Cardiac Effects of Radiation Therapy

Carolyn Taylor, D.Phil.
Oncologist
Nuffield Department of Population Health
University of Oxford
carolyn.taylor@ndph.ox.ac.uk

DCEG Radiation Epidemiology and Dosimetry Course 2019

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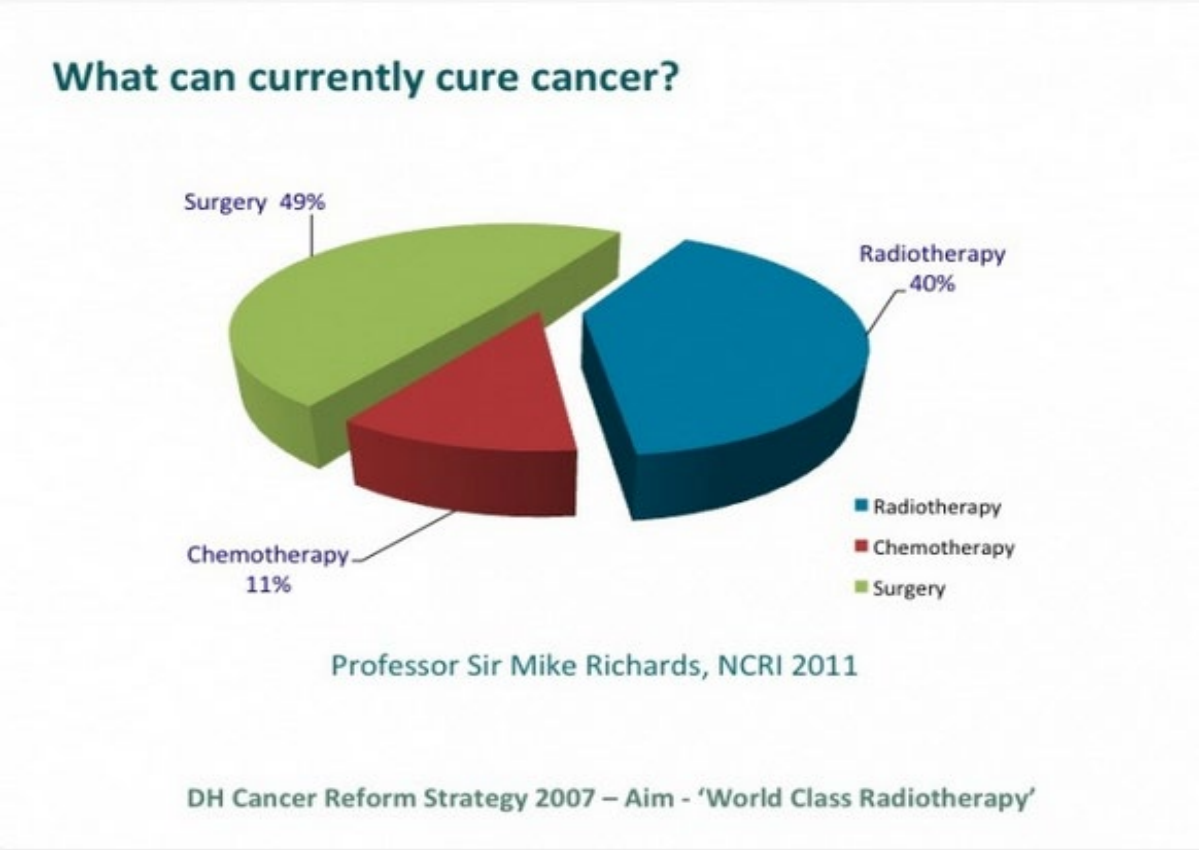
Radiotherapy cures cancers



Types of Epidemiological Study

1. Descriptive studies
2. Randomised trials
3. Cohort studies
4. Nested case-control studies

Types of Epidemiological Study

1. **Descriptive studies 1900s-1970s**

   Case reports

   Case series

Descriptive studies

MANTLE IRRADIATION IN HODGKIN'S DISEASE

An Analysis of Technique, Tumor Eradication, and Complications

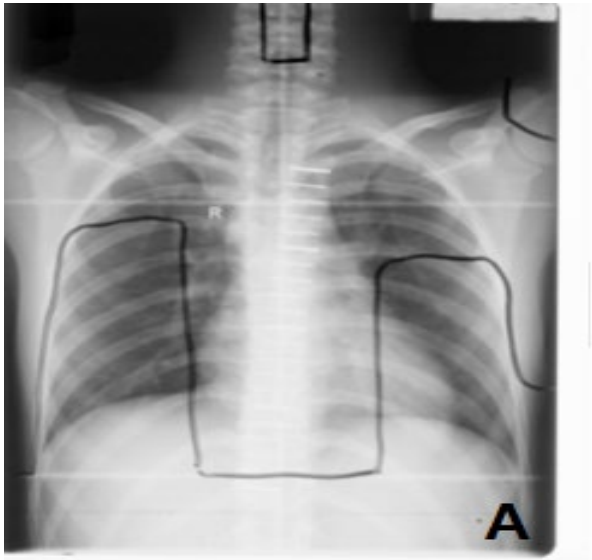
RICHARD J. CARMEL, MD, AND HENRY S. KAPLAN, MD

THE "MANTLE" IS A SINGLE ANTEROPOSTERIOR radiation therapy field designed to treat in continuity the major lymph node-bearing areas above the diaphragm w

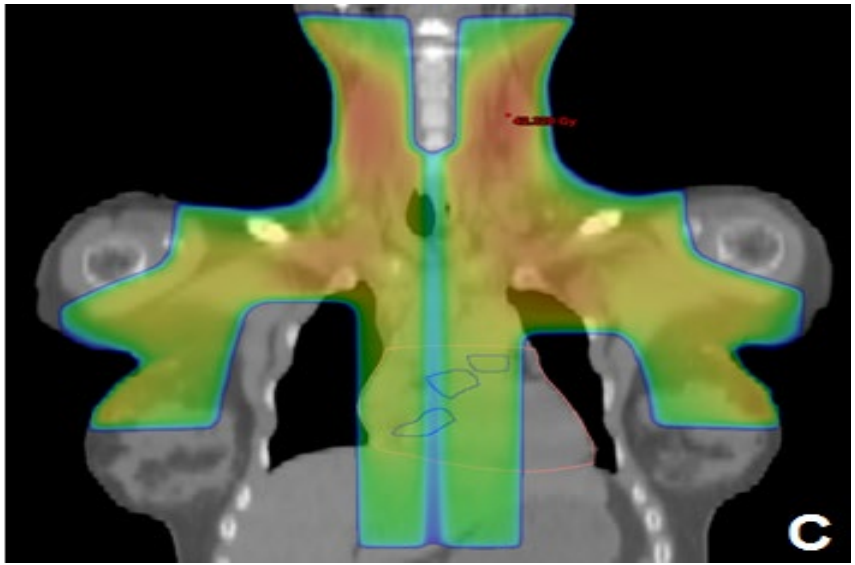
Cancer 37:2813–2825, 1976.

Descriptive studies

Mantle irradiation, Hodgkin Lymphoma



Radiotherapy planning X-ray



Dose reconstructed with modern techniques.

van Nimwegen et al, IJROBP, 2015

Descriptive studies

MANTLE IRRADIATION IN HODGKIN'S DISEASE

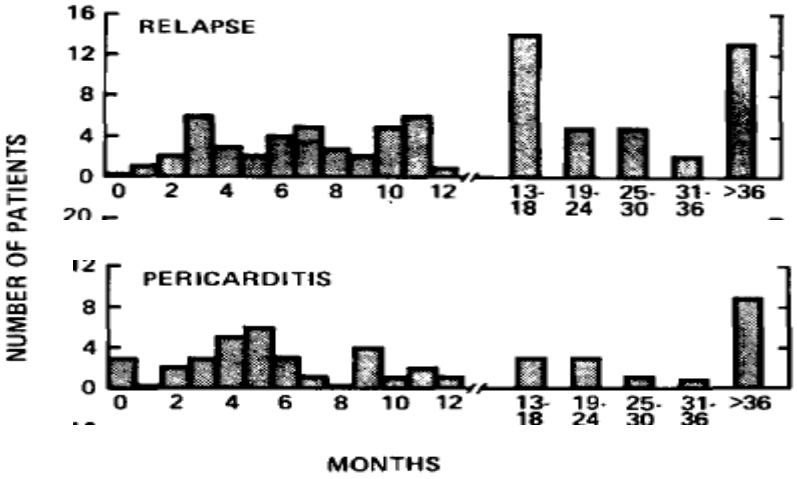
An Analysis of Technique, Tumor Eradication, and Complications

RICHARD J. CARMEL, MD, AND HENRY S. KAPLAN, MD

Mantle Treatment

The 377 patients within the study received mantle irradiation with a mean midline dose to the mediastinum of 4410 rads.

5 deaths from pericarditis

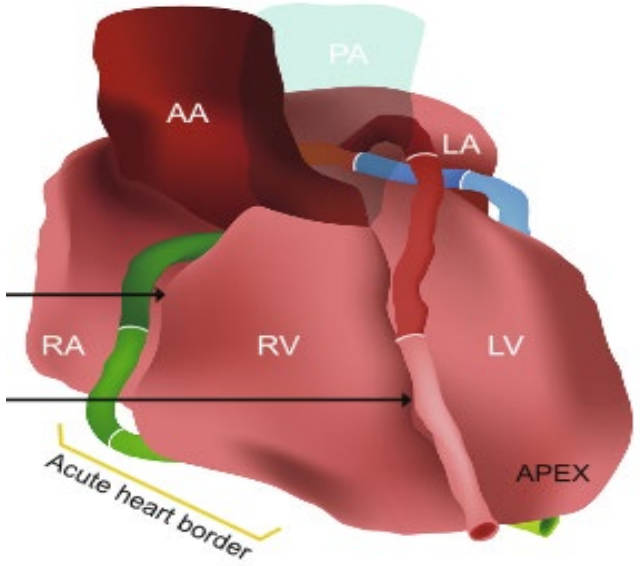


Interval from completion of radiotherapy to relapse/pericarditis

Cancer 37:2813–2825, 1976.

Cardiac Anatomy

- Pericardium
- Coronary arteries
- Valves
- Muscle



Duane, et al Radioth Oncol 2017

Types of Epidemiological Study

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Randomised trial

Experimental: Randomization to exposure

Exposure: Disease:

Yes: → ?

No: → ?

Randomised trials

Randomised to radiotherapy versus not

75 trials, 40,000 women, median entry 1983

Type of surgery	No. of trials	No. of women	Deaths with no recurrence
Mastectomy (for cancer)	36	16,156	2921
Breast conserving (for ca.)	18	11,655	1270
Various (for cancer)	17	9066	1666
All trials	**75**	**40,781**	**6064**

EBCTCG, J Clin Oncol 2017

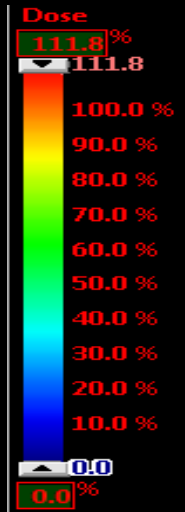
Randomised trials

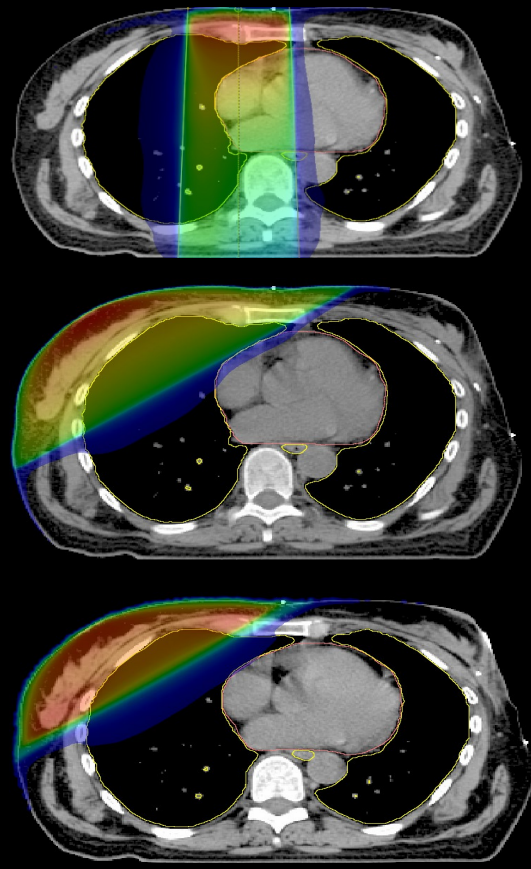
Heart disease mortality

Cause	Total deaths	Excess deaths	Rate ratio (95% CI)	2p
Heart disease	**1253**	**143**	**1.30 (1.15-1.46)**	**<0.0001**
Ischaemic heart dis.	751	90	1.31 (1.13-1.53)	0.0005
Heart failure	96	28	1.94 (1.27-2.98)	0.002
Valve disease	46	14	1.97 (1.07-3.67)	0.03
Other heart disease	360	11	1.08 (0.86-1.35)	0.52

EBCTCG, J Clin Oncol 2017

Radiotherapy by decade in trials



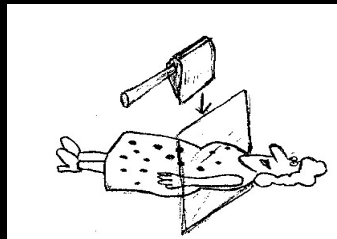


1970s

1980s

1990s

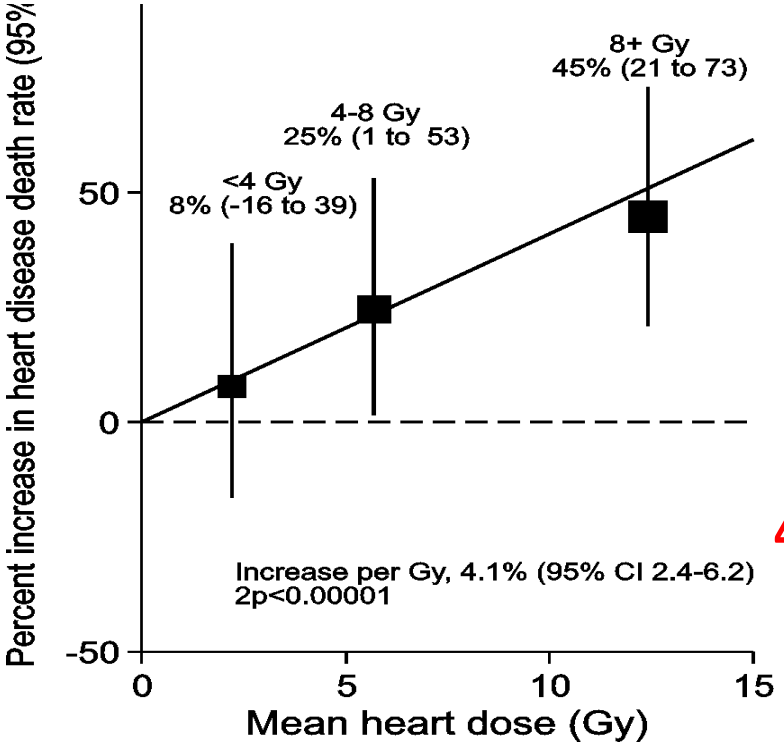
c/o Dr Fran Duane



Randomised trials

Heart dose-response relationship

1253 cardiac deaths in 40,000 women



Very approximate information on heart dose based just on trial description

4.1% (2.4 - 6.2)

EBCTCG, J Clin Oncol 2017

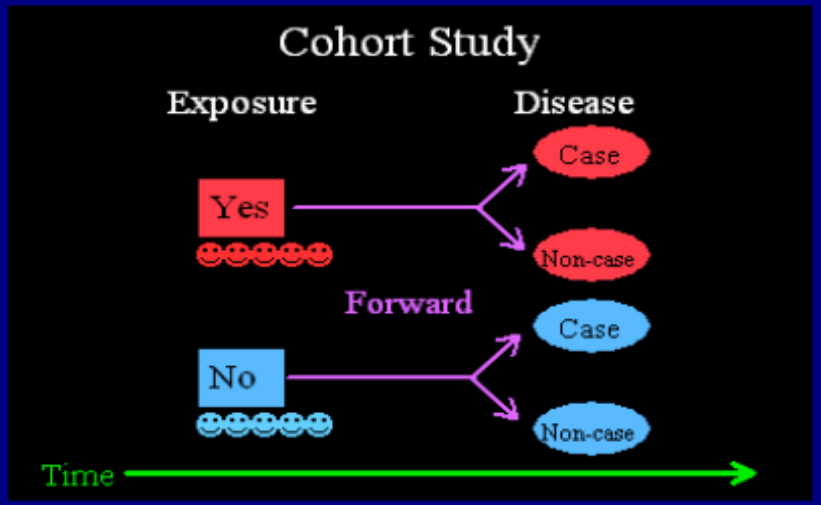
Still need …….

- Large studies in the *general* patient population
- Data on non-fatal and fatal events
- More detailed studies:
  - Individual information on radiation heart dose
  - Medical history at time of cancer diagnosis including, eg pre-existing heart disease

Types of Epidemiological Study

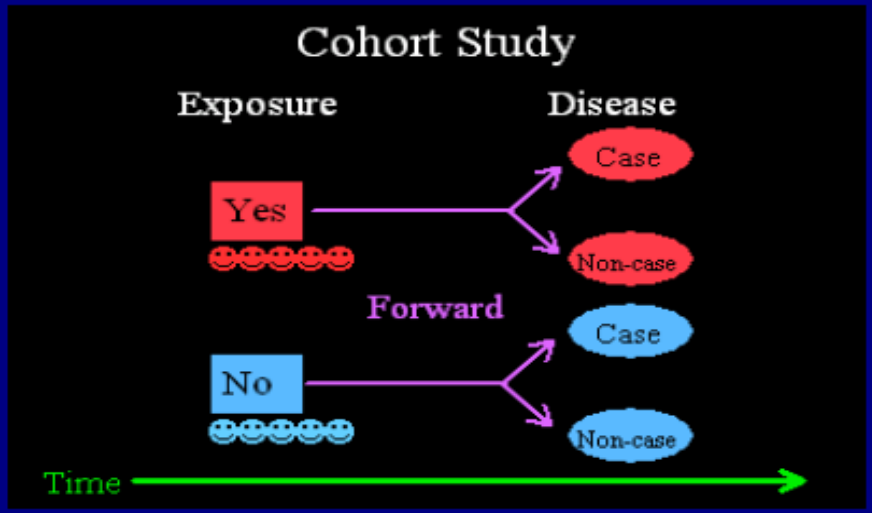
1. Descriptive studies
2. Randomised trials
3. **Cohort studies**
4. Nested case-control studies

Cohort Study



- Compare disease status in exposed vs. non-exposed
- Prospective
- May take many years to follow-up the cohort

Cohort Study



- Compare disease status in exposed vs. non-exposed
- Prospective
- May take many years to follow-up the cohort

Cohort studies

Cardiac mortality: Radiotherapy *versus* not

~2 million women

57 cancer registries in 22 countries

55,000 deaths from heart disease

53% irradiated

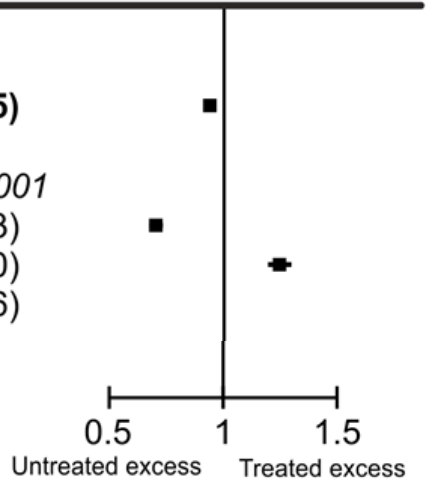
Cardiac mortality ratio, RT *versus* not (95% CI)
All women
0.94 (0.92-0.95)

K Henson 2019 provisional results

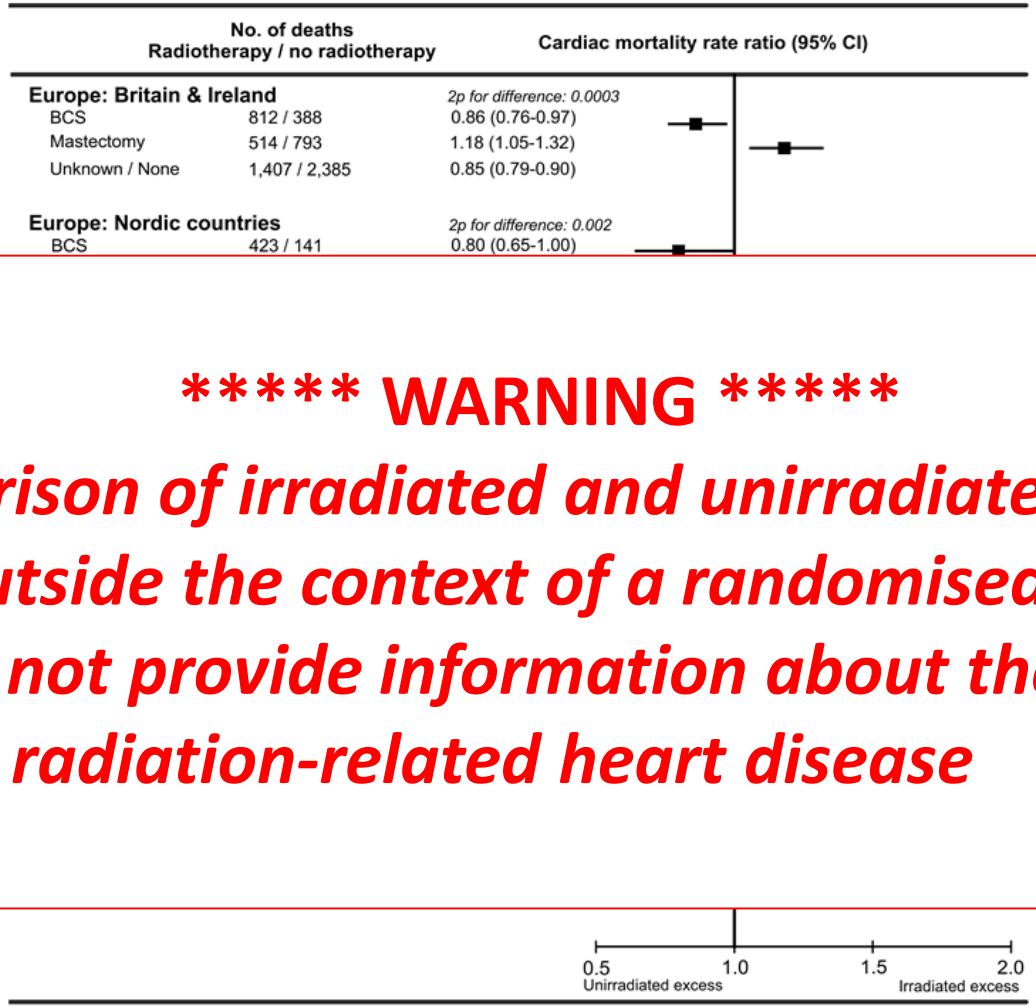
Cohort studies

Cardiac mortality: Radiotherapy *versus* not

	Number of deaths Treatment / no treatment	Cardiac mortality rate ratio (95% CI)
Radiotherapy	**22,100 / 33,164**	**0.94 (0.92−0.95)**
		2p for difference < 0.0001
BCS	5,832 / 3,805	0.70 (0.67−0.73)
Mastectomy	3,315 / 13,727	1.24 (1.19−1.30)
Unknown/None	12,953 / 15,632	1.03 (1.00−1.06)



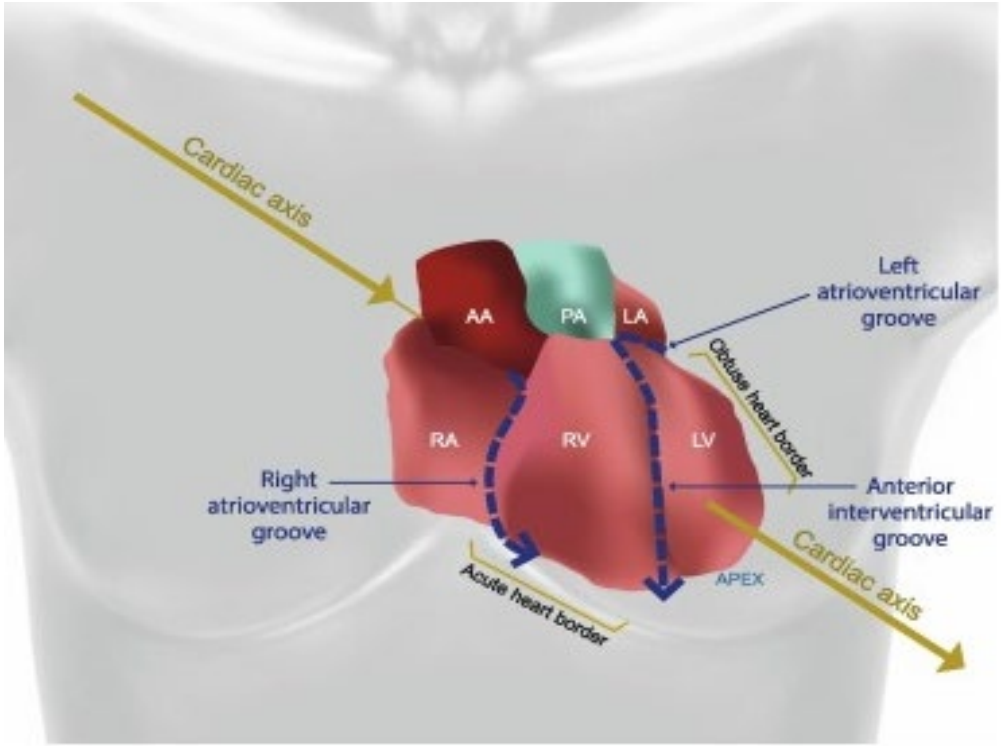
K Henson 2019 provisional results



***** WARNING *****

The comparison of irradiated and unirradiated women outside the context of a randomised trial may not provide information about the risk of radiation-related heart disease

K Henson 2019 provisional results



a

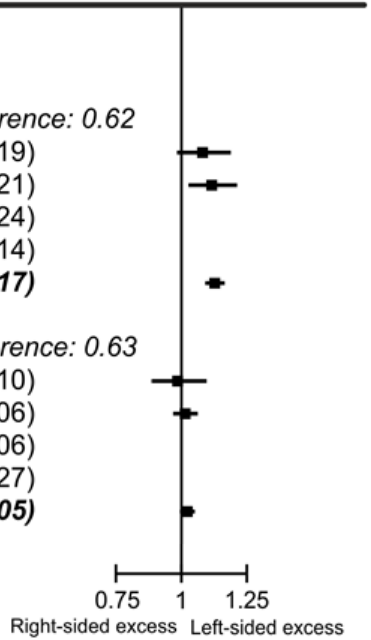
Duane, et al Radioth Oncol 2017

Cohort studies

Cardiac mortality ratios

Left-sided vs right-sided breast cancer

	Number of deaths Left-sided / right-sided	Cardiac mortality rate ratio (95% CI)
Women diagnosed before 1990		
Irradiated women		*2p for difference: 0.62*
BCS	933 / 828	1.08 (0.98−1.19)
Mastectomy	1,249 / 1,052	1.12 (1.03−1.21)
None/unknown	3,536 / 2,823	1.18 (1.13−1.24)
Not recorded	2,094 / 1,831	1.07 (1.01−1.14)
Total	***7,812 / 6,534***	***1.13 (1.09−1.17)***
Unirradiated women		*2p for difference: 0.63*
BCS	714 / 697	0.99 (0.89−1.10)
Mastectomy	3,733 / 3,442	1.01 (0.97−1.06)
None/unknown	5,127 / 4,655	1.02 (0.98−1.06)
Not recorded	764 / 634	1.14 (1.03−1.27)
Total	***10,338 / 9,428***	***1.02 (0.99−1.05)***



K Henson 2019 provisional results

Cohort studies

- If the decision to give radiotherapy did not depend on laterality of the breast cancer, then …..
- we can regard the heart disease rates in women with left-sided and right-sided breast cancer as equivalent to a randomised trial.

Cohort and case control studies

- Large studies in the general patient population
- Data on non-fatal and fatal events
- More detailed studies:
  - Individual information on radiation heart dose
  - Medical history at time of cancer diagnosis

Cohort studies

Contents lists available at ScienceDirect

Radiotherapy and Oncology

journal homepage: www.thegreenjournal.com

Cardiac morbidity

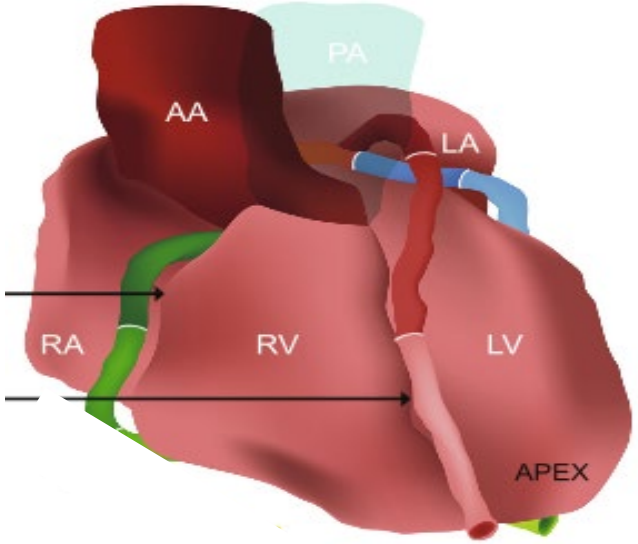
Incidence of heart disease in 35,000 women treated with radiotherapy for breast cancer in Denmark and Sweden

Paul McGale [a], Sarah C. Darby [a,*], Per Hall [b], Jan Adolfsson [c], Nils-Olof Bengtsson [d], Anna M. Bennet [b], Tommy Fornander [e], Bruna Gigante [f], Maj-Britt Jensen [g], Richard Peto [a], Kazem Rahimi [h], Carolyn W. Taylor [a], Marianne Ewertz [i]

Left vs right-sided breast cancer:
Heart disease incidence ratios

Cardiac Anatomy

- Pericardium
- Coronary arteries
- Valves
- Muscle



Duane, et al Radioth Oncol 2017

Cohort studies

Left vs right-sided breast cancer:

35,000 women given breast cancer radiotherapy

Disease category	Events left/right	Incidence ratio, left vs. right (95% CI)	P
Ischaemic heart disease	878/712	1.18 (1.07-1.30)	0.001
Pericarditis	60/36	1.61 (1.06-2.43)	0.03
Valvular heart disease	94/60	1.54 (1.11-2.13)	0.009
Conduction disorders	445/453	0.94 (0.82-1.07)	0.35
Heart failure	310/315	0.95 (0.81-1.11)	0.51
All heart disease	2275/2016	1.08 (1.02-1.15)	0.01

McGale et al, Rad Onc 2011

Cohort and case control studies

- Large studies in the general patient population
- Data on non-fatal and fatal events
- More detailed studies:
  - Individual information on radiation heart dose
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Types of Epidemiological Study

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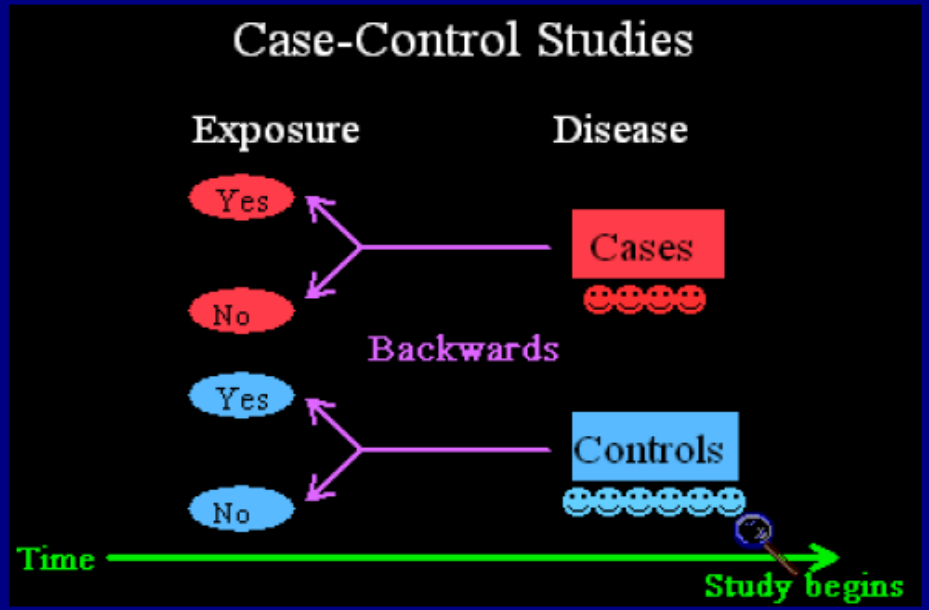
Case-Control Study



- Compare exposure in cases vs. controls
- Retrospective

Case control studies

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 MARCH 14, 2013 VOL. 368 NO. 11

Risk of Ischemic Heart Disease in Women after Radiotherapy for Breast Cancer

Sarah C. Darby, Ph.D., Marianne Ewertz, D.M.Sc., Paul McGale, Ph.D., Anna M. Bennet, Ph.D., Ulla Blom-Goldman, M.D., Dorthe Brønnum, R.N., Candace Correa, M.D., David Cutter, F.R.C.R., Giovanna Gagliardi, Ph.D., Bruna Gigante, Ph.D., Maj-Britt Jensen, M.Sc., Andrew Nisbet, Ph.D., Richard Peto, F.R.S., Kazem Rahimi, D.M., Carolyn Taylor, D.Phil., and Per Hall, Ph.D.

Nested in cohort study

Danish Breast Cancer Cooperative Group and Swedish Cancer Registry

Case control studies

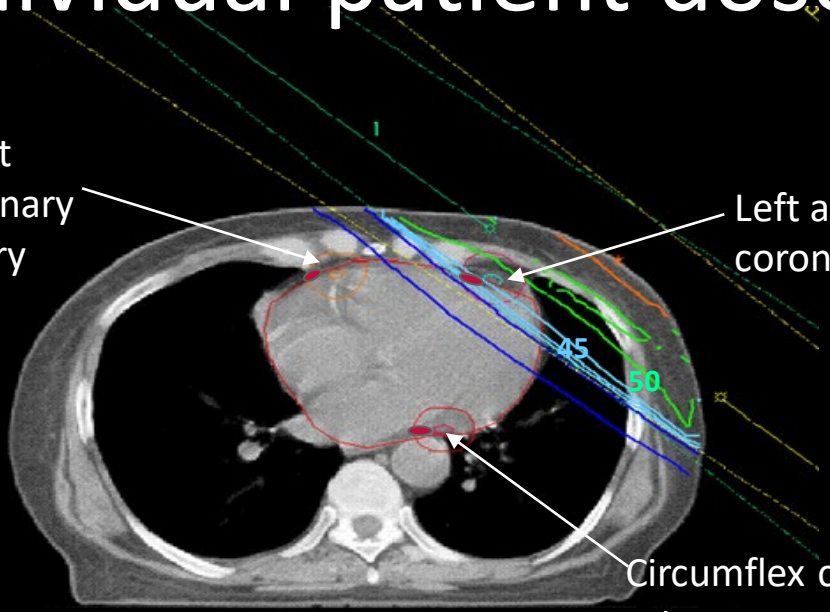
Population-based case-control study of major coronary events

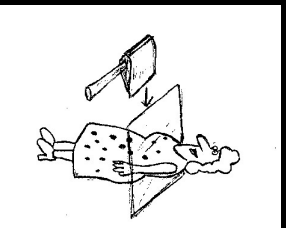
- Population: Women irradiated for breast cancer
- 963 cases (Major Coronary Events)
- 1205 controls also irradiated for breast cancer
- Information from oncology records (medical history and radiotherapy plans)

Darby et al, NEJM 2013

Case control studies

Individual patient doses

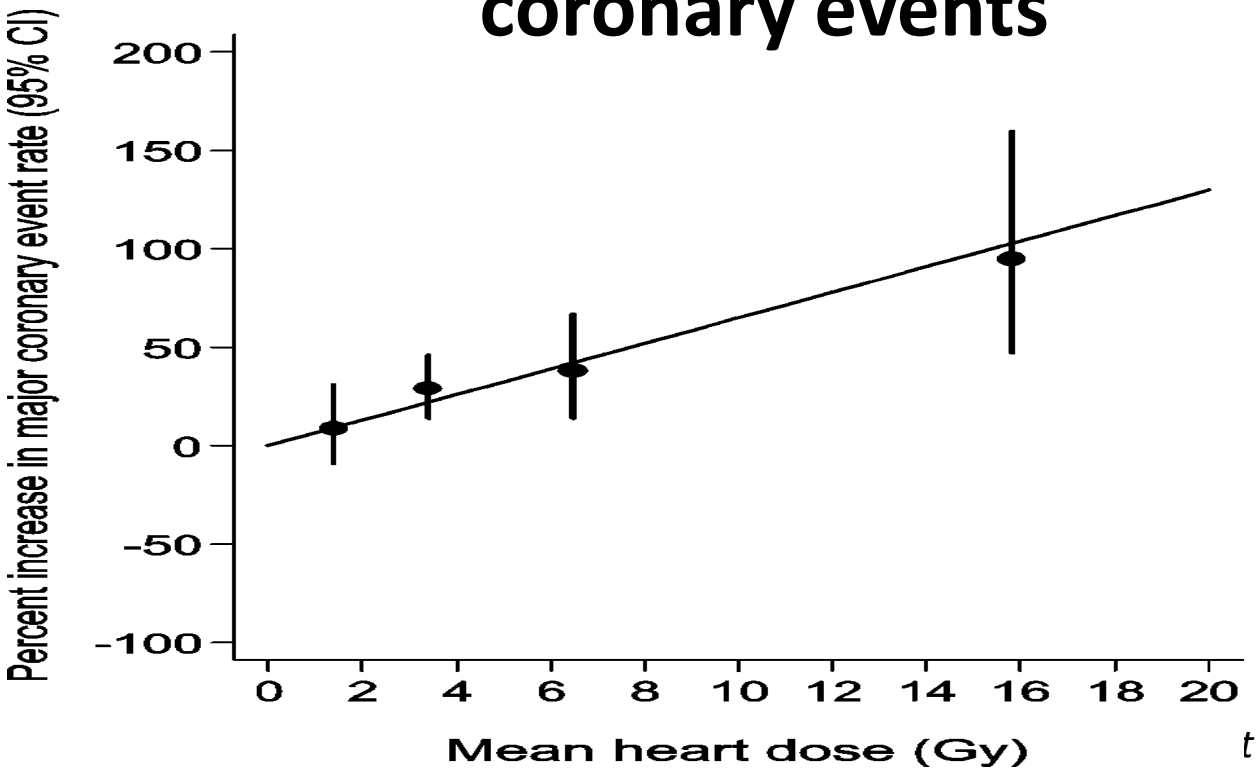




Taylor et al, IJROBP 2007

Case control studies

Dose-response relationship for major coronary events



t al, NEJM 2013

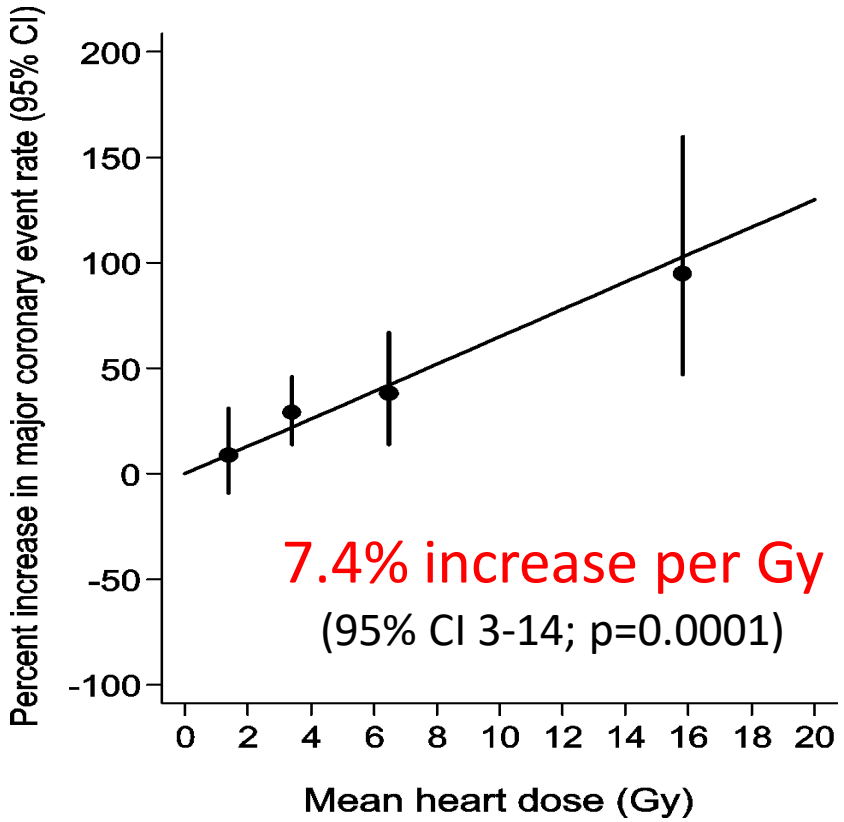
Case control studies

Major coronary event rate per Gy mean heart dose

		Average dose to heart (Gy)	% increase in MCE rate/Gy (95%CI)	2p for diff
Cardiac risk factor	No	5.1	7.4 (2.0-20.3)	0.99
	Yes	4.9	7.4 (1.2-20.1)	

Darby et al, NEJM 2013

Case control studies

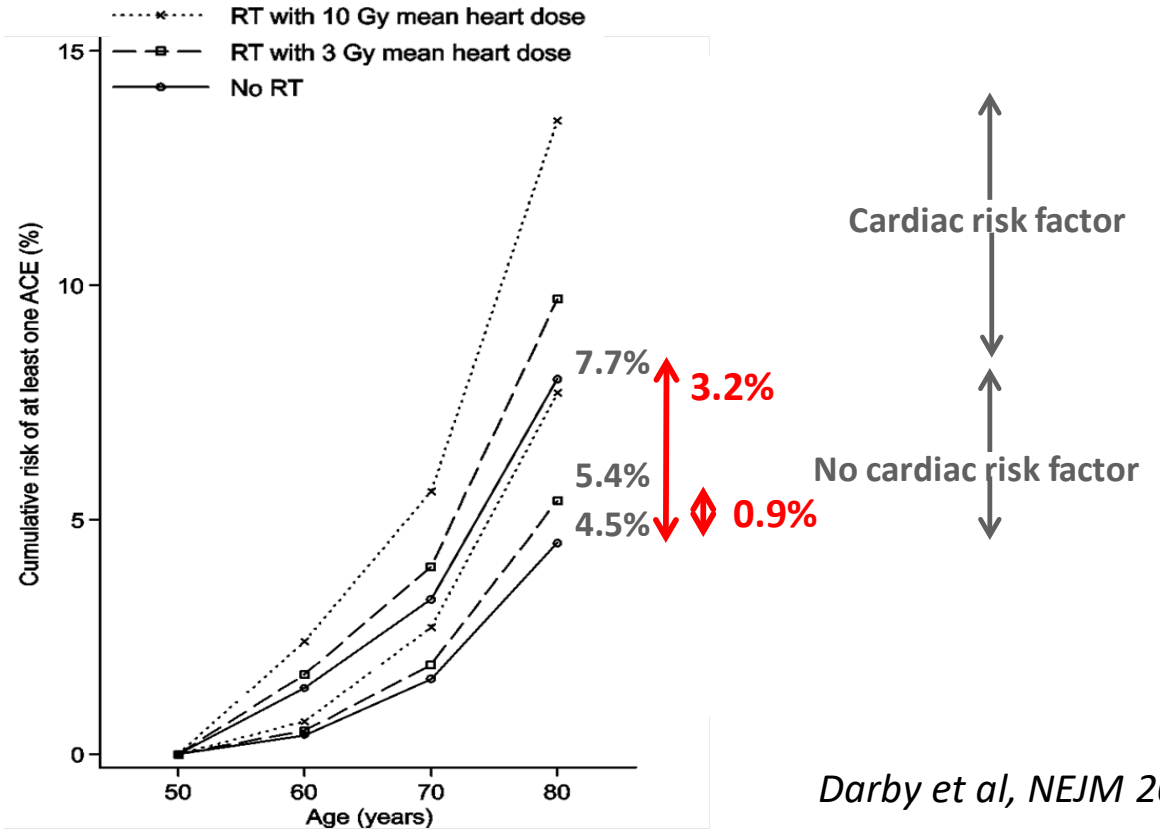


Same slope for women with and without cardiac risk factors at time of breast cancer diagnosis

Darby et al, NEJM 2013

Case control studies

Risks by age 80 of radiotherapy at age 50



Darby et al, NEJM 2013

Ischaemic Heart Disease: Current position

- Risk proportional to whole heart dose
- No known threshold
- Radiation-related risk multiplies pre-existing risk
- Risk starts within first 5 years, continues for several decades

Case control studies

ARTICLE

Risk for Valvular Heart Disease After Treatment for Hodgkin Lymphoma

David J. Cutter*, Michael Schaapveld*, Sarah C. Darby, Michael Hauptmann, Frederika A. van Nimwegen, Augustinus D. G. Krol, Cecile P. M. Janus, Flora E. van Leeuwen, Berthe M. P. Aleman

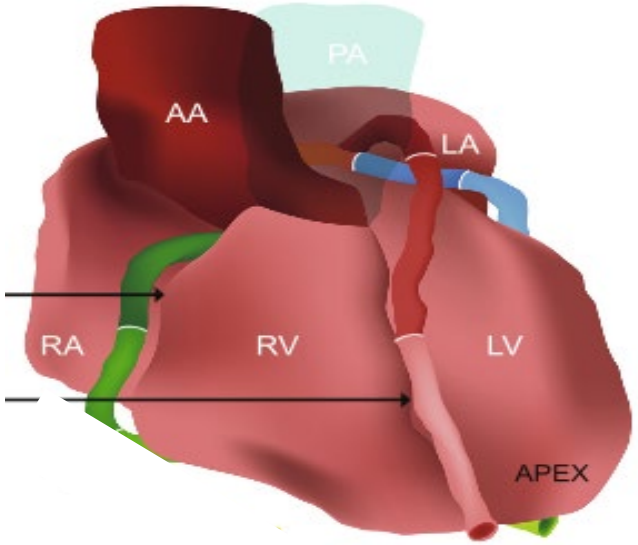
5-year survivors Hodgkin lymphoma

Nested in cohort of 1852 patients

Cases = valvular heart disease after radiotherapy

Cardiac Anatomy

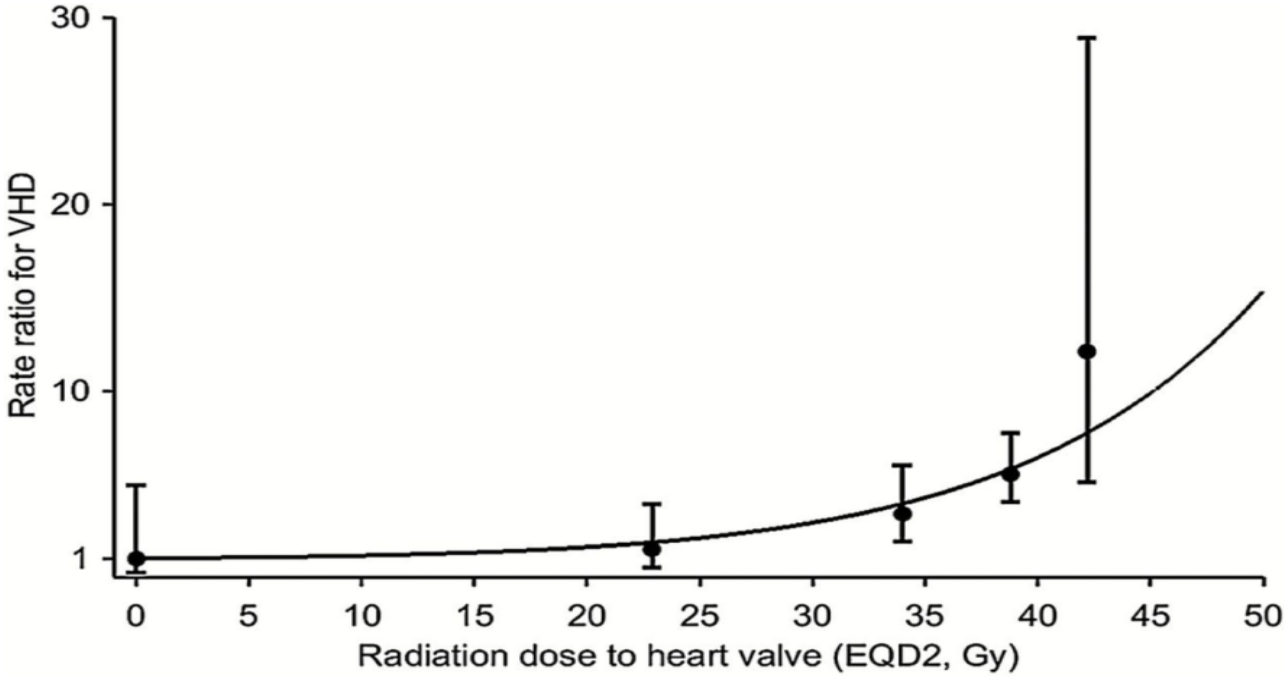
- Pericardium
- Coronary arteries
- Valves
- Muscle



Duane, et al Radioth Oncol 2017

Case control studies

Valvular heart disease



Cutter, Schaapveld, et al JNCI 2015

Case control studies

Valvular Heart Disease: Current position

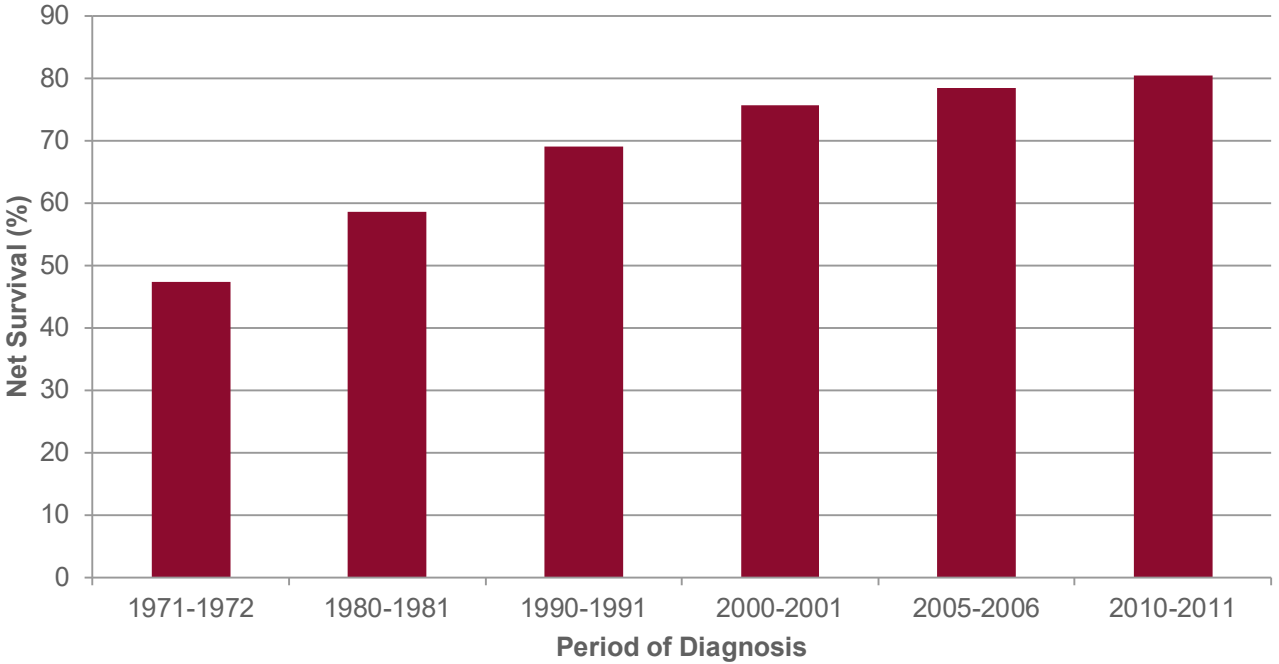
- Radiation increases the risk at >30 Gy
- Little evidence of risk from lower doses
- Risk starts after 10 years

- Muscle: Heart failure can be caused by chemotherapy. Unclear about radiotherapy.

- Examples given for Hodgkin lymphoma and breast cancer.

- Good survival – many patients live a long time

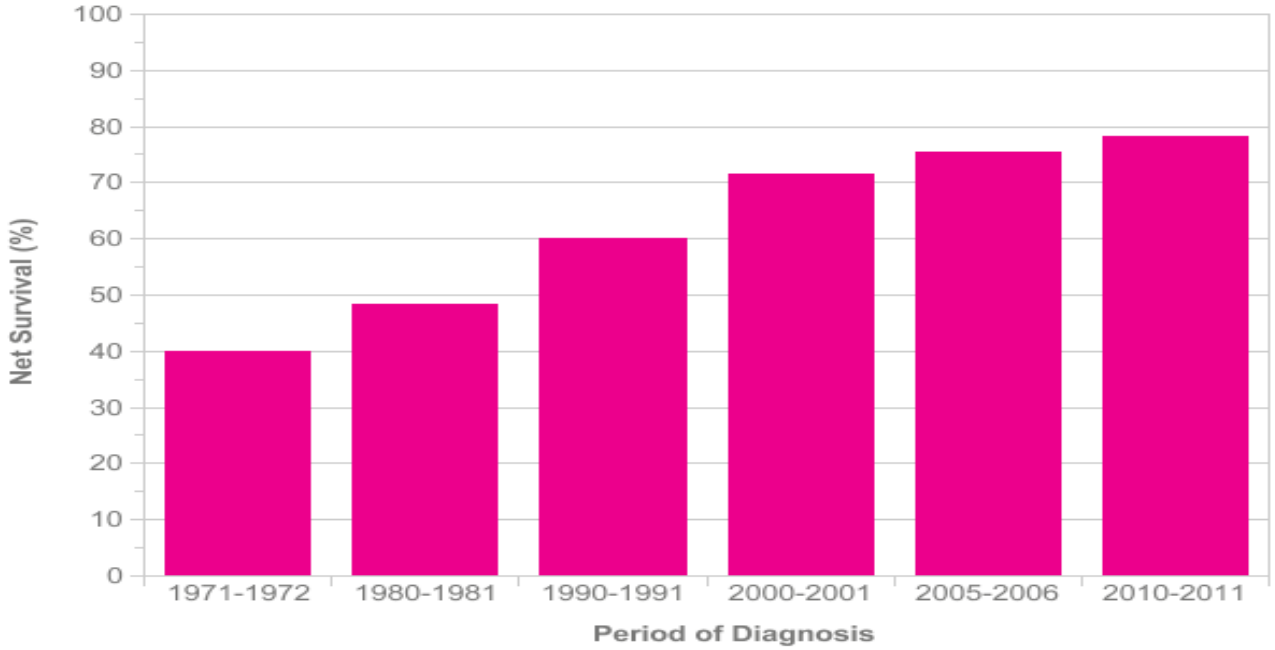
Ten-year survival Hodgkin Lymphoma



Age-Standardised Ten-Year Net Survival, England and Wales

CANCER RESEARCH UK

Ten-year survival Breast cancer



Age-standardised ten-year net survival, England and Wales

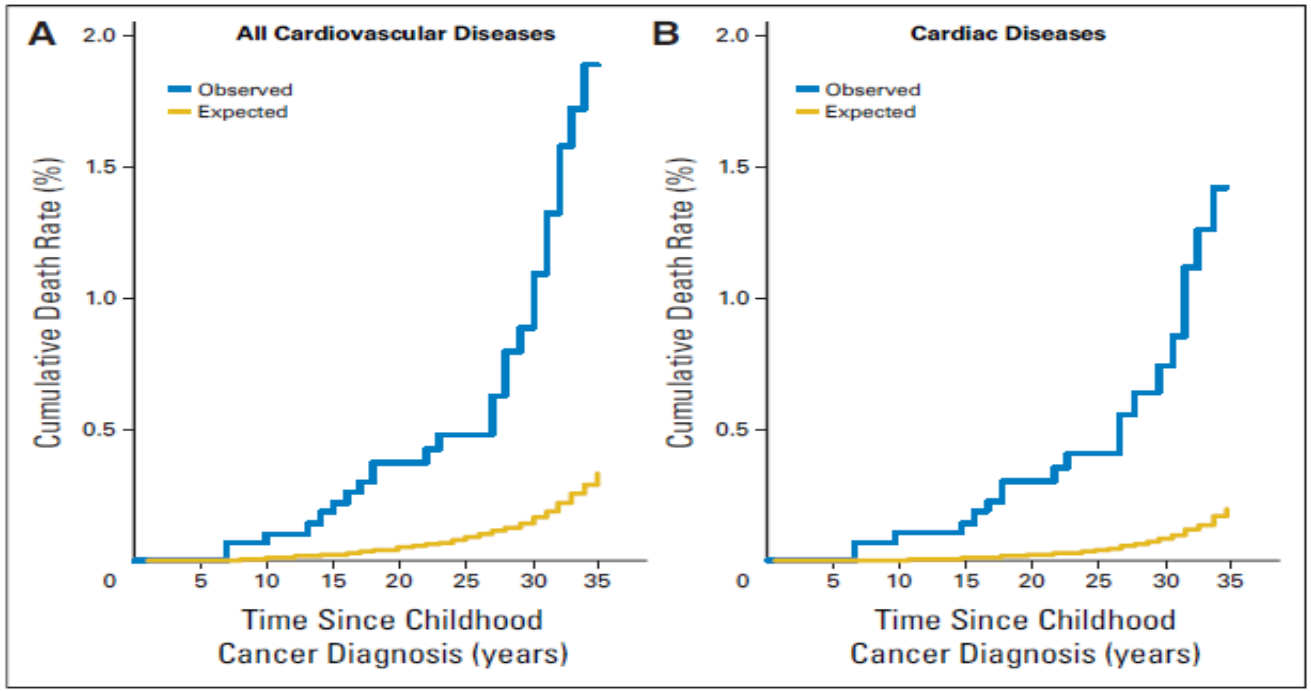
CANCER RESEARCH UK

- Other adult cancers where radiotherapy involves heart:
  - Lung cancer
  - Oesophageal cancer

Survival poorer – few live a long time

Cohort study

Childhood cancer



Tukenova et al, JCO, 2010

Cohort study

Childhood cancer

- Linear relationship between heart dose and risk of cardiac mortality
- Estimated increase: 60% per Gy (7.4% for adults)
- Irradiating heart in childhood may affect growth of the heart

Clinical decisions

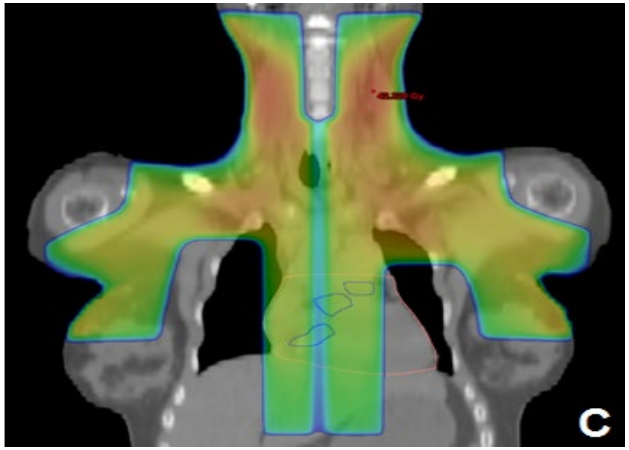
Clinicians need absolute risks …

Heart disease

Cancer recurrence

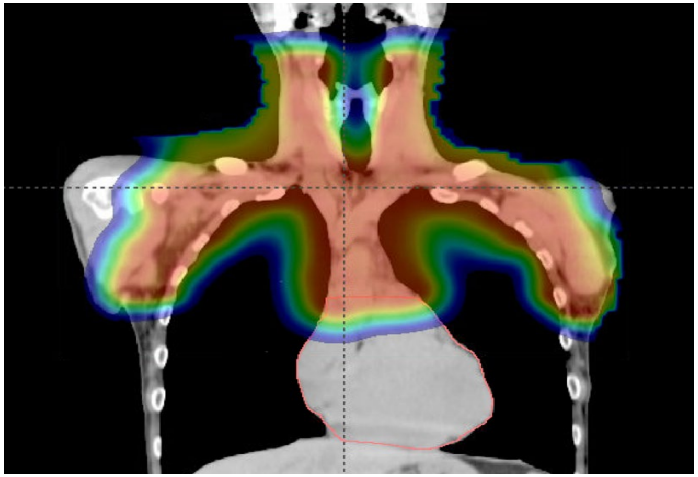
Balance absolute benefit and absolute risk

Radiotherapy has changed Hodgkin lymphoma



1970s

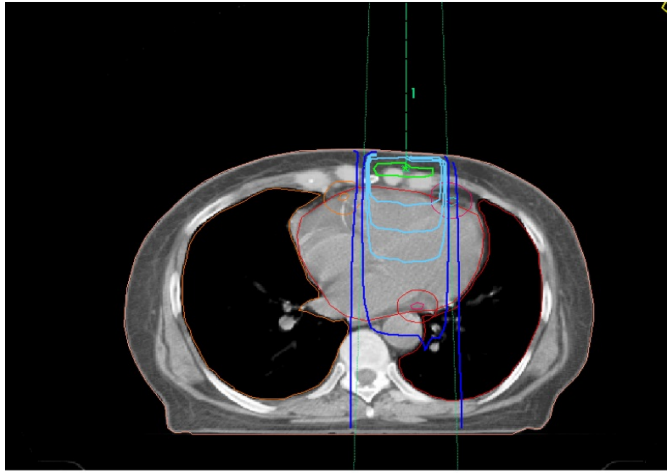
c/o Dr David Cutter



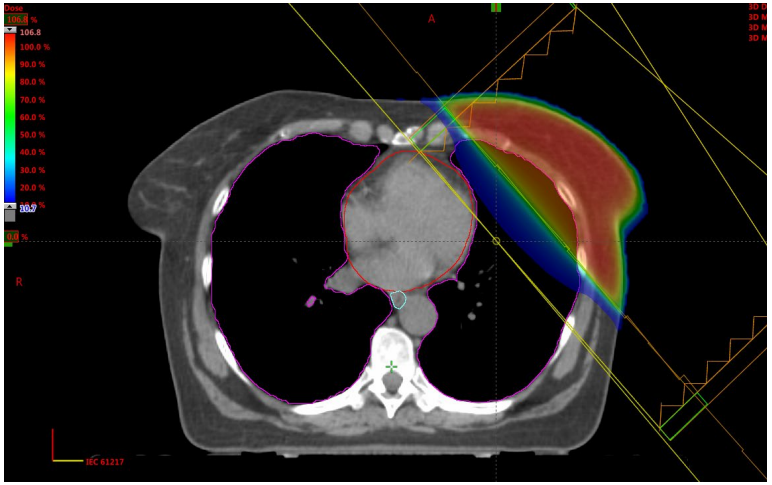
2010s

c/o Dr Georgios Ntentas

Radiotherapy has changed
Breast cancer



1970s



2010s

Thank you

Quiz 1

The commonest type of radiation-induced heart disease is:

a) Heart failure
b) Ischaemic heart disease
c) Valve disease

Quiz 1

The commonest type of radiation-induced heart disease is:

a) Heart failure
b) Ischaemic heart disease
c) Valve disease

Quiz 2

Heart radiation doses from today's radiotherapy are similar to doses from 1970s radiotherapy

True/False

Quiz 2

Heart radiation doses from today's radiotherapy are similar to doses from 1970s radiotherapy

True/False

Quiz 3

The cardiac risks from modern radiotherapy outweigh the benefits for most patients

True/False

Quiz 3

The cardiac risks from modern radiotherapy outweigh the benefits for most patients

True/False

U.S. Department of Health & Human Services

National Institutes of Health | National Cancer Institute

cancer.gov/dceg

1-800-4-CANCER

Produced September 2019