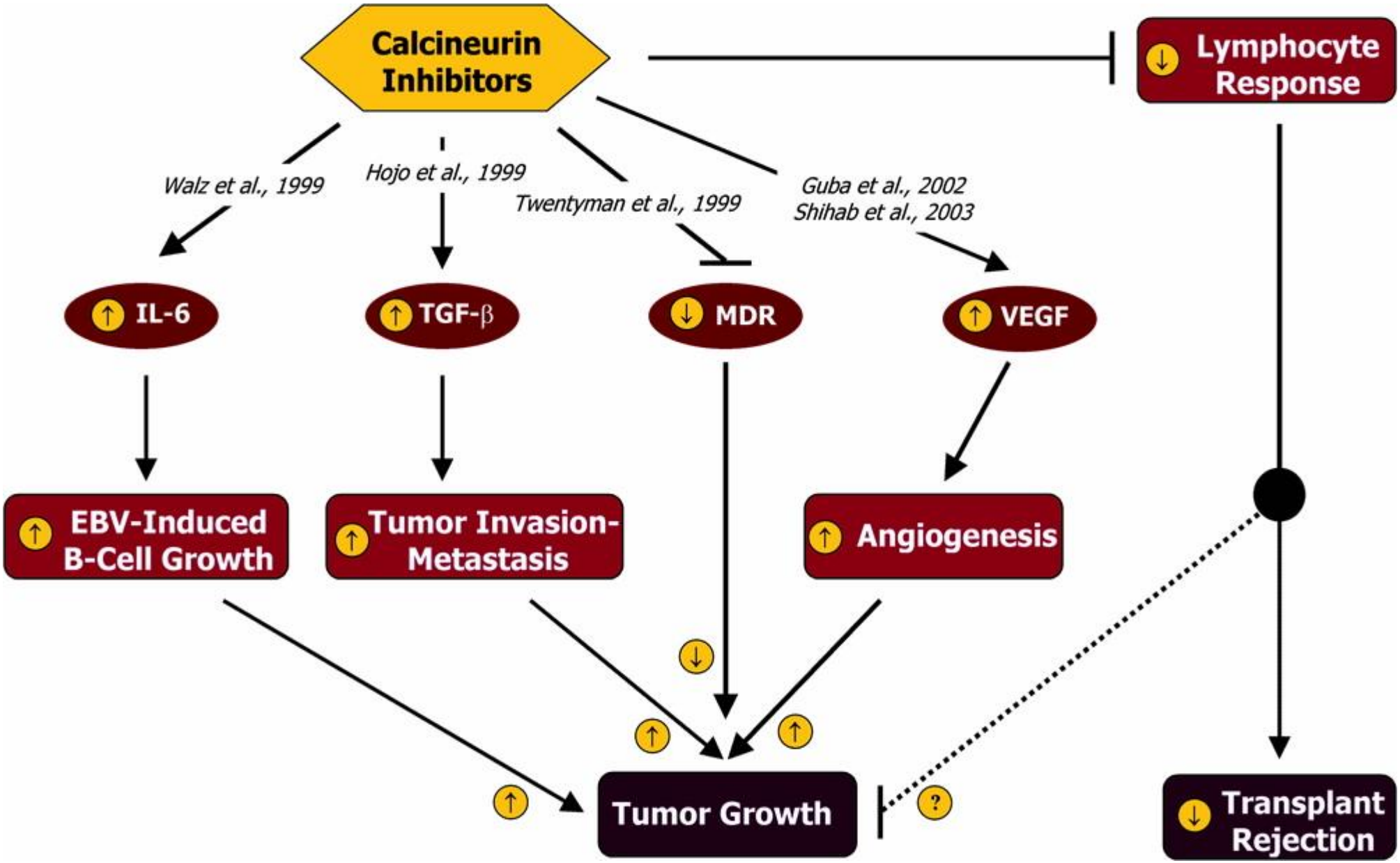
Risk factors for solid organ malignancy



Chapman J R , Campistol J M NDT. 2007

Immunosuppression





Guba M. Transplantation 2004

Azathioprine The mechanism of action is postulated via intercalation of DNA to be the inhibition of repair splicing and induction of codon misreads

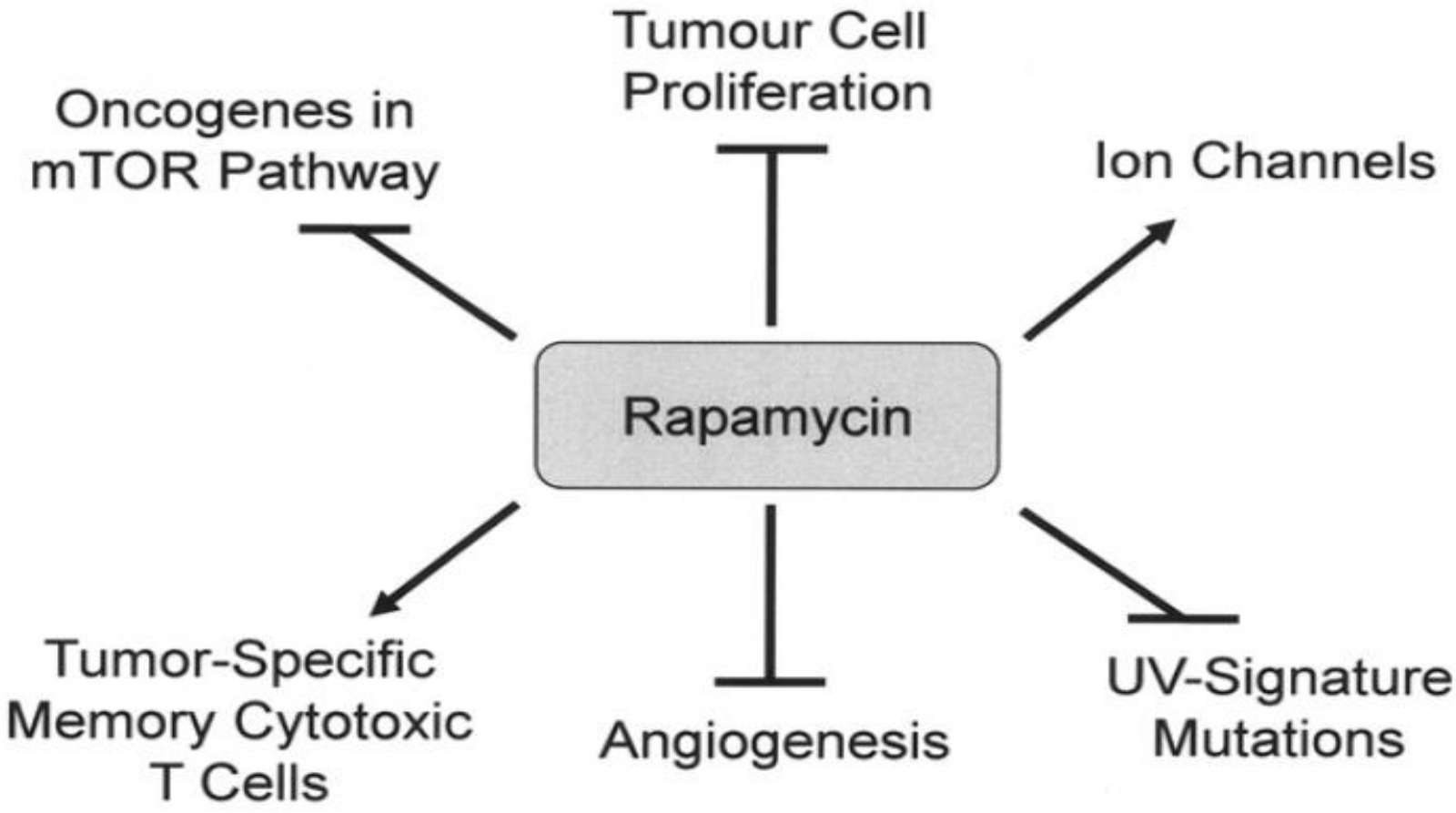
Mycophenolate mofetil impairs lymphocyte function by blocking purine biosynthesis via inhibition of the enzyme, inosine monophosphate dehydrogenase. Some malignancies, including some solid tumors, have dramatic elevations of this enzyme, suggesting that this agent may have some antiproliferative activity

The risk of developing a malignancy is not higher with MMF and may actually be associated with a decreased risk of solid and skin cancers

	Cyclosporine (*N* = 26 250)		Tacrolimus (*N* = 30 942)			Azathioprine (*N* = 3399)		MMF (*N* = 7366)		
	N	%	*N*	%	*P*-value	*N*	%	*N*	%	*P*-value
Any cancer	1275	4.9	1046	3.4	<0.001	211	6.2	1904	4.0	<0.001
Solid	537	2.0	432	1.4	<0.001	85	2.5	801	1.7	<0.001
Skin	576	2.2	382	1.2	<0.001	93	2.7	804	1.7	<0.001
PTLD	174	0.7	224	0.7	NS	37	1.1	302	0.6	<0.01

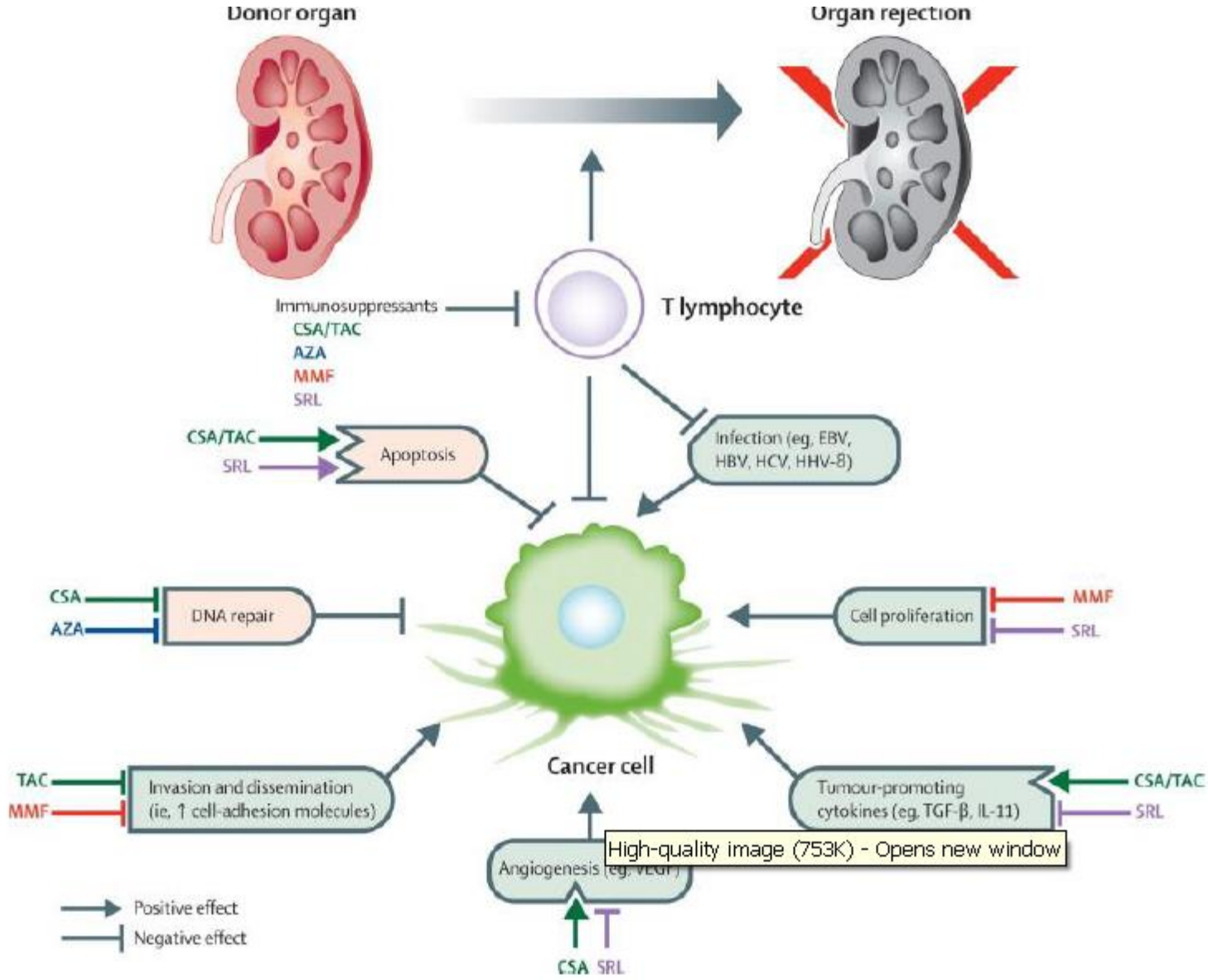
OPTN/UNOS, Organ Procurement and Transplantation Network/United Network for Organ Sharing; PTLD, post-transplant lymphoproliferative disorder; MMF, mycophenolate mofetil.

Kauffman HM. et al., Transplant Int 2006



Compared with controls, sirolimus was associated with a 40 % decrease in the overall risk of malignancy

Geissler EK, Transplant Proc, 2010, 42, S32-S35



CSA=cyclosporin. TAC=tacrolimus. AZA=azathioprine. MMF=mycophenolate mofetil. SRL=sirolimus. HBV=hepatitis B virus. HCV=hepatitis C virus. VEGF=vascular endothelial growth factor. TGF=transforming growth factor. IL=interleukin. ↑=increased quantities. *Ajikhumar TV Lancet oncol. 2007*

Viral agents

Viral Agent	Evidence of Causality		
	Sufficient	Limited	Inconclusive
Hepatitis B virus[14]	Liver		
Hepatitis C virus[14]	Liver		
Human T-cell lymphotropic virus type I[15]	Non-Hodgkin lymphoma*		
Human herpesvirus 8[16]	Kaposi sarcoma, non-Hodgkin lymphoma†		
Epstein-Barr virus[16]	Nasopharynx, Hodgkin disease, non-Hodgkin lymphoma‡		Salivary gland, stomach, lung
Human papillomavirus[17,18]	Tongue, mouth, tonsil, oropharynx, anus, vulva, vagina, cervix, penis	Nonmelanoma skin, periungual skin, larynx, eye§	Esophagus, nasal cavity, colon, lung, breast, ovary, prostate, bladder

*Adult T-cell lymphoma.
†Primary effusion lymphoma.
‡Burkitt lymphoma, sinonasal angiocentric T-cell lymphoma, and immune-suppression related lymphoma.
§Conjunctival carcinoma.

Vajdic CM, Int J Cancer, 2009

Post-transplant malignancies

- Malignancies *de novo*
- Recurrent malignancies
- Donor – transmitted malignancies

Candidates for organ transplantation undergo an extensive age and risk factor-appropriate cancer screening

Milan criteria in liver tranplantation

- single tumour with diameter ≤5 cm,
- or up to 3 tumours each with diameter ≤3 cm
- no extra-hepatic involvement
- no major vessel involvement

Patients with a history of malignancy prior to transplantation may experience recurrent disease.

No waiting period for transplantation is necessary with low-risk tumors

Transplantation should be delayed for at least five years with tumors that carry a high risk of recurrence following transplantation

Guidelines for the minimum time interval between diagnosis and treatment of a cancer and the transplantation

0- 2 years	**minimum 2 years**	**minimum 5 years**
Bladder cancer *in situ* Cervical cancer *in situ* BCC Prostate cancer (Gleason≤3, T1a-T1c)	Wilms tumor Testicular cancer Thyroid cancer Prostate cancer T2 Breast cancer stage 0-2 Bladder cancer invasive RCC symptomatic Lymphoma melanoma *in situ* Colorectal cancer Duke A or B1	Breast cancer stage 3-4 RCC large or invasive Colorectal cancer Duke C Uterine cancer Lung cancer

Batabyal et al. (2012)

Post-transplant malignancies

- Malignancies *de novo*
- Recurrent malignancies
- Donor – transmitted malignancies

TABLE 5. Organ-specific incidence of donor tumor transmission to transplant recipients: UNOS, 4/1/94-12/31/00

Organ	Transmission Number (%)
Liver (n=27,910)	7 (0.025%)
Kidney (n=52,539)	3 (0.006%)
Heart (n=15,379)	2 (0.013%)

Unintended transmission of malignant cells from a donor is very rare

Transplantation, 2002

Risk categories for donor tumor transmission

Risk category		Definition		Recommended clinical use[2]
		Nominal	Frequency estimate (f)[1]	
0	No significant risk	No active malignant tumor or history of tumor found during evaluation	0%	Standard
1	Minimal	The literature suggests minimal risk of tumor transmission	0%<f≤0.1%	Clinical judgment with informed consent[3]
2	Low	The literature suggests low grade risk of tumor transmission	0.1%<f≤1%	Use in recipients at significant risk without transplant. Informed consent required[3]
3	Intermediate	The literature suggests significant risk of tumor transmission	1%<f≤10%	Use of these donors is generally not recommended. On occasion, a lifesaving transplant may be acceptable in circumstances where recipient expected survival without transplantation is short (e.g. a few days or less). Informed consent required[3]
4	High	The literature suggests high risk of tumor transmission	>10%	Use of these donors is discouraged except in rare and extreme circumstances. Informed consent required[3]
U	Unknown risk	Evaluation for risk factors is incomplete or no literature exists to assess risk	N/A	Use should be based on clinical judgment with informed consent[3]

Nalesnik MA AJT 2011

Minimal risk of tumor transmission < 0,1%

Basal cell carcinoma, skin

Squamous cell carcinoma, skin without metastases

Carcinoma *in situ*, skin (nonmelanoma)

In situ cervical carcinoma

In situ vocal cord carcinoma

Superficial (noninvasive) papillary carcinoma of bladder (T0N0M0 by TNM stage) (nonrenal transplant only)

Solitary papillary thyroid carcinoma,≤0.5 cm

Minimally invasive follicular carcinoma, thyroid, ≤ 1.0 cm

(Resected) solitary renal cell carcinoma, ≤1.0 cm, well differentiated (Fuhrman 1–2)

High risk of tumor transmission >10 %

Malignant melanoma

Breast carcinoma >stage 0 (active)

Colon carcinoma >stage 0 (active)

Choriocarcinoma

CNS tumor (any) with ventriculoperitoneal or ventriculoatrial shunt, surgery,irradiation or extra-CNS metastasis, WHO grade III or IV

Lung cancer (stages I–IV)

Leukemia or lymphoma

Renal cell carcinoma >7 cm or stage II–IV

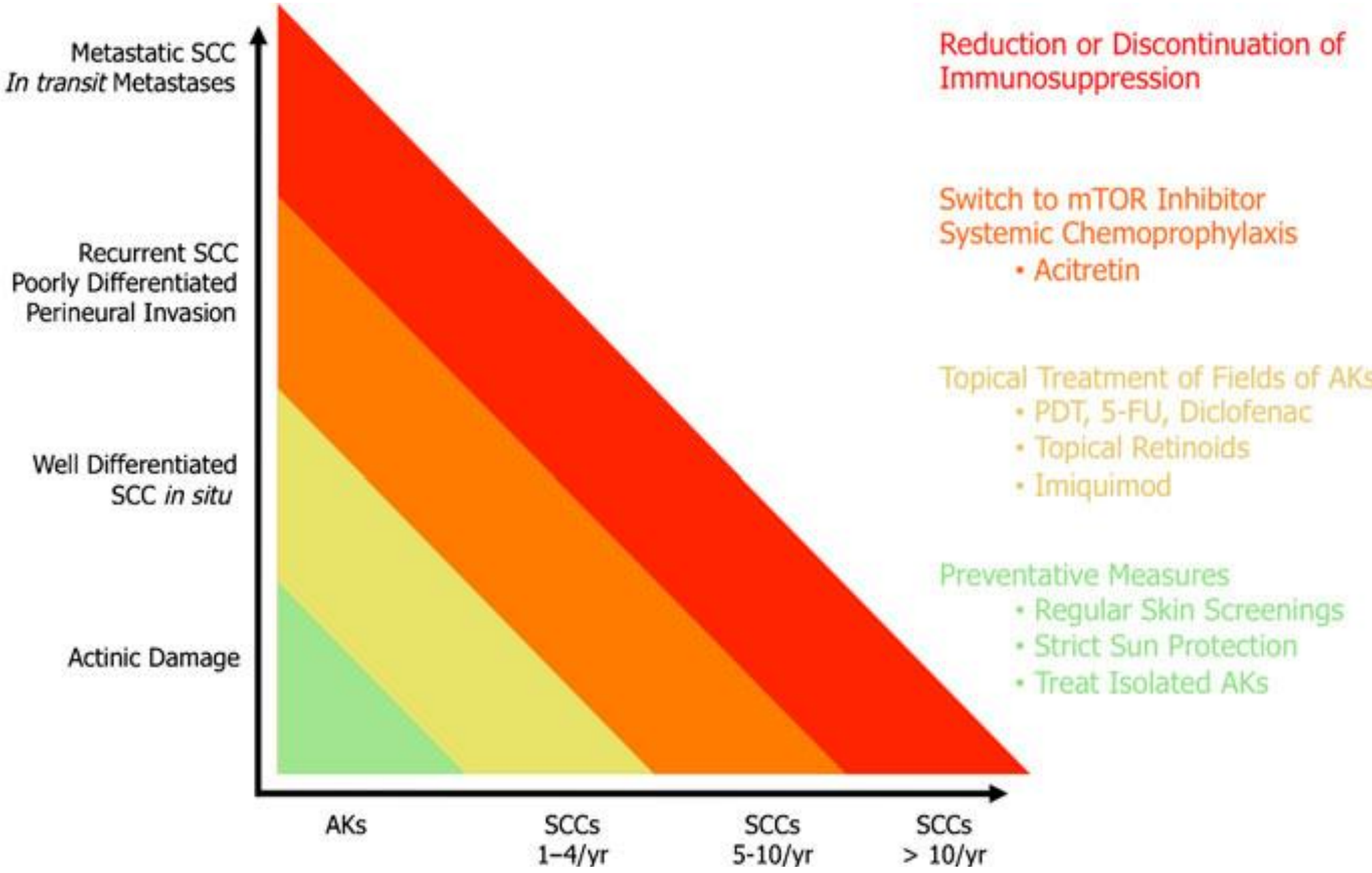
Small cell/neuroendocrine carcinoma, any site of origin

Metastatic carcinoma

Sarcoma

SKIN CANCERS

- especially squamous cell and basal cell carcinomas, but also melanoma, Merkel cell carcinoma (MCC), and KS, are more common than in the nontransplant population



Bangash HK 2012Curr. Treatment Opt. in Oncology (2012)

post-transplant lymphoproliferative disorders (PTLD)

- lymphoid and/or plasmacytic proliferations that occur in the setting of solid organ or allogeneic hematopoietic cell transplantation as a result of immunosuppression.

- the majority appears to be related to the presence of Epstein-Barr virus (EBV) 80% (early <12months post transplant ; late >12 months.)

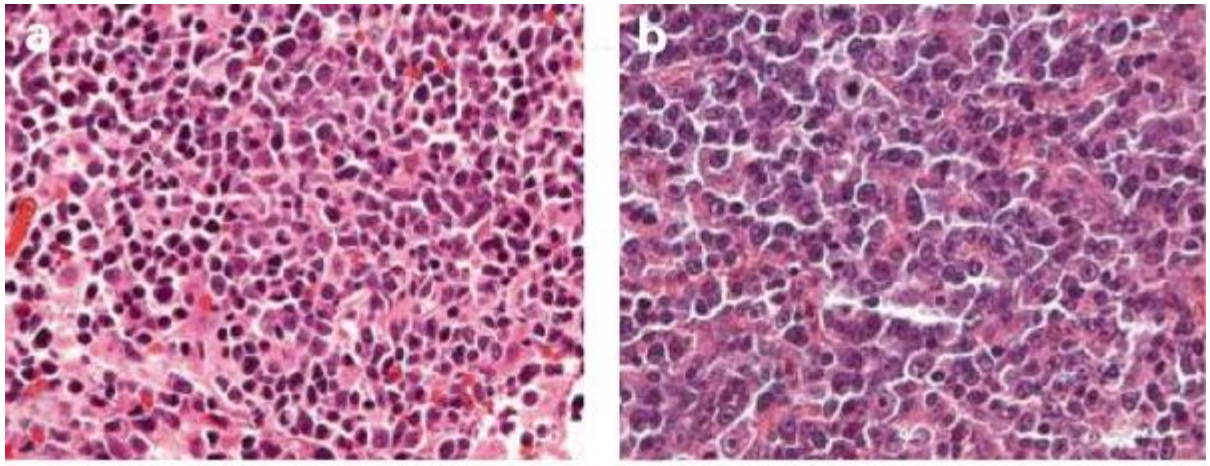
- **risk factors:**
- the degree of T cell immunosuppression
- the EBV serostatus of the recipient
- time post-transplant
- recipient age
- transplanted organ: jejunum 14% > liver 2-5% > heart 2-5% lung 2-3% > pancreas 2.1%> kidney 1%

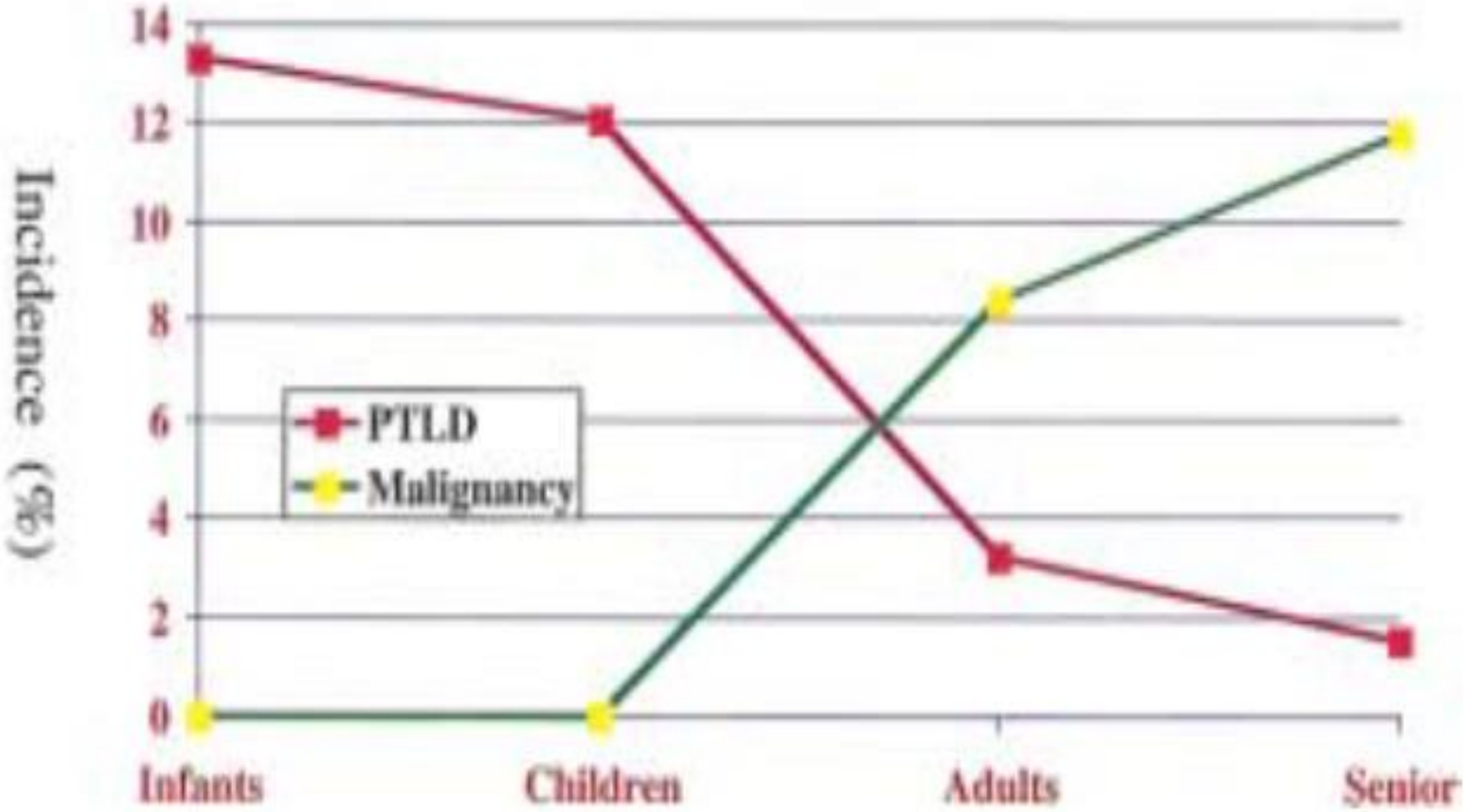
Three general types of PTLD

Early lesions (ie, plasmacytic hyperplasia and infectious mononucleosis-like PTLD) – This presents as an infectious mononucleosis-type acute illness characterized by polyclonal B cell proliferation with no evidence to suggest malignant transformation.

●**Polymorphic PTLD** – Polymorphic PTLD are polyclonal or monoclonal lymphoid infiltrates that demonstrate evidence of malignant transformation but do not meet all of the criteria for one of the B cell or T/NK cell lymphomas recognized in immunocompetent patients.

●**Monomorphic PTLD** – Monomorphic PTLD are monoclonal lymphoid proliferations that meet the criteria for one of the B cell or T/NK cell lymphomas recognized in immunocompetent patients





Fung Liver Transplantation 2003

KAPOSI SARCOMA

classic, endemic, iatrogenic, AIDS-associated

Most cases of posttransplant KS occur in individuals of Mediterranean, Jewish, Arabic, Caribbean, or African descent – (geographic distribution of HHV8)

The clinical presentation is manifested as angiomatous lesions (purplish, reddish blue, or dark brown/black macules, plaques, and nodules on the skin) predominantly affecting the legs and causing lymphedema

Screening

The ability to prevent and detect solid organ malignancies in the transplant patient, particularly early-stage carcinomas, relies upon periodic screening examinations and strict adherence to prophylactic measures.

- **Intensified protocol** (since 2002)

  Examinations were performed annually in all patients regardless of age:
  - chest and abdominal CT,
  - urological evaluation (including measurement of PSA),
  - gynaecological (including Papanicolau smear and mammography) and
  - dermatological screening.
  - Colonoscopy was performed 3 years after LT and every 5 years thereafter, except in patients with an adenoma prior to LT or a history of inflammatory bowel disease. In these patients, the first colonoscopy was performed 1 year after LT.

- **Standard protocol** (<2002) = health maintenance for the general population
  - annual gynecologic examinations (PAP smear) starting at the age of 20 years,
  - mammographies every 2 years starting at the age of 40 years,
  - annual urologic examinations including PSA measuring starting at the age of 45 years and
  - colonoscopies starting at the age of 50, except patients with a positive family history for colorectal malignancies (starting at the age of 40)

- Post-LT HCC surveillance has not changed over the study period. In HCC patients, an annual chest and abdominal CT scan was performed pre- and post-2002.

Finkestedt et. al. AJT 2009

Suggested guidelines for cancer screening in patients undergoing solid organ transplantation

Cancer type	Recommendation
Breast	Women 50 to 69 years: annual screening mammography with or without clinical breast examination; age 40 to 49 years: the benefit of screening is less certain and should be left to the decision of the clinician and patient; ≥70 years of age: annual screening is appropriate as long as estimated life exectancy is ≥8 years.
Skin	Monthly self-examination; clinician examination annually, with early referral for suspected lesions.
Cervical	All women ≥18 years old and sexually active girls <18 years old should undergo an annual pelvic examination and Pap smear.
Anogenital	Yearly physical examination of the anogenital area, including pelvic examination and cytologic studies for women. Insufficient evidence to recommend for or against screening anoscopy and biopsies of anal epithelium.
KS/other sarcomas	Examination of skin, conjunctivae, and oropharyngeal mucosa annually; patients at higher risk (ethnicity, geographic area of residence or serologic positivity for HHV) may benefit from more frequent screening.
Prostate	Annual screening with digital rectal examination and PSA recommended for men ≥age 50 years if their estimated life expectancy is at least 10 years. If positive family history or African-American race, may start annual screening earlier (eg, age 45 years).
Colorectal	Starting at age 50 years: annual FOBT and either sigmoidoscopy every five years or colonoscopy every 10 years*.
PTLD	Complete history and physical examination every three months, particularly in the first posttransplant year; patients at increased risk of PTLND may benefit from more frequent screening.
Lung	Not recommended.
HCC	For patients with chronic hepatitis B or C and cirrhosis, serum AFP and liver ultrasound every 6 to 12 months.
Renal cell	Screening via cytologic or radiographic means is not recommended, except possibly for patients with a history of analgesic abuse.

KS: Kaposi sarcoma; PSA: prostate specific antigen; HHV-8: human herpesvirus 8; FOBT: fecal occult blood testing; PTLD: posttransplant lymphoproliferative disorder; HCC: hepatocellular cancer; AFP: alpha-fetoprotein.

* At some institutions, screening is started at age 40 years or five years after transplant, whichever comes first.

Modified from: Kasiske BL, Vazquez MA, Harmon WE, et al. Recommendations for the outpatient surveillance of renal transplant recipients. American Society of Transplantation. J Am Soc Nephrol 2000; 11 Suppl 15:S1.