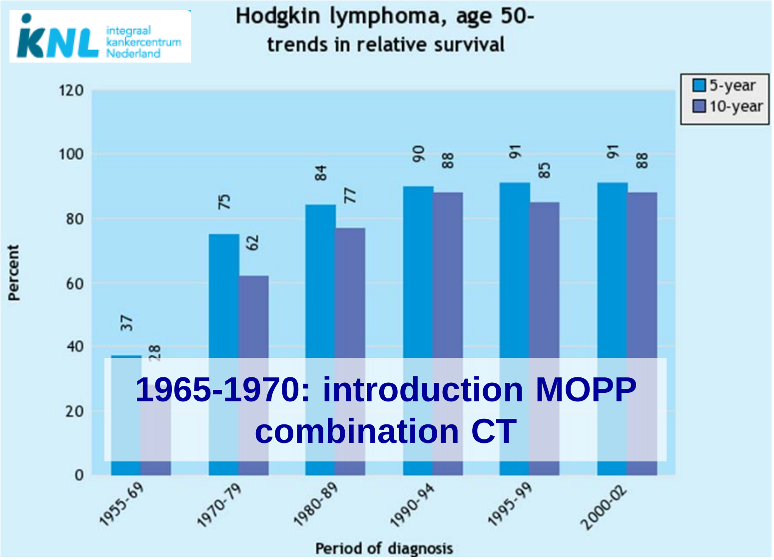
Flora van Leeuwen, Ph.D.
Professor & Head, Department of Psychosocial Research & Epidemiology
the Netherlands Cancer Institute

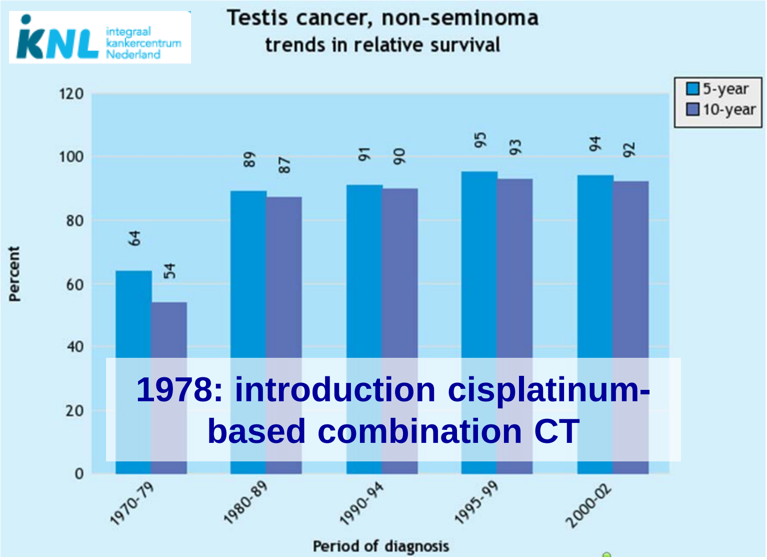
Cancer Risks from Radiation Therapy

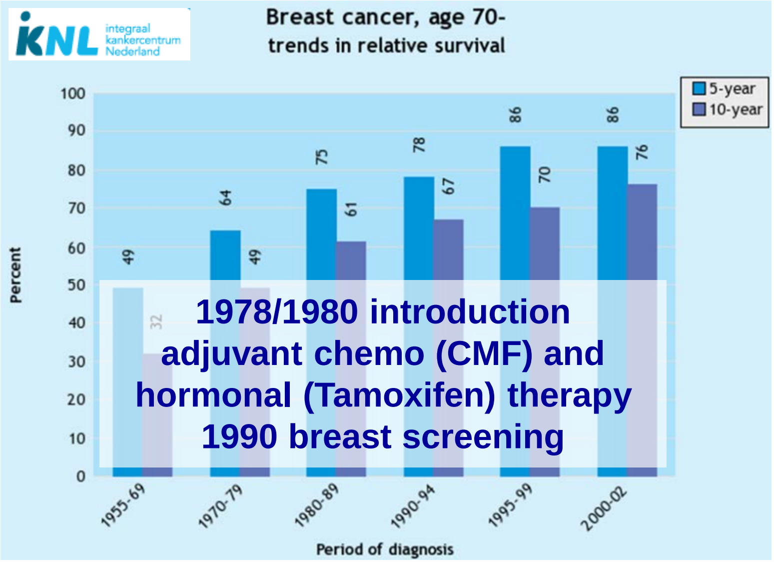
Radiation Epidemiology & Dosimetry Course

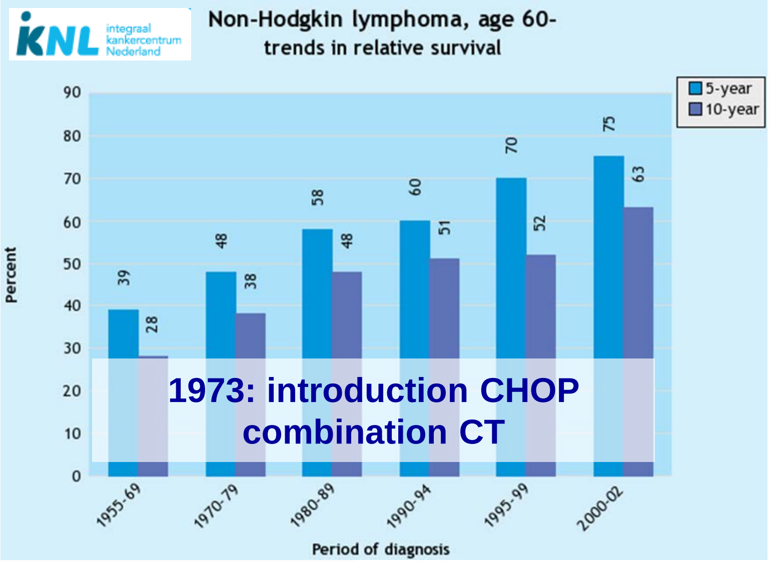
National Cancer Institute www.dceg.cancer.gov/RadEpiCourse

Cancer prognosis has improved over the last decades



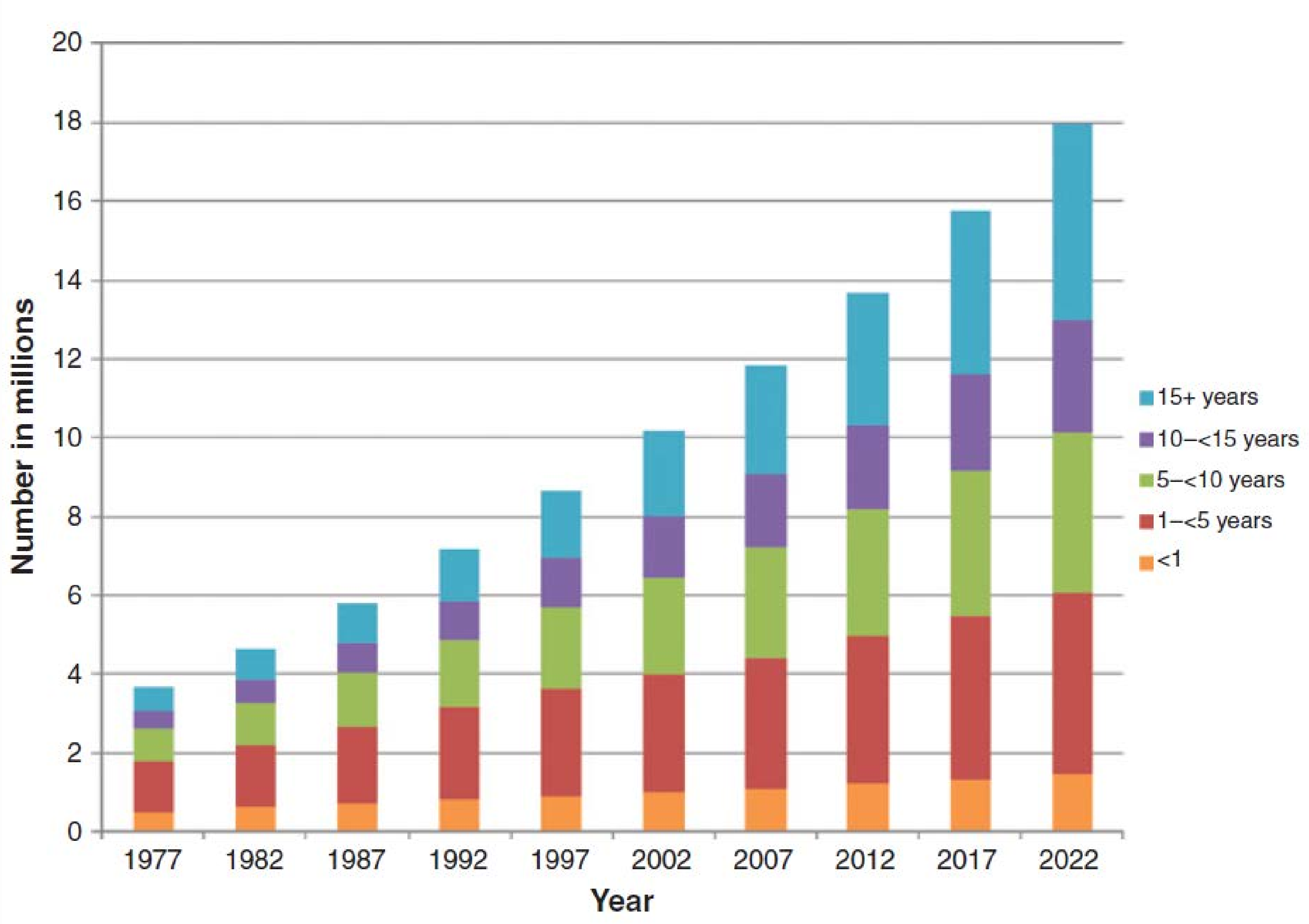






Increasing numbers of cancer survivors

Estimated and projected number of cancer survivors in the US up to 2022 by years since diagnosis



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

Cancer Treatment & Survivorship Facts & Figures

2014-2015

American Cancer Society®

Estimated Numbers of Cancer Survivors by State as of January 1, 2014

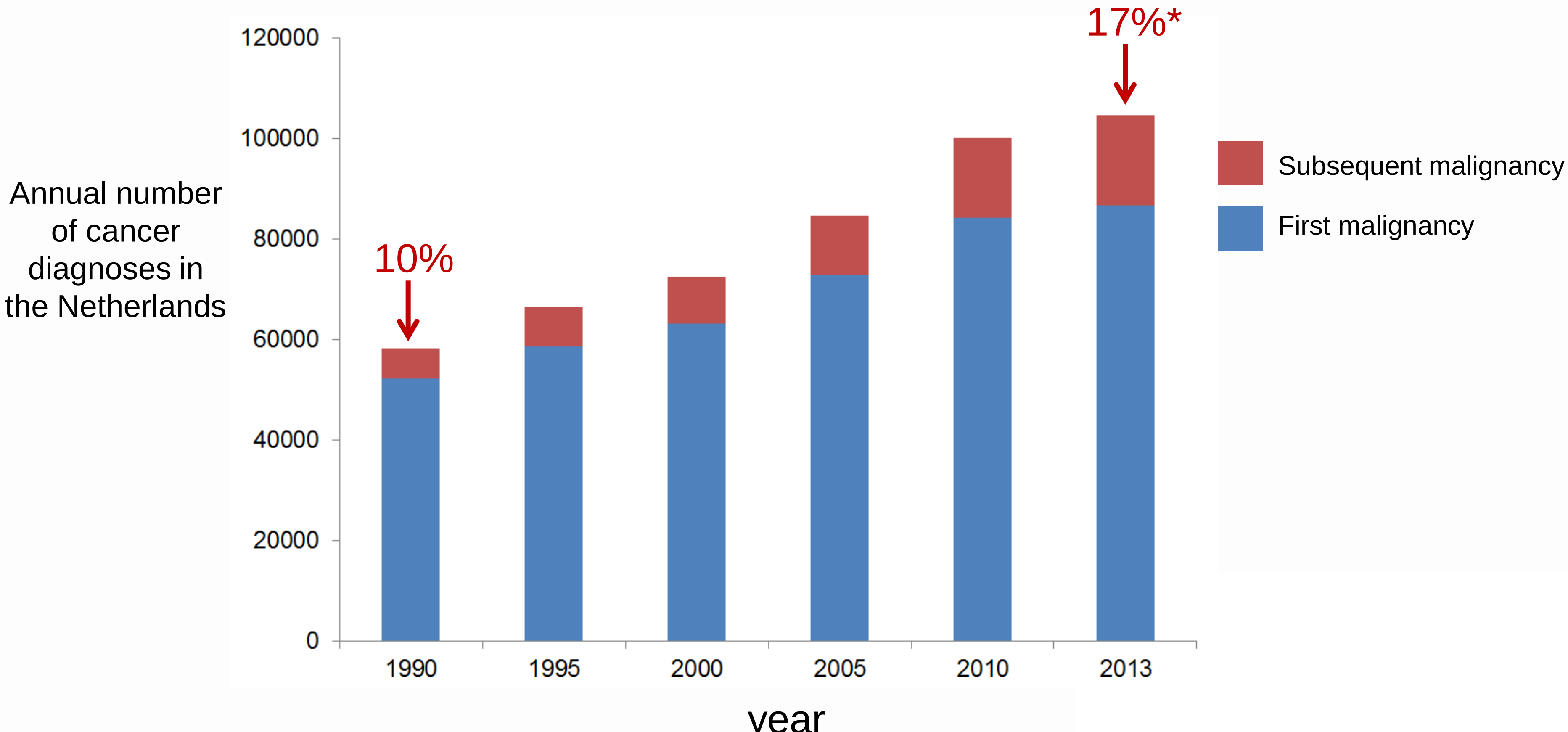
Note: State estimates do not sum to US total due to rounding.

Total prevalence in 2014

US Total 14,483,830

1 in 20 U.S. citizens = cancer survivor

More frequent diagnosis of subsequent cancers



Source: Netherlands Cancer Registry

*19% in 9 U.S. SEER registries

Second primary malignancy

- Originates in a new primary site/tissue
- Not a recurrence or metastasis

Synonyms

Second cancer / malignancy / neoplasm

Second primary (…)

Subsequent (…)

Multiple primaries / (…)

SMN

SPN

SPM

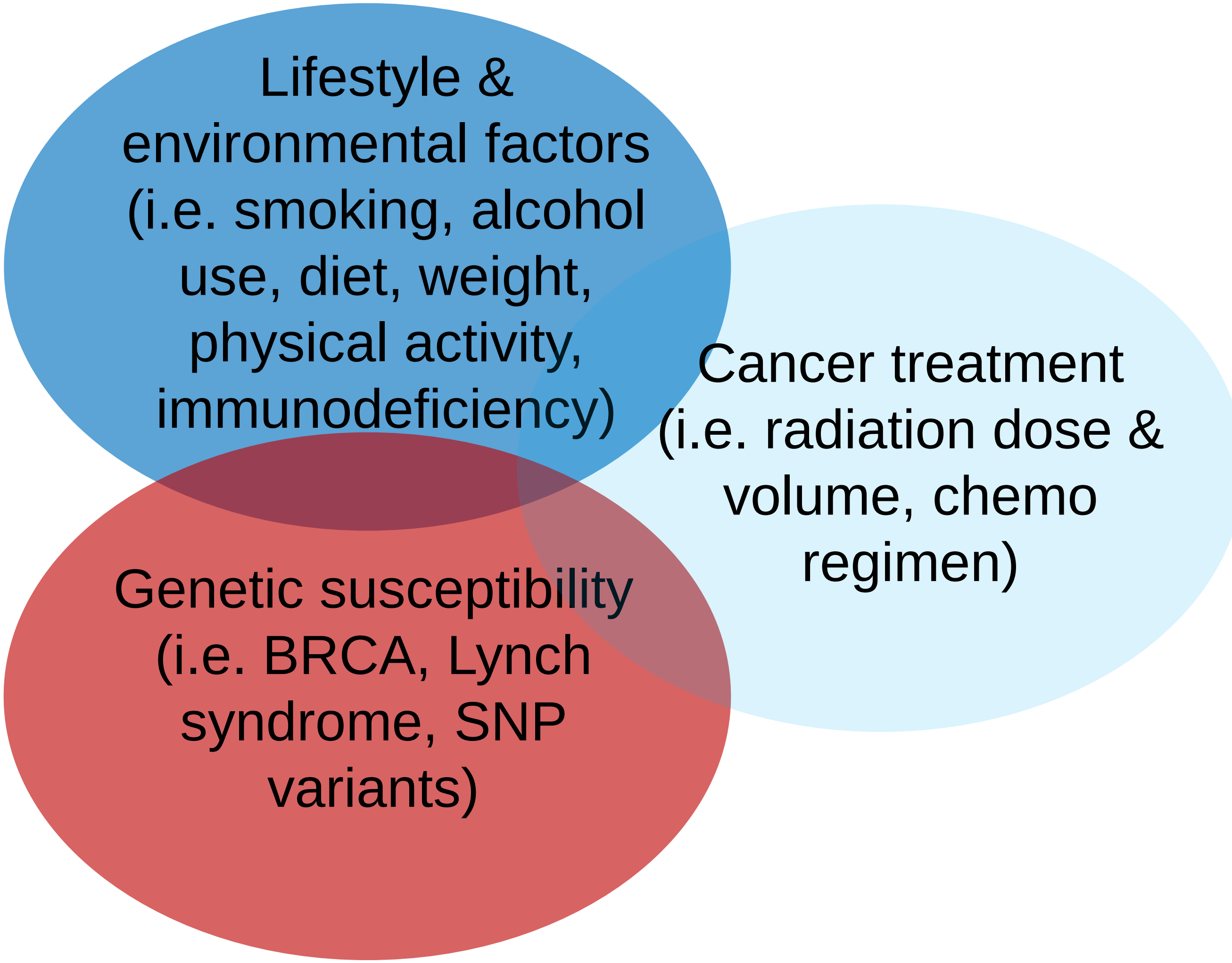
New primary cancers

~~Secondary cancer~~

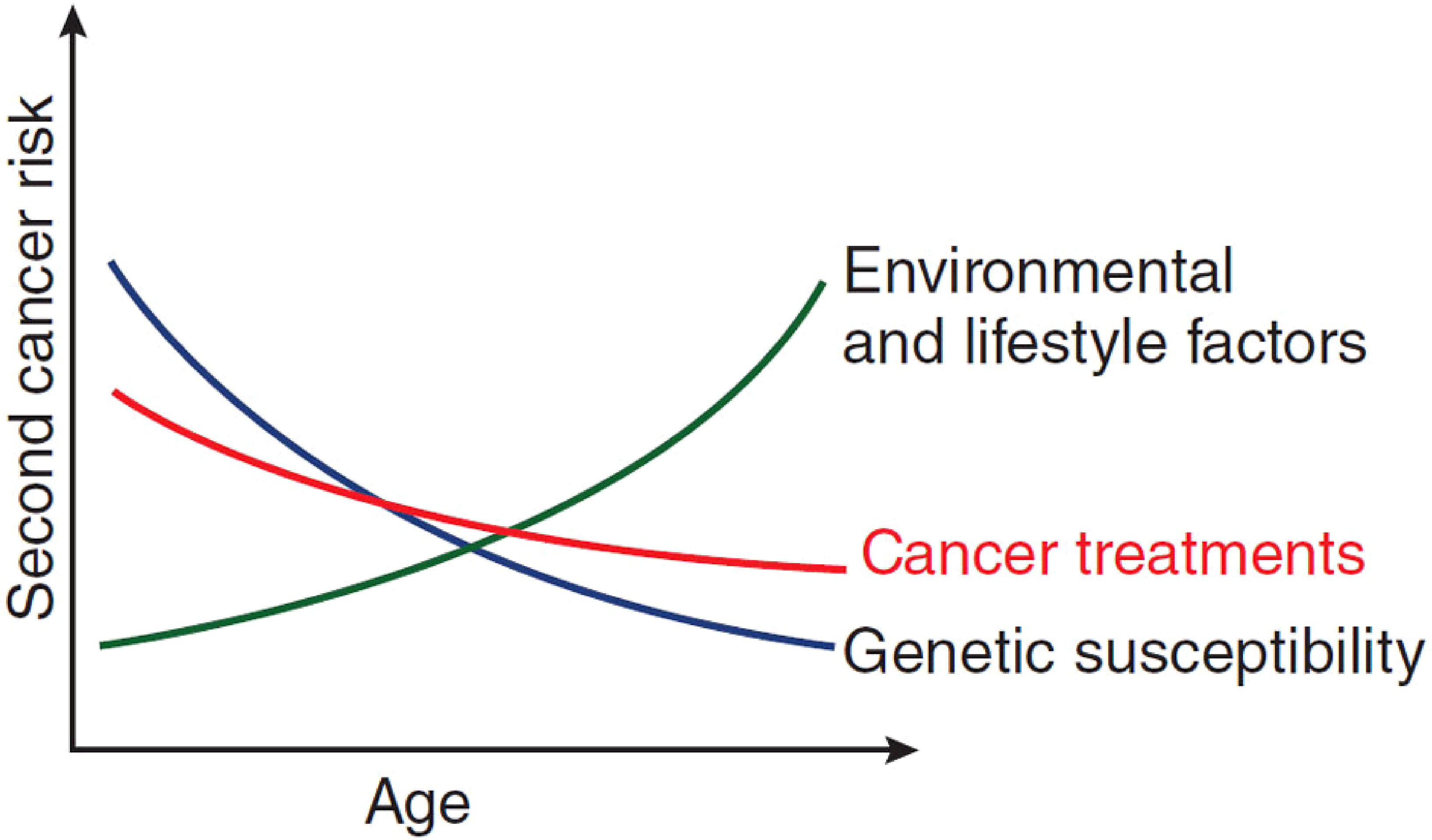
Explanations for occurrence of 2 primary malignancies in one person

- Host susceptibility factors
  (genetic predisposition, immunodeficiency)
- Common carcinogenic influences (smoking, obesity, alcohol use)
- Treatment for the first tumor
- “Chance” (risk factors unrelated to first cancer)

Causes of second cancers



Causes of second cancers in relation to age



Morton & Chanock. *Nat Med* 2011 17(8):924-5

Second cancers: impact of treatment

Treatment has **largest** impact on second cancer risk among patients treated for a **first cancer**:

- at a young age
- with excellent prognosis

Therefore second cancer research has a strong focus on survivors of:

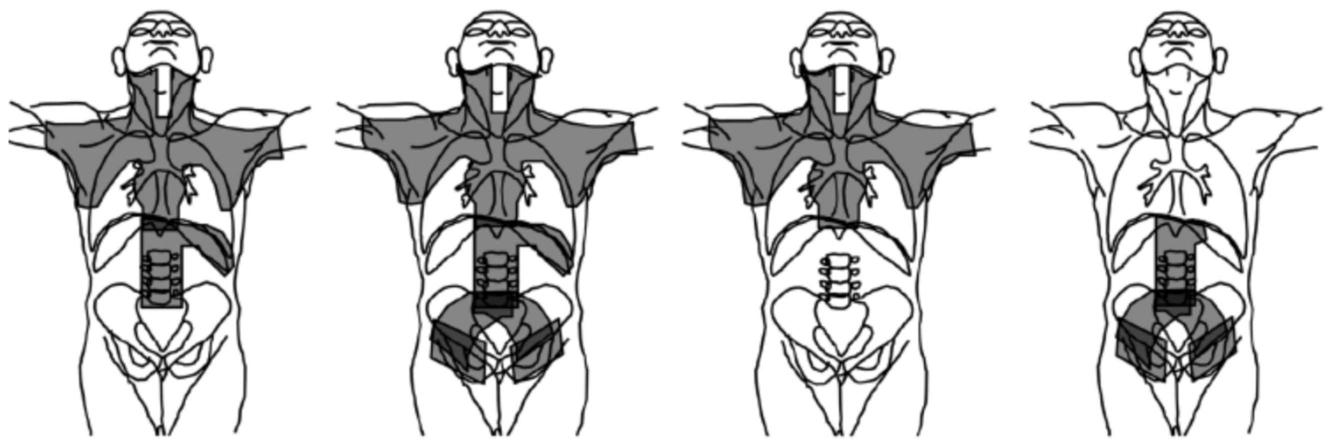
- Childhood cancer
- Hodgkin lymphoma
- Breast cancer
- Testicular cancer

~ 27% of all cancer survivors

Classic radiation fields in treatment of Hodgkin lymphoma and testicular cancer

Hodgkin Lymphoma

36-44 Gray
2-Gray fractions

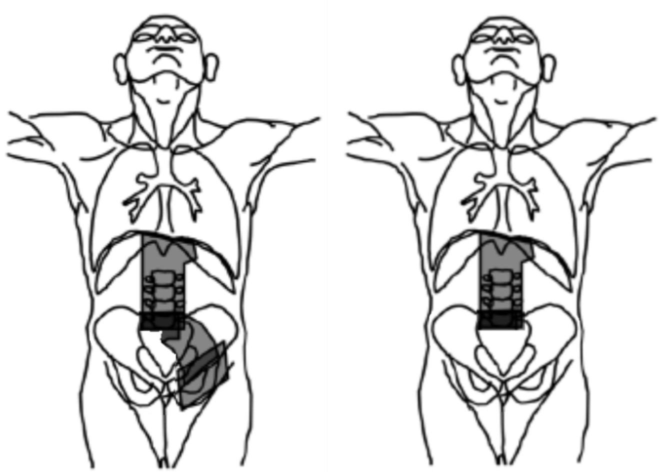


Subtotal nodal irradiation | Total nodal irradiation | Mantle field irradiation | Inverted-Y irradiation

Testicular cancer

Seminoma subtype
26-40 Gray
2-Gray fractions

Non-seminoma
40-50 Gray
2-Gray fractions

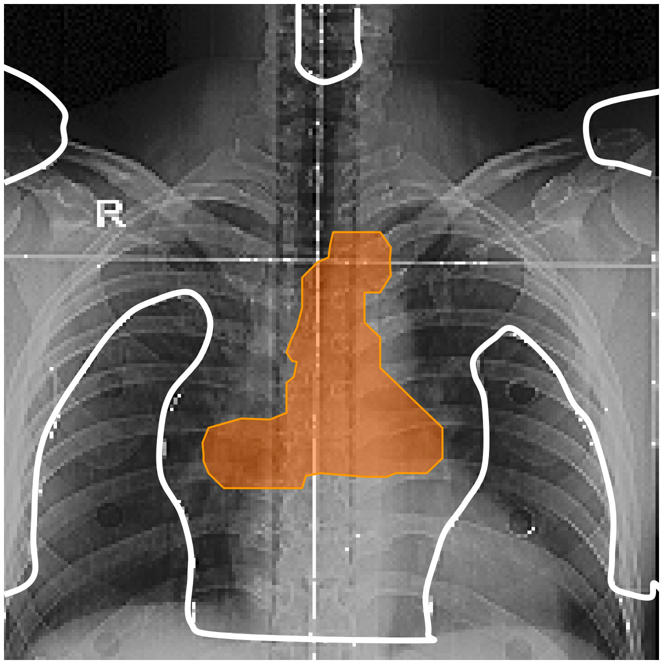


Dog-leg irradiation | Para-aortal irradiation

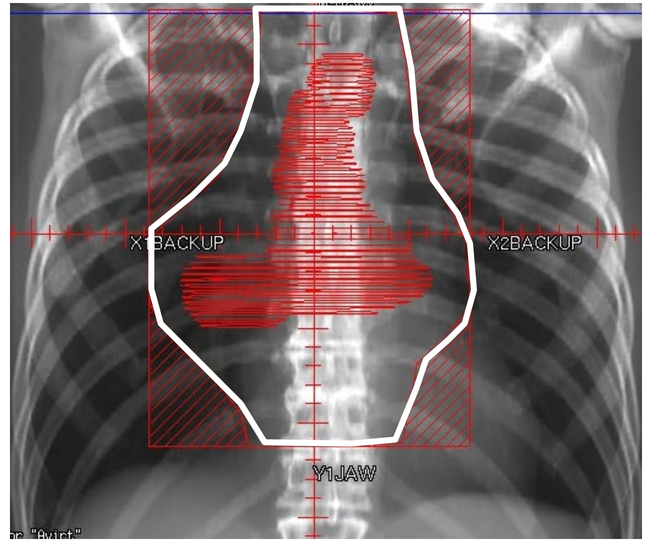
Organs in field

	Hodgkin	Testis
Salivary glands	✓	X
Thyroid	✓	X
Esophagus	✓	X
Pharynx/ Larynx	✓	X
Trachea/ Lung	✓	X
Breast	✓	X
Stomach	✓	✓
Pancreas	✓	✓
Colon	✓	✓
Rectum	✓	✓
Bladder	✓	✓
Uterus	✓	X
Skin	✓	✓

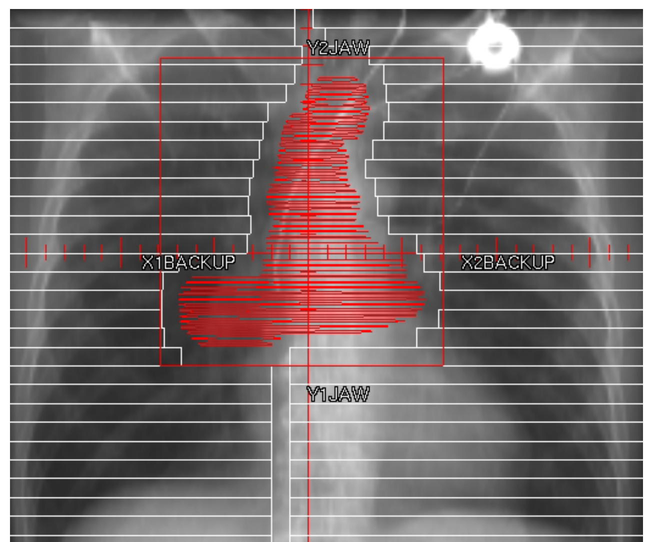
Changes in Hodgkin RT volumes



Mantle field radiotherapy



EORTC
H9
IFRT



EORTC
H10
INRT

Courtesy: R vd Maazen Radboud
University Nijmegen Medical Center

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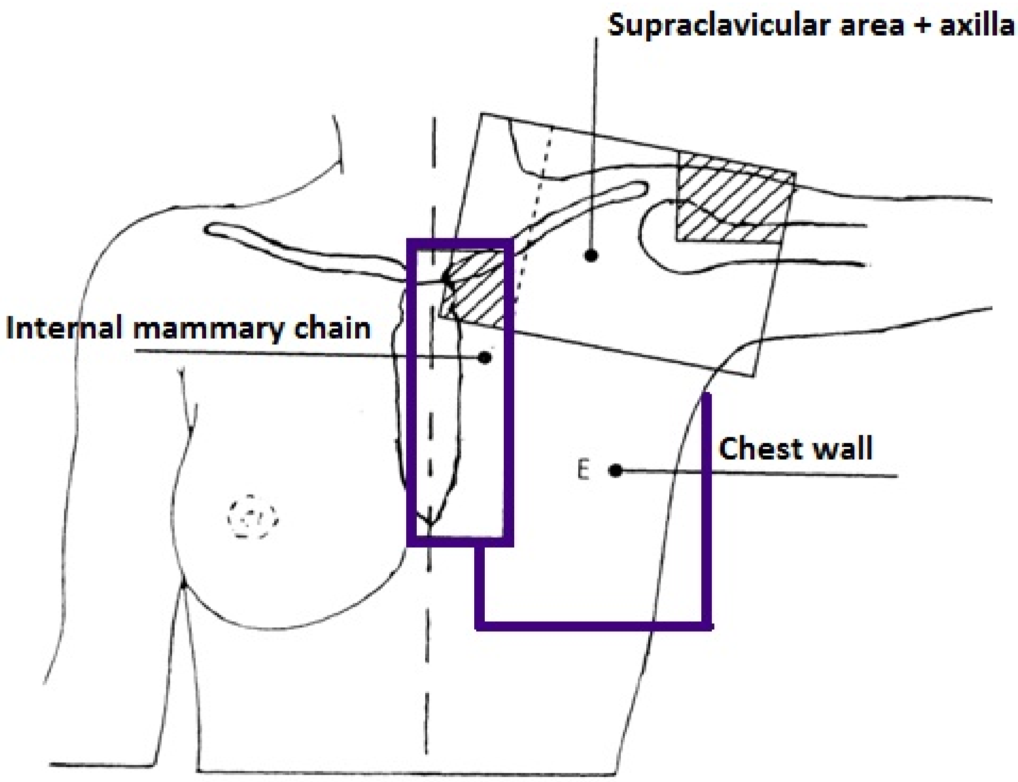
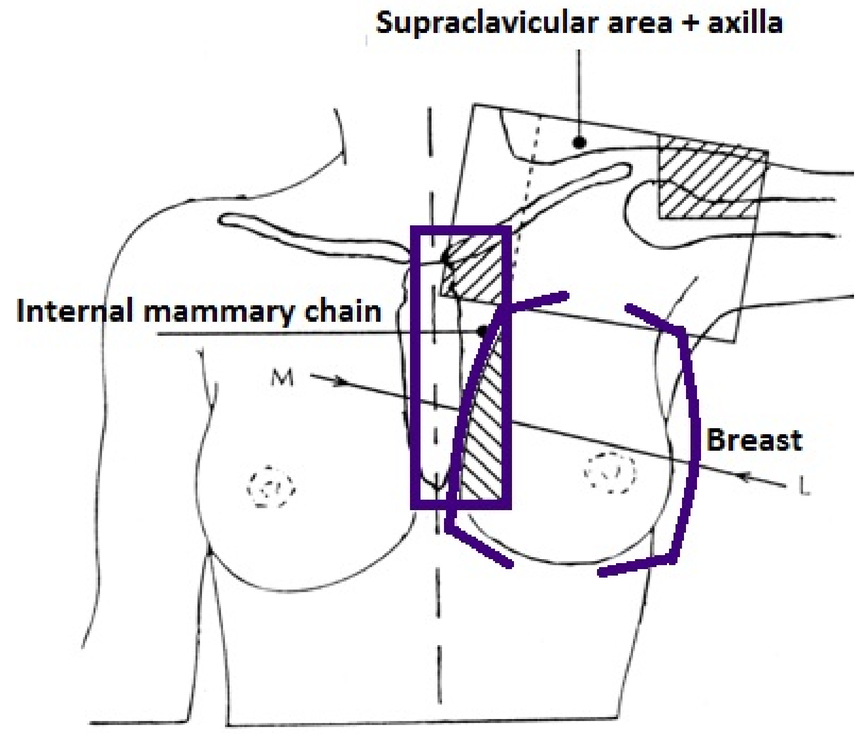
Breast cancer radiation fields





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Clinical epidemiology

- Comparison with risk in general population
- Comparison between treatments

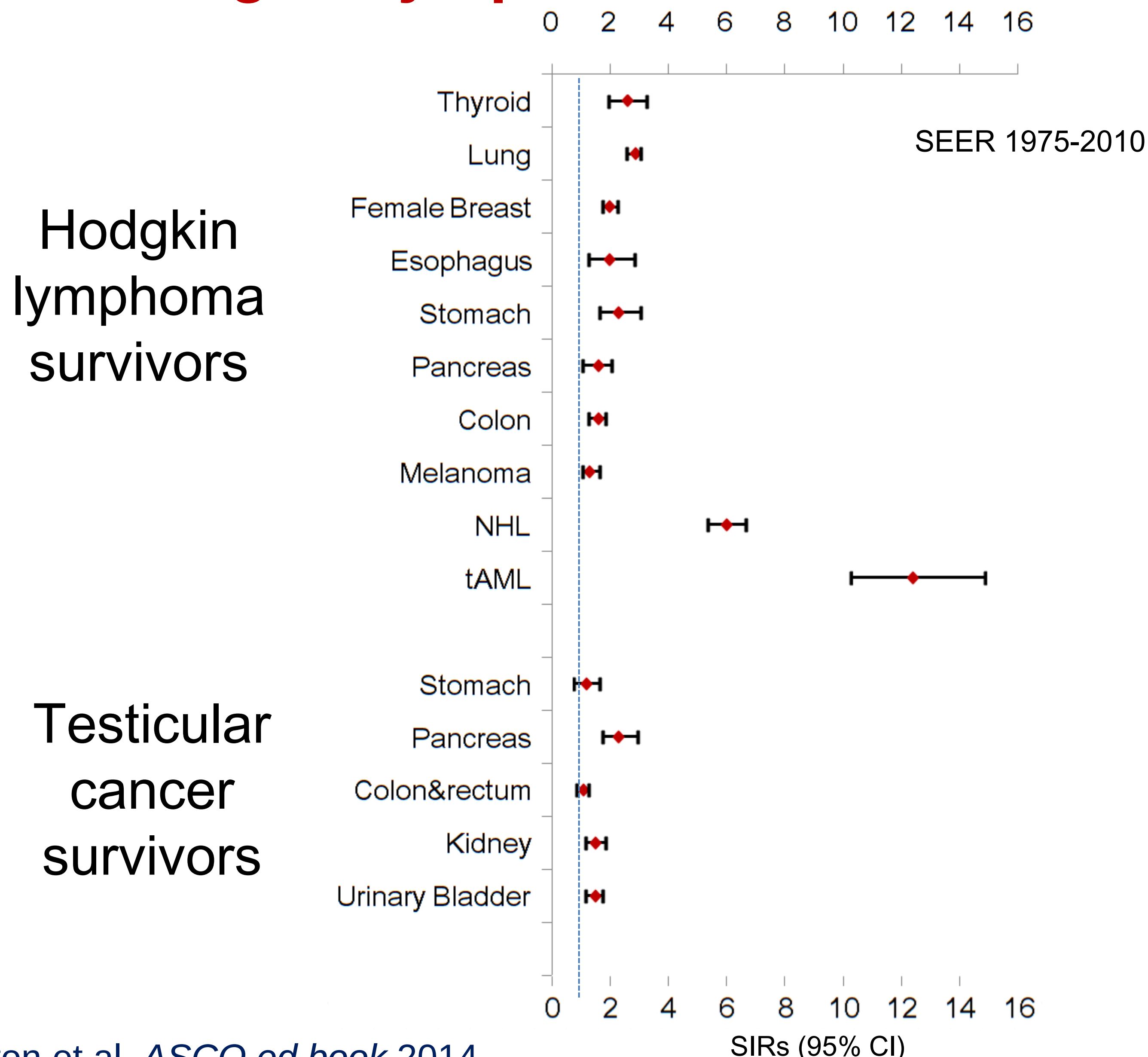
APPROPRIATE STUDY DESIGNS

- Cohort study
- Case-control study

Risk measures

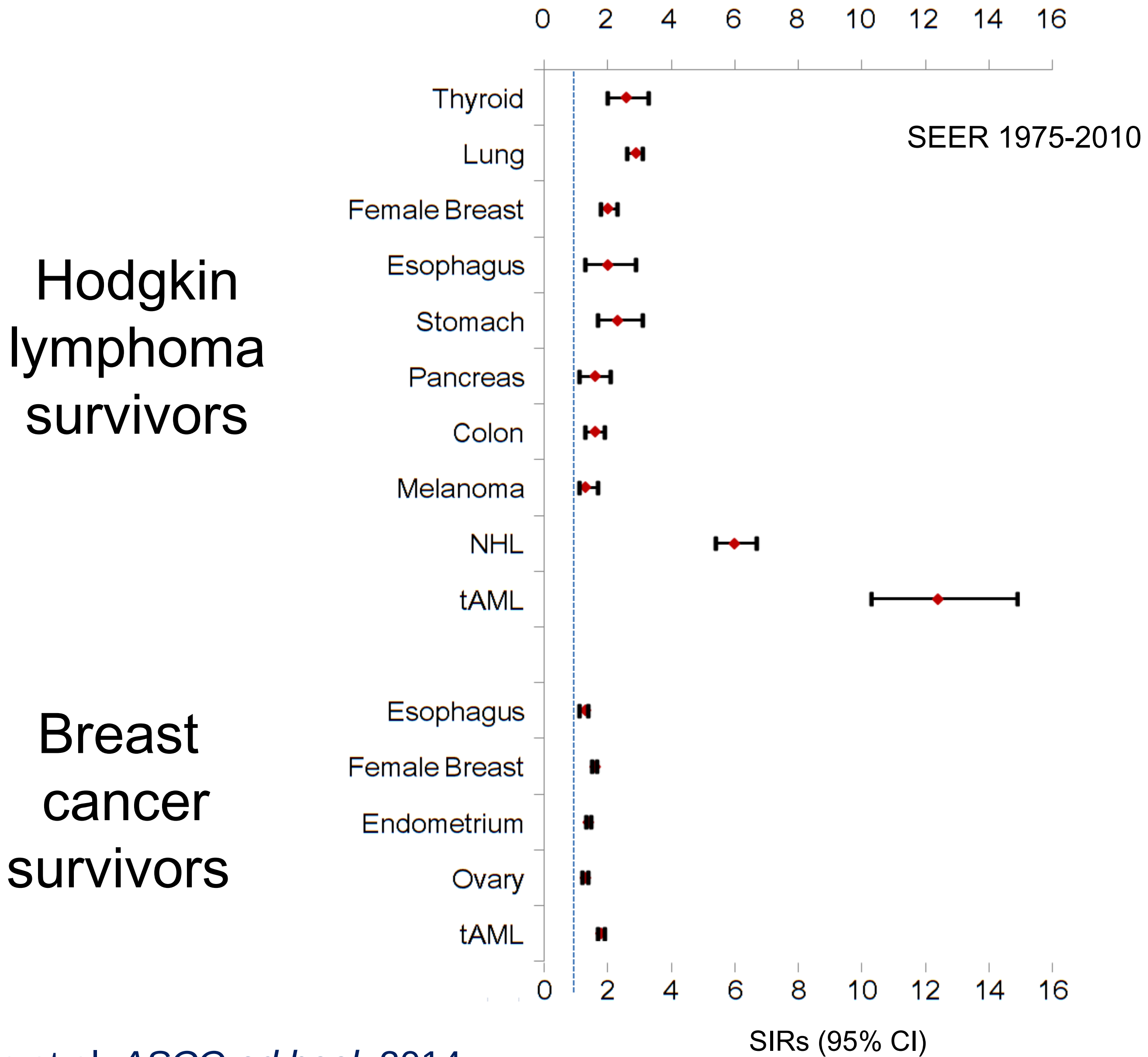
- Relative risk (SIR, HR)
- Absolute risk (AER, Cum. incidence)

Risks for selected second malignancies after Hodgkin lymphoma and testicular cancer



Morton et al. *ASCO ed book* 2014

Risks for selected second malignancies after Hodgkin lymphoma and breast cancer



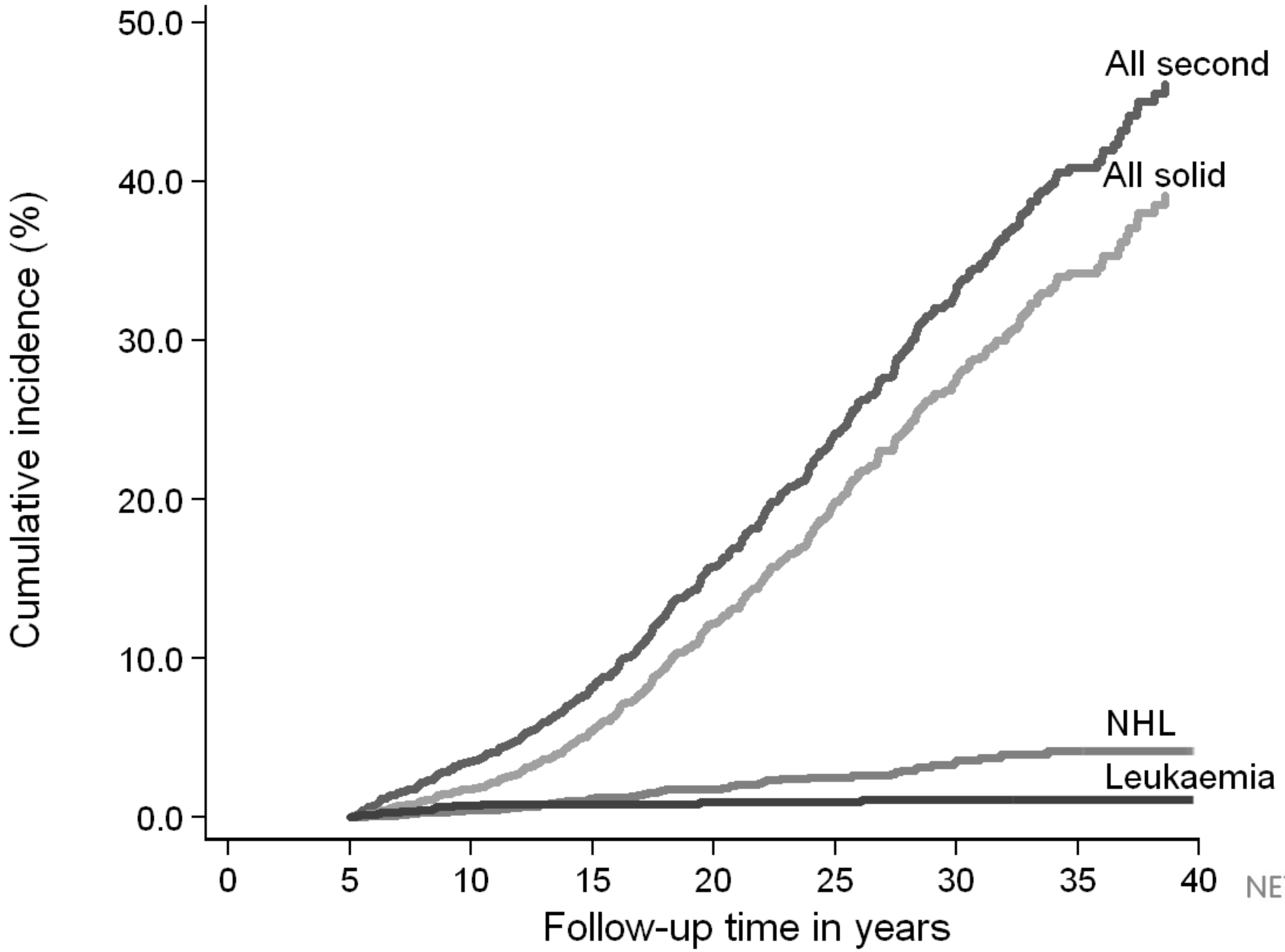
Morton et al. *ASCO ed book* 2014

Risk of second malignancy, Dutch Hodgkin cohort; 3940 5-yr survivors, 15-50 yr at dx, 1965 - 2000

Cancer site	SCs	SIR	(95%CI)
All Malignancies	**709**	**4.5**	**(4.2-4.9)**
Oral cavity/pharynx	15	**3.1**	(1.7-5.1)
Esophagus	23	**7.1**	(4.5-10.7)
Stomach	33	**8.9**	(6.1-12.5)
Colon	25	**2.4**	(1.5-3.5)
Rectum & Rectosigmoid	18	**2.5**	(1.5-4.0)
Lung & Bronchus	129	**6.5**	(5.4-7.7)
Pleura	12	**14.9**	(7.7-26.1)
Female breast	138	**4.4**	(3.6-5.2)
Melanoma	27	**2.7**	(1.8-3.9)
Bladder	13	**3.4**	(1.8-5.8)
Prostate	14	**1.1**	(0.6-1.8)
Thyroid	17	**12.7**	(7.4-20.4)
Soft tissue sarcoma	19	**13.6**	(8.2-21.2)
Leukemia	33	**12.4**	(8.6-17.5)
Non-Hodgkin Lymphoma	78	**11.3**	(9.0-14.2)

Schaapveld et al., submitted

Cumulative incidence of second malignancies, in the presence of competing risks
Updated results of Dutch HL cohort 1965-2000



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Absolute excess risk

- Excess number of second malignancies beyond number expected, per 10,000
- AER = (Obs – Exp)/Person-years x 10,000
- Most appropriate measure to judge which SCs contribute most to SC burden

Large absolute excess risk for solid cancers

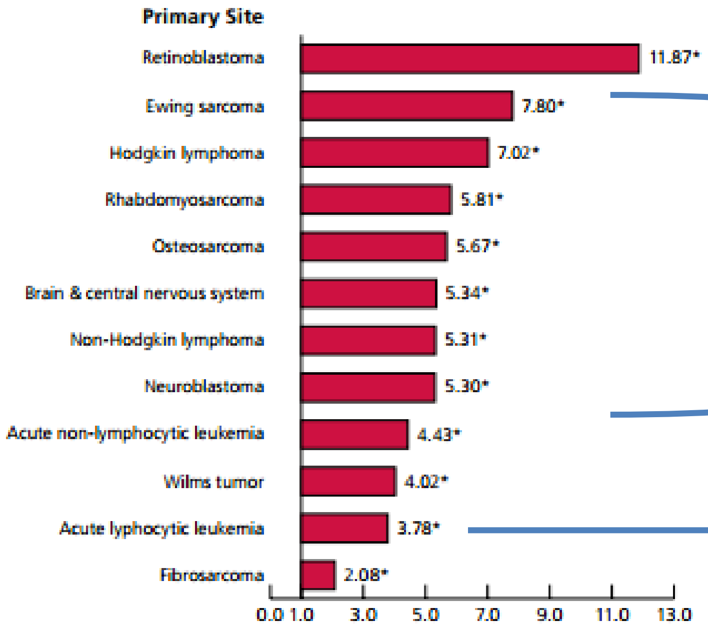
SIRs and AERs of second malignancy, Dutch Hodgkin cohort; 3940 5-yr survivors, 15-50 yr at dx, 1965 - 2000

Cancer site	SCs	SIR	AER/10,000
All Malignancies	**709**	**4.5**	**114.7**
Oral cavity/pharynx	15	3.1	2.1
Esophagus	23	7.1	3.0
Stomach	33	8.9	6.1
Colon	25	2.4	3.0
Rectum & Rectosigmoid	18	2.5	2.3
Lung & Bronchus	129	**6.5**	**22.6**
Pleura	12	14.9	2.3
Female breast	138	**4.4**	**49.2**
Melanoma	27	2.7	3.5
Bladder	13	3.4	1.9
Prostate	14	1.1	0.3
Thyroid	17	**12.7**	**3.2**
Soft tissue sarcoma	19	**13.6**	**3.7**
Leukemia	33	**12.4**	**6.3**
Non-Hodgkin Lymphoma	78	11.3	14.8

AER=absolute excess cases per 10,000/yr

Risks for second cancers after childhood cancer in U.S. - SEER

Figure 17. Observed-to-expected (O/E) Ratios for Subsequent Cancers by Primary Site, Ages 0-19, 1973-2010



*p<0.05

Note: Observed-to-expected ratio is the number of cancers observed in a population of cancer survivors divided by the number of cancers expected.

Source: Surveillance Epidemiology, and End Results (SEER) Program, 18 SEER Registries, 1973-2010, Division of Cancer Control and Population Sciences, National Cancer Institute.[33]

American Cancer Society, Surveillance and Health Services Research, 2014

Retinoblastoma: 11.9*

Hodgkin L / sarcoma 5 - 10*
CNS, NHL, neuroblastoma
AnLL

Acute Lymphoblastic Leukemia (ALL): 3.8*

Risk of second malignancy in U.S. Childhood Cancer Survivor Study

14,359 5-yr survivors 1970-86, median follow-up 23 yrs

SMN	Obs. (O)	**SIR**	95% CI	Median time to SMN y	AER/ 10,000 py
All SMNs	802	**6.0**	5.5 – 6.4	12	26.3
Leukemia	41	**6.1**	4.5 – 8.2	7	1.3
CNS tumor	77	**10.4**	8.3 – 13.1	13	2.8
Breast cancer	188	**9.8**	8.4 – 11.5	21	6.7
Bone cancer	45	**19.0**	14.2 – 25.5	10	1.7
Soft-tissue sarcoma	73	**8.1**	6.4 – 10.2	15	2.5
Thyroid ca	128	**10.9**	9.1 – 12.9	19	4.6
Melanoma	48	**3.3**	2.4 – 4.5	19	1.3
Colorectal	27	**4.6**	3.2 – 6.8	23	0.8

Friedman et al JNCI 2010: 102: 1083-98

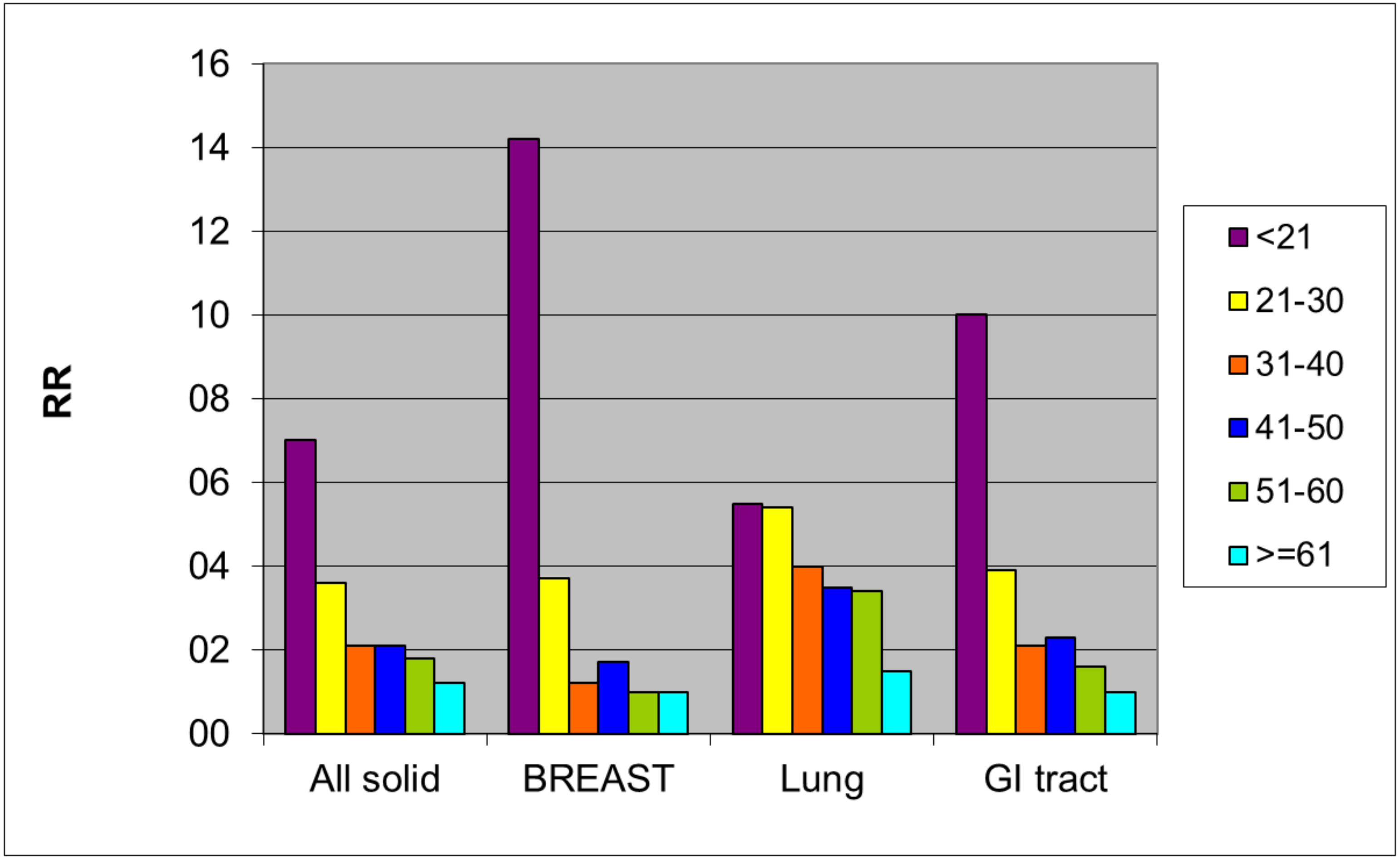
Second malignancy after radiation treatment

- **Patient-related factors**
  - *Age at diagnosis/treatment*
  - *Follow-up time*
  - Lifestyle (smoking, hormone use)
  - Genetic factors
- **Treatment-related factors**
  - Radiation dose to various organs
  - Radiation volume
  - CT regimen (doses and combination)
    - ➢Indirect effects: premature menopause
- **Interaction RT/CT/age at treatment/smoking**

Decreasing relative risks of solid tumors with increasing age at HL treatment

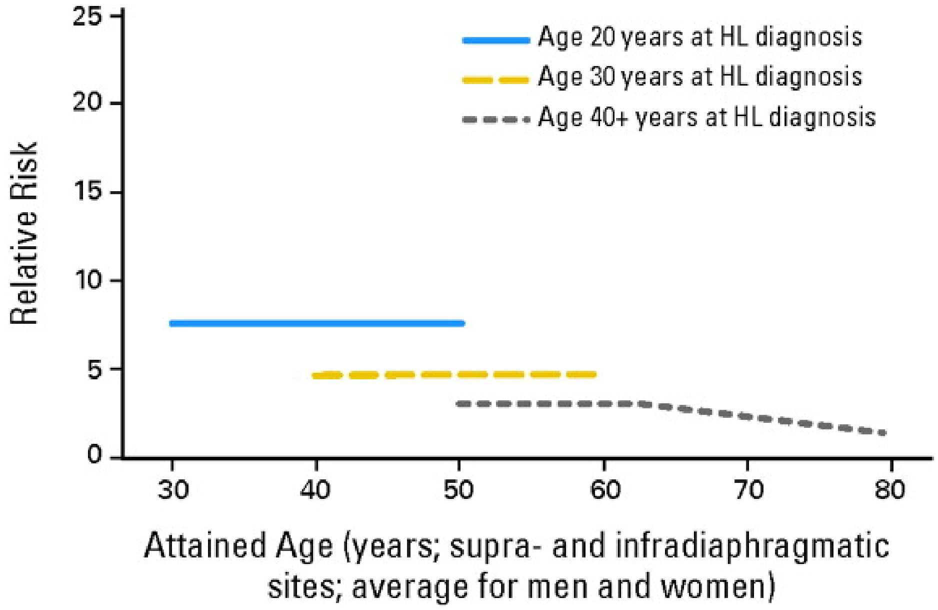
International cohort study: 32,591 HL patients

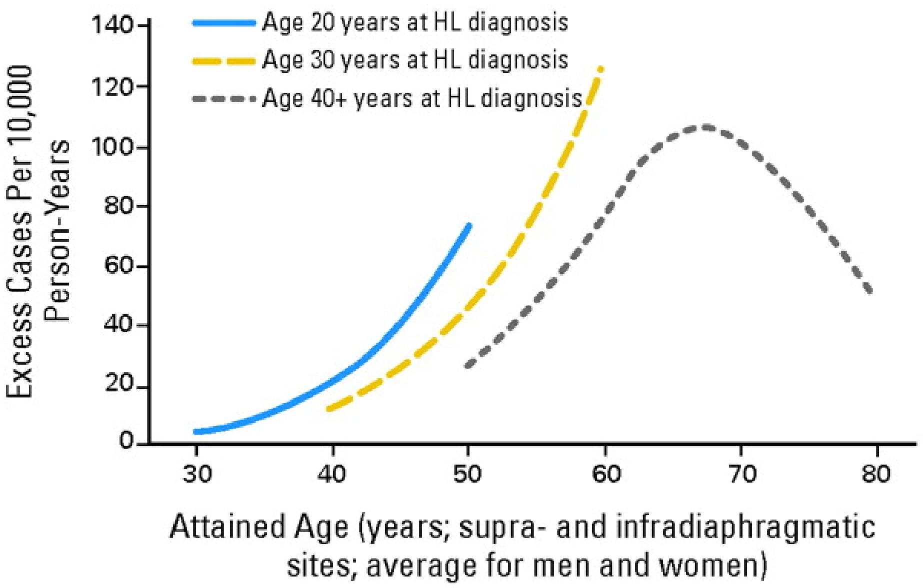
1,111 25-years survivors, population-based



(Adapted from Dores JCO 2002;20:3484)

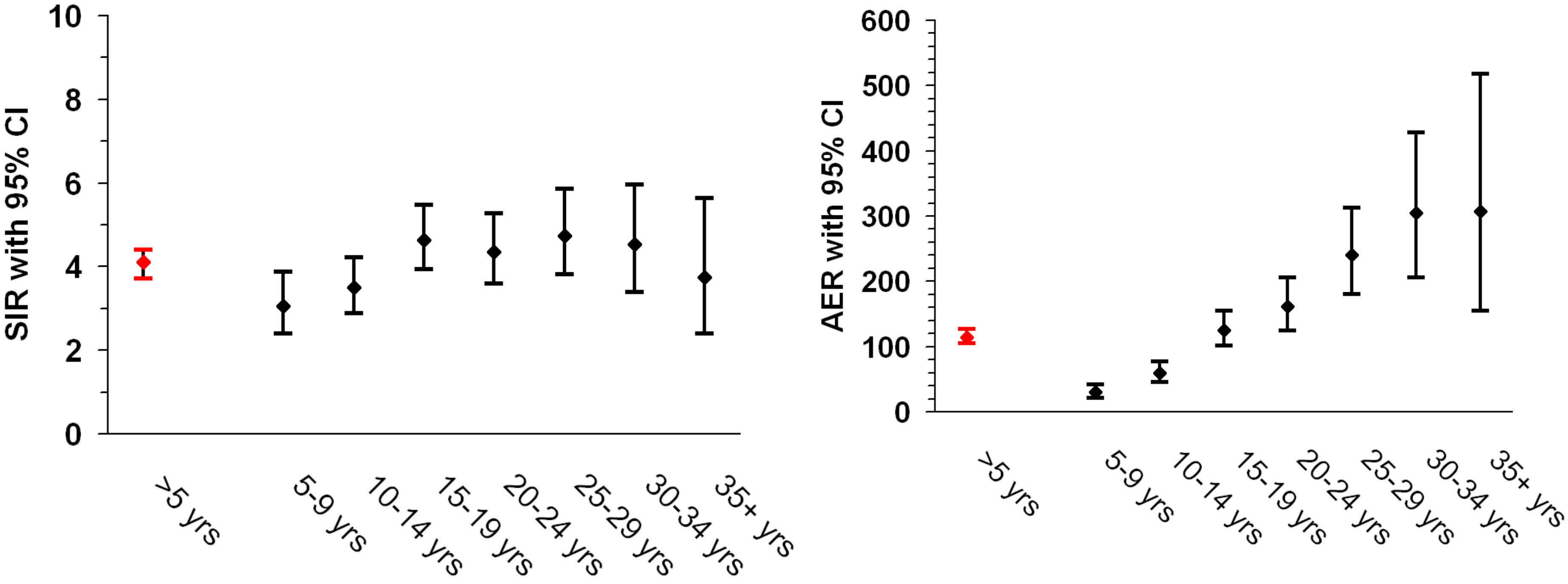
RR and AER of second cancers according to age at HL diagnosis and attained age.





Hodgson et al. J Clin Oncol 2007; 25(12): 1489-1497

Solid cancer risk increased for >35 yrs Dutch Hodgkin cohort



AER per 10,000 patients/yrs

Schaapveld et al. submitted

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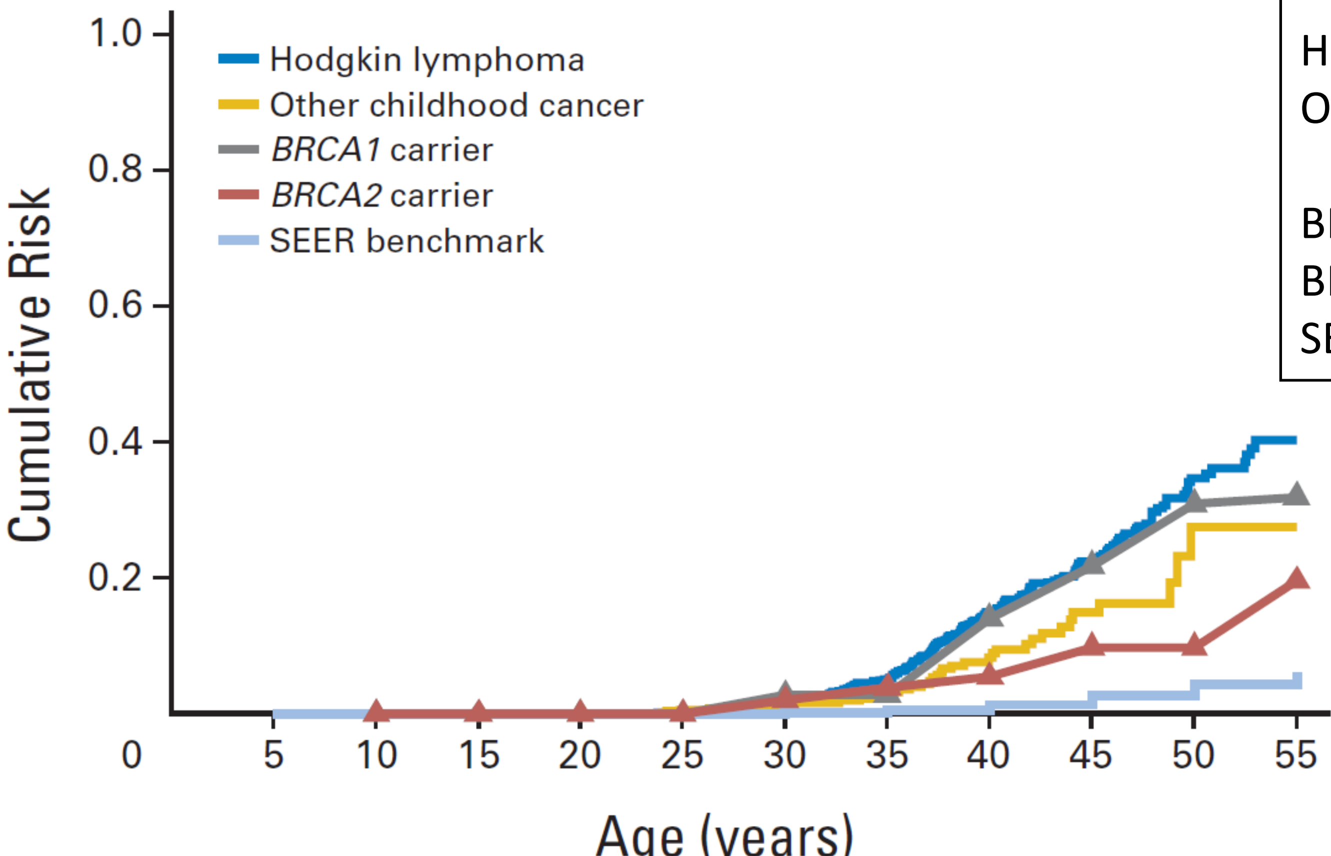
Breast cancer risk after childhood cancer: High burden after chest radiotherapy



Cum. risk at age 50 yrs:

HL	35%
Other CC	(age 45) 15%
BRCA1	31%
BRCA2	10%
SEER	<5%

Moskowitz et al JCO, 2014; 32(21):2217-23

Radiation dose – response for second cancer risk

Linear increase with higher dose for:

- Breast cancer
- Lung cancer
- Stomach cancer
- Pancreatic cancer
- Esophageal cancer
- Sarcoma
- Glioma
- Meningioma

For thyroid cancer decreasing risk after 20-30 Gy
For leukemia decreasing risk after 4 Gy

Based on retrospective radiation dosimetry (simulation films, old RT charts, phantoms)

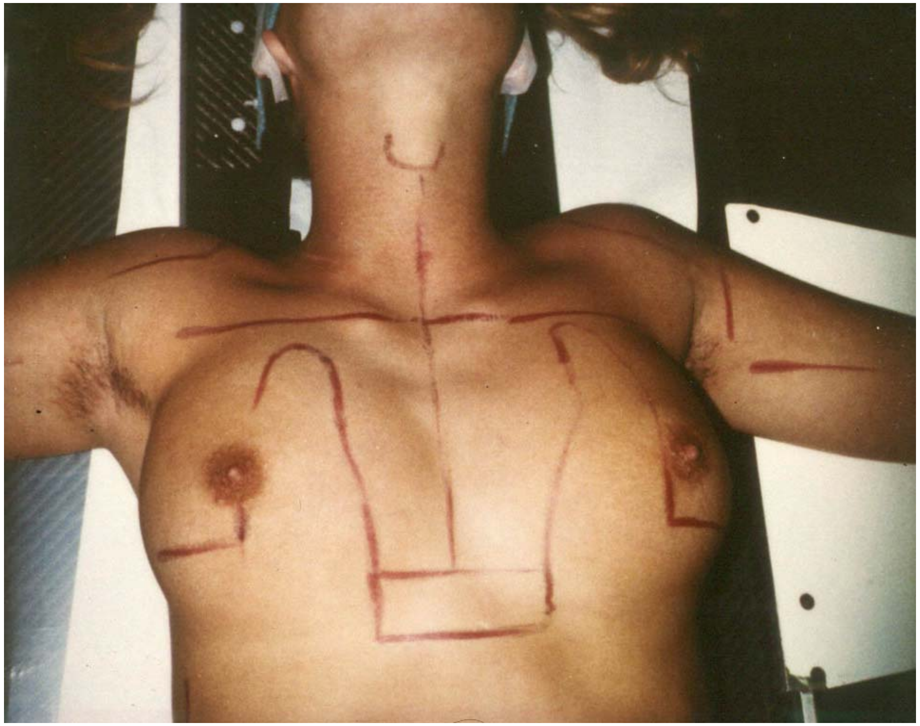
Breast cancer case-control study to assess radiation dose-response

- Compare treatment between:
  - Cases with breast cancer after HL
  - Matched controls without breast cancer

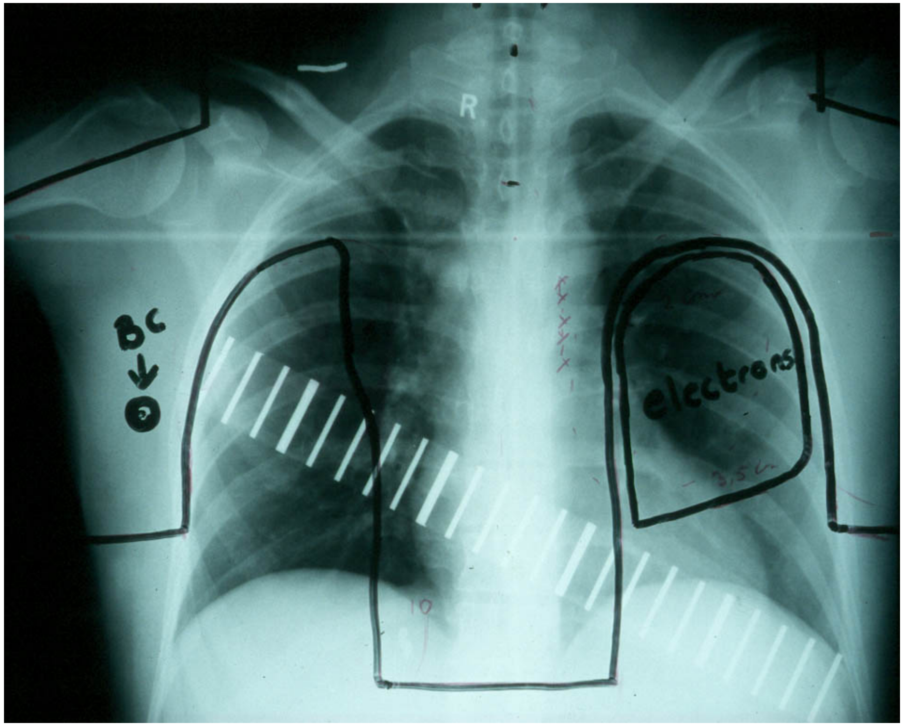
- Treatment information from medical records

- Irradiated patients: individual radiation dosimetry; radiation dose *to the site of breast cancer development*, based on radiation charts, simulation films of previous RT treatment and mammograms (M. Stovall, M.D. Anderson, Houston)

Breast cancer after HL



Mantle field RT



Mantle field 1974,
BC= Site of subsequent
breast cancer 2002

Radiation dose ⬆ ⟹ Breast cancer risk ⬆

- International nested case-control study, 105 cases with breast cancer, 266 matched controls
- Radiation dosimetry: dose to affected site in breast

Radiation dose	RR	95% CI
0-4 Gy	**1.0**	Ref.
4-7 Gy	**1.8**	0.7-4.5
7-23 Gy	**4.1**	1.4-12.3
23-28 Gy	**2.0**	0.7-5.9
28-37 Gy	**6.8**	2.3-22.3
37-40 Gy	**4.0**	1.3-13.4
41-61 Gy	**8.0**	2.6-26.4

Linear ERR per Gy 0.15 (95%CI 0.04-0.73)

Travis JAMA 2003; 290:465

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JOURNAL OF CLINICAL ONCOLOGY

ORIGINAL REPORT

Stomach Cancer Risk After Treatment for Hodgkin Lymphoma

Lindsay M. Morton, Graça M. Dores, Rochelle E. Curtis, Charles F. Lynch, Marilyn Stovall, Per Hall, Ethel S. Gilbert, David C. Hodgson, Hans H. Storm, Tom Børge Johannesen, Susan A. Smith, Rita E. Weathers, Michael Andersson, Sophie D. Fossa, Michael Hauptmann, Eric J. Holowaty, Heikki Joensuu, Magnus Kaijser, Ruth A. Kleinerman, Frøydis Langmark, Eero Pukkala, Leila Vaalavirta, Alexandra W. van den Belt-Dusebout, Joseph F. Fraumeni Jr, Lois B. Travis, Berthe M. Aleman, and Flora E. van Leeuwen

Author affiliations appear at the end of this article.

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ABSTRACT

Purpose

Treatment-related stomach cancer is an important cause of morbidity and mortality among the growing number of Hodgkin lymphoma (HL) survivors, but risks associated with specific HL treatments are unclear.

Patients and Methods

We conducted an international case-control study of stomach cancer nested in a cohort of 19,882 HL survivors diagnosed from 1953 to 2003, including 89 cases and 190 matched controls. For each patient, we quantified cumulative doses of specific alkylating agents (AAs) and reconstructed radiation dose to the stomach tumor location.

- **Radiation dose to stomach**
- **Procarbazine dose**

Risk of stomach cancer after HL by radiation dose to the stomach tumor location

Morton et al., JCO, 2013 Sep 20;31(27):3369-77.

Radiation dose (Gy)	Cases	Controls	OR* (95% CI)
0	9	27	**1.0** (referent)
0.1-0.9	13	41	**1.3** (0.4-4.1)
1.0-4.9	13	17	**1.0** (0.3-3.5)
5.0-24.9	4	20	**0.5** (0.1-2.7)
25.0-34.9	12	11	**4.6** (1.2-20.5)
35.0-39.9	24	16	**8.2** (2.6-29.7)
>40.0	12	16	**4.2** (1.2-15.6)
$\mathbf{P_{trend}}$			**<0.001**

ERR per Gy: 0.09 (95% CI 0.04-0.21)

* Adjusted for alkylating agent CT

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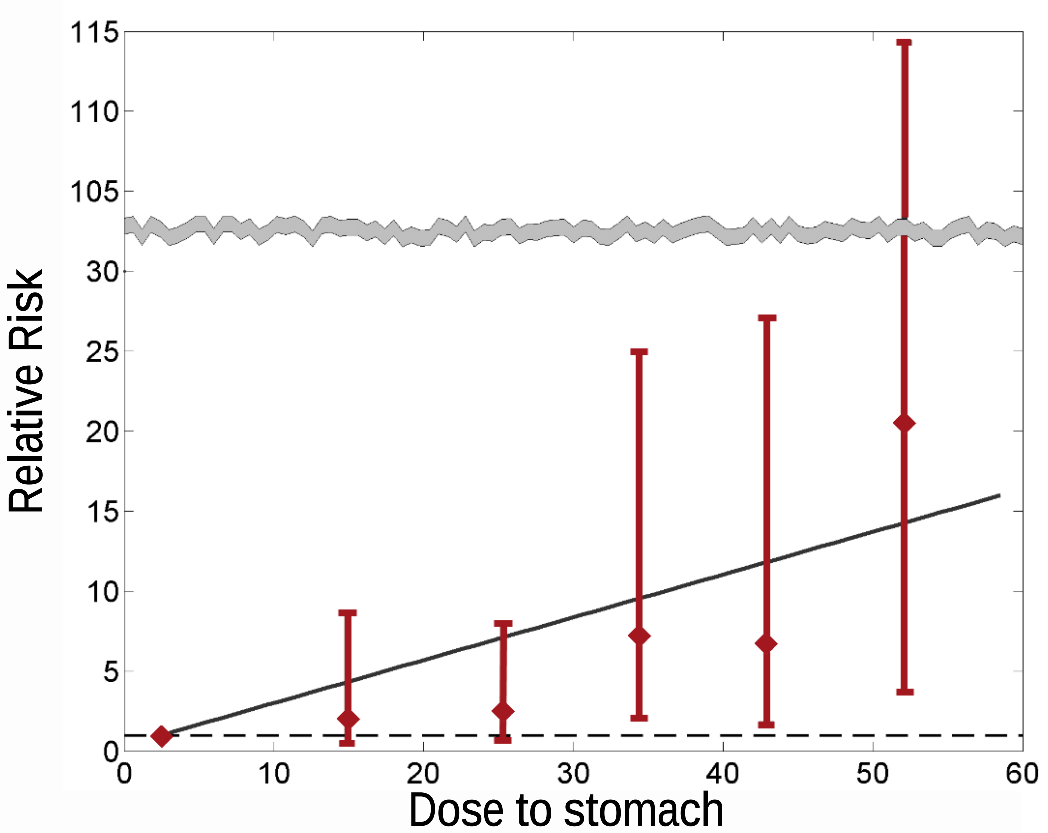
Radiation dose and stomach cancer risk in testicular cancer survivors

International nested case-control study, 87 stomach cancer cases and 151 matched controls; Radiation dosimetry to estimate dose to area of stomach tumor



Hauptmann et al. BJC *2014;112(1):44-510*

Excess Relative Risk per Gray 0.27 (95%CI 0.054-1.44)

Risk of pancreatic cancer after Hodgkin by radiation dose to pancreatic tumor location

Radiation dose (Gy)	Cases	Controls	OR* (95% CI)
0 - <0.5	9	25	**1.0** (referent)
0.5 - <5	6	24	**0.5** (0.1-2.0)
10-<40	10	12	**1.8** (0.5-8.1)
>40	9	6	**9.1** (1.7-77)

$P_{trend} = 0.005$

ERR per Gy: 0.098 (95% CI 0.015-0.42)

* Adjusted for number of alkylating CT cycles

Dores et al., Ann Oncology 2014, 25: 2073-79

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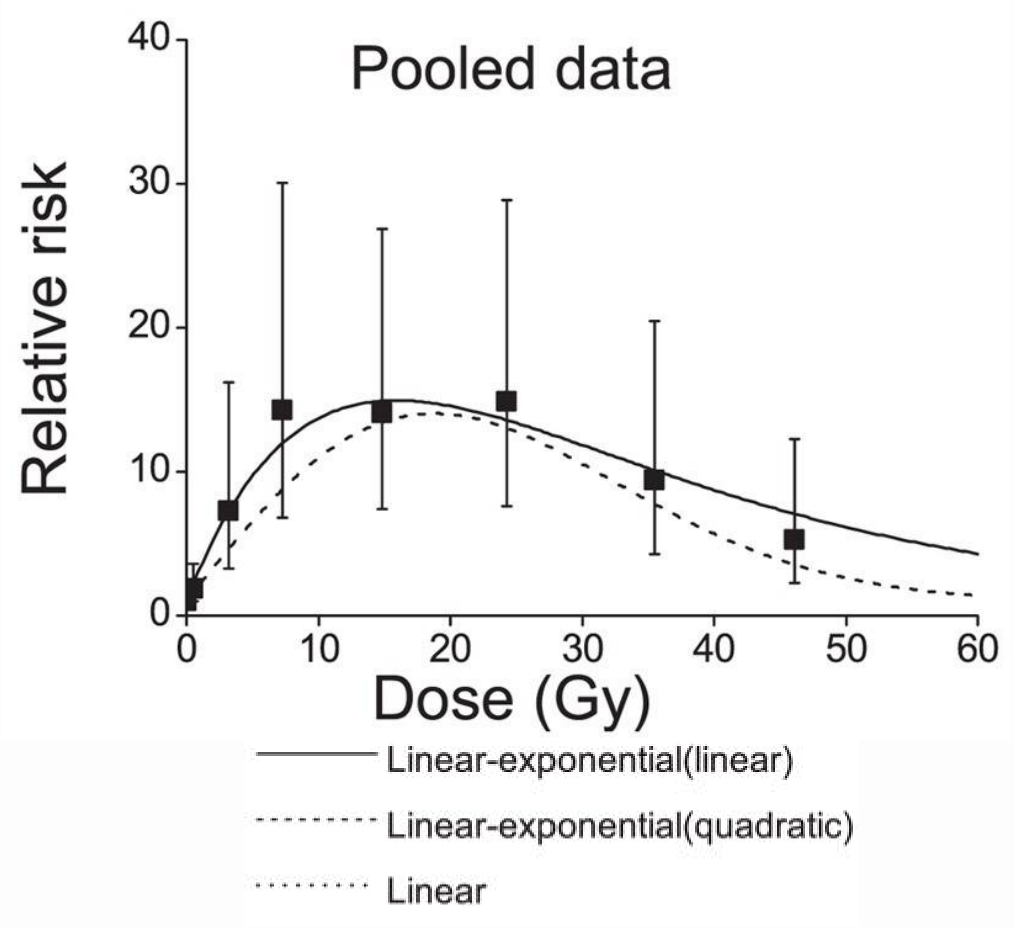
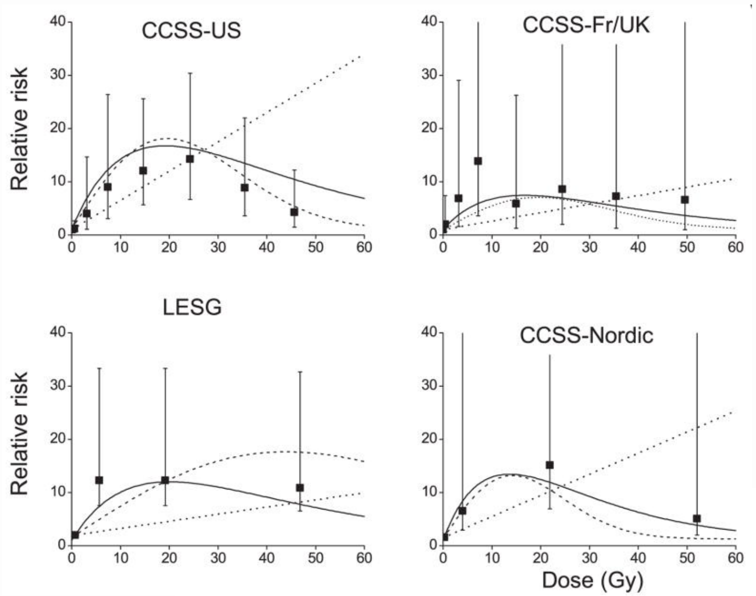
Radiation dose and thyroid cancer risk in childhood cancer survivors

International pooled analysis (2 cohort and 2 case-control studies), 187 thyroid cancer cases. Veiga et al. Radiat Res 2012; 178:365



Individual studies



Radiation dose and sarcoma risk

Berrington de Gonzalez *et al. Clinical Sarcoma Research* 2012, **2**:18
http://www.clinicalsarcomaresearch.com/content/2/1/18

CLINICAL SA

REVIEW

Sarcoma risk after radiation exposure

Amy Berrington de Gonzalez*, Alina Kutsenko and Preetha Rajaraman

Linear dose response

- bending off >40 Gy ?

Little excess risk <10 Gy

- Radium dial painters (Rowland ea 1978)
- Abomb survivors (Preston ea 2007)

Genetic component
(e.g. Li Fraumeni Syndrome)

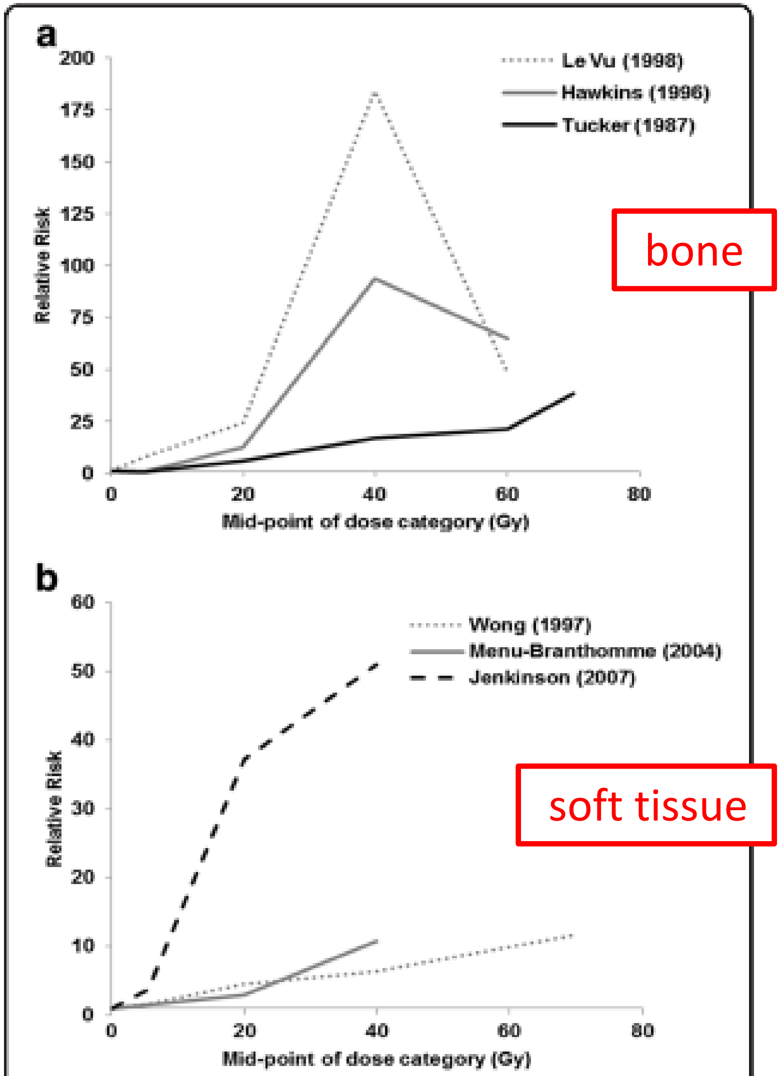


Figure 1 Relative risk of sarcoma according to radiation dose (Gy) after radiotherapy for childhood cancer. a) Bone sarcoma. b) Soft tissue sarcoma.

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Critical Review

Second Solid Cancers After Radiation Therapy: A Systematic Review of the Epidemiologic Studies of the Radiation Dose-Response Relationship

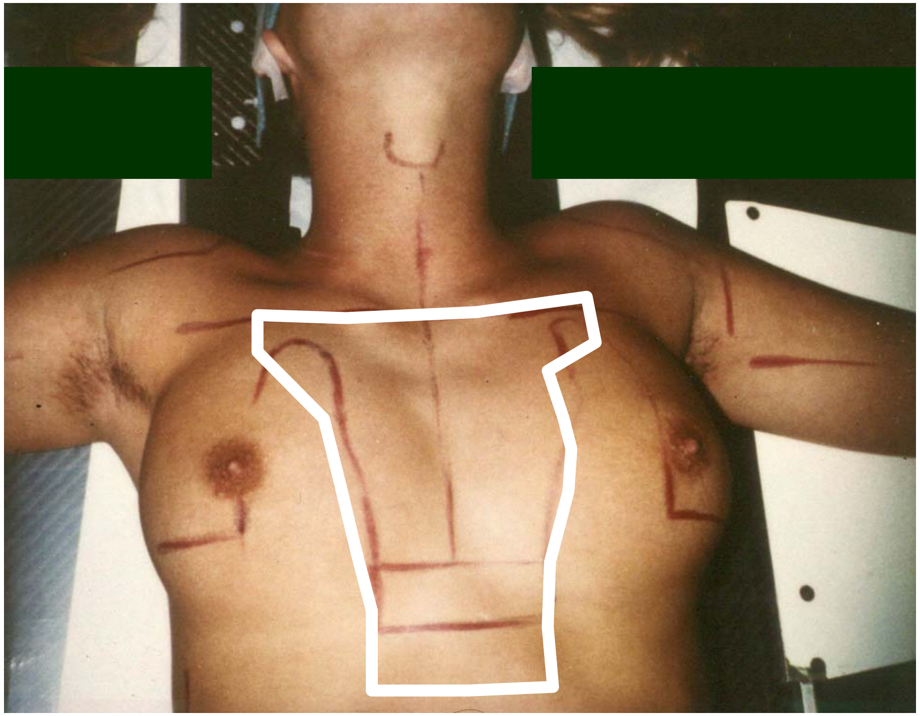
Amy Berrington de Gonzalez, DPhil, Ethel Gilbert, PhD, Rochelle Curtis, MA, Peter Inskip, ScD, Ruth Kleinerman, MPH, Lindsay Morton, PhD, Preetha Rajaraman, PhD, and Mark P. Little, DPhil

Radiation Epidemiology Branch, Division of Cancer Epidemiology & Genetics, National Cancer Institute, National Institutes of Health, Bethesda, Maryland

Received Apr 17, 2012, and in revised form Aug 30, 2012. Accepted for publication Sep 1, 2012

Berrington de Gonzalez et al. Int J Radiat Oncol Biol Phys. 2013 Jun 1;86(2):224-33.

Effect of radiation volume: changes in RT fields



With mediastinal RT less breast tissue in RT volume

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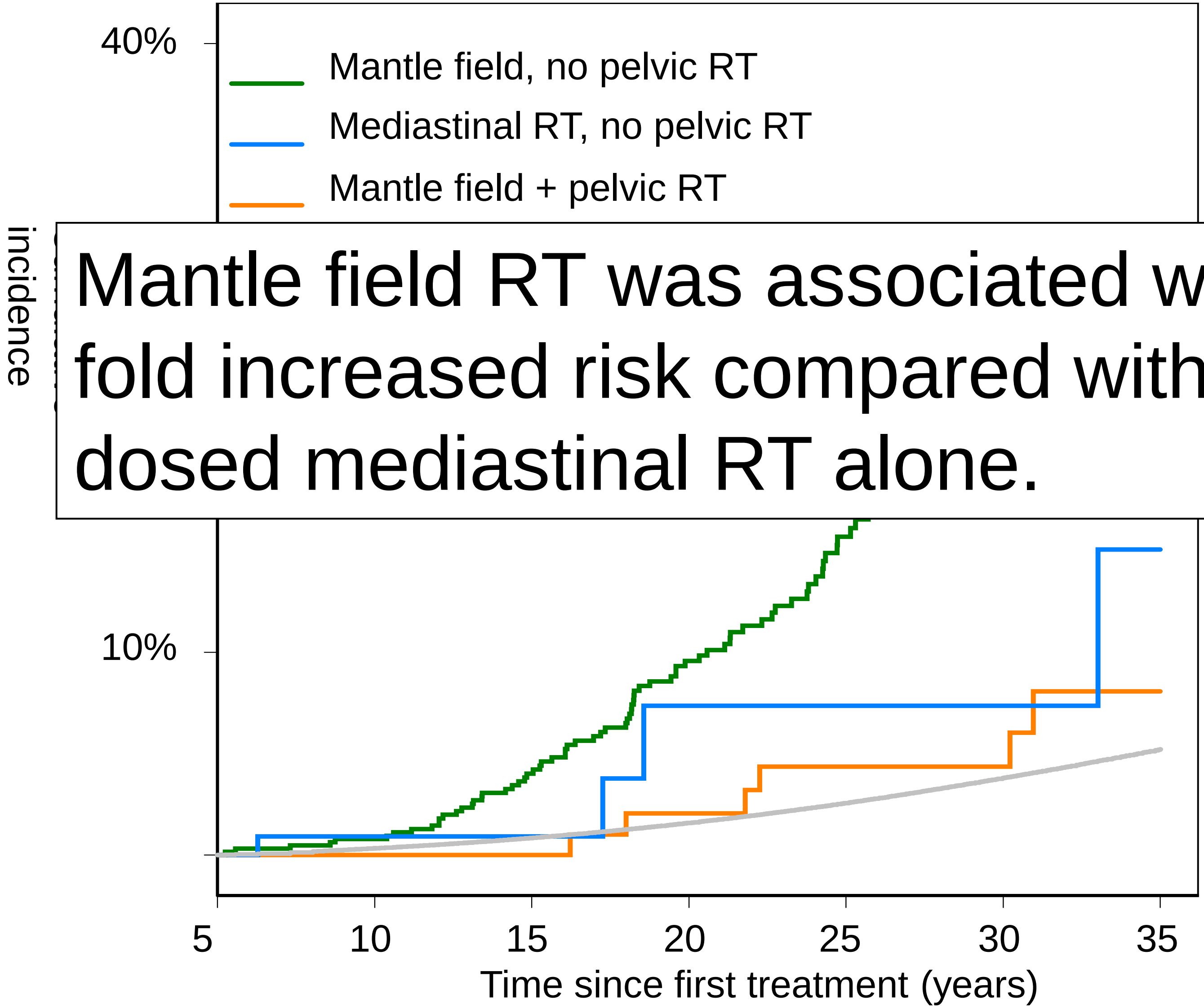
Impact of RT volume
Risk of breast cancer after HL according to RT volume



Mantle field RT was associated with a 2.7-fold increased risk compared with similarly dosed mediastinal RT alone.

De Bruin M, J. Clin Oncol 2009; 27(26): 4239-4246

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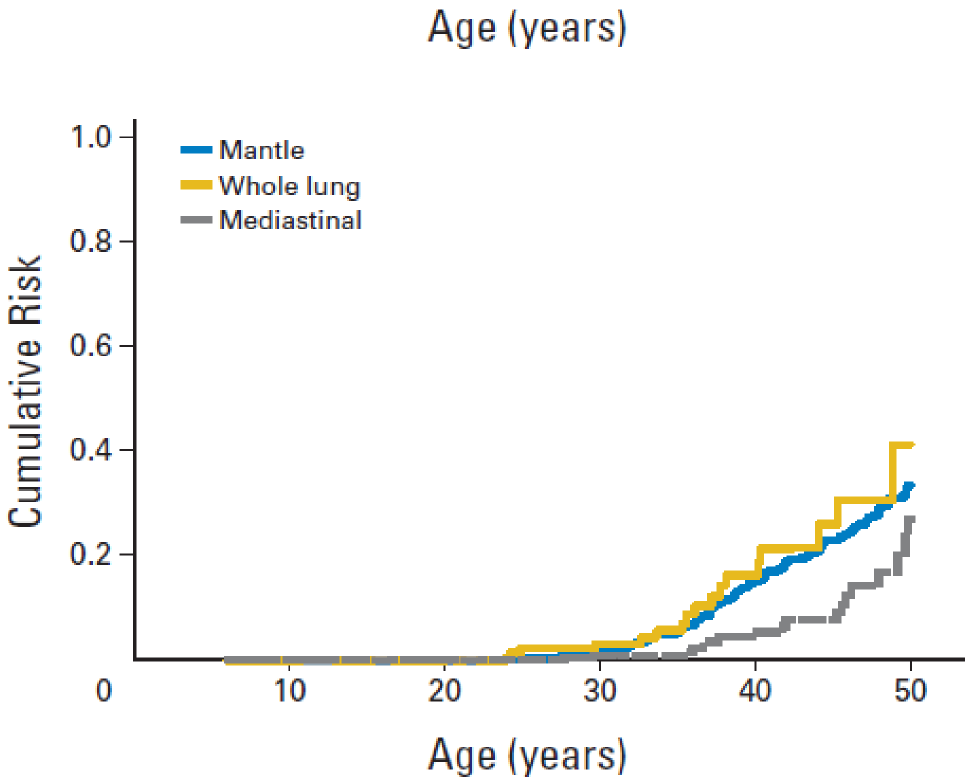
Breast cancer after childhood cancer: Role of irradiated breast volume

Whole lung Irradiation (e.g. Wilms) similar risk as Mantle radiation (HL); higher than mediastinal irradiation, although RT dose is typically lower (10-19 Gy vs >20 Gy)

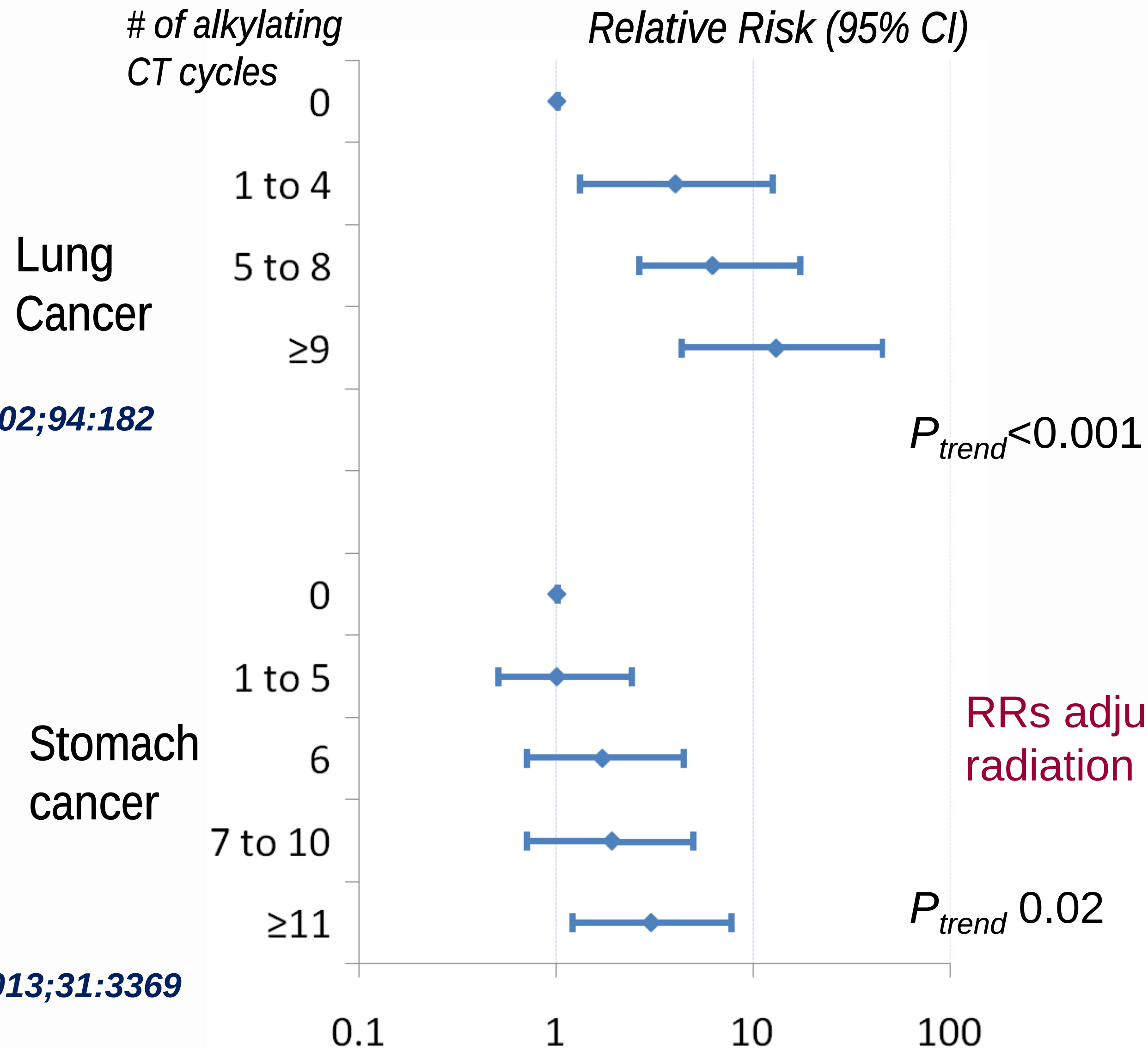


Moskowitz et al J Clin Oncol, 2014; 32(21):2217-23

Potential modifiers of radiation-associated risk

- Age
- Chemotherapy
- Hormonal factors
- Smoking
- Genetic factors

Some chemotherapy regimens also increase solid cancer risk



Travis et al. JNCI 2002;94:182

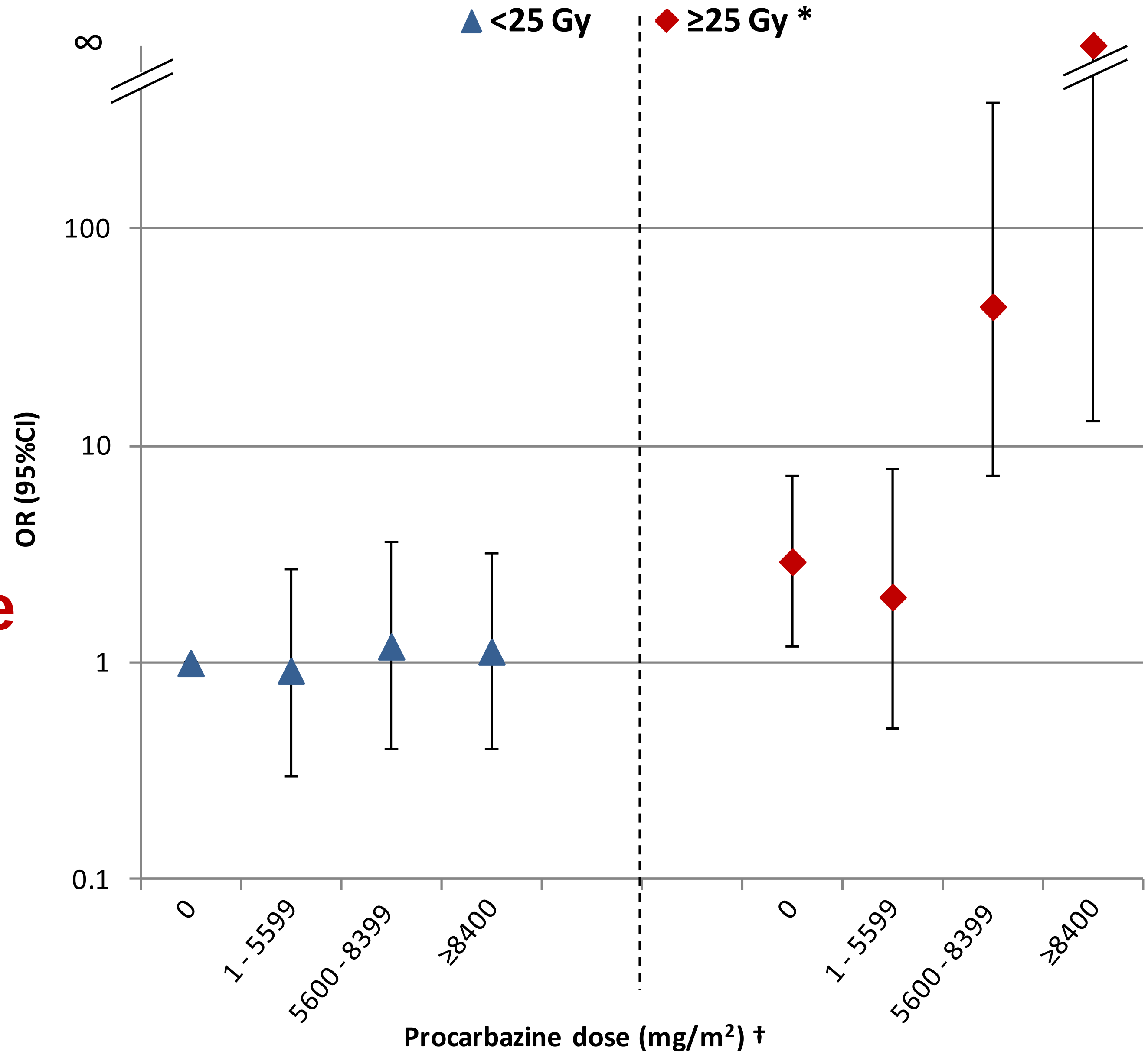
P_{trend}<0.001

RRs adjusted for radiation dose

P_{trend} 0.02

Morton et al. JCO 2013;31:3369

Stomach cancer after HL: interaction between radiation dose and procarbazine



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Morton et al., JCO, 2013 Sep 20;31(27):3369-77.

Risk of bone sarcoma after childhood cancer by radiation dose and alkylator score

Table 3. Matched Relative Risk of Bone Sarcoma, According to Radiation Dose and Alkylator Score.

Radiation Dose	Alkylator Score		
	0	*1 or 2*	*≥3*
None			
Relative risk	1.0*	4.8	8.5†
<1000 rad			
Relative risk	1.3	0.4	1.3
≥1000 rad			
Relative risk	37.4‡	14.2‡	59.2‡

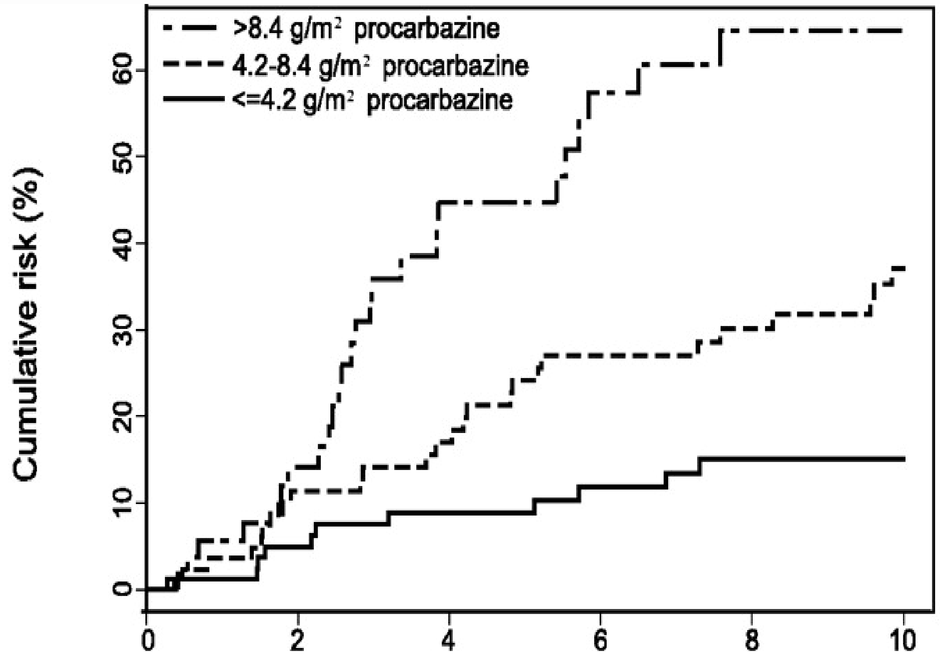
*Referent category.

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

‡$P<0.05$.

Hawkins MM J Natl Cancer Inst. 1996 Mar 6;88(5):270-8.

Cumulative risk of premature menopause (< 40yrs) by cumulative procarbazine dose among female HL survivors



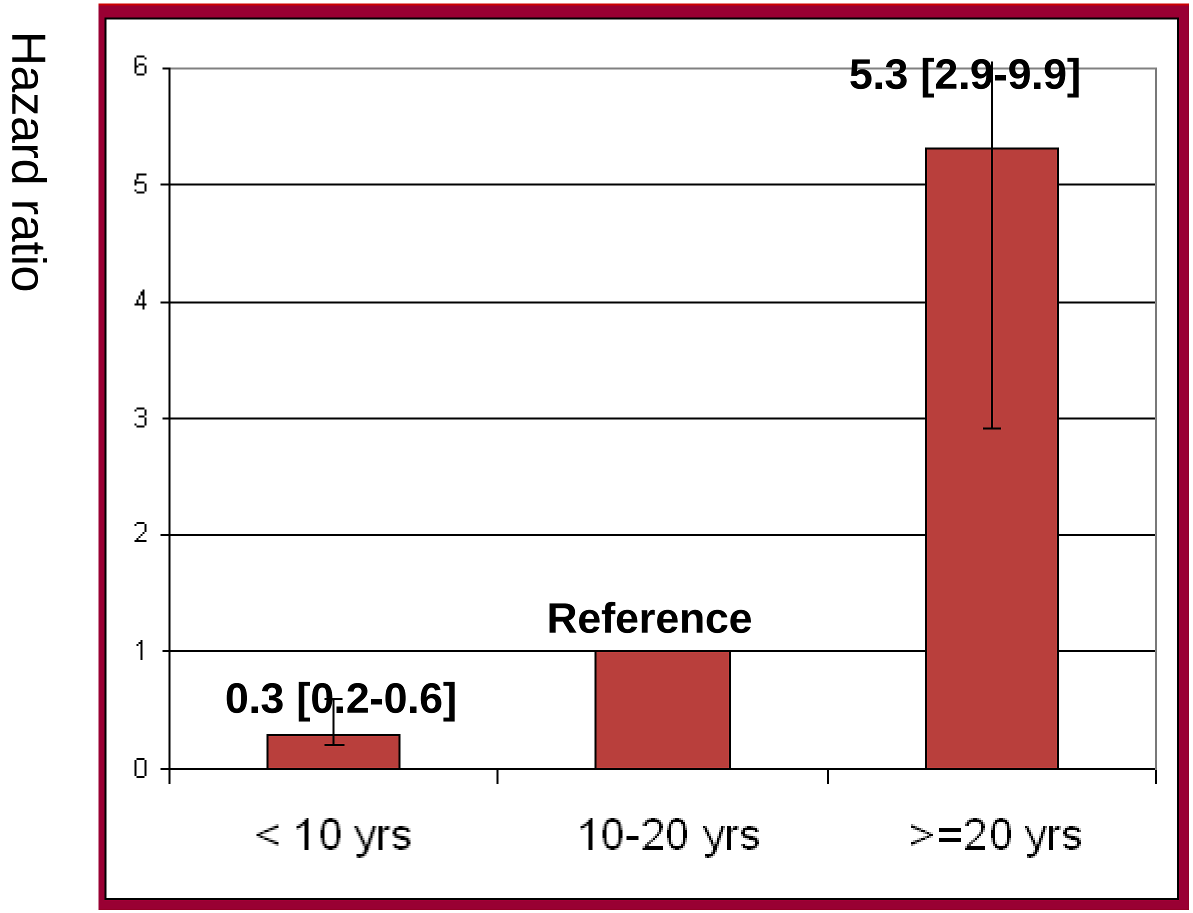
Time since first treatment (years)

Numbers at risk							Cumulative risk 10 years after treatment
<=4.2 g/m² procarbazine (n=85)	85	76	66	58	51	41	15% [6-23%]
4.2-8.4 g/m² procarbazine (n=86)	86	68	59	51	44	36	37% [24-48%]
>8.4 g/m² procarbazine (n=55)	55	39	19	14	9	7	65% [44-78%]

De Bruin et al. Blood 2008;111:101

Modifiers of RT-induced cancers

Risk of breast cancer after RT for HL, by duration of ovarian function after RT

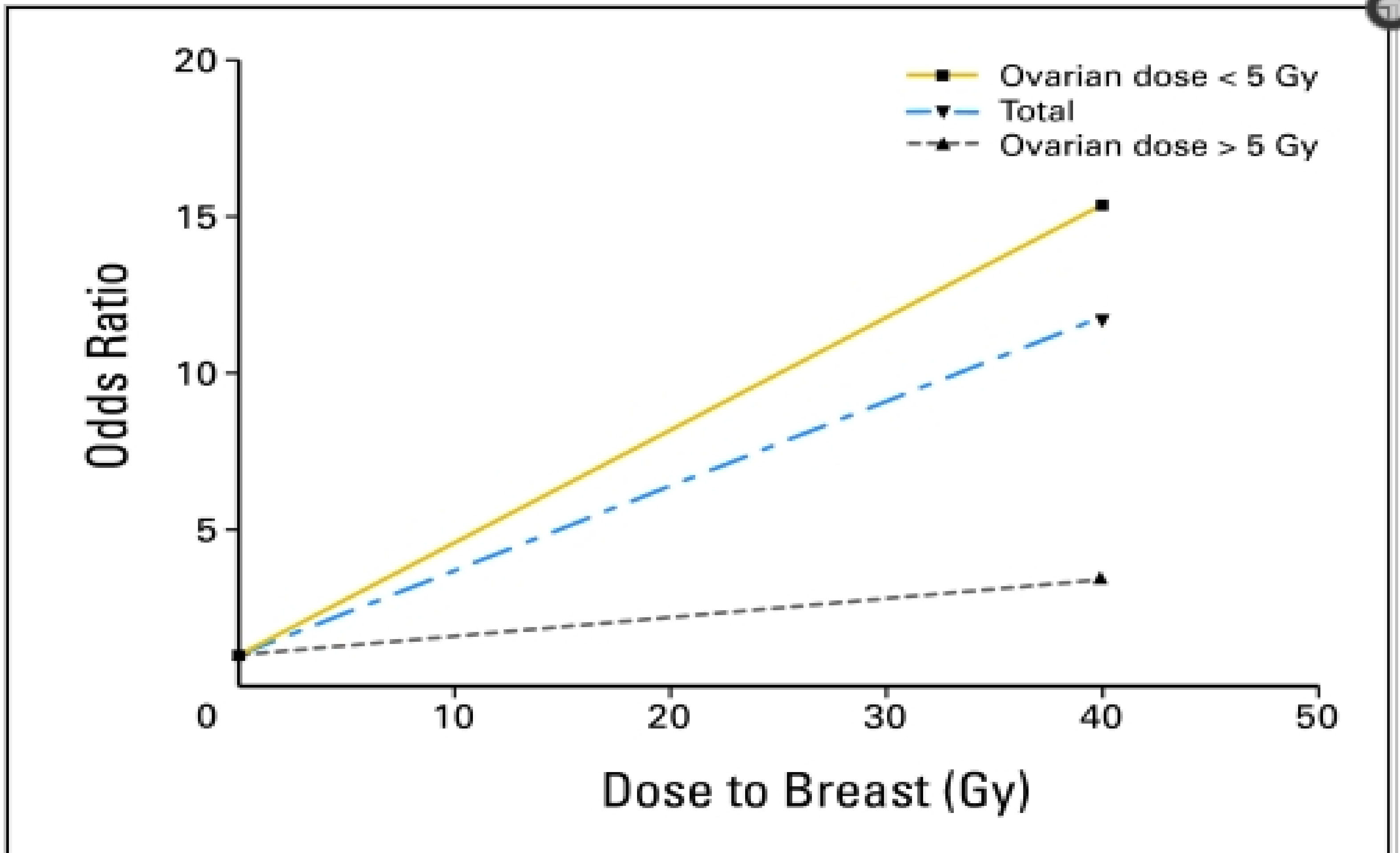


years of intact ovarian function after RT

➡ Ovarian hormones crucial in radiation-induced breast carcinogenesis

De Bruin M, JCO 2009; 27(26): 4239-4246

Breast cancer risk after childhood cancer according to radiation dose to breast and ovarian radiation



Inskip et al. JCO 2009; 27(24): 3901-07

Lung cancer after HL
Joint effects of smoking and treatment

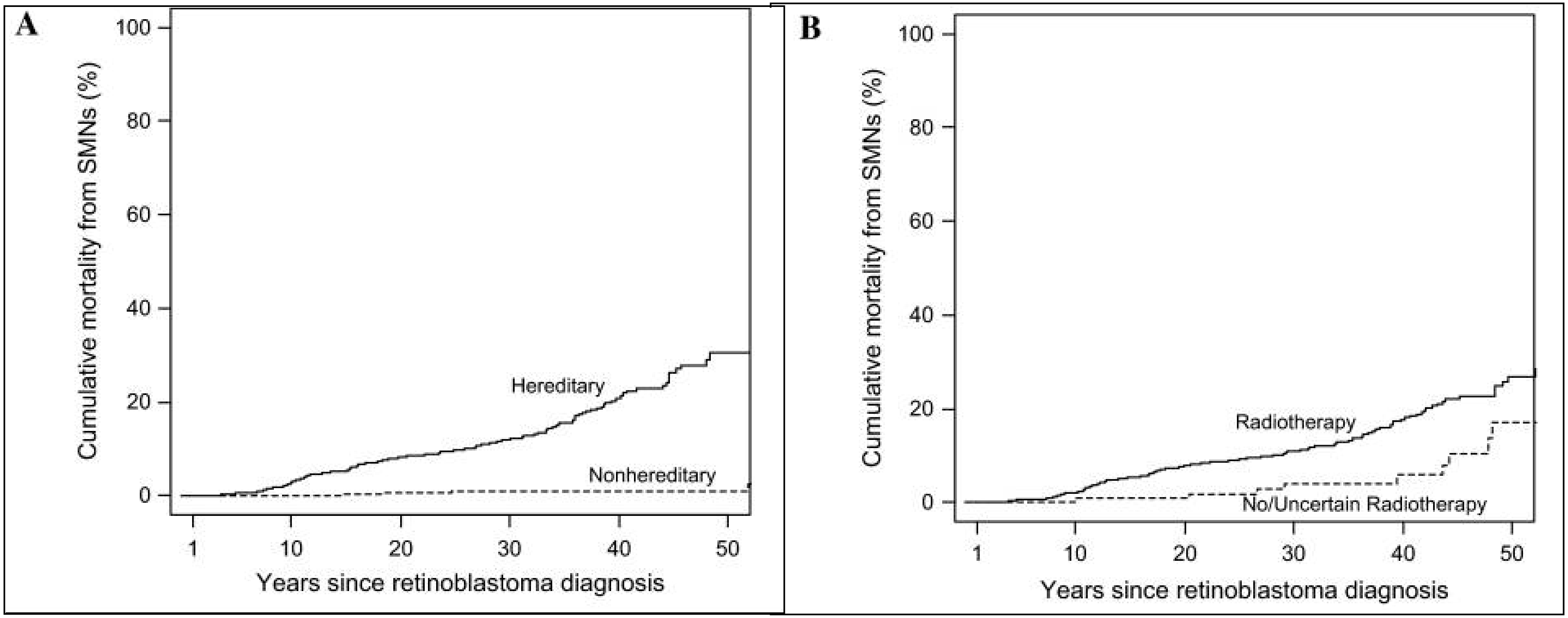
Risks from smoking multiply risks from RT and CT

	RR non/light smokers	RR smokers
No RT (< 5 Gy), no CT	1.0 (ref)	6.0 (1.9-20.4)
RT (≥ 5 Gy), no CT	7.2 (2.9-21.2)	20.2 (6.8-68)
No RT (< 5 Gy), CT	4.3 (1.8-11.7)	16.8 (6.2-53)
RT (≥ 5 Gy), CT	7.2 (2.8-21.6)	49.1 (15.1-187)

10% of lung cancers due to treatment alone
24% of lung cancers due to smoking alone
63% of lung cancers due to treatment + smoking in combination

Travis et al. JNCI 2002; 94:182

Cumulative mortality due to second cancer after retinoblastoma



Yu C et al. J Natl Cancer Inst 2009; 101: 581-91

Relative rates of mortality from second cancer after retinoblastoma according to RT and hereditary status

Nonirradiated, nonhereditary	**1.0**	**(ref)**
Nonirradiated, hereditary	7.12	(95%CI 2.70-20.7)
Irradiated, nonhereditary	7.20	(95%CI 2.25-23.0)
Irradiated, hereditary	17.9	(95%CI 8.55-45.8)
P interaction = 0.12		

Yu C et al. J Natl Cancer Inst 2009; 101: 581-91

Genetic susceptibility for treatment-induced second cancers?

nature medicine

Brief report

FGFR2 genotype and risk of radiation-associated breast cancer in Hodgkin lymphoma

Yussanne P. Ma,[1] Flora E. van Leeuwen,[2] Rosie Cooke,[3] Annegien Broeks,[4] Victor Enciso-Mora,[1] Bianca Olver,[1] Amy Lloyd,[1] Peter Broderick,[1] Nicola S. Russell,[5] Cecile Janus,[6] Alan Ashworth,[7] Richard S. Houlston,[1] and Anthony J. Swerdlow[3]

Ma YP et al., Blood 2012; 119(4): 1029-31

Variants at 6q21 implicate *PRDM1* in the etiology of therapy-induced second malignancies after Hodgkin's lymphoma

Timothy Best[1], Dalin Li[2], Andrew D Skol[3], Tomas Kirchhoff[4], Sarah A Jackson[3], Yutaka Yasui[5], Smita Bhatia[6], Louise C Strong[7], Susan M Domchek[8], Katherine L Nathanson[8], Olufunmilayo I Olopade[3], R Stephanie Huang[3], Thomas M Mack[2,9], David V Conti[2], Kenneth Offit[4], Wendy Cozen[2,9], Leslie L Robison[10] & Kenan Onel[1,11]

Best T et al., Nat Med 2011; 17(8): 941-43

Few studies examined tumor characteristics of second cancers

RESEARCH ARTICLE

Characterization of Genomic Alterations in Radiation-Associated Breast Cancer among Childhood Cancer Survivors, Using Comparative Genomic Hybridization (CGH) Arrays

Xiaohong R. Yang[1]*, J. Keith Killian[2], Sue Hammond[3], Laura S. Burke[1], Hunter Bennett[1], Yonghong Wang[2], Sean R. Davis[2], Louise C. Strong[4], Joseph Neglia[5], Marilyn Stovall[6], Rita E. Weathers[6], Leslie L. Robison[7], Smita Bhatia[8], Kiyohiko Mabuchi[1], Peter D. Inskip[1], Paul Meltzer[2]

Broeks et al.,IJROB 2010; 76:540-47

0360-3016/10/$–see front matter

ELSEVIER

doi:10.1016/j.ijrobp.2009.09.004

BIOLOGY CONTRIBUTION

RADIATION-ASSOCIATED BREAST TUMORS DISPLAY A DISTINCT GENE EXPRESSION PROFILE

Annegien Broeks, Ph.D.,* Linde M. Braaf, B.S.,* Lodewyk F. A. Wessels, Ph.D.,[†‡] Marc van de Vijver, M.D., Ph.D.,[§] Marie L. De Bruin, Ph.D.,[¶] Marilyn Stovall, Ph.D.,[||] Nicola S. Russell, M.D., Ph.D.,** Flora E. van Leeuwen, Ph.D.,[¶] and Laura J. Van 't Veer, Ph.D.*[§]

Risk of multiple primary malignancies

blood

Prepublished online April 16, 2014;
doi:10.1182/blood-2013-10-532184

Risk of multiple primary malignancies following treatment of Hodgkin lymphoma

Anna M. van Eggermond, Michael Schaapveld, Pieternella J. Lugtenburg, Augustinus D. G. Krol, Jan Paul de Boer, Josée M. Zijlstra, John M. M. Raemaekers, Leontien C. M. Kremer, Judith M. Roesink, Marieke W. J. Louwman, Berthe M. P. Aleman and Flora E. van Leeuwen

Van Eggermond AM, et al. Blood 2014;124(3):319-27

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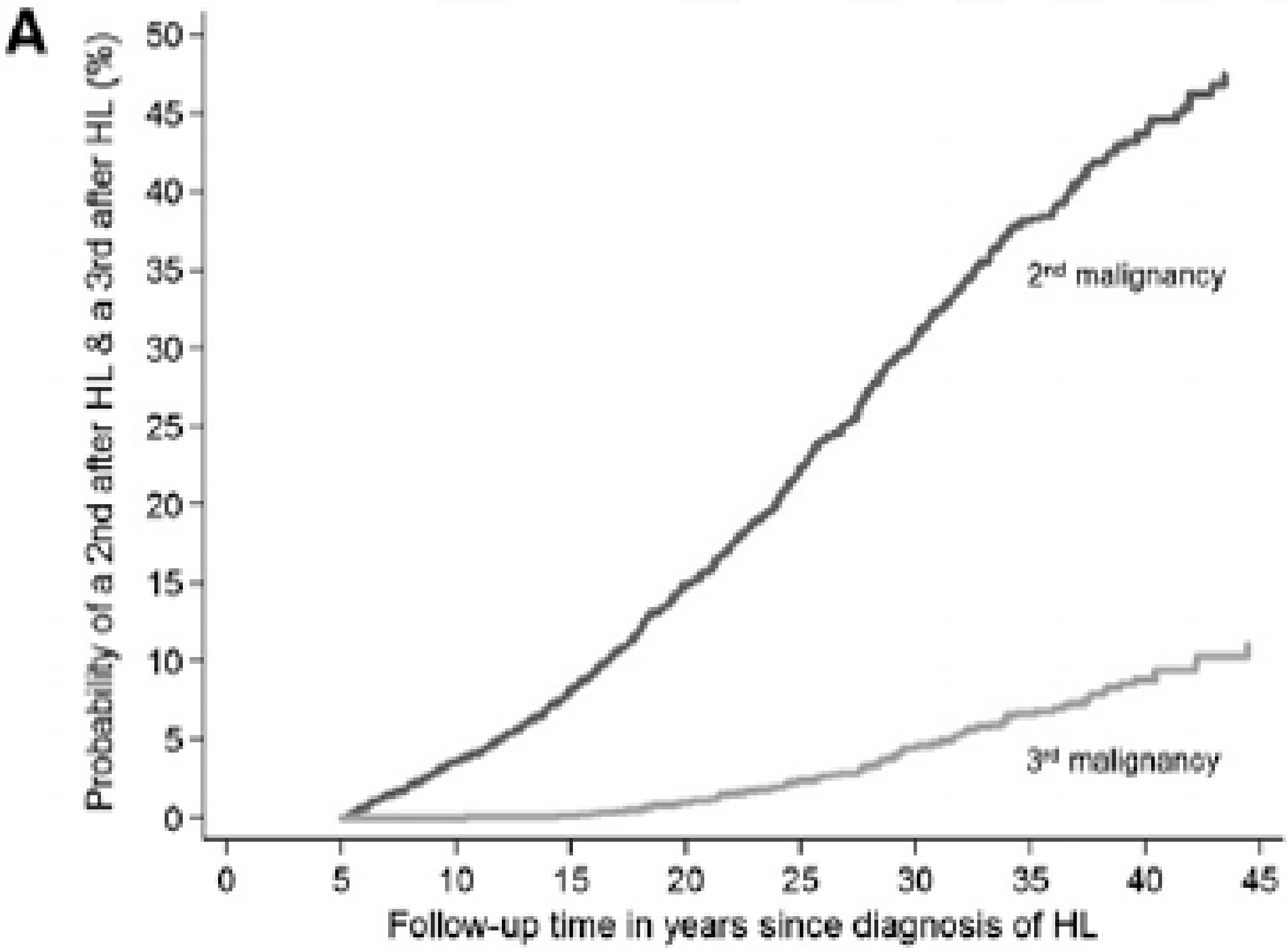
Risk of multiple malignancies following treatment for Hodgkin lymphoma

- 3,122 5-year HL survivors
- After median follow-up of 22.6 years
  - 832 second malignancies, SIR =4.7
  - 126 third malignancies, SIR = 5.4
  - Patients with SMN, treated before age 25, compared to those free of SMN: 2.2-fold increased risk of subsequent cancer

Cumulative incidence of a second and third malignancy in HL survivors



Van Eggermond AM, et al. Blood 2014;124(3):319-27

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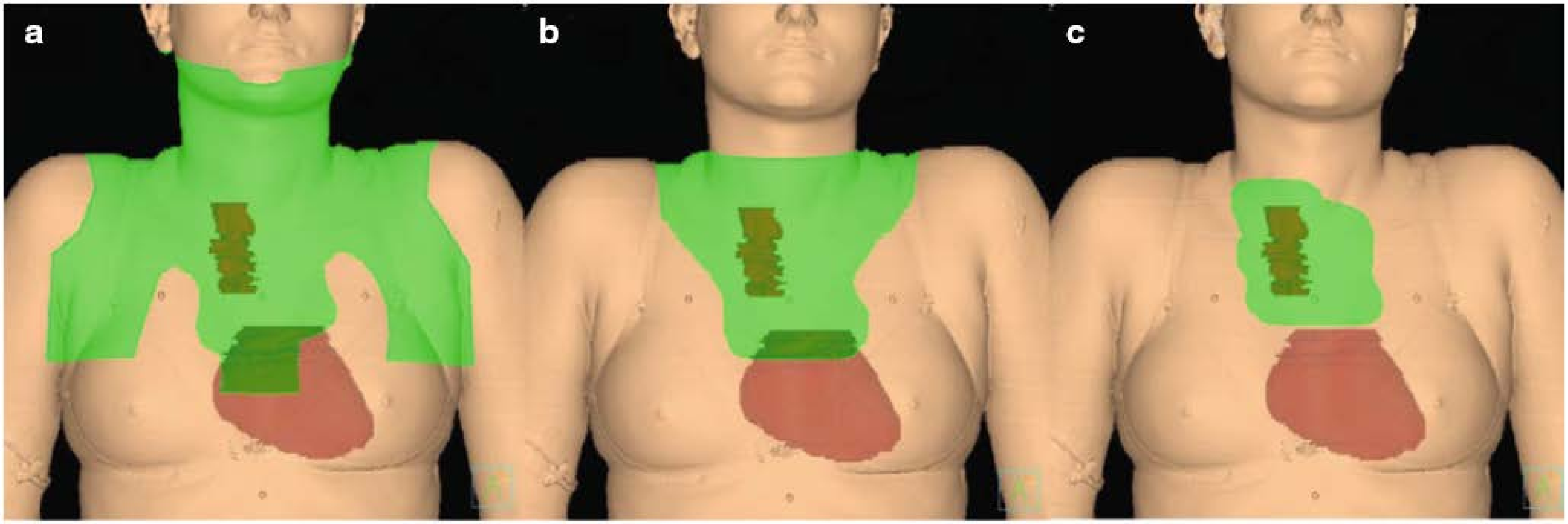
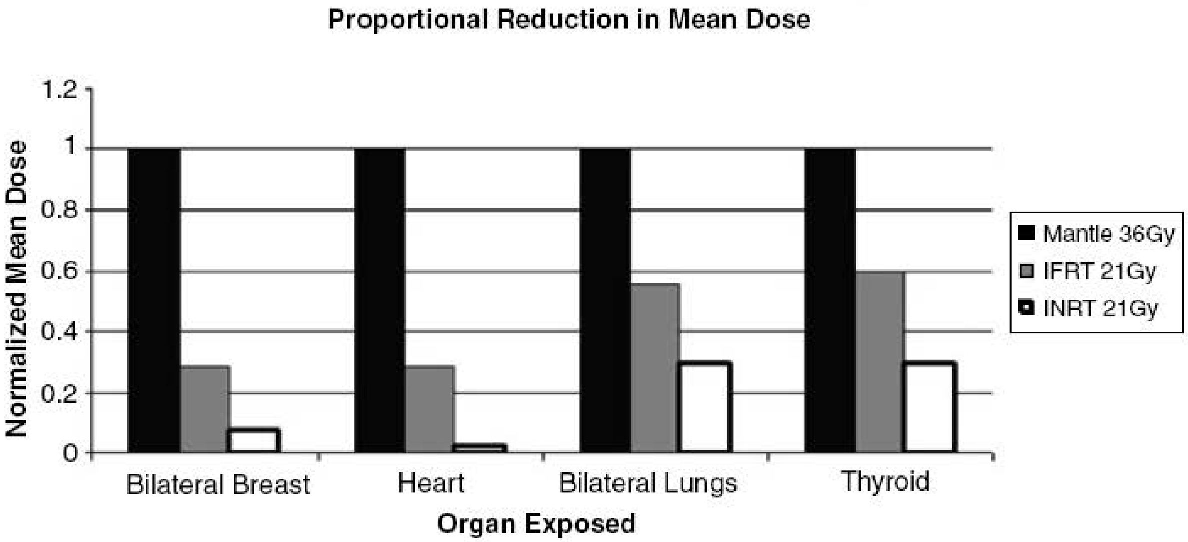
Proportional reduction mean RT dose





Summary of second cancer findings

- Solid cancer risk after radiotherapy remains increased for >35 years
- Higher relative risk with RT at younger age
- Higher risk with larger RT doses (linear dose-response) and radiation volumes
- Emerging data that some **CT regimens** increase solid cancer risk, potential interaction with RT
- Chemotherapy, smoking, premature menopause can modify solid cancer risk

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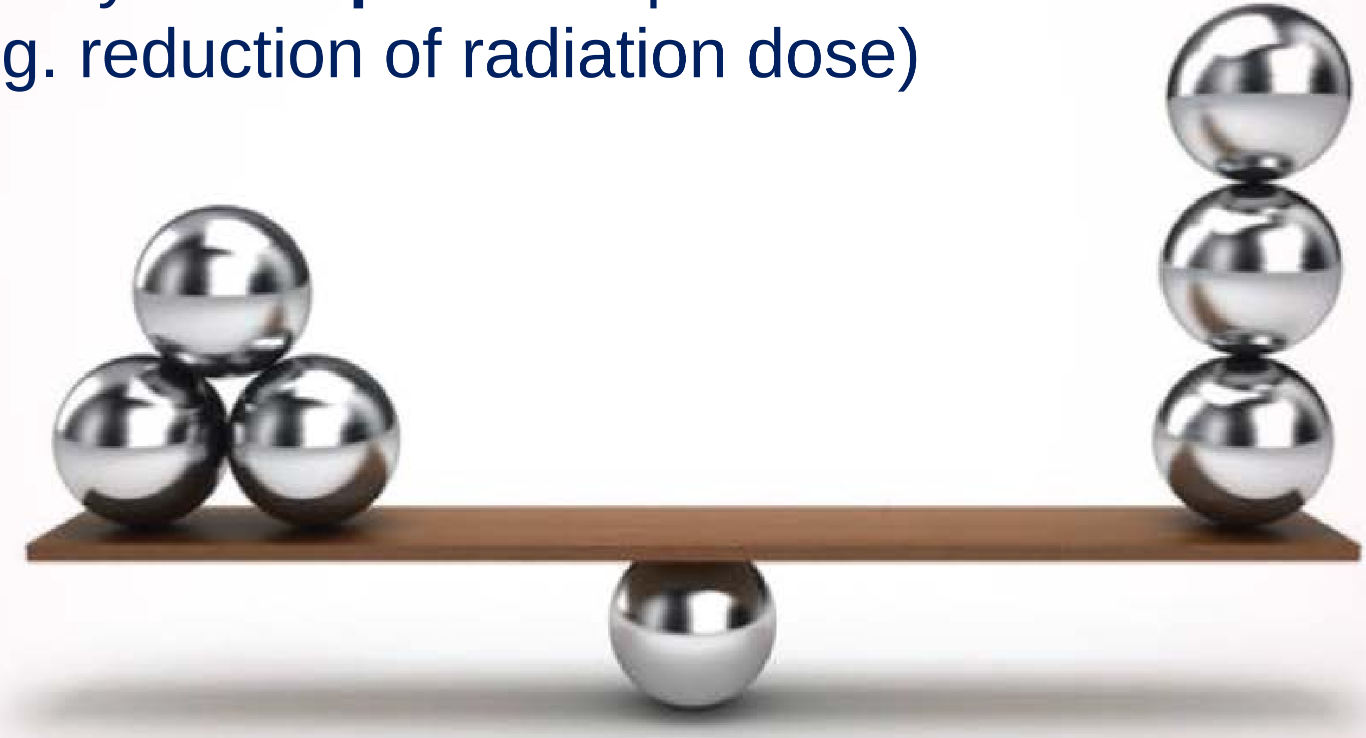
Implications of late effect studies

- Identification of patient groups at high risk of SC → **screening** if effective methods available

- Development of new treatment protocols with lower toxicity and **equal** therapeutic effectiveness (e.g. reduction of radiation dose)



Challenges for future research

1. Contemporary RT regimens, IMRT, protons; lower doses to larger volumes
2. RT dose/volume effects (combination)
3. Interaction between RT and chemotherapy
4. Search for susceptibility genes for RT/CT-associated second cancers
5. Interaction between treatment and lifestyle (premature menopause, smoking)
6. Risk prediction models
7. Tumor characteristics and prognosis second cancers
8. Efficacy of screening
9. Chemoprevention?

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Netherlands Cancer Registry

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Questions

- What is more detrimental for risk of second cancer in a specific organ/tissue, a high radiation dose to a small volume or a low dose to a larger volume? And how should we study this?

- What is the most efficient way to study gene-treatment interactions in the etiology of second cancers?

- Is there a radiation signature in radiation-associated cancers?

Questions and Answers

U.S. Department of Health and Human Services
National Institutes of Health | National Cancer Institute
www.dceg.cancer.gov/RadEpiCourse
1-800-4-CANCER

Produced May 2015