Risk of subsequent malignancies after radiotherapy among adults

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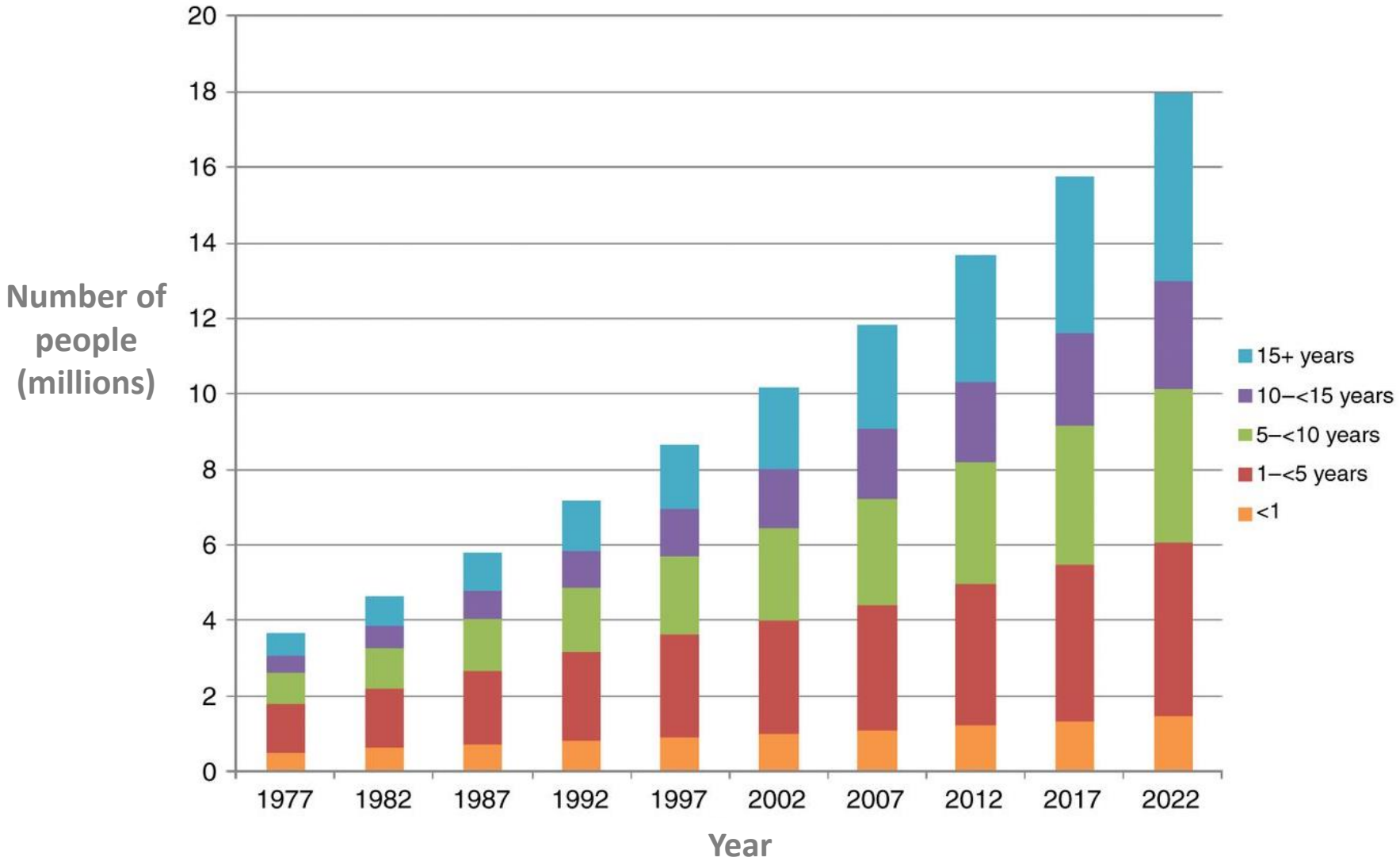
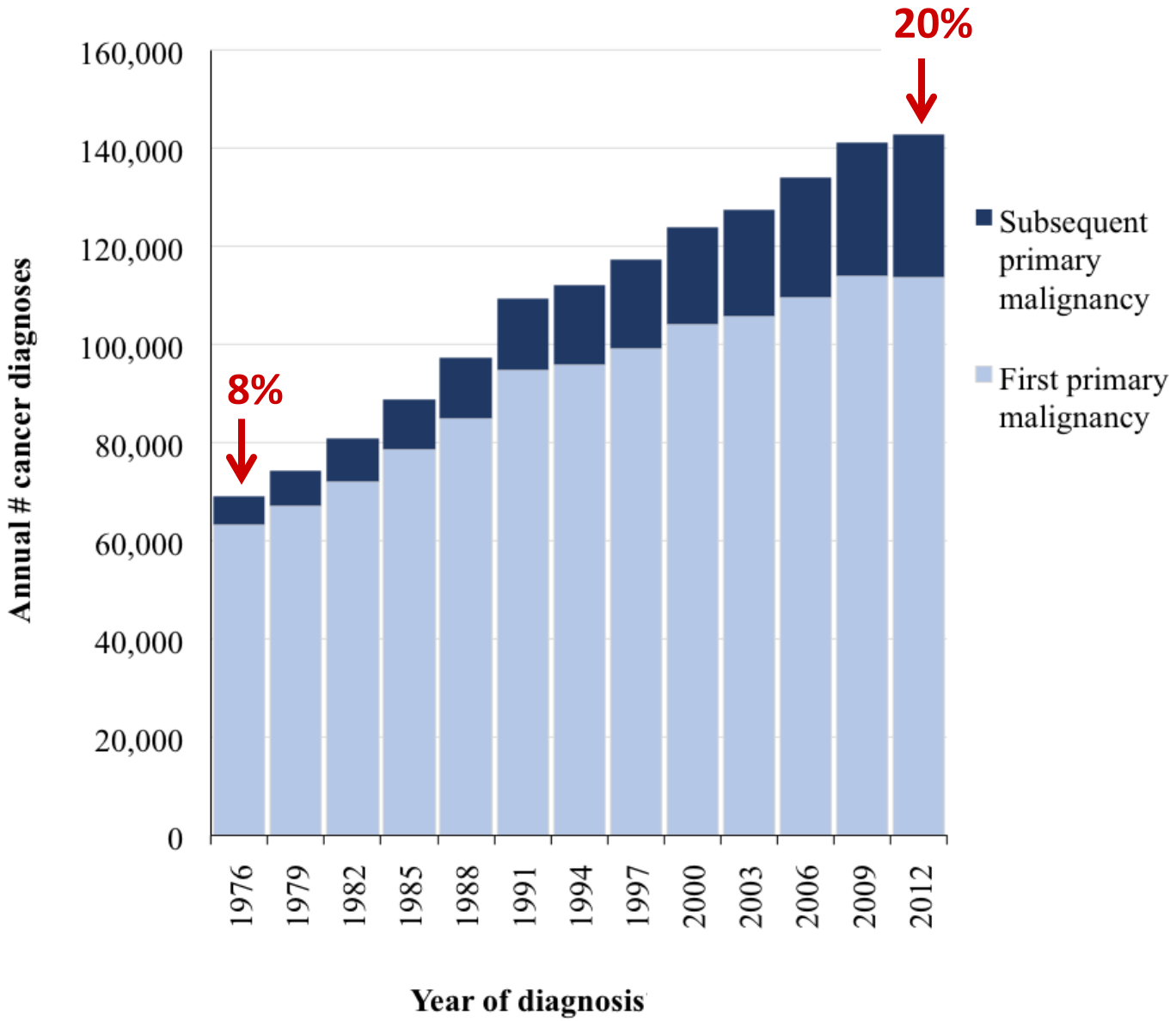
Division of Cancer Epidemiology & Genetics

Increasing Population of Survivors

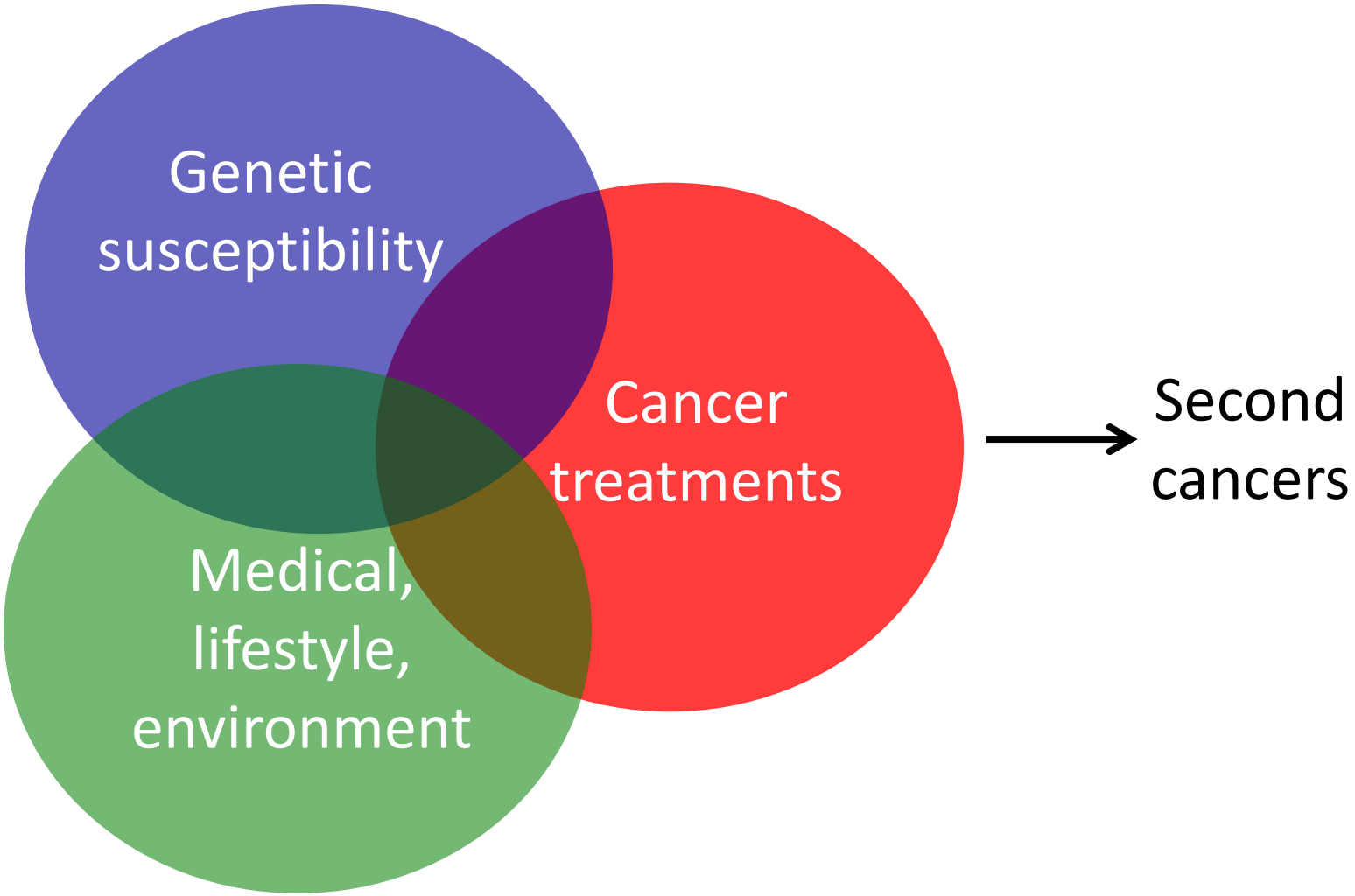


de Moor JS et al. *Cancer Epidemiol Biomarkers Prev* 2013

Increasing 2nd Cancer Burden

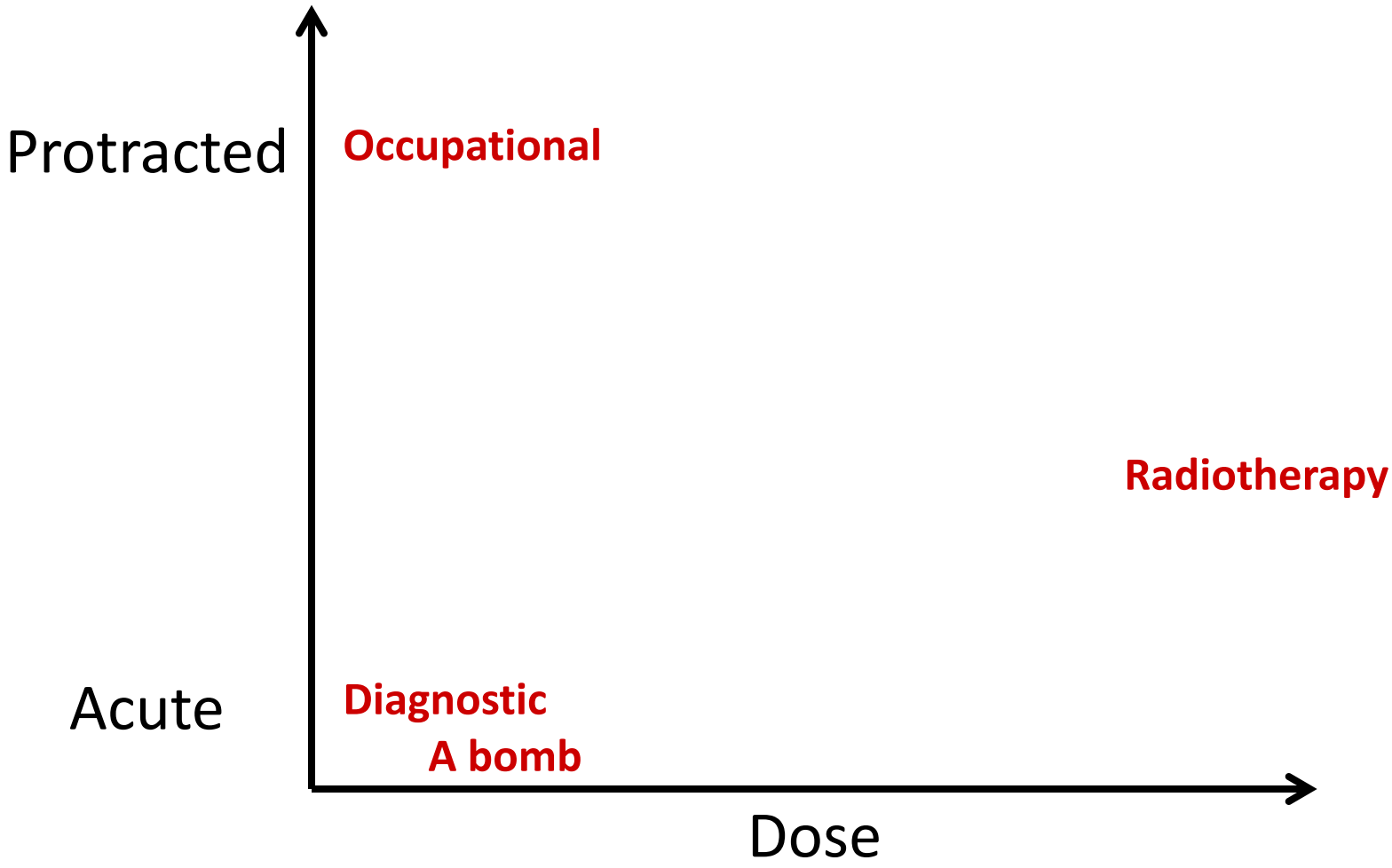


Causes of Second Cancers



Radiotherapy & 2nd Cancer Risks

- Ionizing radiation → established carcinogen



Radiotherapy & 2nd Cancer Risks

- Ionizing radiation → established carcinogen

- Key research questions:
  - Magnitude and shape of radiation dose-response relation
  - Modifiers

- Detailed treatment data → quantify risks
  - Follow-up patients treated in the past
  - Project risks associated with current treatments

Radiation Dose-Response Relation

Radiation Dose-Response Relation

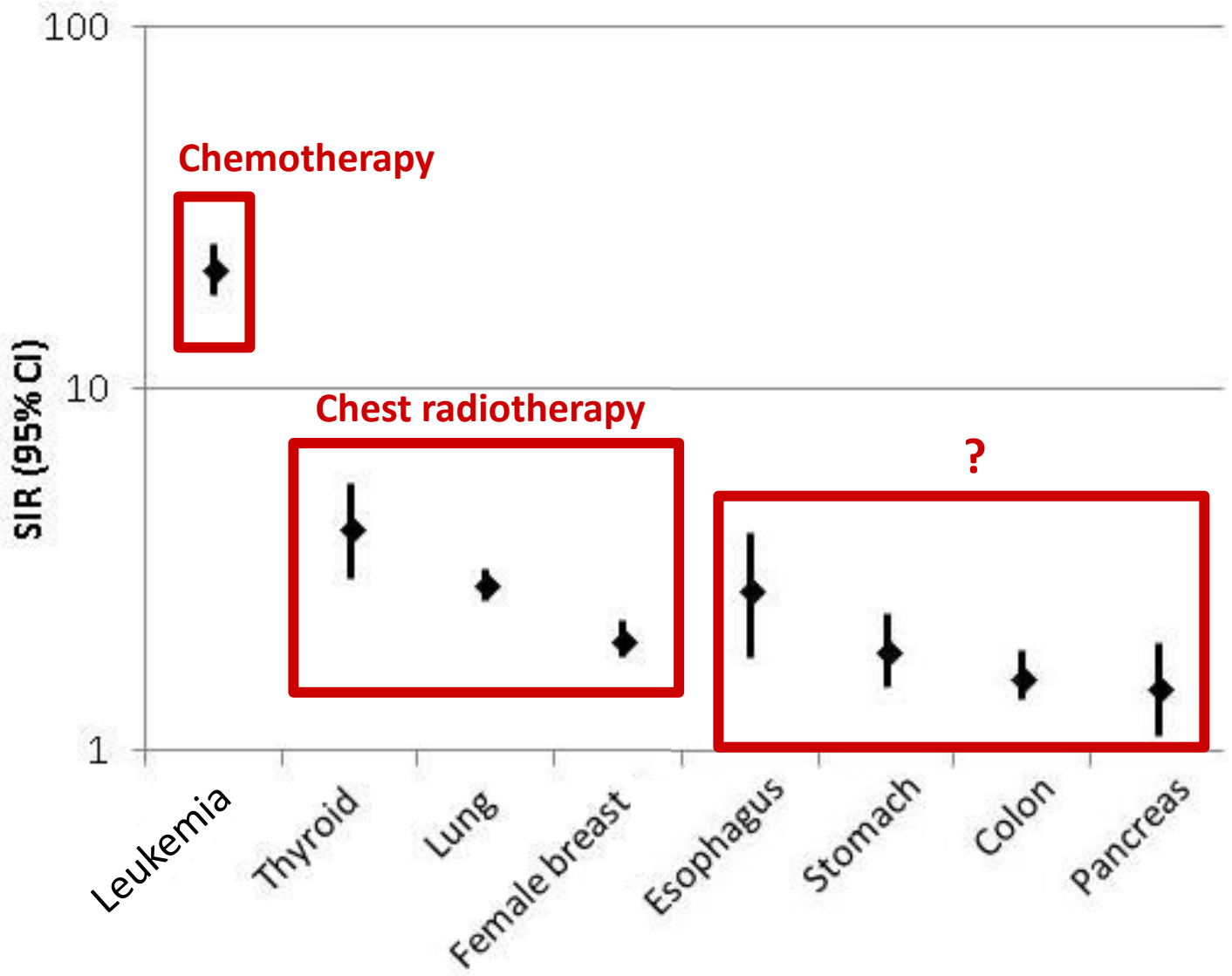
- Tissue sensitivity to radiation varies substantially

- Highest risks:
  - Leukemia
  - Basal cell carcinoma
  - Sarcoma
  - Meningioma
  - Thyroid
  - Breast

- Risk for certain malignancies after radiotherapy poorly understood

Berrington de González et al. *Int J Radiat Oncol Biol Phys* 2013

2nd Cancers after Hodgkin lymphoma



Dores et al. *J Clin Oncol* 2002

2nd Gastrointestinal Cancer Study

Denmark, Finland, Iowa, Netherlands, Norway, Ontario, Sweden

First cancer	Second Cancer: Esophagus	Stomach	Pancreas
Breast cancer	X		
Hodgkin lymphoma	X	X	X
Testicular cancer		X	X
Cervical cancer		X	

Case-Control Study Methods

- Cohort of ~20,000 HL survivors
  - Diagnosed during 1943-1996
  - Followed through 2003

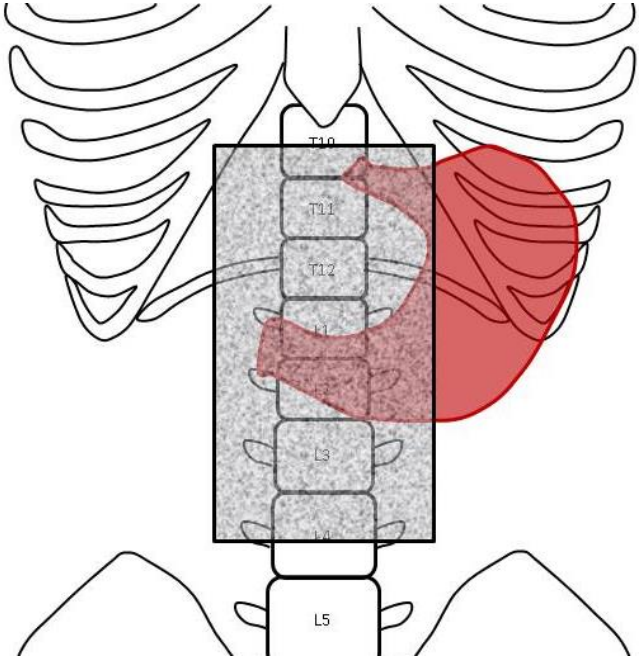
- Controls individually matched to cases (2:1)

	Esophagus	Stomach	Pancreas
Cases	36	89	36
Controls	71	190	70

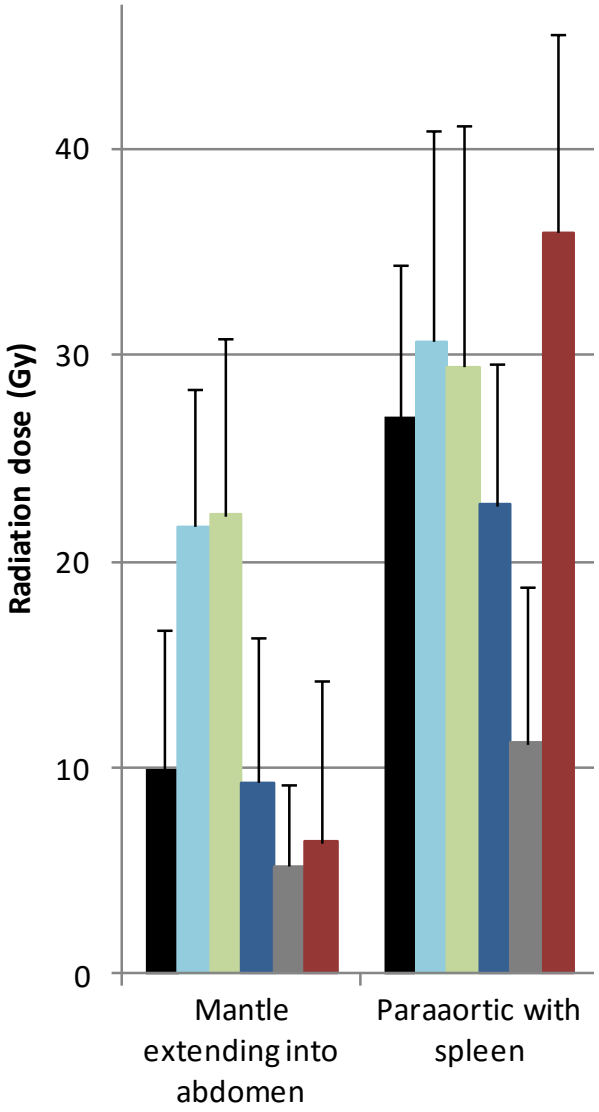
Case-Control Study Methods

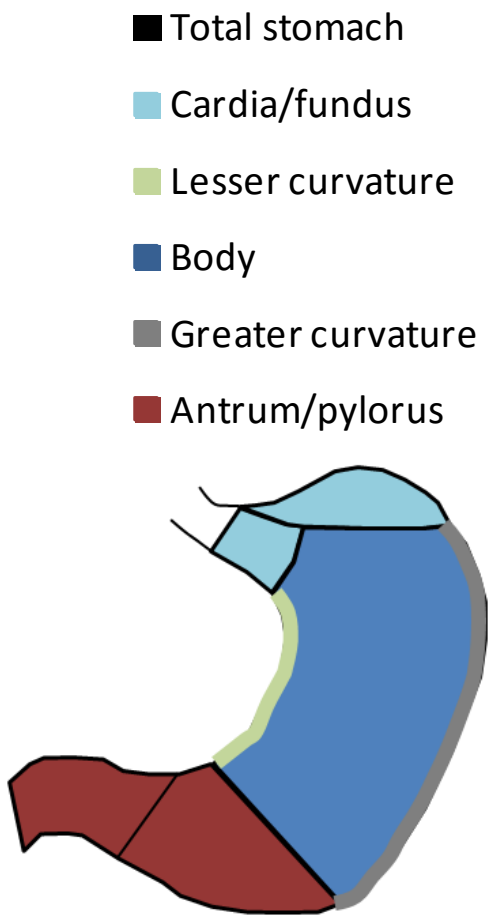
- Medical record abstraction
  - HL and GI cancer diagnoses
  - Detailed HL treatment data

- Radiation dose reconstruction
  - Beam energy
  - Treatment fields
  - Normal tissue blocking
  - Prescribed target dose
  - Tumor location



Dose by Field and Stomach Region



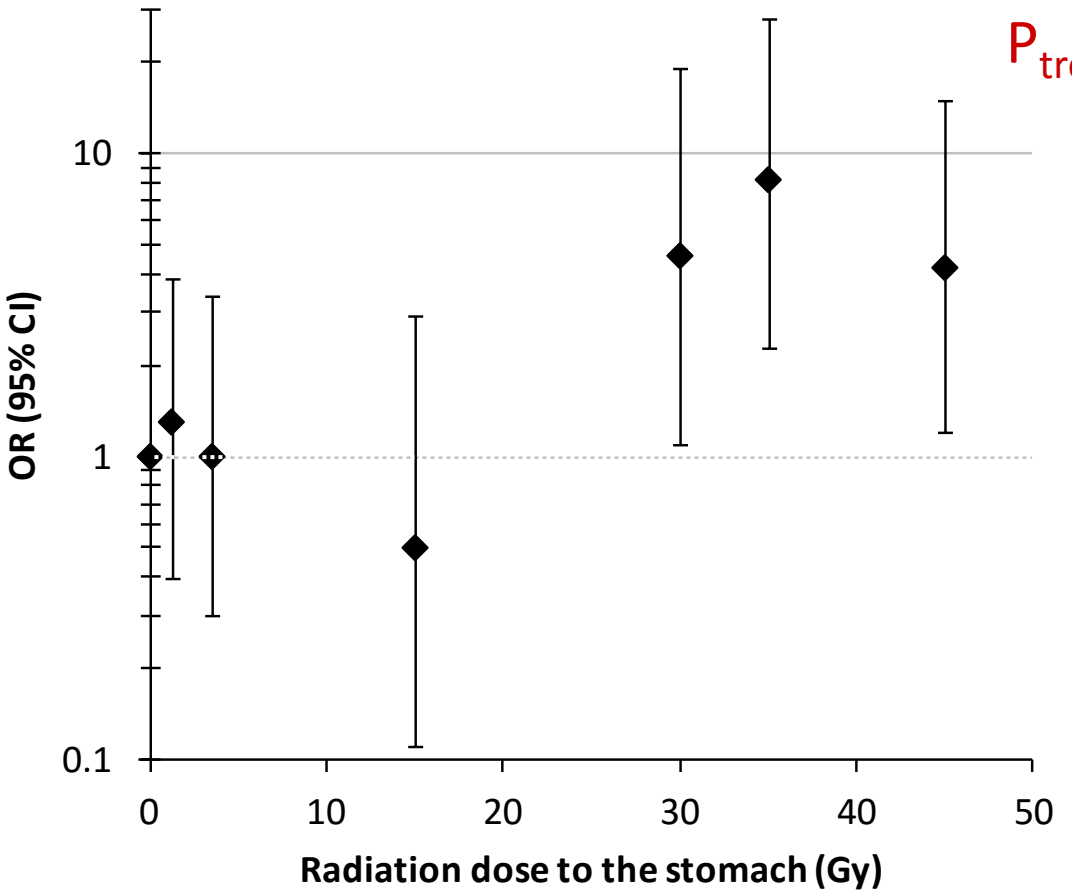


Morton et al. *J Clin Oncol* 2013

Radiotherapy → Stomach Cancer

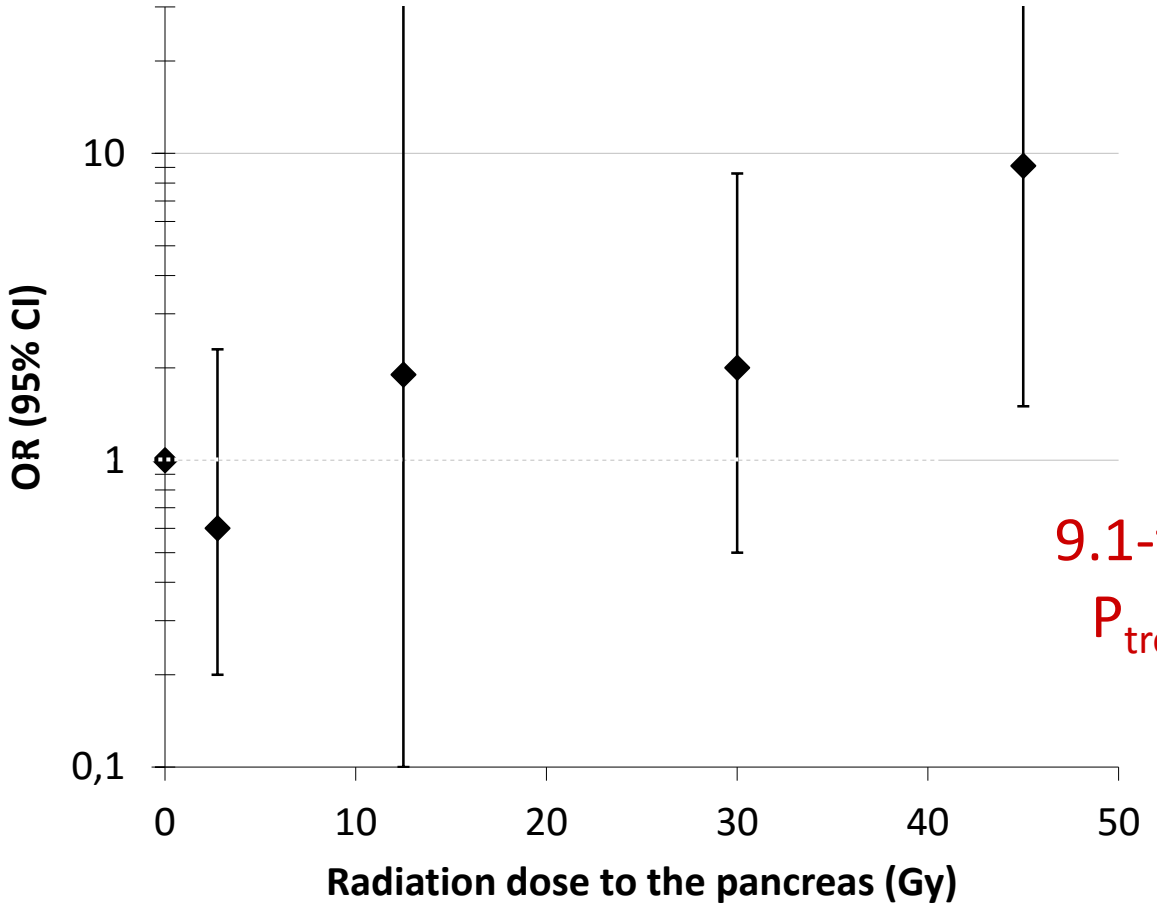
4.2-fold ↑ risk

P_{trend}<0.001



Morton et al. *J Clin Oncol* 2013

Radiotherapy → Pancreatic Cancer



9.1-fold ↑ risk

P_{trend}=0.004

Dores et al. *Ann Oncol* 2014

Radiation Dose-Response Relation

Reference	First cancer	Cases / Controls	ERR/Gy (95% CI)
Lung			
Gilbert et al., 2003	HL	227 / 455	0.15 (0.06-0.39)
Inskip et al., 1994 *	Breast	61 / 120	0.20 (-0.62-1.03)
Grantzau et al., 2014	Breast	151 / 443	0.09 (0.03-0.23)

* Organ dose rather than tumor dose. § Mean dose <5 Gy.

Modifiers of Radiation Dose-Response Relation

Potential Modifiers

- Age
- Latency
- Radiotherapy exposure
  - Proton vs. photon
  - Volume of tissue irradiated
- Systemic therapy
- Genetic susceptibility
- Lifestyle factors/medical history

Childhood Cancer Treatments → Sarcoma

Radiation Dose	Alkylator Score		
	0	*1 or 2*	*≥3*
None			
Relative risk	1.0*	4.8	8.5†
No. cases:controls	6:44	1:4	3:3
<1000 rad			
Relative risk	1.3	0.4	1.3
No. cases:controls	5:43	1:13	3:14
≥1000 rad			
Relative risk	37.4‡	14.2‡	59.2‡
No. cases:controls	21:45	11:26	13:12

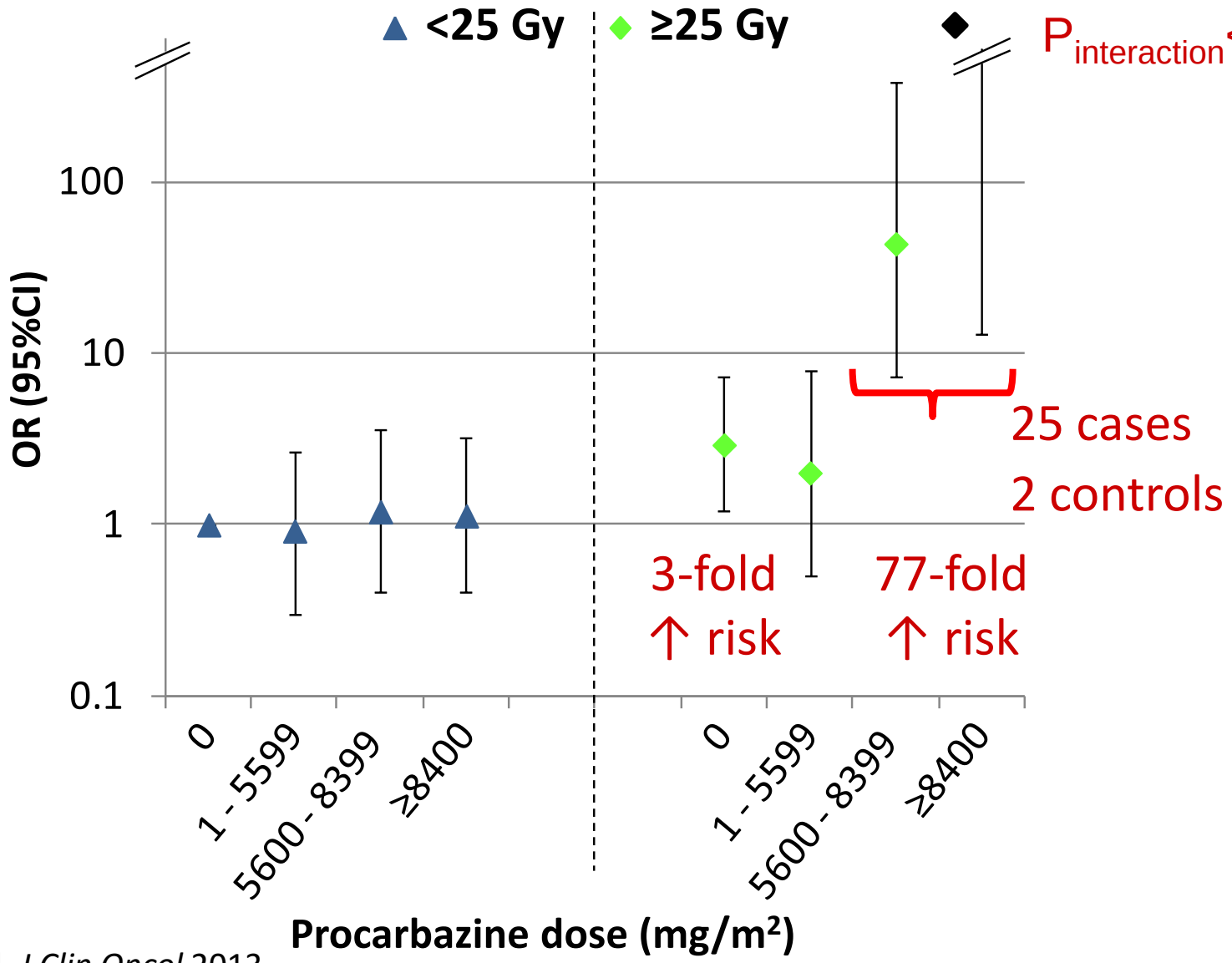
*Referent category.

†Trend in alkylator score in subjects not exposed to radiation, P = 0.05.

‡P<0.05.

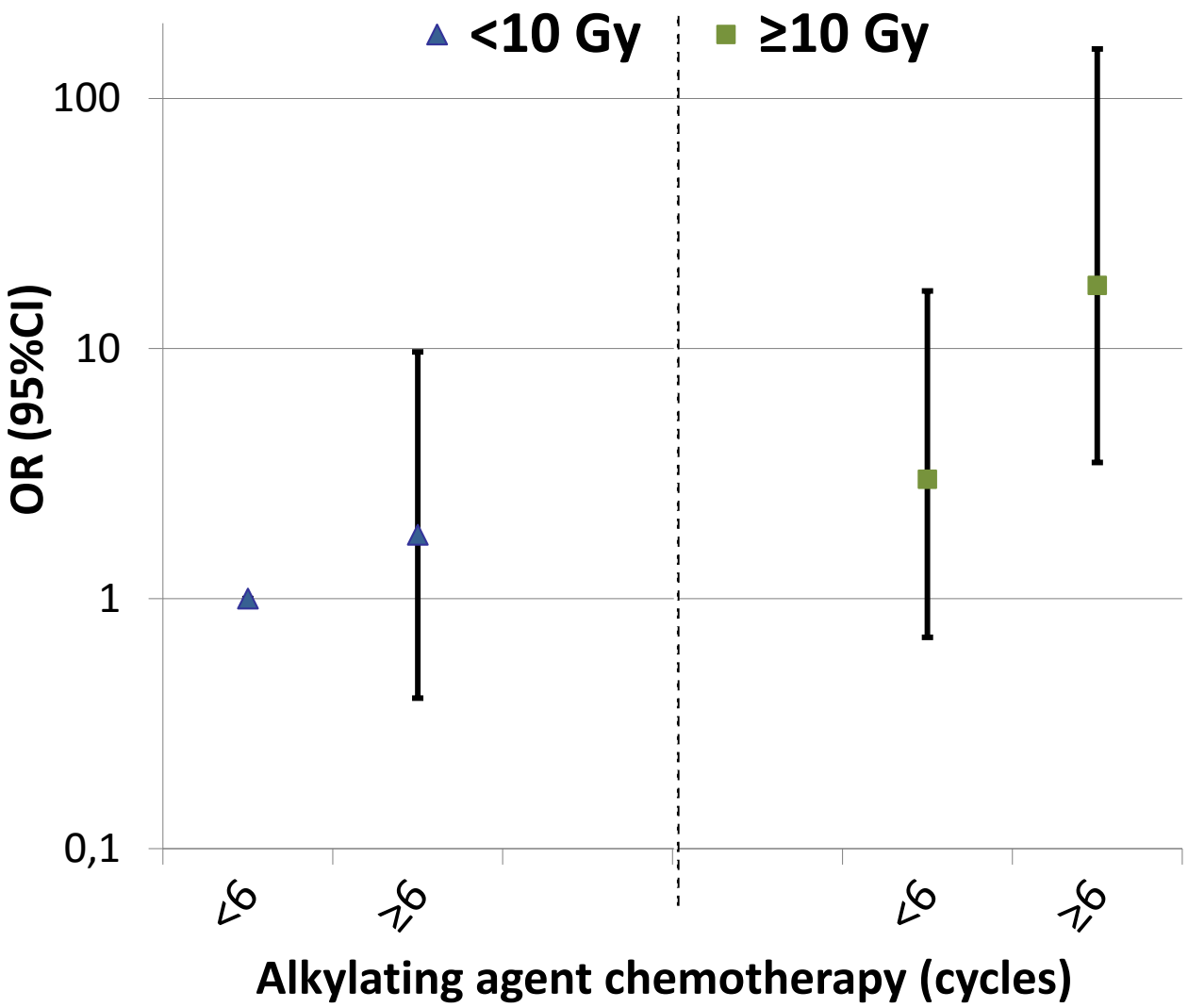
Tucker et al. *New Engl J Med* 1987

HL Treatments → Stomach Cancer



Morton et al. *J Clin Oncol* 2013

HL Treatments → Pancreatic Cancer



Multiplicative:

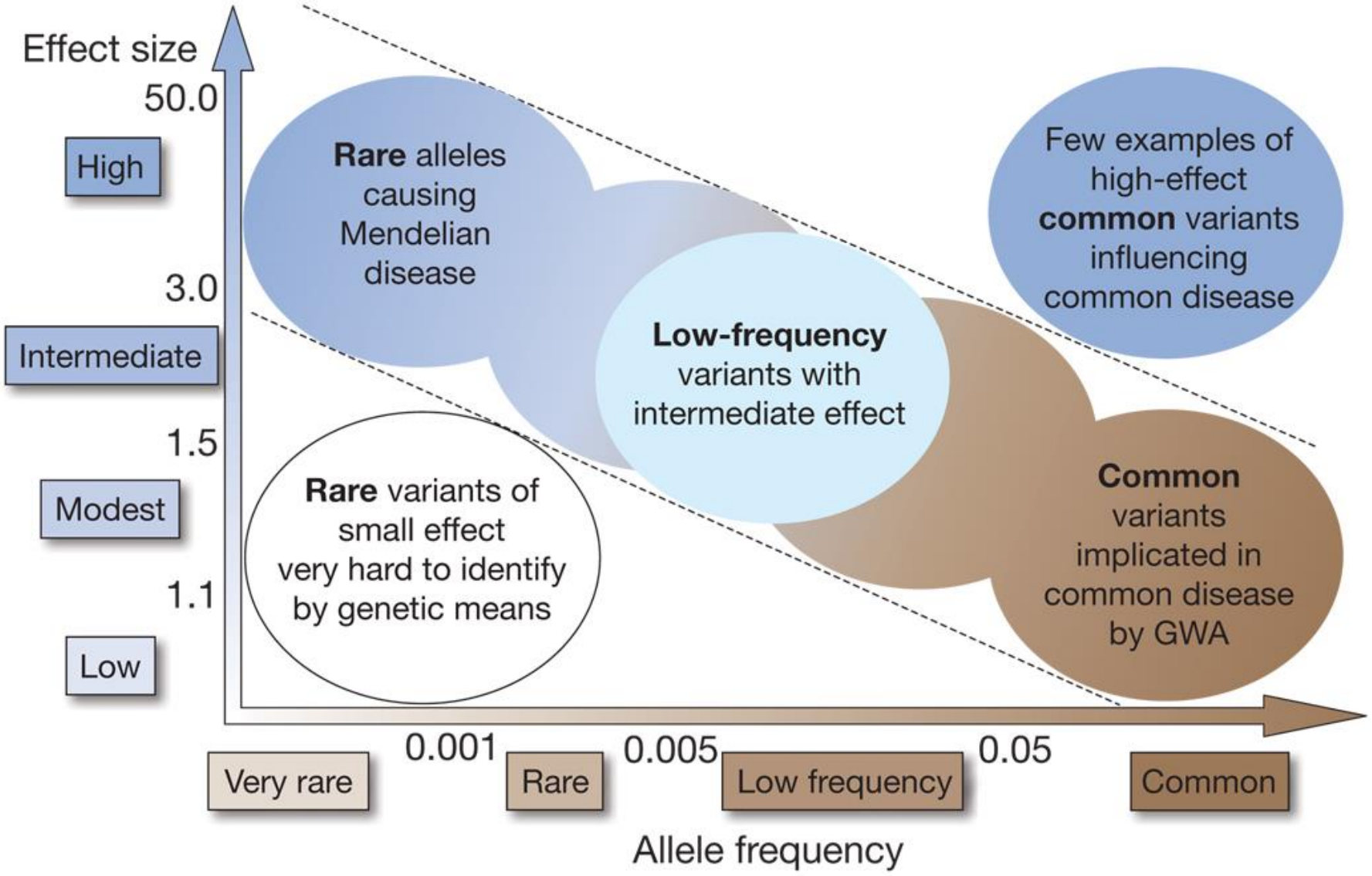
$P_{interaction}$=0.29

Additive:

$P_{interaction}$=0.041

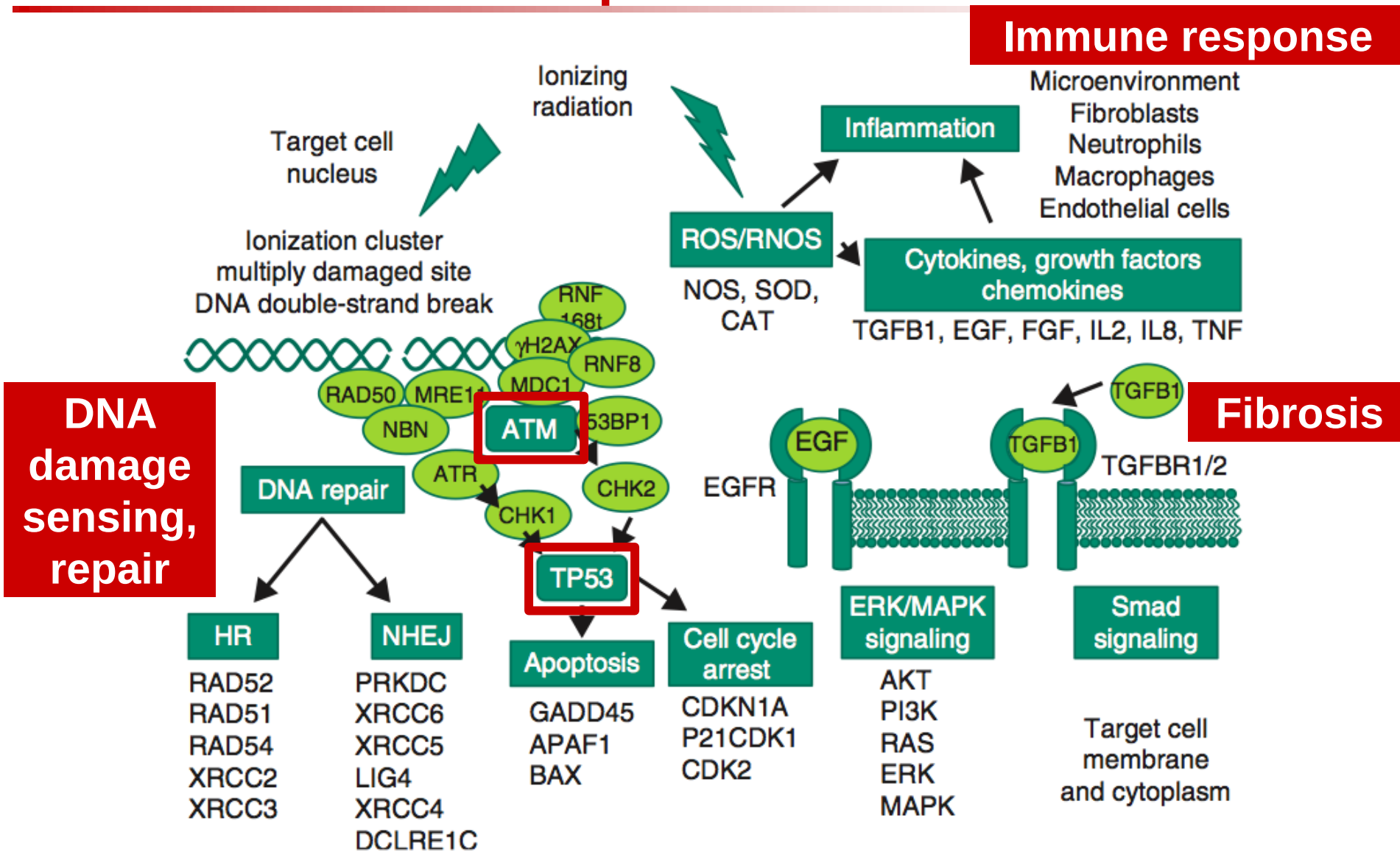
Dores et al. *Ann Oncol* 2014

Types of Genetic Variation



Manolio et al. *Nature* 2009

Radiation Response



West & Barnett *Genome Med* 2011

Rare Inherited Disorders

- Li-Fraumeni syndrome (17p13.1, *TP53*)
- Ataxia-telangiectasia (11q22.3, *ATM*)
- Nijmegen breakage syndrome (8q21.3, *NBS1*)
- Fanconi anaemia (16q24.3, *FANCA*)

Barnett et al. *Nat Rev Cancer* 2009

Candidate Gene Study Examples

- WECARE Study: Contralateral breast cancer
  - ➢ among *BRCA1/2* mutation carriers

Population	Breast Cancer Risk
BRCA1/2 mutation carrier vs. no mutation	4.5*
No mutation, ≥1 vs. <1 Gy	1.2*
BRCA1/2 mutation carrier, ≥1 vs. <1 Gy	1.0

* P<0.05

Bernstein et al. *Eur J Cancer* 2013

Risks Associated with Current Treatments

2nd Cancers after Prostate Cancer

- New technologies frequently used
  - 3D conformal radiotherapy (3D-CRT)
  - Intensity-modulated radiotherapy (IMRT)

  ➢Changes in volumes of tissue irradiated at treatment, intermediate, and low doses

- Review of planning studies suggested increase in second cancer risks with IMRT (Murray et al. *Radiat Oncol* 2013)

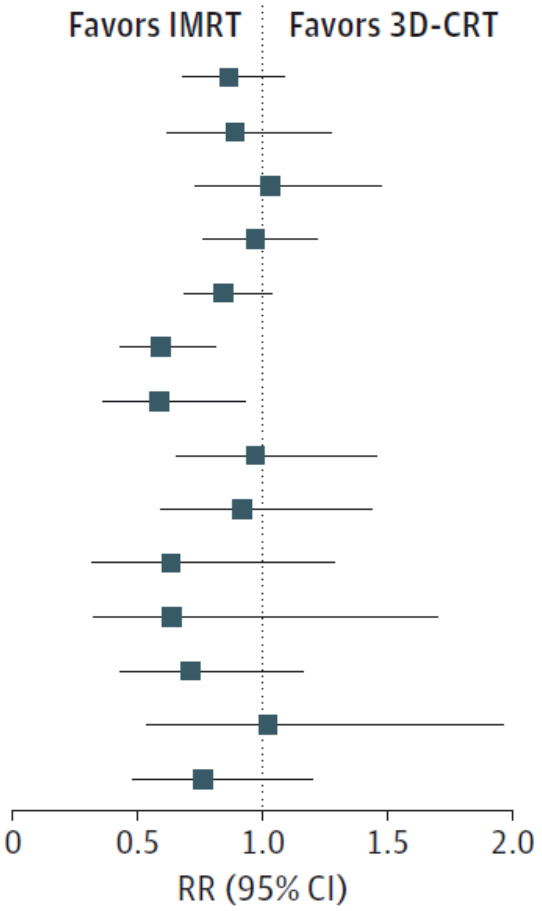
2nd Cancers after Prostate Cancer

Characteristic	No. (%)	
	IMRT	3D-CRT
Patients, No.	27 904	11 124
Age at diagnosis, y		
65-69	6847 (24.5)	2922 (26.3)
70-74	10 415 (37.3)	4235 (38.1)
75-79	7933 (28.4)	3028 (27.2)
≥80	2709 (9.7)	939 (8.4)
Year at diagnosis		
2002-2003	3684 (13.2)	6840 (61.5)
2004-2005	7296 (26.2)	2808 (25.2)
2006-2007	9555 (34.2)	1147 (10.3)
2008-2009	7369 (26.4)	329 (3.0)
Tumor grade		
1 to 2	11 525 (41.3)	6083 (54.7)
3 to 4	16 379 (58.7)	5041 (45.3)

Journy et al. *JAMA Oncol* 2016

2nd Cancers after Prostate Cancer

Source	IMRT No. of Cases	IMRT Incidence Rate	3D-CRT No. of Cases	3D-CRT Incidence Rate	RR (95% CI) for IMRT vs 3D-CRT
All leukemia and myelodysplasia[a]	135	168	108	201	0.86 (0.68-1.09)
Non-CLL leukemia	49	61	37	69	0.89 (0.62-1.28)
Myelodysplasia	63	79	43	80	1.03 (0.72-1.48)
Lymphoma[a]	130	162	91	170	0.97 (0.76-1.22)
All solid cancers[b]	318	1015	440	1392	0.84 (0.68-1.04)
Colon	25	80	47	149	0.59 (0.43-0.81)
Rectum	<11		13	41	0.58 (0.36-0.93)
Urinary bladder	66	211	80	253	0.97 (0.65-1.46)
Other urinary organs and tracts	20	64	25	79	0.92 (0.59-1.44)
Pancreas	<11		16	51	0.63 (0.30-1.29)
Stomach	<11		15	47	0.63 (0.24-1.70)
Other digestive organs	15	48	24	76	0.71 (0.43-1.16)
Lung and bronchus	94	300	110	348	1.02 (0.53-1.96)
Head and neck	31	99	46	146	0.76 (0.48-1.20)



Journy et al. *JAMA Oncol* 2016

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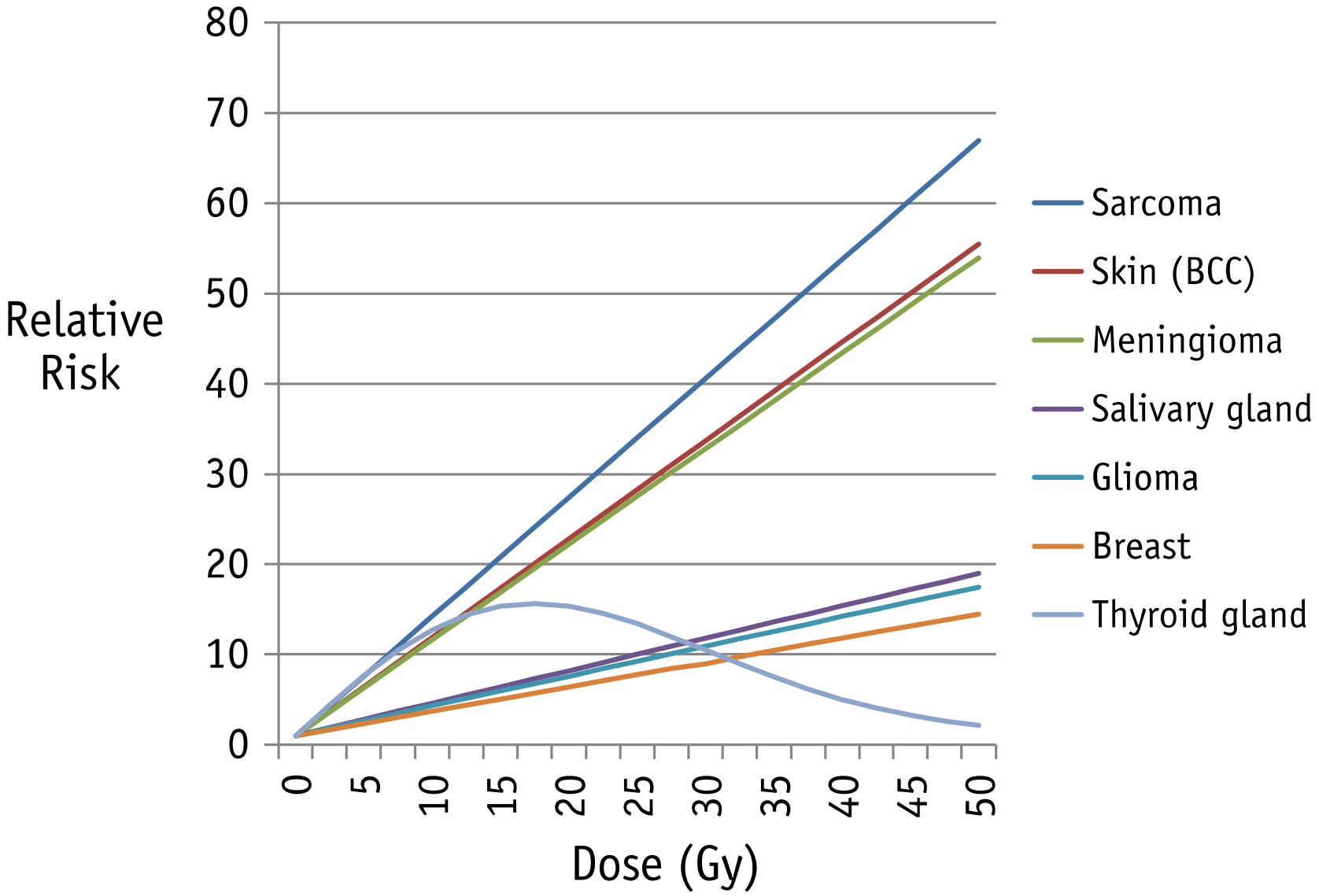

Inskip et al. *Int J Radiat Oncol Biol Phys* 2016

	ERR
	30
Bladder	1.23
Other solid	0.91
Female breast	0.87
Lung	0.81
Brain, CNS	0.62
Ovary	0.61
Thyroid	0.57
Colon	0.54
Esophagus	0.52
Oral cavity	0.39
Stomach	0.34
Liver	0.3
Pancreas	0.26
Rectum	0.19
NMSC	0.17
Renal cell	0.13
Prostate	0.11
Uterus	0.1
Gallbladder	-0.05

Preston et al. *Radiat Res* 2007; Table 11