Cancer Risks from Conventional Radiotherapy

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DCEG Radiation Epidemiology and Dosimetry Course 2019

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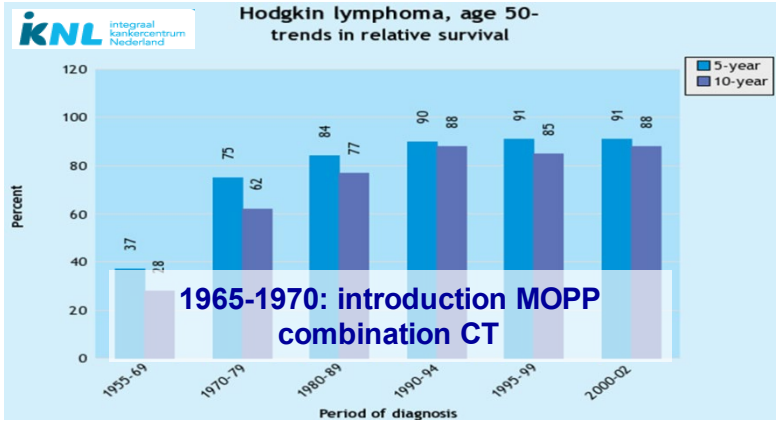
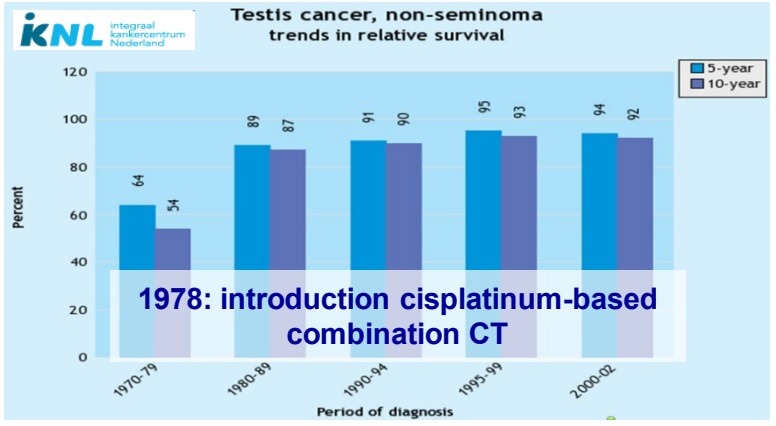
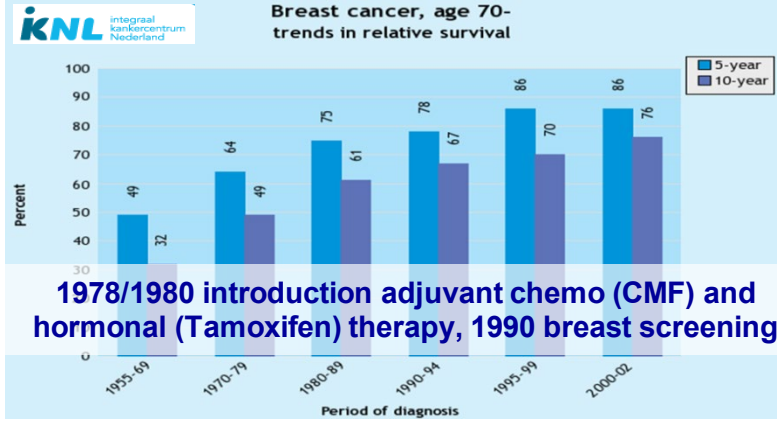
Cancer prognosis has improved over the last decades







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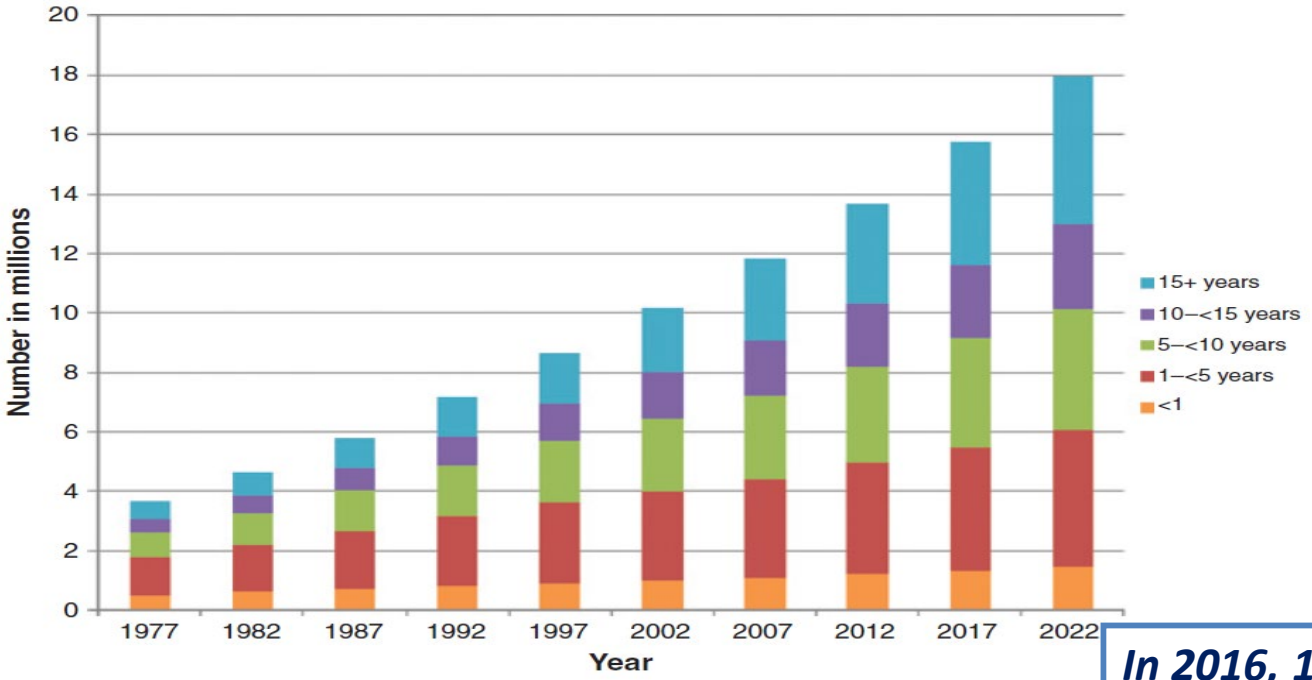
Increasing numbers of cancer survivors

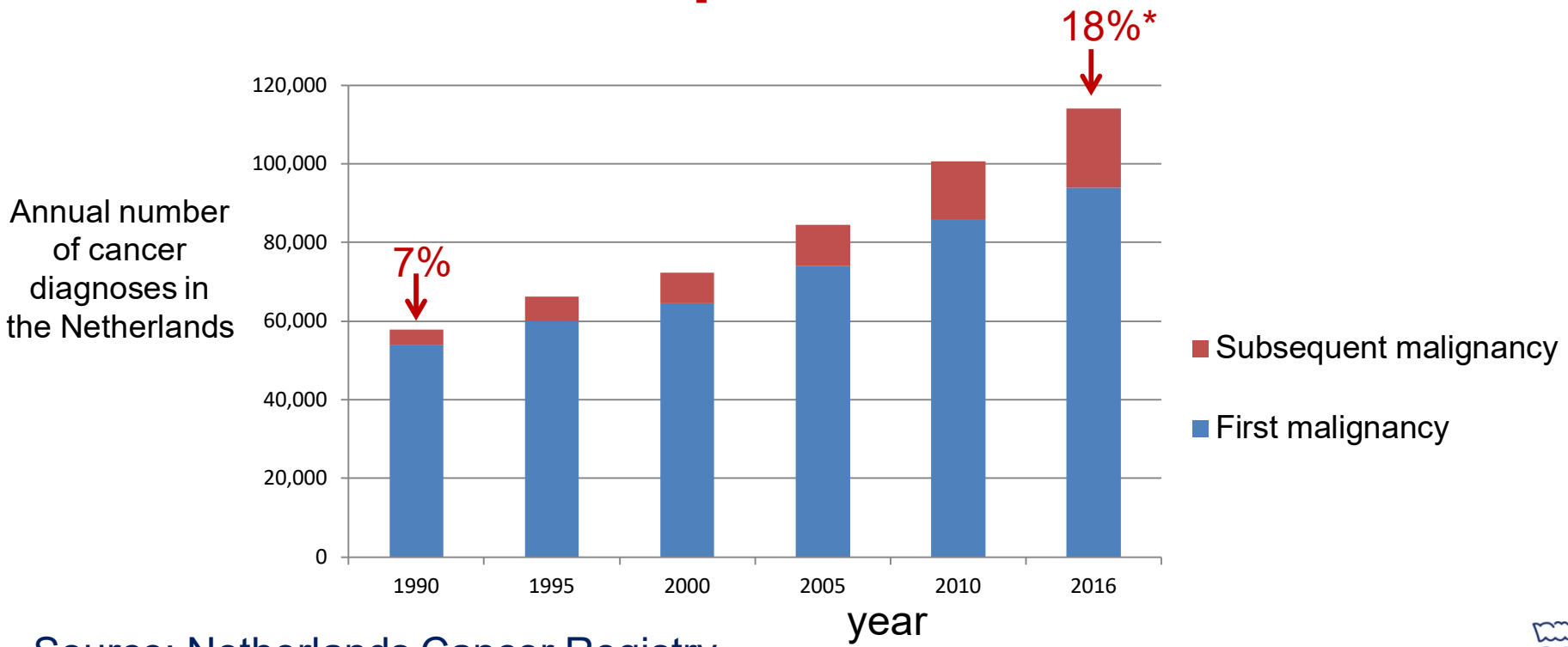
Estimated and projected number of cancer survivors in the US up to 2022 by years since diagnosis



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

In 2016, 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

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Cancer Risks from Conventional Radiotherapy

- **Introduction on second malignancy**
- Magnitude of risks for various *second* malignancies after selected *first* primary malignancies
- Radiotherapy, dose and volume
- Modifying factors of radiation-associated risk (age, chemotherapy)
- Clinical implications

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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~~

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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

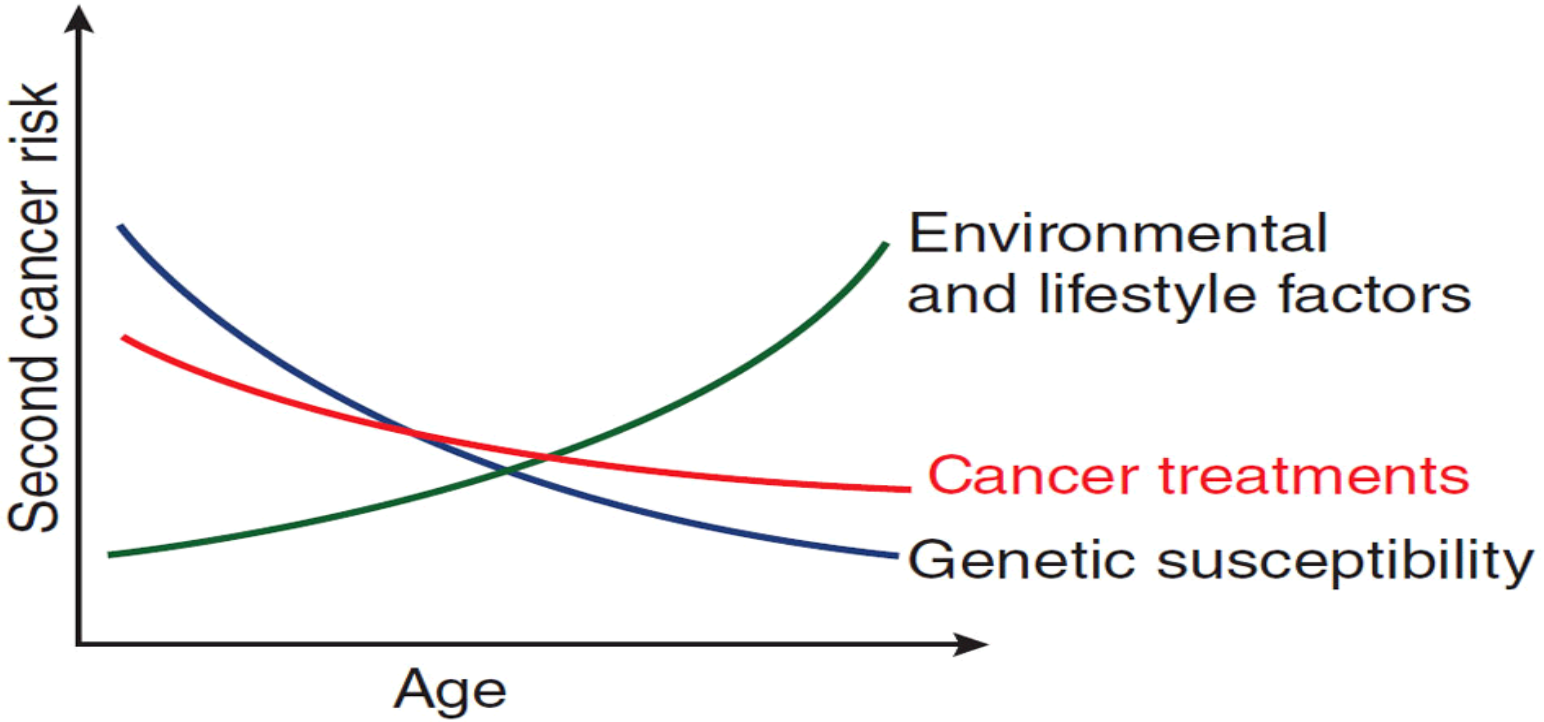
Lifestyle & environmental factors (i.e. smoking, alcohol use, diet, weight, physical activity)

Cancer treatment (i.e. radiation dose & volume, chemo regimen)

Host susceptibility

- Genetic susceptibility (i.e. BRCA, Lynch syndrome, SNP variants)
- Immunodeficiency

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

Cancer Risks from Conventional Radiotherapy

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Radiotherapy

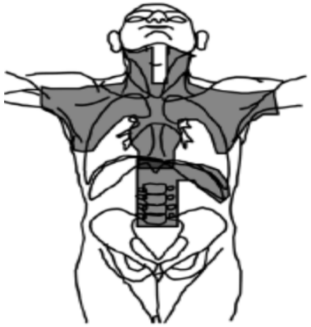
Classic radiation fields in treatment of Hodgkin lymphoma and testicular cancer

Hodgkin Lymphoma

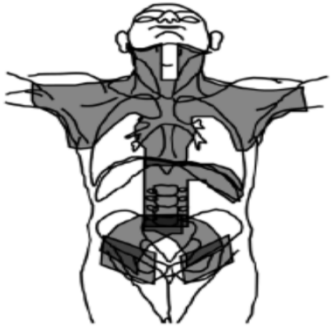
36-44 Gray
2-Gray fractions

Testicular cancer

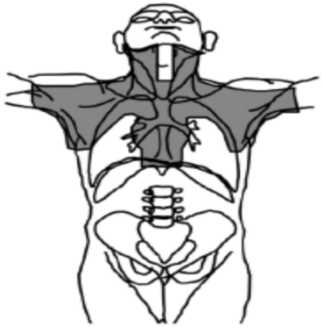
Seminoma subtype
26-40 Gray
2-Gray fractions



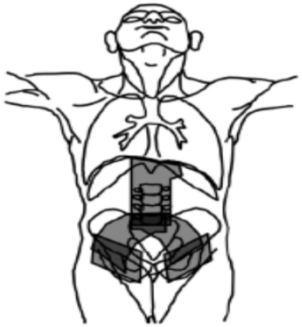
Subtotal nodal irradiation



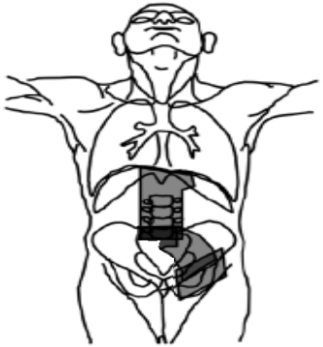
Total nodal irradiation



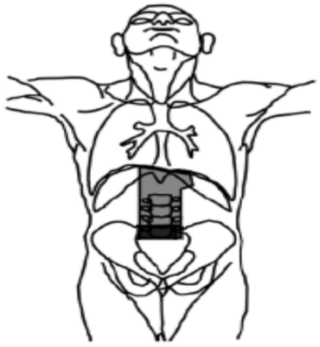
Mantle field irradiation



Inverted-Y irradiation



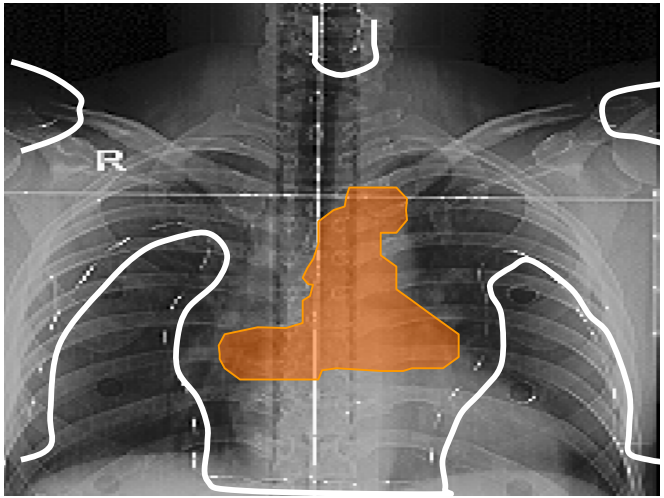
Dog-leg irradiation



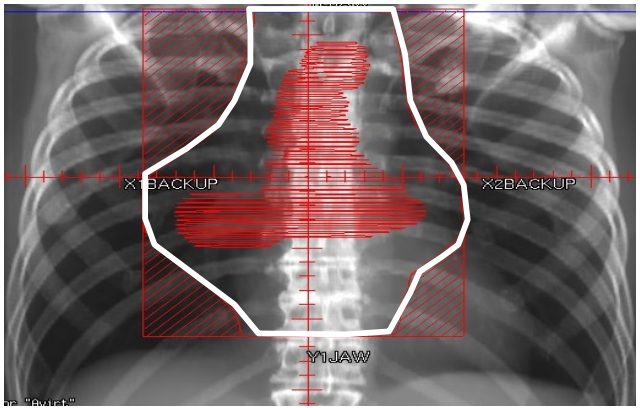
Para-aortal irradiation

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	✓	✓

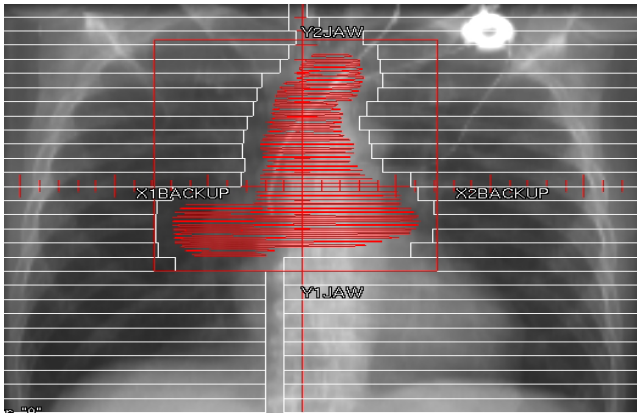
Changes in Hodgkin RT volumes



Mantle field radiotherapy
till late 1980s



EORTC
H9
Involved Field
Radiotherapy
From 1985

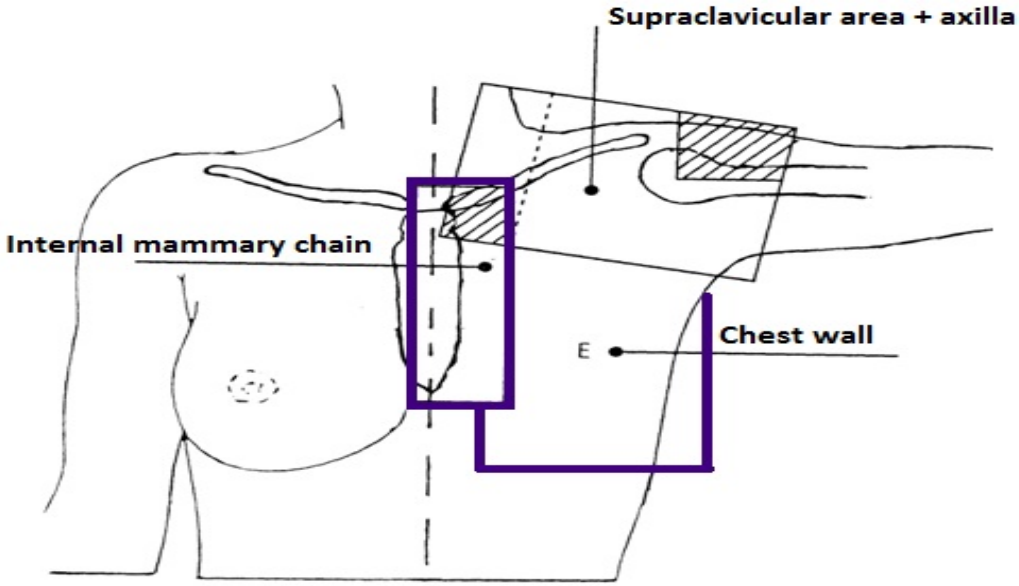


EORTC
H10
Involved Node
Radiotherapy
After 2000

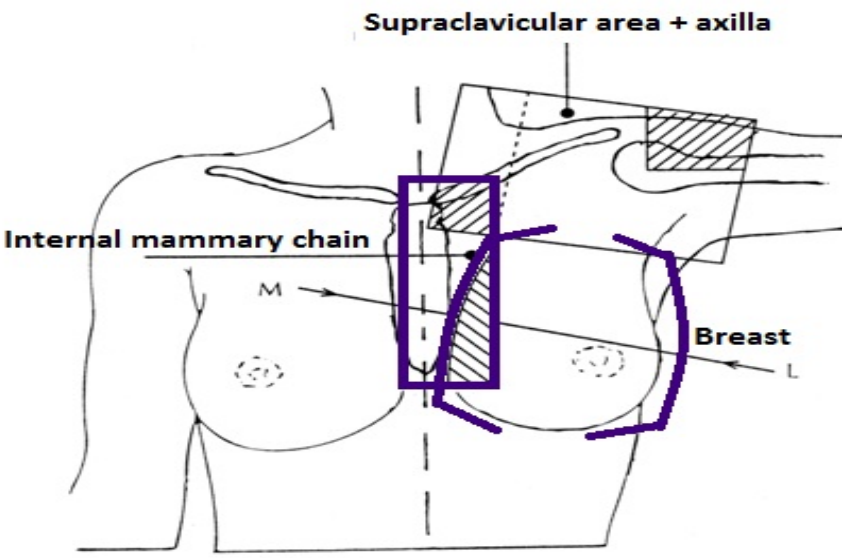
Courtesy: R vd Maazen Radboud
University Nijmegen Medical Center

Breast cancer radiation fields

After mastectomy



After breast conserving treatment



Clinical epidemiology

- Comparison with risk in general population
- Comparison between treatments

APPROPRIATE STUDY DESIGNS

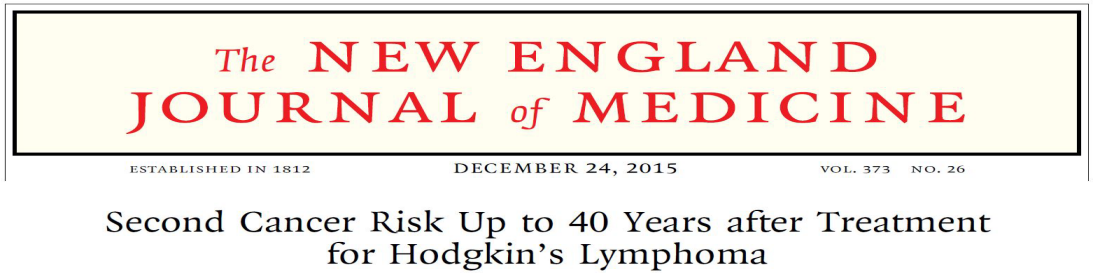
- Cohort study
- Case-control study

Risk measures

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

Dutch HL cohort

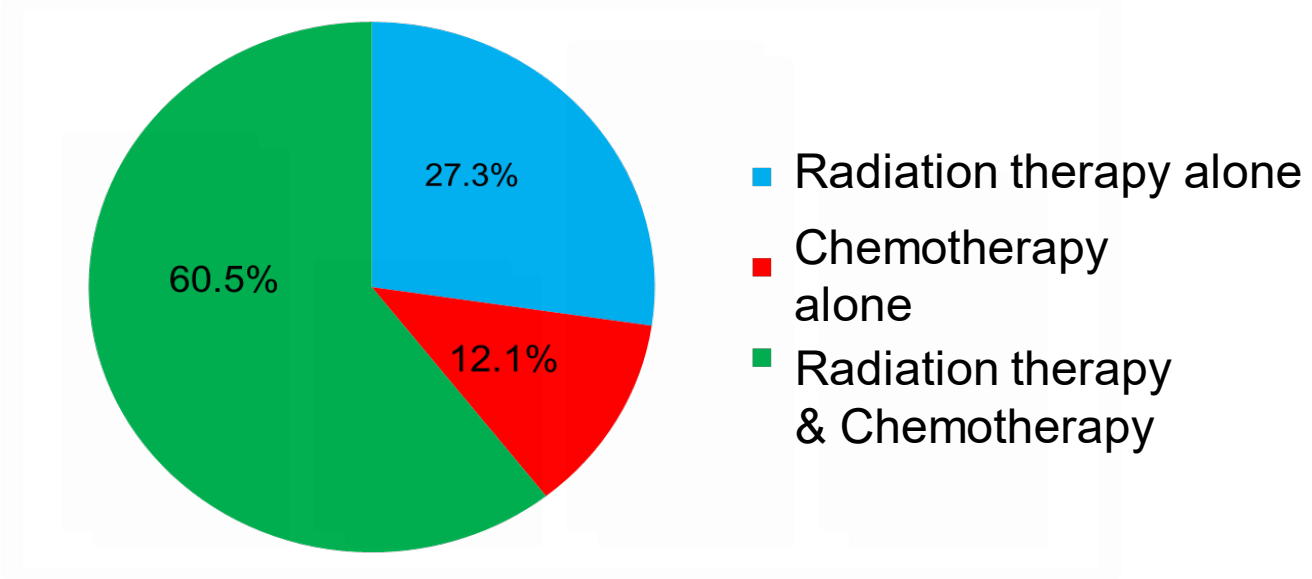
- 3,905 HL patients from 6 (University Medical) Cancer Centers & 41 community hospitals
- Treatment period: 1965-2000
- Age at HL diagnosis: 15-50 years
- > 5-year survivors
- Follow-up through linkage with the Netherlands Cancer Registry
- 96% complete follow-up for second cancers



Schaapveld M et al.
NEJM 2015;373(26):2499

Patient characteristics

- 3,905 HL survivors
- Median age at HL: 28.6 years
- Median follow-up time: 19 years, range: 5-47 yrs



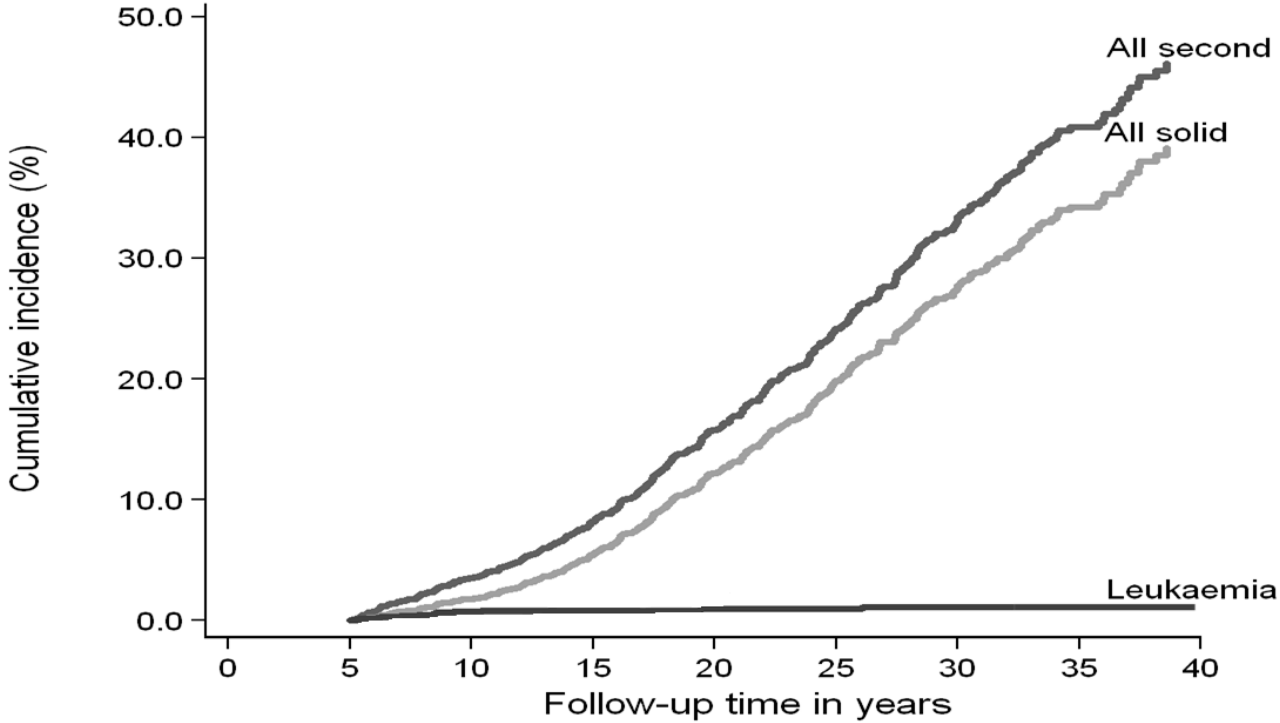
Risk of second malignancy, Dutch HL cohort; 3,905 5-yr survivors, 15-50 yr at dx, 1965-2000

Cancer site	Observed sec. cancers	SIR
All Malignancies	**884**	**4.6**
Oral cavity/pharynx	20	**3.2**
Esophagus	38	**9.5**
Stomach	39	**7.4**
Colon	42	**2.9**
Lung & Bronchus	176	**6.4**
Pleura	17	**15.1**
Rectum & Rectosigmoid	25	**2.6**
Pancreas	23	**5.7**
Female breast	183	**4.7**
Melanoma	34	**2.8**
Bladder	22	**4.1**
Thyroid	23	**14.0**
Soft tissue sarcoma	22	**12.0**
Leukemia	41	**9.5**

SIR = Standardized Incidence Ratio

Schaapveld M et al. *NEJM* 2015;373(26):2499

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



High relative risk
≠
High absolute risk

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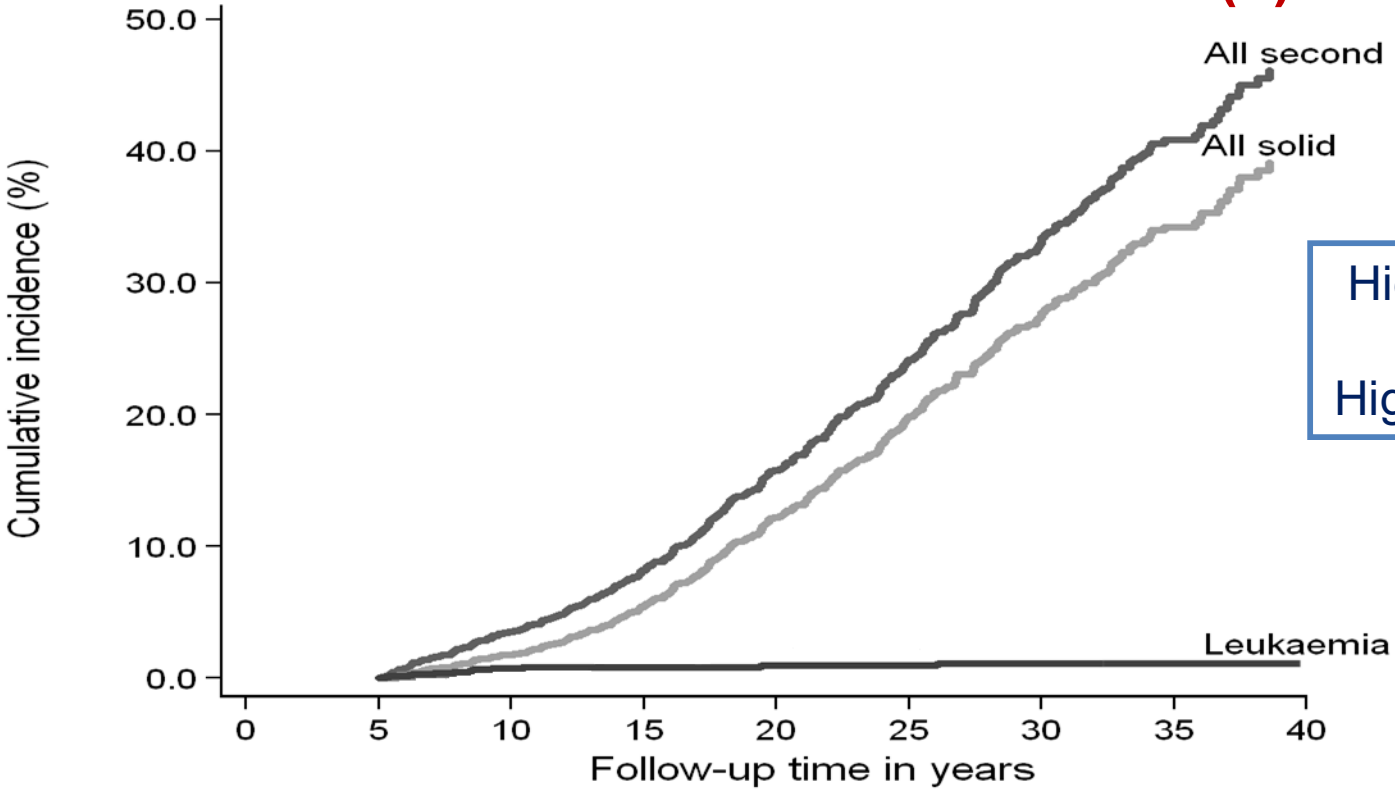
Cumulative incidence of second malignancies, in the presence of competing risks, Dutch HL cohort 1965-2000 (2)



High relative risk
≠
High absolute risk

40-year risk of breast cancer = 22%

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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 second cancers contribute most to SC burden

Large absolute excess risk for solid cancers

SIRs and AERs of second malignancy, Dutch HL cohort; 3,905 5-yr survivors, 15-50 yr at dx, 1965-2000

Cancer site	SCs	SIR	AER/10,000
All Malignancies	**884**	**4.6**	**121.8**
Oral cavity/pharynx	20	3.2	2.3
Esophagus	38	9.5	5.6
Stomach	39	7.4	5.6
Colon	42	2.9	4.6
Rectum & Rectosigmoid	25	2.6	2.6
Pancreas	23	5.7	3.1
Lung & Bronchus	176	**6.4**	**24.6**
Pleura	17	15.1	2.6
Female breast	183	**4.7**	**54.3**
Melanoma	34	2.8	3.6
Bladder	22	4.1	2.8
Thyroid	23	**14.0**	**3.5**
Soft tissue sarcoma	22	**12.0**	**3.3**
Leukemia	41	**9.5**	**6.1**

AER= absolute excess number of cases per 10,000 patients/yr

Risk of second cancer after testicular cancer
Dutch nationwide testicular cancer cohort

- 5,848 1-year survivors
- Treated 1976-2007
- Median follow up: 14 years
- 50% seminoma, 50% non-seminoma
- **82% of seminoma patients received RT**
- 58% of non-seminoma patients received platinum-based chemotherapy
- 38% of non-seminoma patients had orchidectomy alone

H. Groot, *JCO* 2018;36(24):2504-2513

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Standardized incidence ratios for second malignancies after testicular cancer

Seminoma (N=2,827)

Cancer site	Observed	SIR	95%CI
Any solid SMN	180	**1.5**	(1.3-1.8)
Lung	22	**1.0**	(0.7-1.6)
Gastrointestinal tract	52	**1.9**	(1.4-2.4)
- Stomach	7	**1.7**	(0.7-3.5)
- Colon	13	**1.3**	(0.7-2.1)
- Rectum	8	**1.0**	(0.4-2.0)
- Pancreas	14	**4.4**	(2.4-7.4)
Urinary tract	28	**2.7**	(1.8-3.9)
- Kidney	10	**2.1**	(1.0-3.8)
- Bladder	17	**3.4**	(2.0-5.4)
- Prostate	26	**1.2**	(0.8-1.8)
Melanoma	15	**1.8**	(1.0-2.9)

H. Groot, *JCO* 2018;36(24):2504-2513

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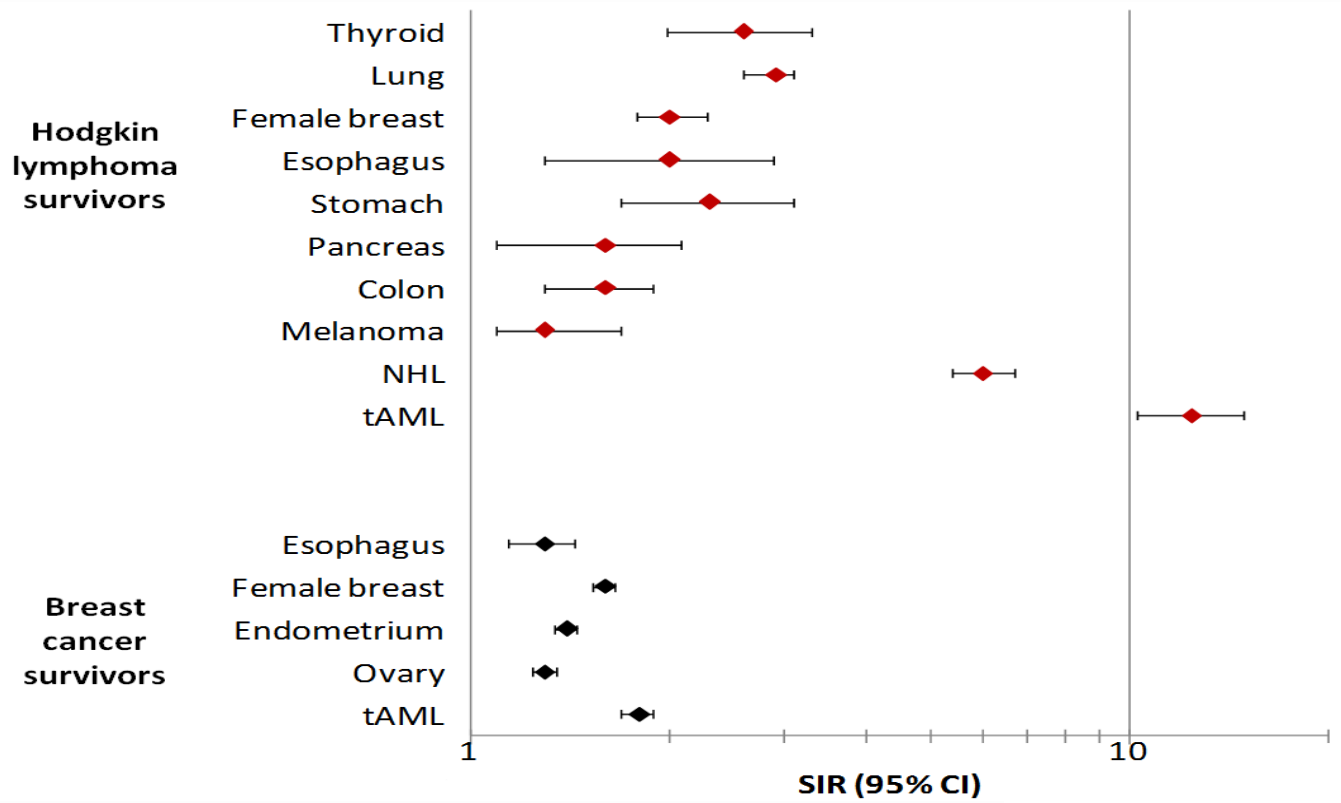
Risks for selected SMNs after Hodgkin lymphoma and breast cancer *(SEER 1975-2010)*



Morton et al. *ASCO ed book 2014*

Risk of second malignancy in Dutch childhood cancer survivors (DCOG-LATER cohort)

6,665 5-yr survivors 1963-2001, median follow-up 21 yrs

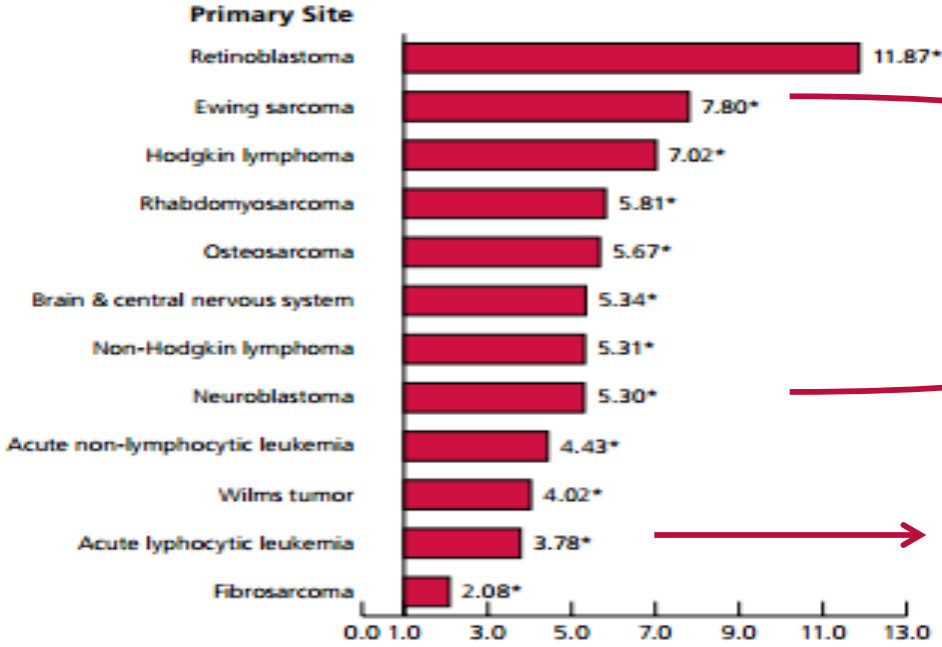
Sec. Malign. Neopl.	Obs.	SIR (95% CI)	AER/10,000 PY
All SMNs	**261**	**5.2 (4.6-5.8)**	**20.3**
Leukemia	17	**6.1** (3.6-9.8)	1.3
All solid	230	**5.5** (4.8-6.2)	18.1
Breast	45	**5.1** (3.8-6.9)	7.6
Bone	21	**17.1** (10.6-26.1)	1.9
Soft tissue	24	**19.3** (12.4-28.7)	2.2
CNS	24	**8.5** (5.4-12.6)	2.0
Thyroid	25	**17.1** (11.1-25.3)	2.2
Digestive tract	17	**4.1** (2.4-6.6)	1.2
Lung	8	**4.3** (1.9-8.5)	0.6

SIR: Standardized Incidence Ratio, AER: Absolute Excess Risk

Teepen et al. *J Clin Oncol* 35:2288-2298, 2017

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



Retinoblastoma: 11.9*

Hodgkin lymphoma, sarcoma, CNS, NHL, neuroblastoma 5 - 8*

Acute Lymphoblastic Leukemia (ALL): 3.8*

Source: SEER 1973-2010

American Cancer Society

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- Modifying factors of radiation-associated risk (age, chemotherapy)
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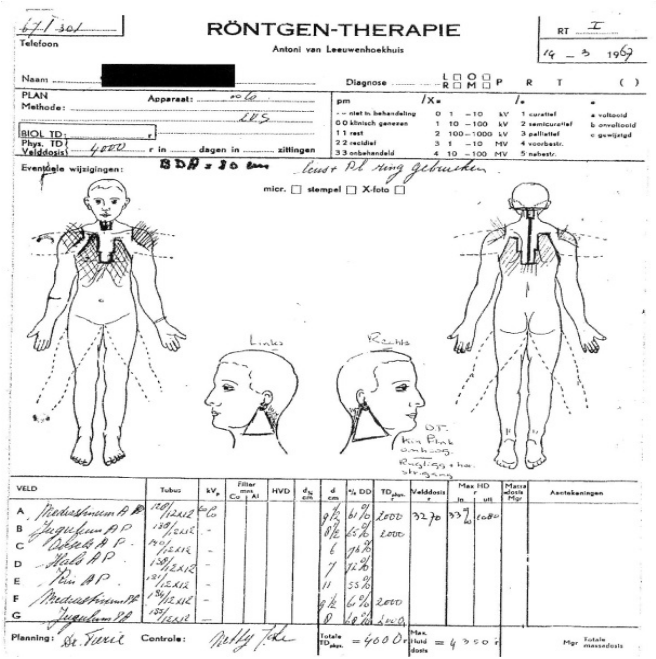
Radiation dose – response for second cancer risk

Linear increase with higher dose for:

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



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

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

Radiation dose – response for second cancer risk

Linear increase with higher dose for:

- Breast cancer
- Lung cancer
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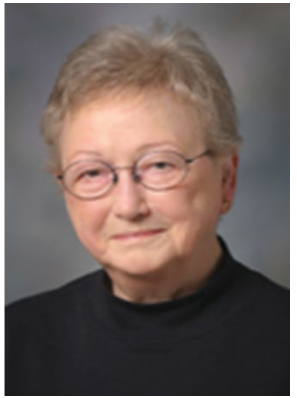
- Meningioma

Individual radiation dosimetry



Marilyn Stovall,
MD Anderson Houston

For leukemia decreasing risk after 4 Gy
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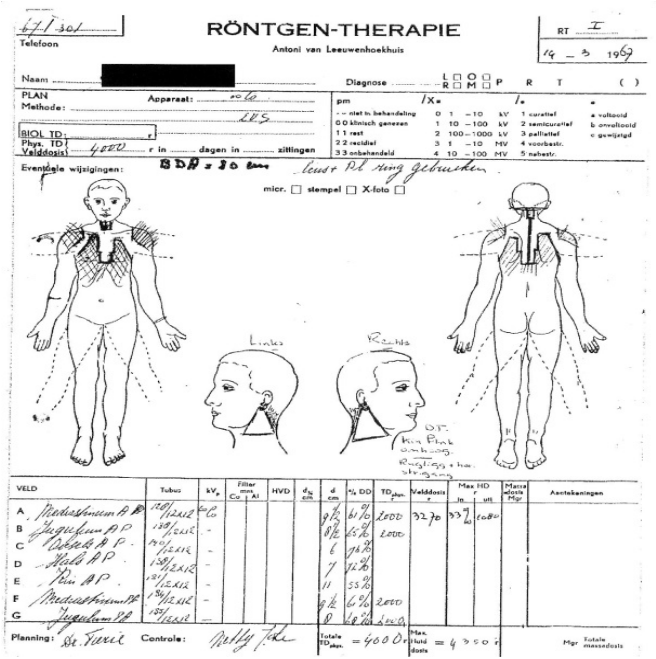
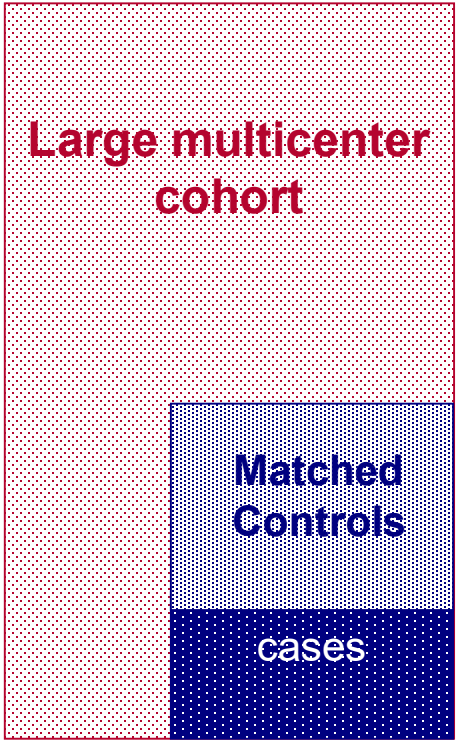


For leukemia decreasing risk after 4 Gy
For thyroid cancer decreasing risk after 20-30 Gy

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)



Inskip et al, *JCO* 2009, Van Leeuwen *JNCI* 2003, Travis *JAMA* 2003

Radiation dose ⟹ Breast cancer risk

- International NCI-coordinated nested case-control study, 105 cases with breast cancer after HL, 266 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 0.05 – 0.15

Travis *JAMA* 2003; 290:465

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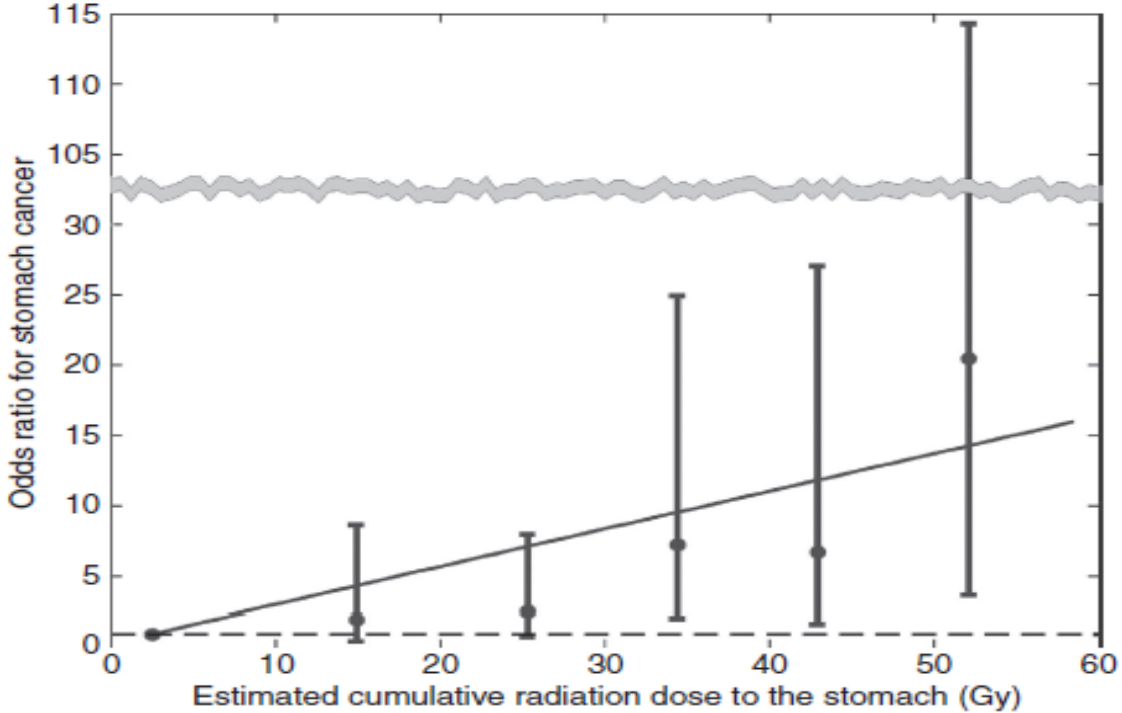
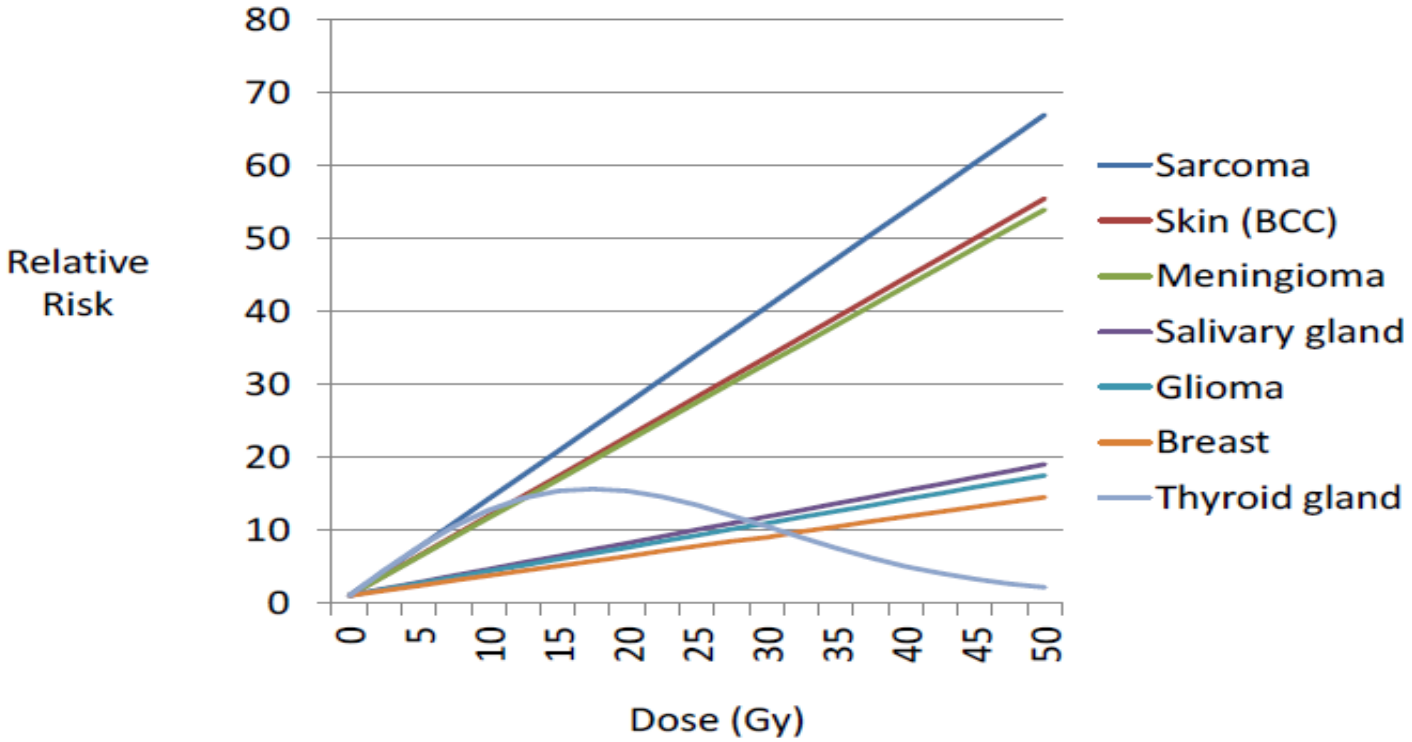
Radiation dose–response relationship for stomach cancer following testicular cancer based on 92 cases and 180 controls

An international NCI-coordinated case-control study



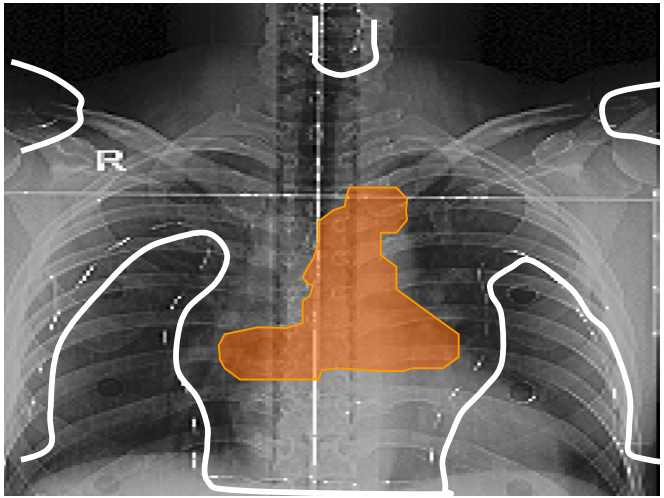
Hauptmann M *Br J Cancer*. 2015;112(1):44-51.

Fitted radiation dose-response by type of second cancer, based on previous CCSS reports

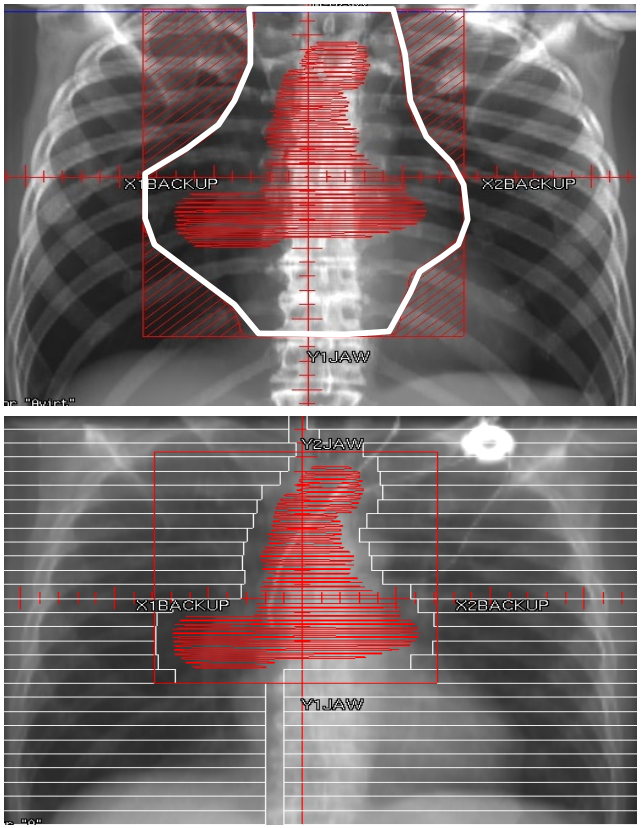


Turcotte et al. *J Clin Oncol.*, 2018

Changes in Hodgkin RT volumes



Mantle field radiotherapy
till late 1980s



EORTC
H9
Involved Field
Radiotherapy
From 1985

EORTC
H10
Involved Node
Radiotherapy
After 2000

Courtesy: R vd Maazen Radboud
University Nijmegen Medical Center

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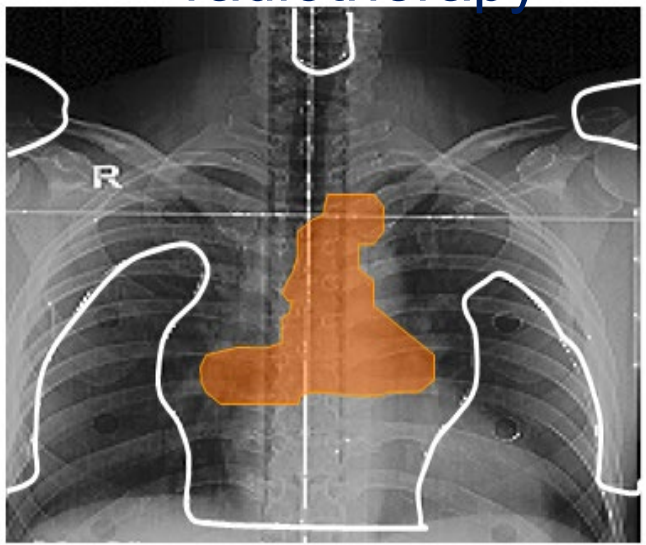
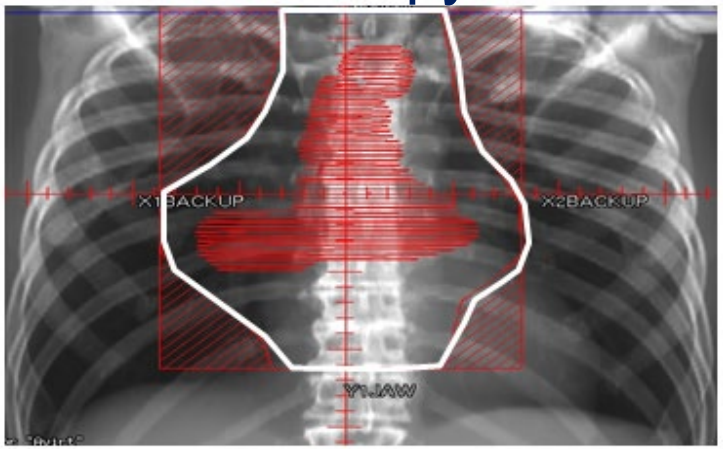
Lower risk with smaller radiation volumes

Mantle field radiotherapy



Involved Field Radiotherapy



60% reduction of breast cancer risk

De Bruin et al. *JCO* 2009; 27(26): 4239-4246

Schaapveld M et al. *NEJM* 2015;373(26):2499

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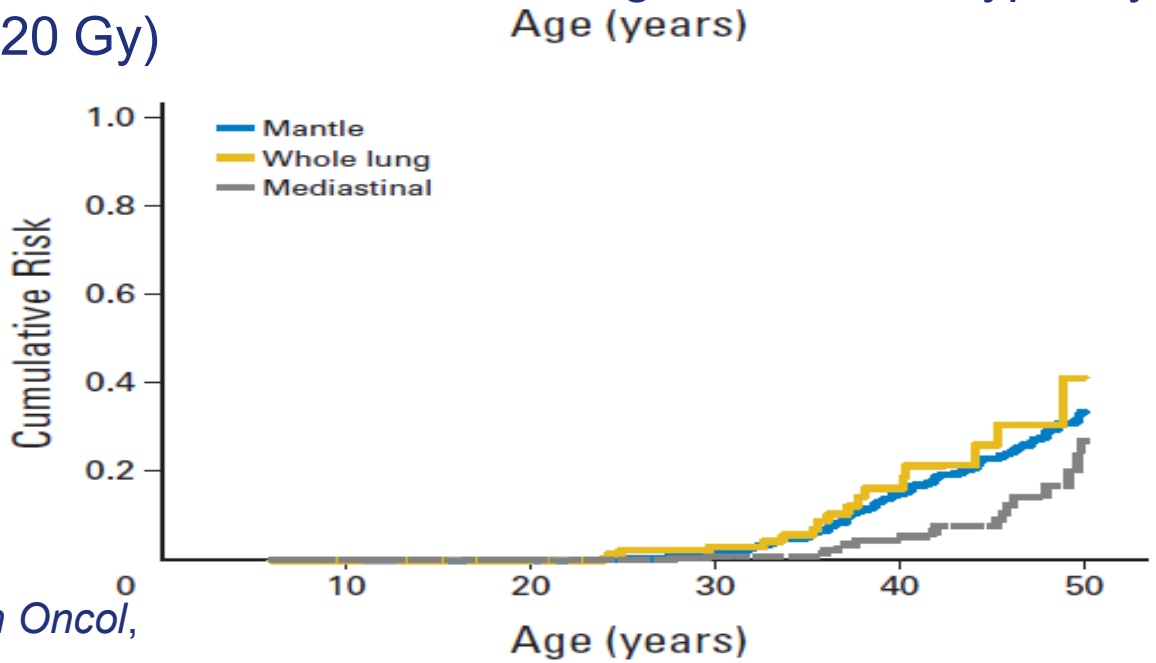
Breast cancer after childhood cancer: Role of irradiated breast volume

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

Separate and joint effects of RT dose and volume

What is worse:

- A lot (of dose) to a little (volume)
- A little (dose) to a lot (of volume)
- Dose-volume parameters
  V40 = part of organ that received 40 Gy or more

Which part of second cancers can be attributed to radiotherapy?

- Cohort study in SEER cancer registries
- 647,672 5-yr survivors, ≥ 20 yr at diagnosis (1973-2002)
- Mean follow-up 12 yrs
- 60,271 (9%) with second solid tumor

- **~ 8% of all solid tumors (~3.266) in irradiated patients attributable to RT**

- % differs with tumor type

Berrington de Gonzalez et al. *Lancet Oncology* 2011

	Number of second solid cancers in patients treated with radiotherapy*	Number of patients	Excess cancers (95% CI)†	Attributable risk (95% CI)
Oral/pharynx	3683	24 880	182 (53 to 310)	5% (1 to 8)
Salivary gland‡	309	3007	37 (1 to 71)	12% (0 to 23)
Rectum‡	1568	21 841	112 (41 to 184)	7% (3 to 12)
Anus	323	3444	32 (−14 to 74)	10% (−4 to 23)
Larynx	3583	17 070	193 (32 to 350)	5% (1 to 10)
Lung (non-small cell)	2395	51 270	152 (82 to 223)	6% (3 to 9)
Soft tissue (non-limbs)	120	1602	18 (−2 to 39)	15% (−2 to 32)
Female breast	12 450	150 661	660 (454 to 866)	5% (4 to 7) → 5%
Cervix‡	1289	14 685	214 (130 to 295)	17% (10 to 23)
Endometrium‡	3269	29 338	286 (165 to 407)	9% (5 to 12)
Prostate‡	11 292	128 582	1131 (956 to 1307)	10% (8 to 12)
Testes (seminomas)	628	7862	150 (56 to 233)	24% (9 to 37) → 24%
Eye and orbit	112	1085	4 (−12 to 22)	4% (−11 to 20)
Brain/CNS	314	13 220	28 (−11 to 66)	9% (−3 to 21)
Thyroid‡	959	16 934	67 (6 to 128)	7% (1 to 13)
Total	42 294	485 481	3266 (2862 to 3670)	8% (7 to 9)

*In all patients (defined as ≥1 year survivors). †Estimated in 5 year or longer survivors calculated with the results from the Poisson regression model (figure 1). ‡Second cancers of the same site were excluded because standard treatment usually involves surgical removal of the affected organ or because of second cancer coding rules (prostate).

Table 4: Estimated number of excess second solid cancers related to radiotherapy treatment and attributable risk in those treated with radiotherapy by first cancer site

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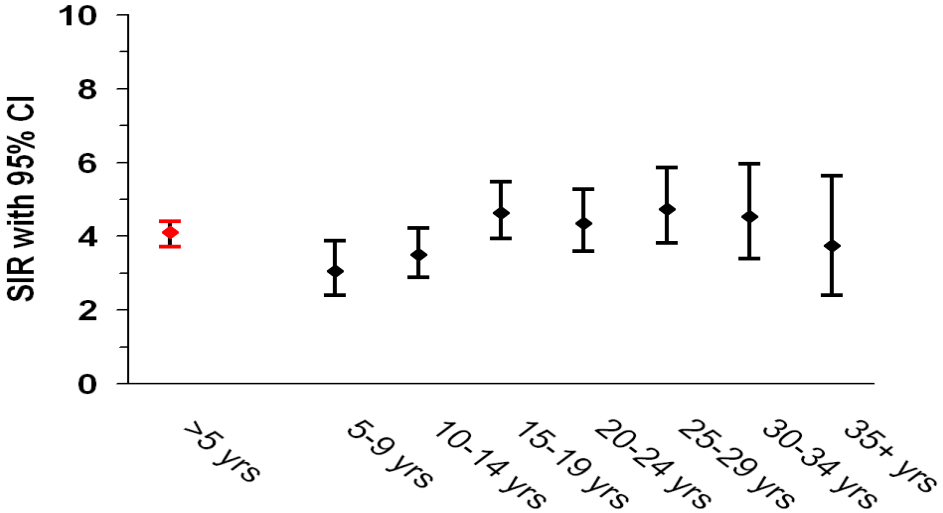
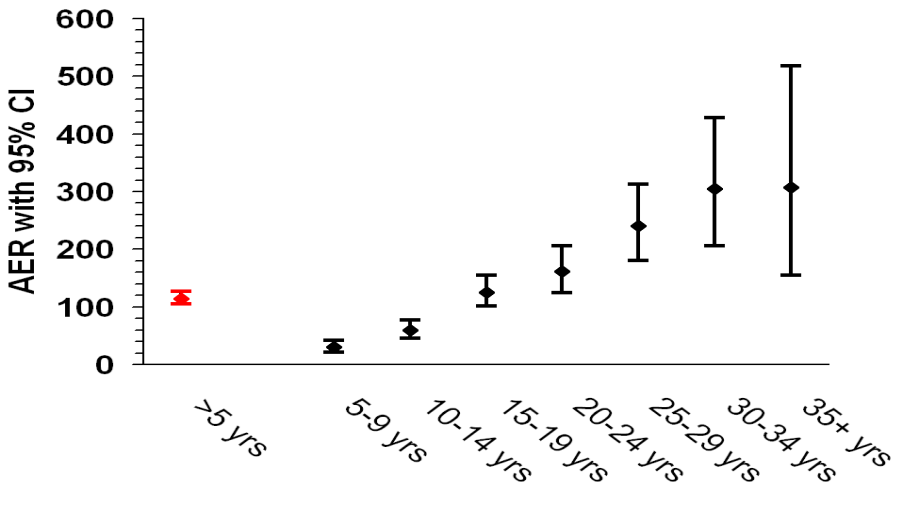
Solid cancer risk increased for >35 yrs
Dutch Hodgkin cohort (n=3940, 1965-2000)





AER per 10,000 patients/yrs

Schaapveld M et al.*NEJM* 2015;373(26):2499

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- **Mean follow-up only 12 yrs!!**
- 60,271 (9%) with second solid tumor

- **~ 8% of all solid tumors (~3.266) in irradiated patients attributable to RT**

- **overall estimate 15-25%**
- **% differs with tumor type: 40-50% for long-term Hodgkin survivors,**

Berrington de Gonzalez et al. *Lancet Oncology* 2011

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Cancer Risks from Conventional Radiotherapy

- Introduction on second malignancy
- Magnitude of risks for various *second* malignancies after selected *first* primary malignancies
- Radiotherapy, dose and volume
- **Modifying factors of radiation-associated risk**
- Clinical implications

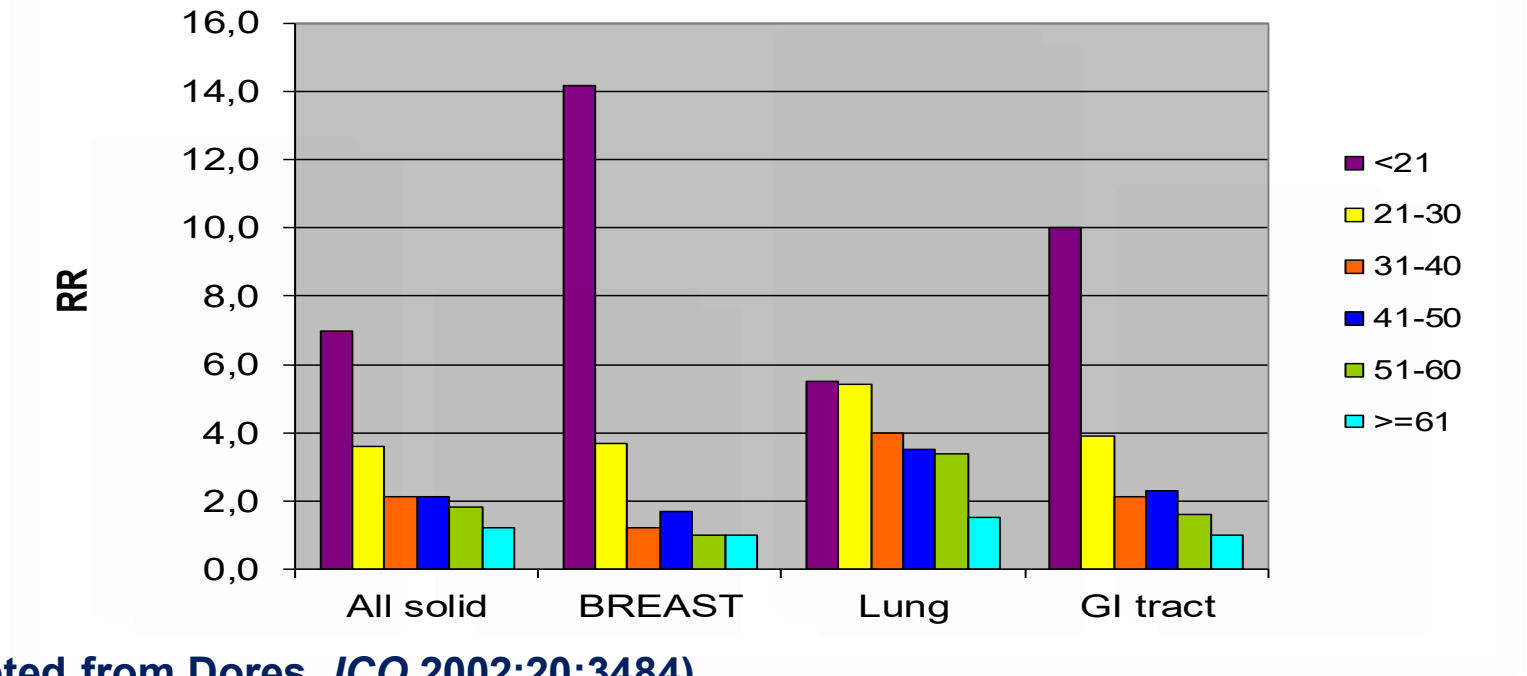
Potential modifiers of radiation-associated risk

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

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

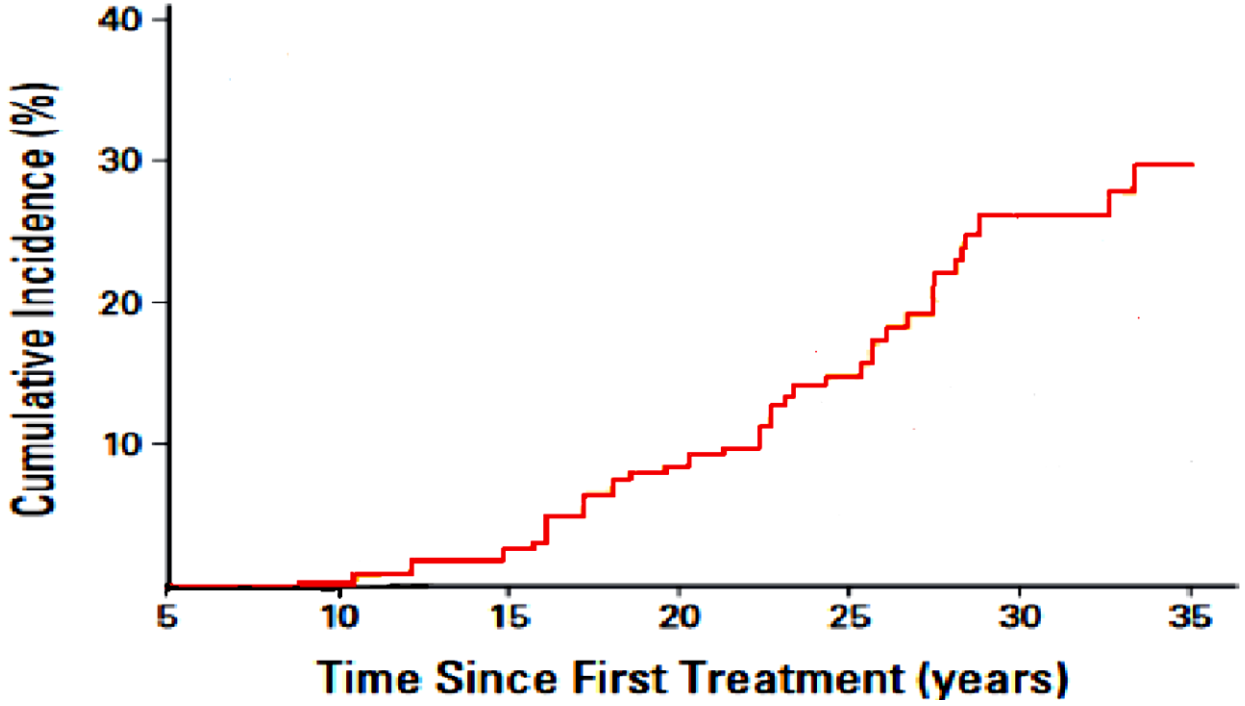
International cohort study: 32,591 HL patients

1,111 25-year survivors, population-based



(Adapted from Dores *JCO* 2002;20:3484)

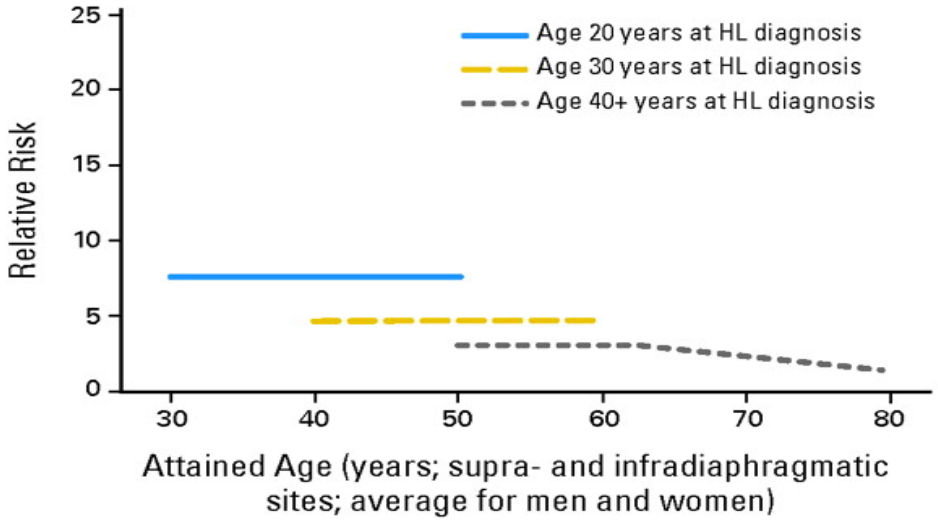
Cumulative incidence of breast cancer after HL
5-yr survivors treated before age 21

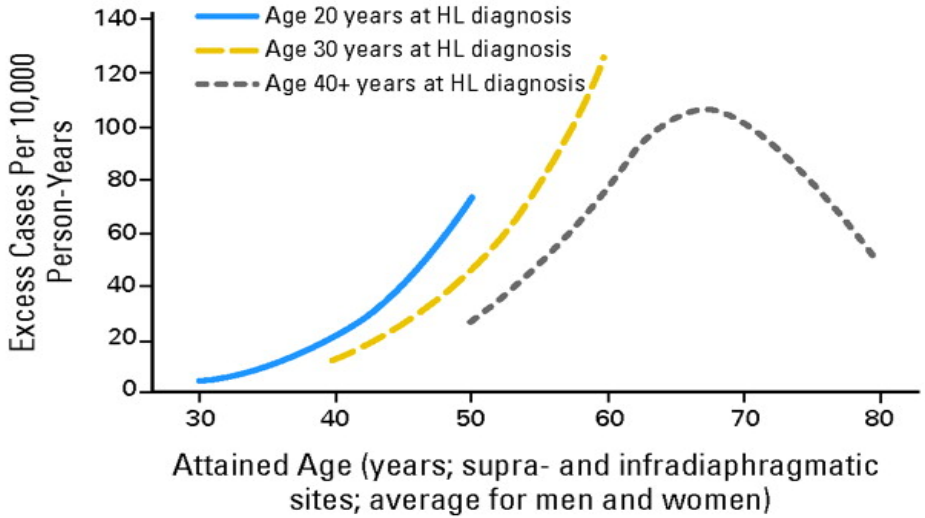


Comparable to risk in BRCA 1 carriers

De Bruin et al. *JCO* 2009; 27(26): 4239-4246. Similar estimates in Swerdlow et al. *JCO* 2012;30(22):2745-2752, Schaapveld *NEJM* 2015; 373(26): 2499-2511, Moskowitz et al. *JCO* 2014

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



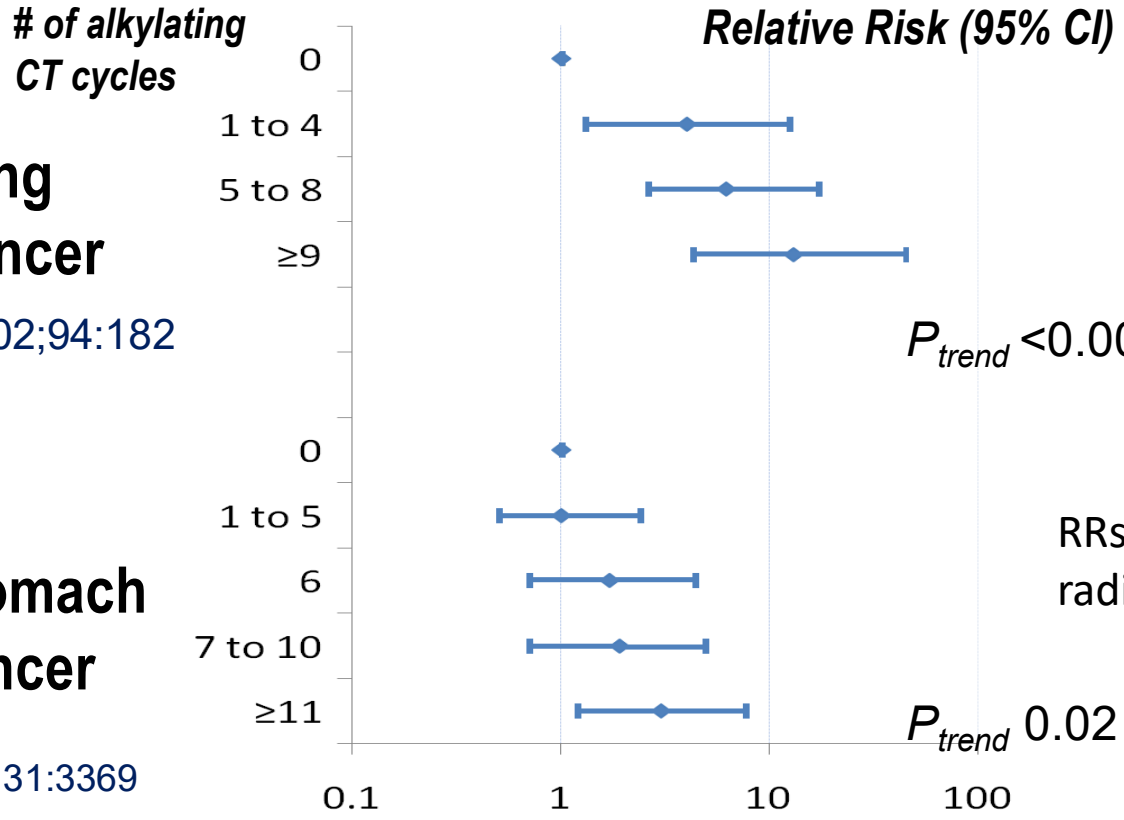


Hodgson et al. *J Clin Oncol* 2007; 25(12): 1489-1497

Potential modifiers of radiation-associated risk (2)

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

Some chemotherapy regimens also increase solid cancer risk after Hodgkin lymphoma



Travis et al. JNCI 2002;94:182

RRs adjusted for radiation dose

Morton et al. *JCO* 2013;31:3369

Risk of stomach cancer after HL according to procarbazine dose

An international NCI-coordinated case-control study

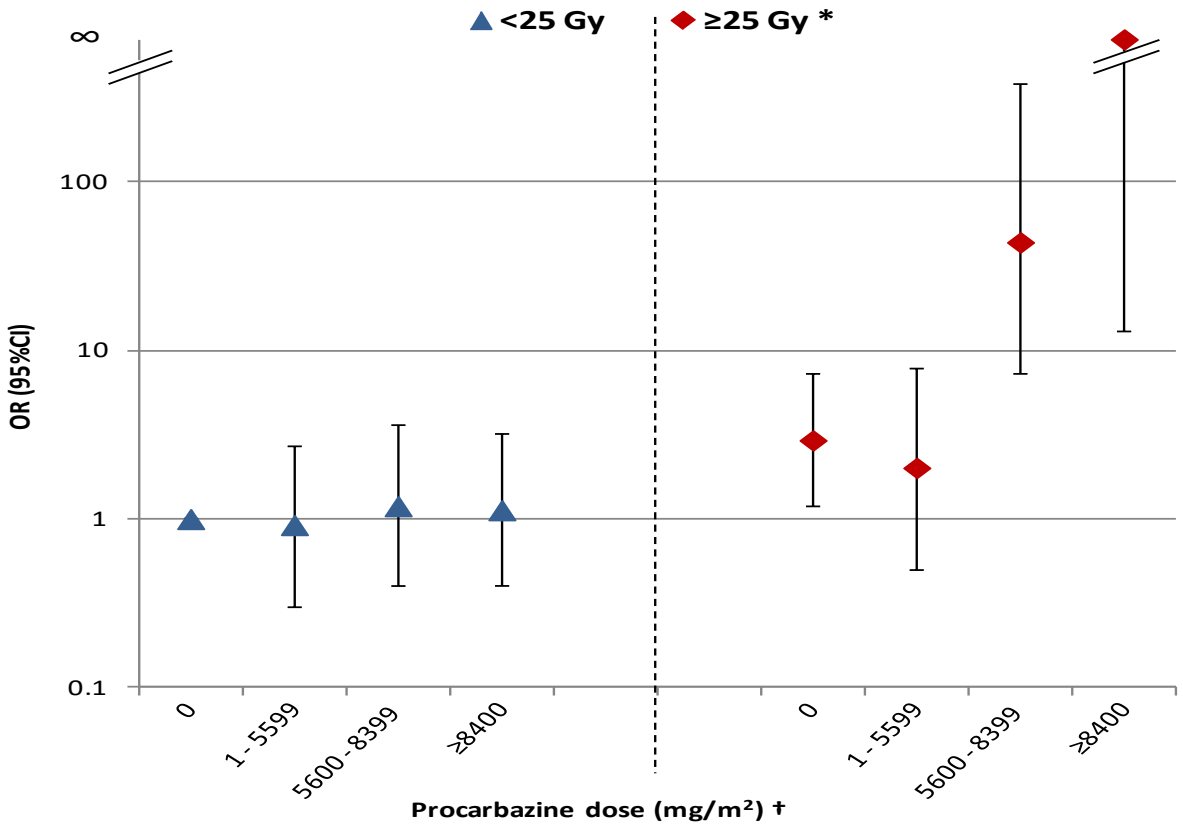
Dose (mg/m²)	**Cases**	**Controls**	**Mean**	**OR*** (95% CI)
0	37	103	0.0	**1.0** (referent)
1-5599	12	39	3403	**0.8** (0.3-1.9)
5600-8399	22	29	6938	**2.9** (1.2-7.0)
≥8400	18	19	12,316	**2.3** (1.0-5.5)

$P_{trend} = 0.009$

* Adjusted for radiation dose and other alkylating agents.

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

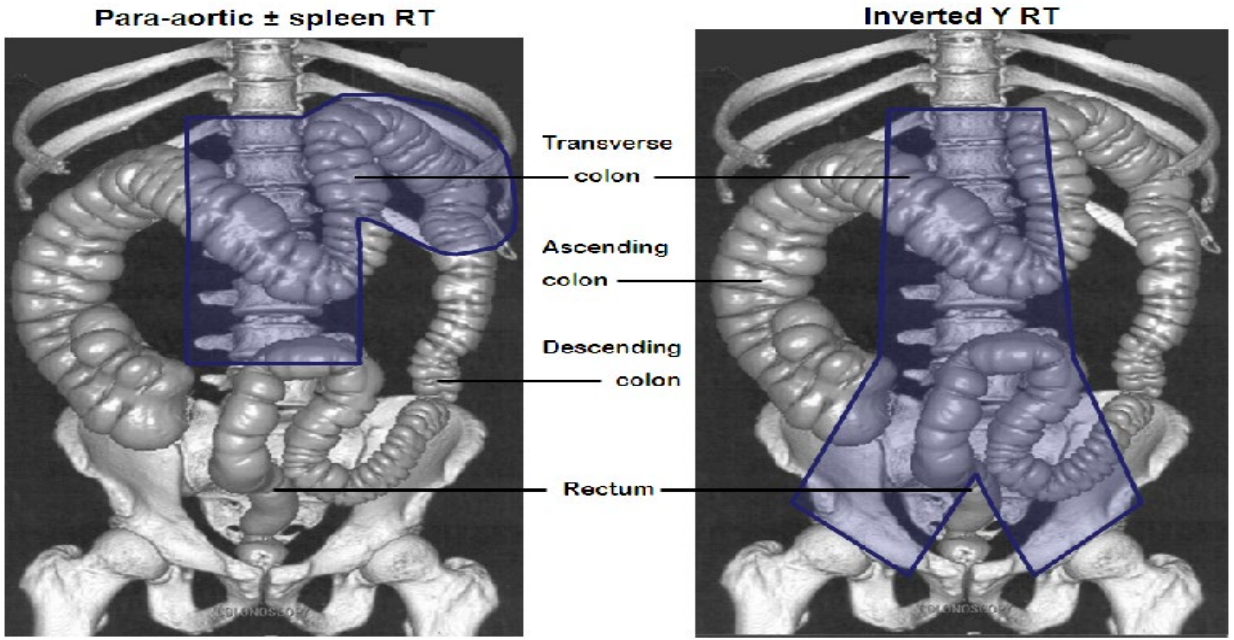
Stomach cancer after HL: interaction between radiation dose and procarbazine



Morton et al., *JCO*, 2013 Sep 20;31(27):3

Colorectal cancer risk in HL patients

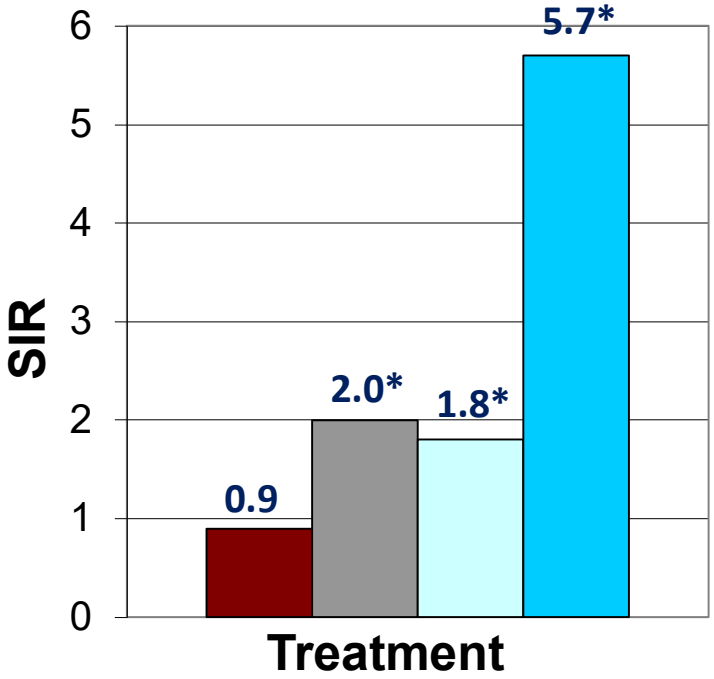
- Radiotherapy



- Chemotherapy (procarbazine)

Anja M. van Eggermond, *Br J Cancer* 2017

Risk of colorectal cancer by HL treatment



Supra RT only

Supra RT + CT

Infra RT (+/- supra RT), no CT

Infra RT (+/- supra RT) + CT

Supra = supradiaphragmatic,
Infra = infradiaphragmatic

Higher risks for cancers in transverse colon!

Anja M. van Eggermond, *Br J Cancer* 2017

*** P < 0.05**

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.

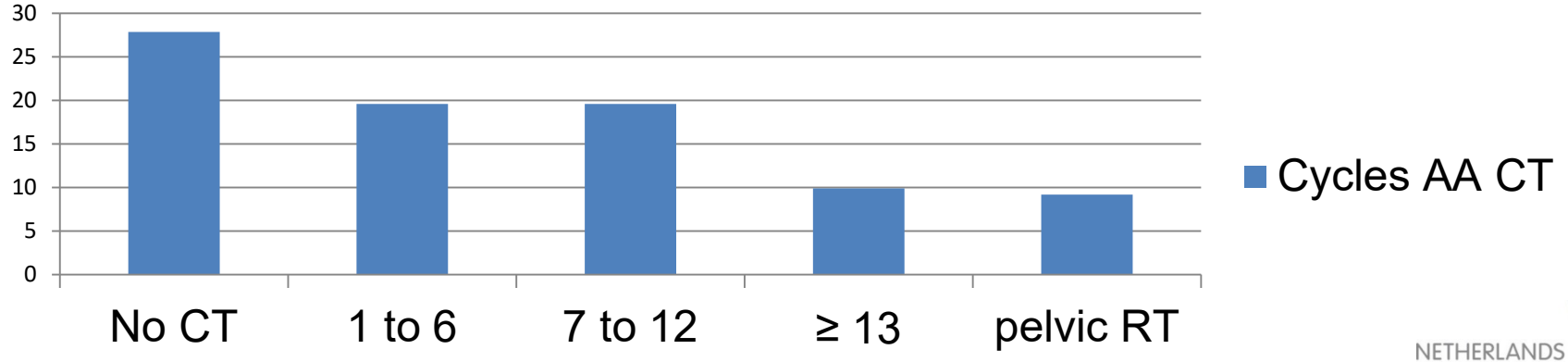
Potential modifiers of radiation-associated risk (3)

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

Reduced risk of RT-induced breast cancer after alkylating chemotherapy or pelvic RT

- Van Leeuwen et al. *JNCI* 2003; 95(13):971-89
- Travis et al. *JAMA* 2003; 290(4):465-75
- De Bruin et al. *JCO* 2009; 27(26):4239-46
- Swerdlow et al. *JCO* 2012; 30(22):2745-52
- Schaapveld et al. *NEJM* 2015; 373(26):2499-511

40-yr cumulative risk of breast cancer after chest RT by no. of cycles of alkylating CT



Swerdlow et al. *JCO* 2012; 30(22):2745-52

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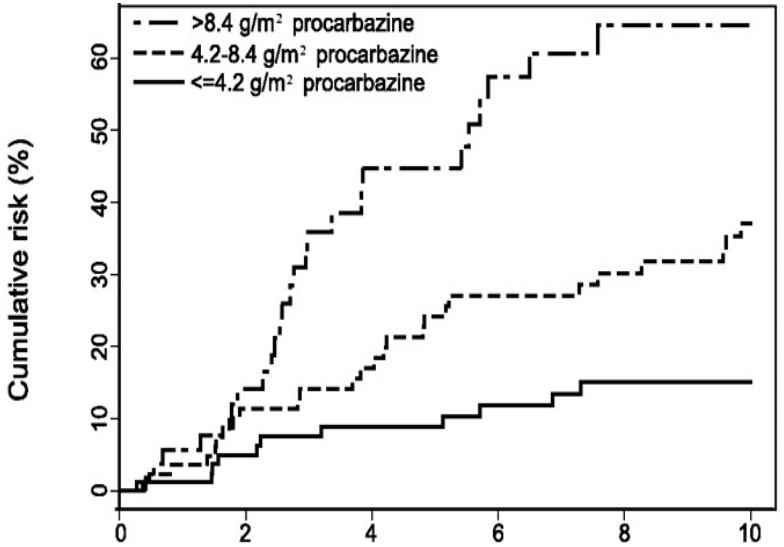
Cumulative risk of premature menopause (< 40 yrs) by cumulative procarbazine dose in HL survivors

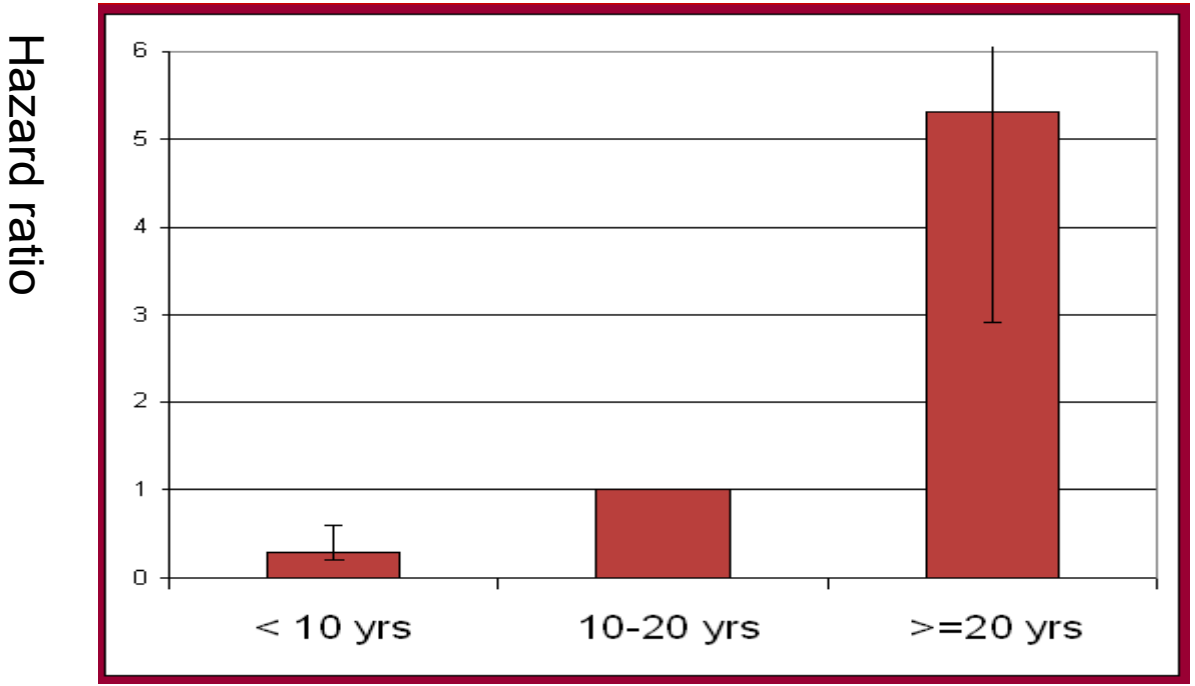


Numbers at risk	Time since first treatment (years)						Cumulative risk 10 years after treatment
<=4.2 g/m² procarbazine (n=85)	85	76	66	58	51	41	15% [6-23%]
4.2-8.4 g/m² procarbazine (n=86)	86	68	59	51	44	36	37% [24-48%]
>8.4 g/m² procarbazine (n=55)	55	39	19	14	9	7	65% [44-78%]

De Bruin et al. *Blood 2008;111:101*

Modifiers of RT-induced cancers

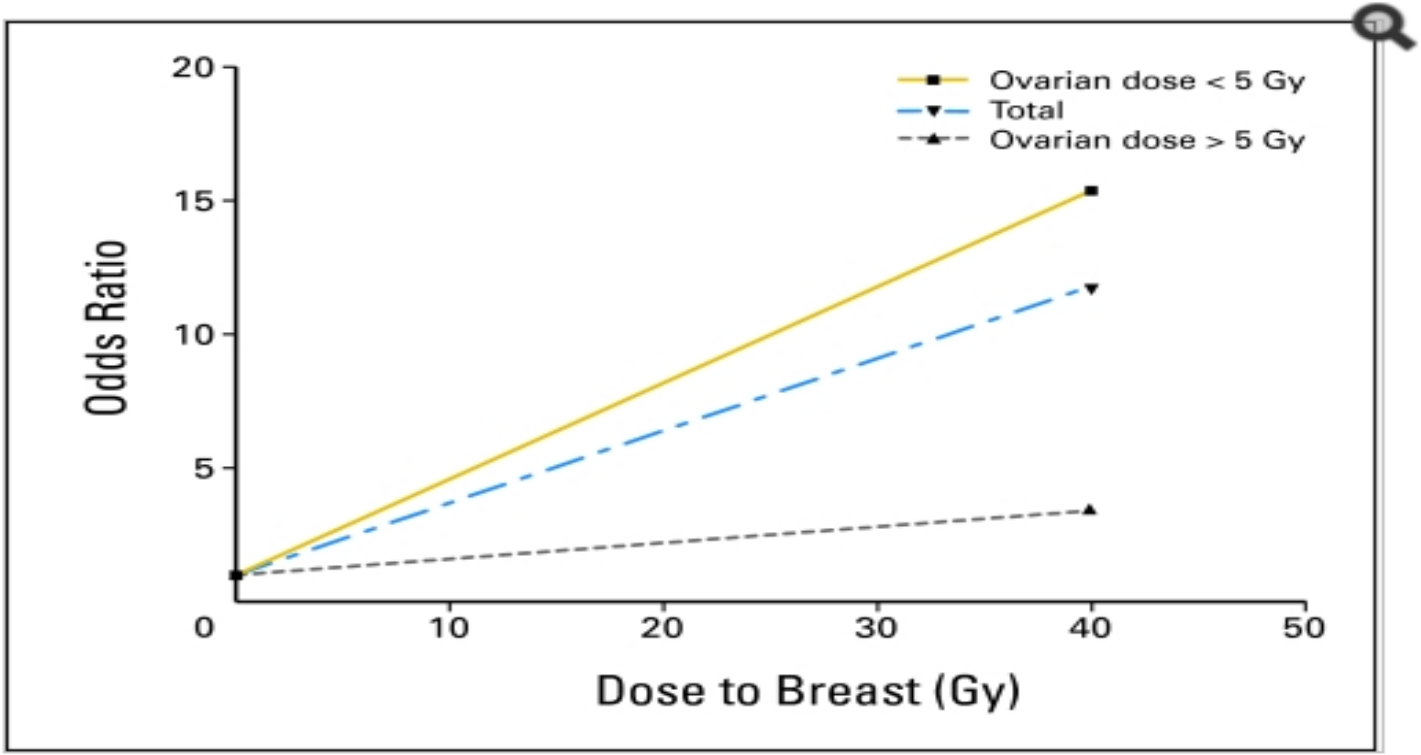
Risk of breast cancer after RT for HL, by duration of ovarian function after RT



Ovarian hormones crucial in radiation-induced breast carcinogenesis

De Bruin M, *JCO* 2009; 27(26): 4239-4246; Krul I, *Int J Rad Onc Biol Phys* 2017

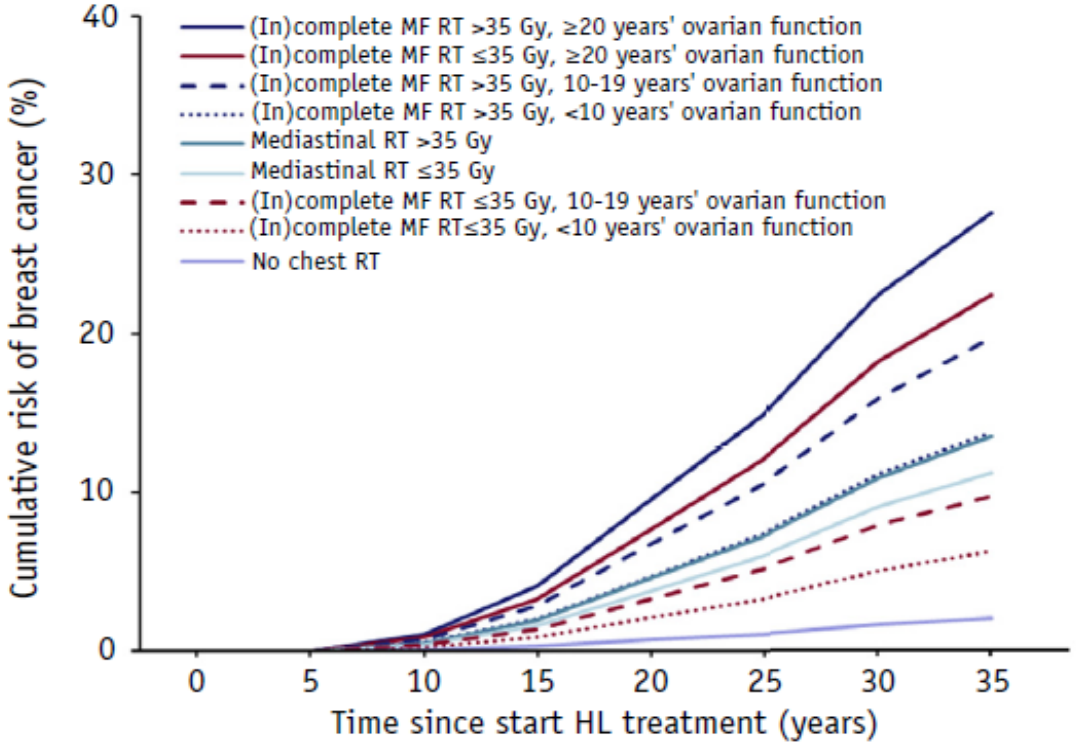
Breast cancer risk after childhood cancer according to radiation dose to breast and ovarian radiation



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

Cumulative incidence of breast cancer in HL survivors according to RT field, prescribed dose, and duration of post-RT intact ovarian function.

MF = mantle field
RT = radiation therapy



Krul IM, *Int J Radiat Oncol Biol Phys*. 2017;99(4):843.

➡ ***Ovarian hormones, RT dose and volume equally important***

Lung cancer after HL
Joint effects of smoking and treatment

Risks from smoking multiply risks from RT and CT

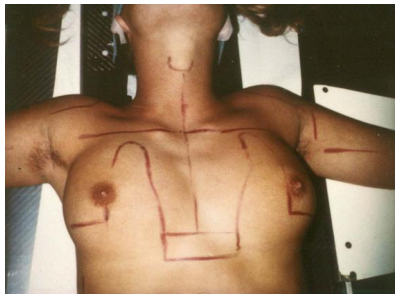
	RR non/light smokers	RR smokers
No RT (< 5 Gy), no CT	1.0 (ref)	6.0 (1.9-20.4)
RT (≥ 5 Gy), no CT	7.2 (2.9-21.2)	20.2 (6.8-68)
No RT (< 5 Gy), CT	4.3 (1.8-11.7)	16.8 (6.2-53)
RT (≥ 5 Gy), CT	7.2 (2.8-21.6)	49.1 (15.1-187)

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

Breast cancer after HL:
It's not just chest radiotherapy…

- High radiation dose
- Large irradiation volume
- Young age at treatment with RT
- Protective effect of premature menopause



Mantle field radiotherapy

About 60% of women who received high-dose chest RT (without gonadotoxic CT) do NOT develop breast cancer

Genetic susceptibility?

Genetic susceptibility for radiation-induced breast cancers?

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, Van Leeuwen FE et al., *Blood* 2012; 119(4): 1029-31

- Examined 14 breast cancer SNPs from general population
- 232 cases with breast cancer after HL, 461 controls
- OR of 1.59 (per allele) associated with FGFR2

OXFORD

JNCI J Natl Cancer Inst (2017) 109(11): djx058

doi: 10.1093/jnci/djx058
First published online May 26, 2017
Article

ARTICLE

Genome-Wide Association Study to Identify Susceptibility Loci That Modify Radiation-Related Risk for Breast Cancer After Childhood Cancer

Lindsay M. Morton*, Joshua N. Sampson*, Gregory T. Armstrong*, Ting-Huei Chen, Melissa M. Hudson, Eric Karlins, Casey L. Dagnall, Shengchao Alfred Li, Carmen L. Wilson, Deo Kumar Srivastava, Wei Liu, Guolian Kang, Kevin C. Oeffinger, Tara O. Henderson, Chaya S. Moskowitz, Todd M. Gibson, Diana M. Merino†, Smita Bhatia‡, Stephen J. Chanock‡, Margaret A. Tucker‡, Leslie L. Robison‡

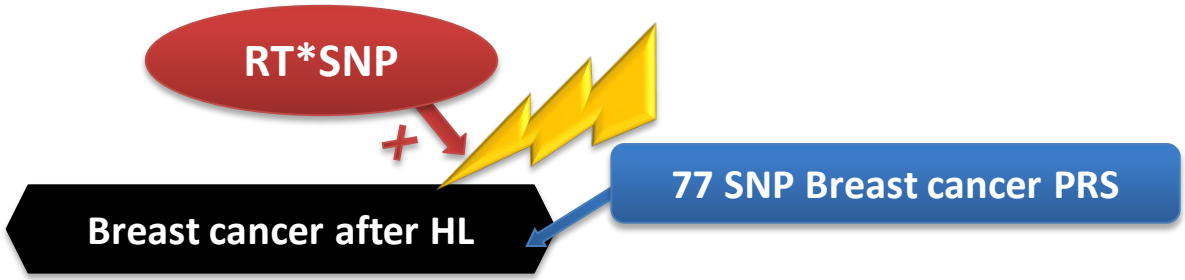
- GWAS of 207 patients with breast cancer after childhood cancer
- Comparison with 2274 CCS without second malignancy
- ~ 2-fold risk increase per allele for a genetic variant at 1q41 (nearest gene PROX1), only for survivors with ≥ 10Gy breast exposure

Morton et al. *J Natl Cancer Inst* 2017;109(11)

Dutch International Collaborative study: Genetic susceptibility for breast cancer after chest RT for Hodgkin lymphoma

Aim: To examine the influence of

- Genetic variants interacting with radiotherapy
- 77 genetic variants associated with breast cancer in the general population



Opstal-van Winden et al., *Blood* 2019

Dutch study: Genetic susceptibility for breast cancer after chest RT for Hodgkin lymphoma

- Based on 327 cases with breast cancer after chest RT for HL from Dutch and UK Hodgkin cohorts and U.S. Childhood Cancer Survivor study
- 4,671 first primary breast cancers from BCAC
- 491 patients with chest RT for Hodgkin who did not develop breast cancer

1. iCOGS SNP-array (211,000 SNPs) → 9 SNPs interacting with RT (False Discovery Rate <20%)
2. Polygenic Risk Score based on these 9 SNPs
3. Internal validation in case-control study

Opstal-van Winden et al., *Blood* 2019

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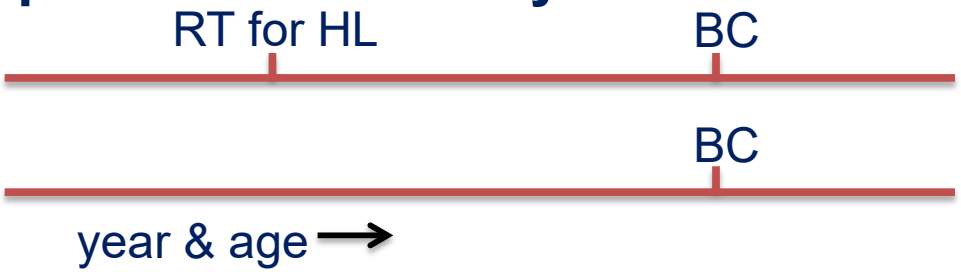
Study design

1st step: Case-Case study



327 BC following HL cases

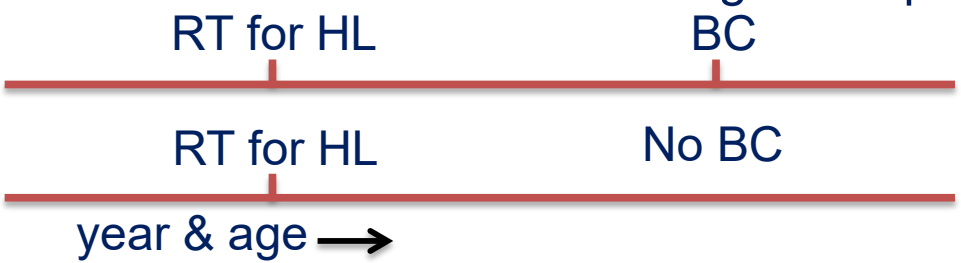
4,671 1st primary BC cases

2nd step: Case-Control study

– Compose Polygenic Risk Score (risk-weighted sum) of:

- 9 SNPs significantly interacting with RT (**RT-interaction PRS**)
- 77 SNPs associated with BC in general population* (**BC-PRS**)

Test difference between

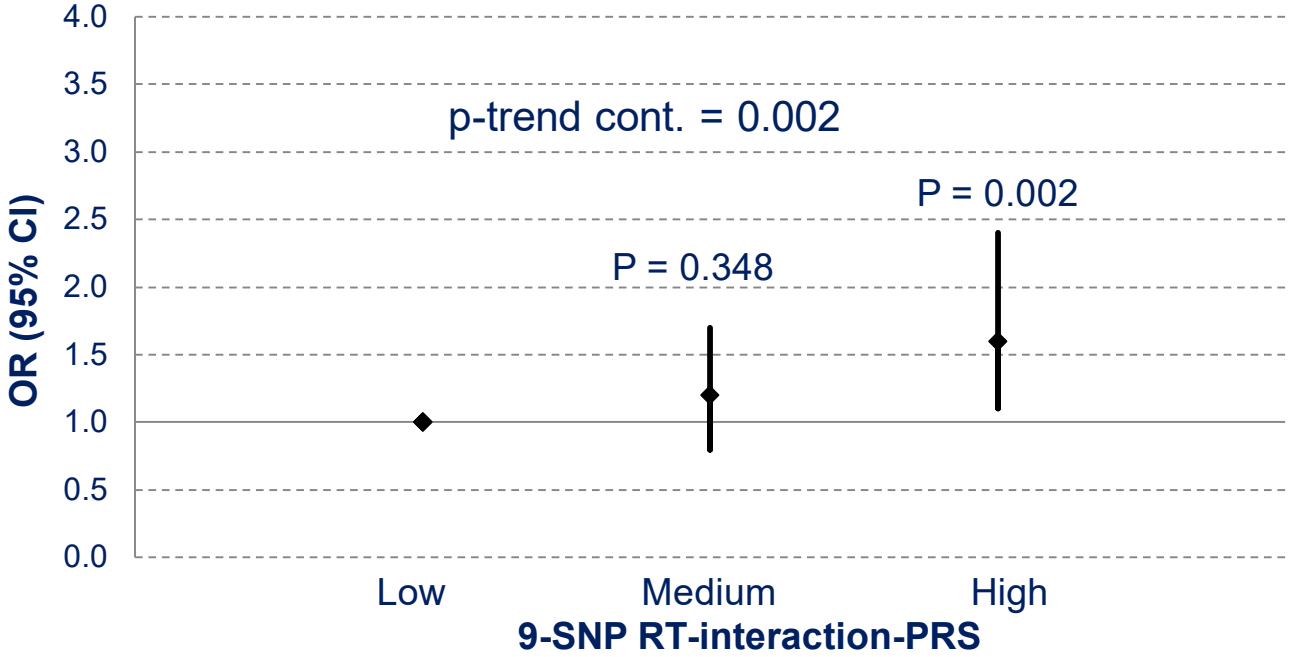


327 BC following HL cases

491 HL controls

Opstal-van Winden et al., *Blood* 2019

Risk of breast cancer after HL by RT-interaction Polygenic Risk Score



BC following HL cases, n (%)	94 (28.7)	105 (32.1)	128 (39.1)
HL controls, n(%)	168 (34.2)	176 (35.8)	147 (29.9)

Opstal-van Winden et al., *Blood* 2019

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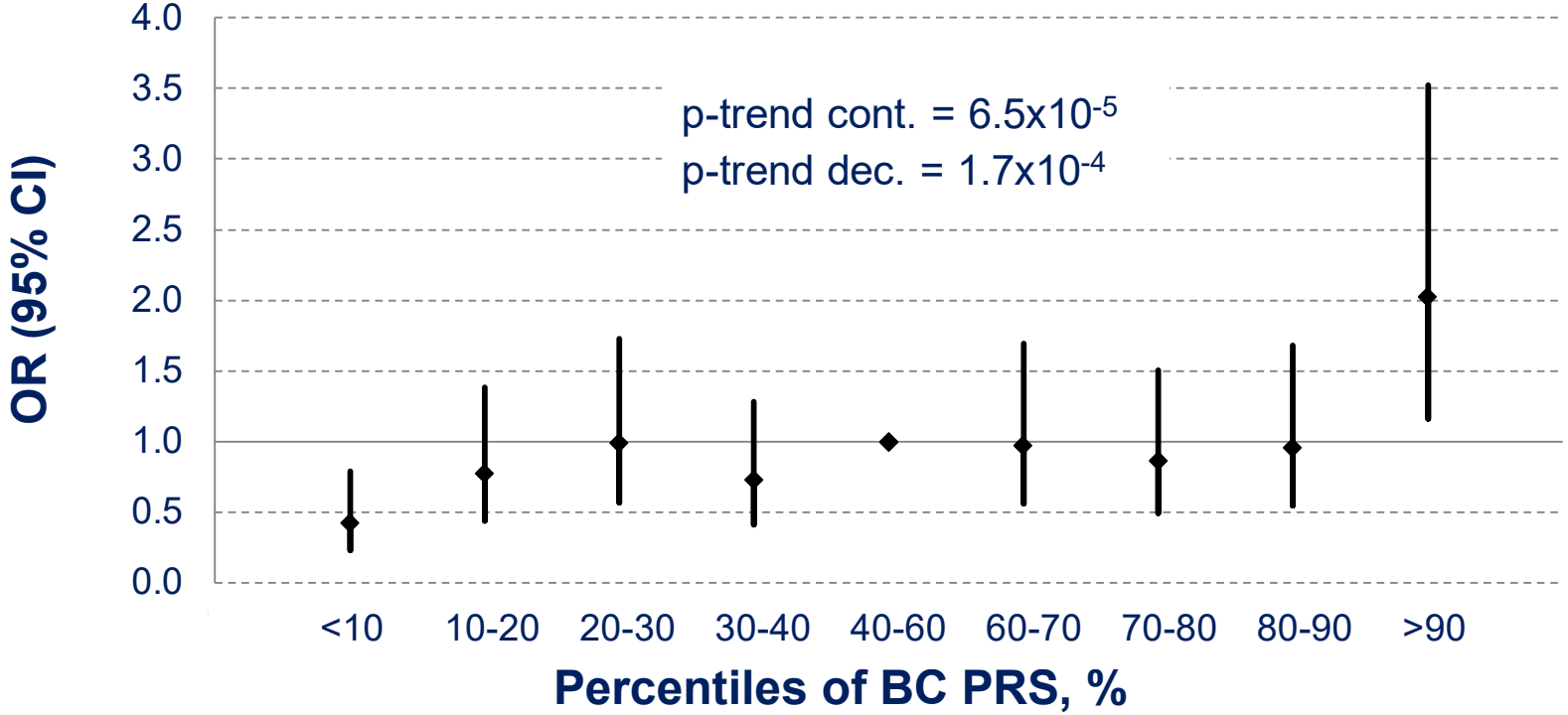
Risk for breast cancer after HL by 77 SNP BC Polygenic Risk Score based on general population data*



Significantly different risk for 20% of female HL survivors with extreme BC-PRS

Opstal-van Winden et al., *Blood* 2019

* Mavaddat et al. *JNCI* 2015

Conclusions genetic susceptibility for RT-induced breast cancer

Genetic susceptibility plays a role in RT-induced breast cancer
Independent effects of:

- PRS for breast cancer in the general population; implementation in risk prediction models for HL patients
- PRS based on 9 SNPs interacting with RT →
- Validation of RT-interaction PRS required: ***ongoing collaboration with NCI and Childhood Cancer Survivor Study: Lindsay Morton***

Summary of findings on second cancer risk

- **Lower risk after testicular and breast cancer than after HL and childhood cancer**
- **Solid cancer** risk after **radiotherapy** remains increased for >35 years
  - Higher risk with larger RT doses (linear dose-response) and volumes
  - Higher relative risk with treatment at younger age
- **Chemotherapy also affects second cancer risk and can modify radiation-associated risk**
  - *Procarbazine* ⟶ *GI tract cancers, lung cancer*
  - *Alkylating agents and anthracyclines* ⟶ *sarcoma*
- **Genes, hormones and lifestyle appear to modify RT-associated solid cancer risk**

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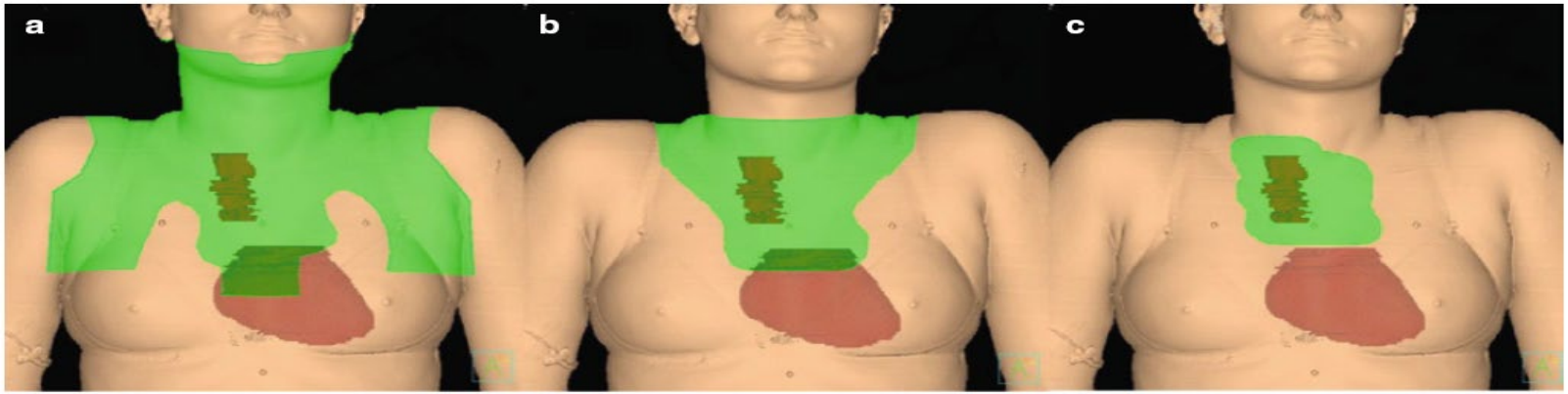
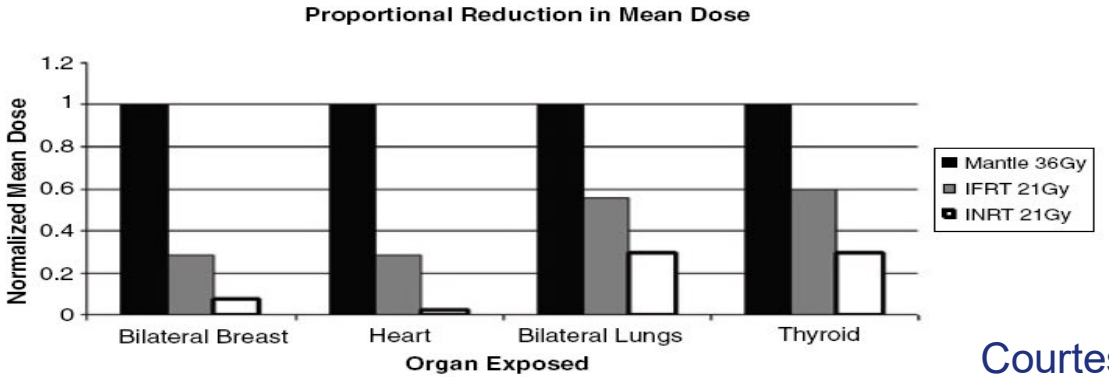
Implications of second cancer studies

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

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

Reduction of RT dose with modern treatments





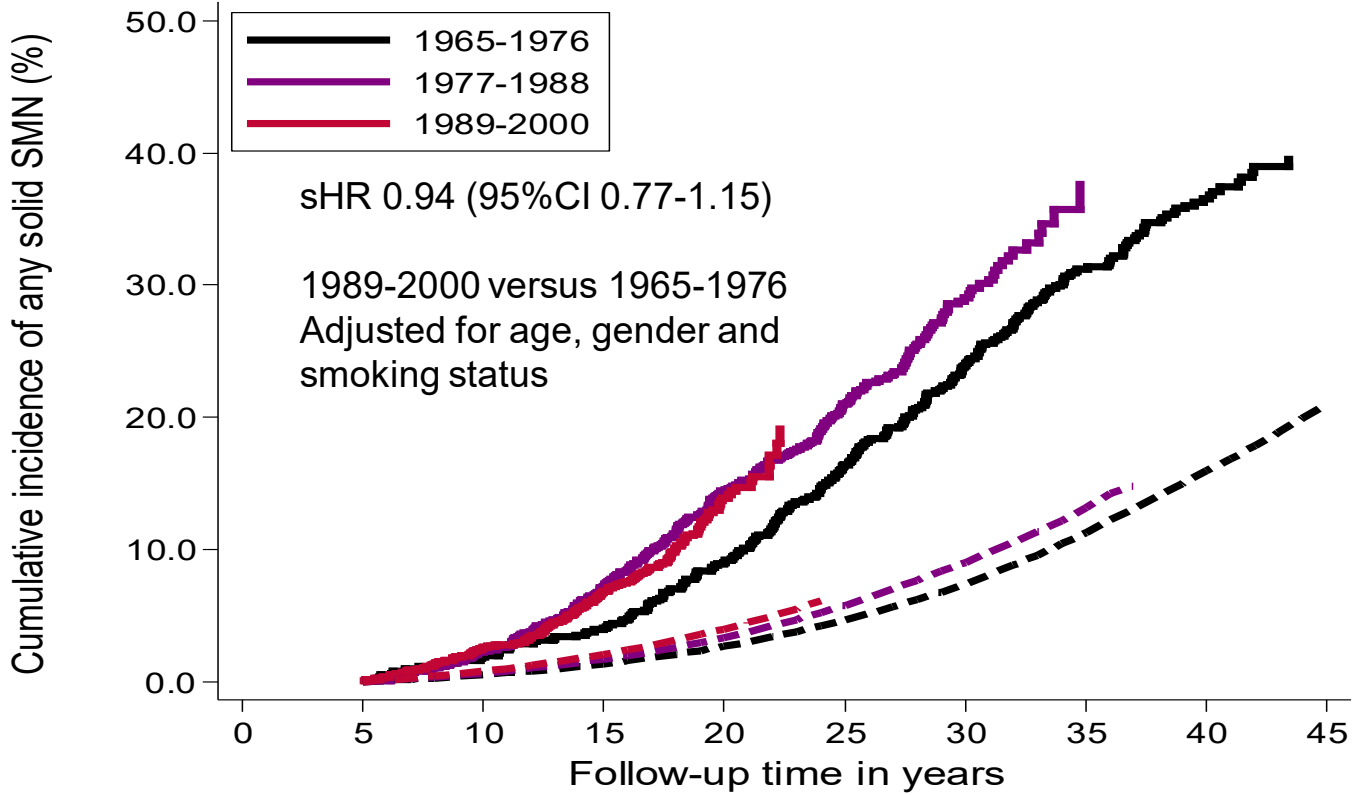
Courtesy: D. Hodgson

Is second cancer risk lower in more recent treatment periods?

- Evolution of second cancer risk in HL patients treated before age 51 between 1965-2000

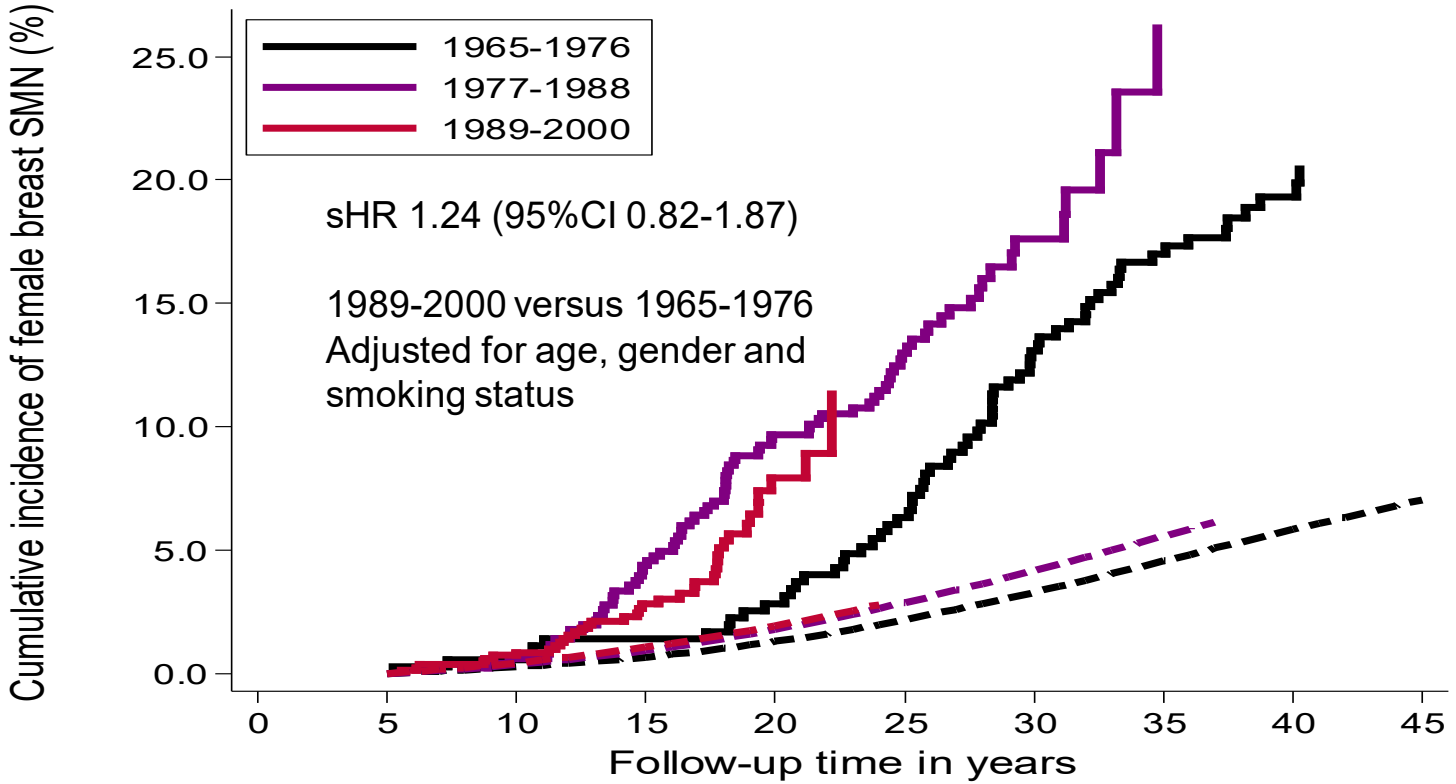
Schaapveld M et al. *NEJM* 2015;373(26):2499

Cumulative incidence of solid cancers by treatment period



Schaapveld M et al. *NEJM* 2015;373(26):2499

Cumulative incidence of breast cancer by treatment period



Schaapveld M et al. *NEJM* 2015;373(26):2499

Why does solid tumor risk not decrease in recent treatment period?

- **Favorable and unfavorable treatment changes**
  - Less use of mantle field → breast cancer ↓
  - Less use of high dose gonadotoxic CT → breast cancer ↑
    → opposite effects on breast cancer risk
  - Anthracyclines?

- **Surveillance (breast!)** ↑

- **Too early yet** to observe a decline in second cancer risks; smaller RT volumes introduced rather recently!

A Dutch nationwide survivorship care program for lymphoma survivors
The “BETER”-project

Better care after (non-)Hodgkin lymphoma:

Evaluation of long-term

Treatment

Effects and screening

Recommendations

BETER Consortium: 26 hospitals

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BETER: evidence-based guidelines based on previous treatments

- Second malignancies
- Cardiovascular disease
- Thyroid disease
- Splenic dysfunction
- Fertility and osteoporosis
- Neck complaints

Patient recall: all HL 5-year survivors treated at ages 15 – 60 yrs

Challenges for future research

1. Contemporary RT regimens, IMRT, protons; lower doses to larger volumes
2. Dose-volume parameters
3. Search for susceptibility genes for RT/CT-associated second cancers
4. Genomic alterations in second cancers
5. Risk prediction models
6. Efficacy of screening

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Which proportion of second malignancies can be attributed to radiotherapy?

A. > 75%
B. < 5%
C. 10 – 25%

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B. < 5%
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The risk of breast cancer after chest radiotherapy increases with:

A. Radiation dose and younger age at treatment
B. Radiation dose, number of alkylating chemotherapy cycles and younger age at treatment
C. Radiation dose, number of alkylating chemotherapy cycles and older age at treatment
D. Radiation dose, longer exposure to ovarian hormones and younger age at treatment

The risk of breast cancer after chest radiotherapy increases with:

A. Radiation dose and younger age at treatment
B. Radiation dose, number of alkylating chemotherapy cycles and younger age at treatment
C. Radiation dose, number of alkylating chemotherapy cycles and older age at treatment
D. Radiation dose, longer exposure to ovarian hormones and younger age at treatment

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