Statistical methods in radiation epidemiology

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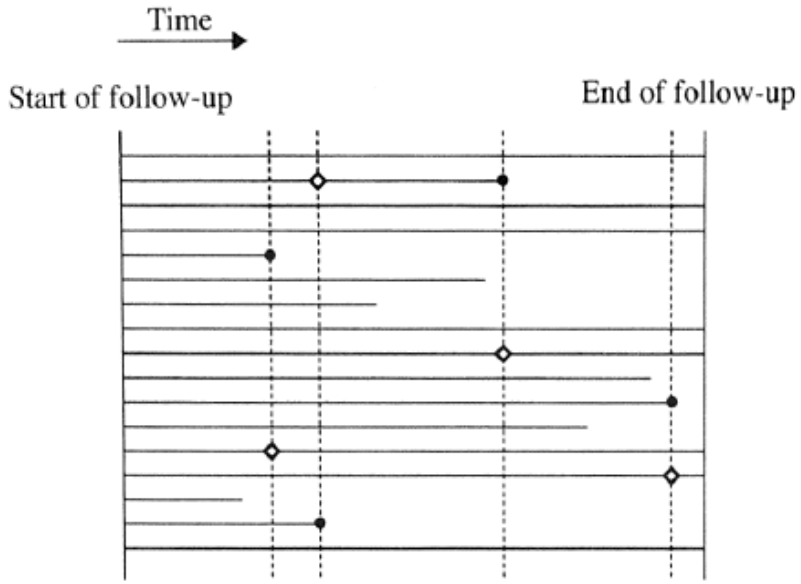
Methods specific to radiation epidemiology

- Nested case-control study
- Linear excess relative risk model
- Shape of dose-response relationship
- Interaction
- Choice of dose metric

Relevant study designs

- Primary & secondary cancers rare
- Start with large patient series = cohort studies
- Detailed treatment information needed to assess radiation risks
  - Organ dose
  - Other (treatment) factors as confounders
- Nested case-control study: detailed treatment information and dose estimation for sample of all cases & subset of controls

Incidence density sampling



- Matching on other factors to control for confounding, e.g., age, calendar year of diagnosis

- The more controls per case the better for power, little improvement beyond 5 controls/case

- Conditional logistic regression analysis

Example: Stomach cancer after testicular cancer

- Cohort: 22,269 5-yr survivors of primary testicular cancer (1959-1987)
- 6 European & North-American population-based cancer registries plus Dutch hospital cohort
- 92 stomach cancer cases (1975-2004)
- 180 controls with testicular cancer individually matched by age & yr of testicular cancer, gender, ethnicity, registry & stomach cancer-free survival

Treatment data

- Medical records: cancer diagnoses, cancer treatment, radiotherapy fields & target dose, chemotherapy cycles & doses

- Dose calculated to the stomach based on typical stomach configuration

- Custom-designed dose program, measurements in water & anthropomorphic phantoms constructed of tissue-equivalent material (Stovall et al., 2006)

Overview of patients

	Cases (N=92)		Controls (N=180)	
	N	%	N	%
Year of testicular cancer diagnosis				
1959-1969	28	30.4	51	28.3
1970-1979	44	47.8	87	48.3
1980-1987	20	21.7	42	23.3
Age at testicular cancer diagnosis (yrs)				
18-29	17	18.5	36	20.0
30-39	35	38.0	70	38.9
40-71	40	43.5	74	41.1
Testicular cancer treatment				
No chemotherapy, no radiotherapy	3	3.3	16	8.9
Chemotherapy only	1	1.1	13	7.2
Radiotherapy only	74	80.4	141	78.3
Both	13	14.1	10	5.6
Unknown	1	1.1	0	0
Interval from testicular cancer to stomach cancer (yrs)				
7-9	9	9.8		
10-14	26	28.3		
15-19	23	25.0		
20-24	23	25.0		
25-39	11	12.0		

Risk models

Exponential failure rate model

$$\lambda\left[t, Z(t), D(t)\right] = \lambda\left[t, Z_0(t)\right] e^{\beta D(t)}$$

- $Z(t)$ risk factor history up to time t
- $Z_0(t)$ standard covariate history
- $\lambda[t, Z(t), D(t)]$ failure rate at t for covariate history $Z(t)$ and dose $D(t)$
- Relative risk

$$\mathrm{RR}\left[t, Z(t), D(t)\right] = \frac{\lambda\left[t, Z(t), D(t)\right]}{\lambda\left[t, Z_0(t)\right]} = e^{\beta D(t)}$$

- Exponential appealing because: nonnegative RR & multiplicative joint effects

Excess risk models

- Excess absolute risk (EAR)

- Excess relative risk (ERR)

Excess absolute risk model

$$RR(D) = \lambda_0 + f(\beta, D)$$

where λ_0=background risk

- Additive model

- Excess risk is independent of baseline risk

Excess relative risk model

$$RR(D) = \lambda_0[1 + f(\beta, D)]$$

where λ_0=background risk

- Relative model

- Excess risk is multiple of baseline risk

Motivation for linear excess relative risk (ERR) model

$$\mathrm{RR}(D) = 1 + \beta D$$

- Biological/mechanistic (Kellerer and Rossi 1971 & 1976)
- Linear no threshold (LNT)
- Additive joint effect = independence
  Synergism/antagonism = departure from additive
  (Rothman, Greenland, Walker 1980)

Properties of the linear ERR model

- Software: EPICURE, David Richardson's SAS macro, David Morina's R package

- Poor asymptotic normality of maximum likelihood estimates for small samples

- Positivity constraint

$$1 + \beta D > 0 \quad \Rightarrow \quad \beta \in \left(-\frac{1}{\max D}, \infty \right)$$

Properties of maximum likelihood estimators

- Essentially no optimal properties for finite samples

- Asymptotic properties

  - Consistency: converges in probability to the value being estimated

  - Asymptotic normality: as sample size increases, distribution of MLE tends to the Gaussian distribution with mean & covariance matrix equal to the inverse of the Fisher information matrix

  - Efficiency: achieves the Cramer-Rao lower bound when sample size tends to infinity, i.e., no asymptotically unbiased estimator has lower asymptotic mean squared error than MLE

Asymptotic normality

- Finite-sample bias: bias negligible for large enough samples, how large is large enough?

- Degree of finite-sample bias tends to be directly proportional to number of variables in model $\Rightarrow$ adjustment for many potential confounders can increase bias

- Sample size required for the Wald method is impractically large

- Ordinary Wald tests and intervals for parameters in additive RR models can be grossly invalid, even at large sample sizes

Alternative: Likelihood ratio or profile likelihood estimation

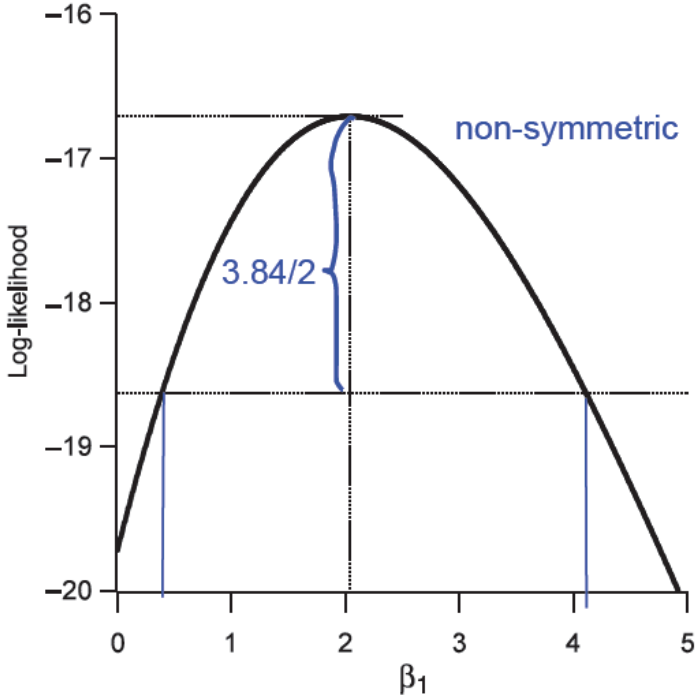


Figure 1. Profile log-likelihood for the log odds ratio, β_1.

(StataCorp LP, College Station, Texas) (9). Appendix 2 gives a method for plotting profile log-likelihoods.

Fitting the logistic model by ML to Table 1, we get $\hat{\beta}_1 = 2.043$ and $\hat{s} = 0.915$, which yields an odds ratio of 7.71. The Wald 95% confidence interval for the odds ratio is $\exp(2.043 \pm 1.96 \times 0.915) = (1.28, 46.3)$. The 95% LR confidence interval is 1.47, 61.1, as can be read off the profile log-likelihood plot in Figure 1 (or found numerically with the data used to generate the plot). The lower horizontal reference

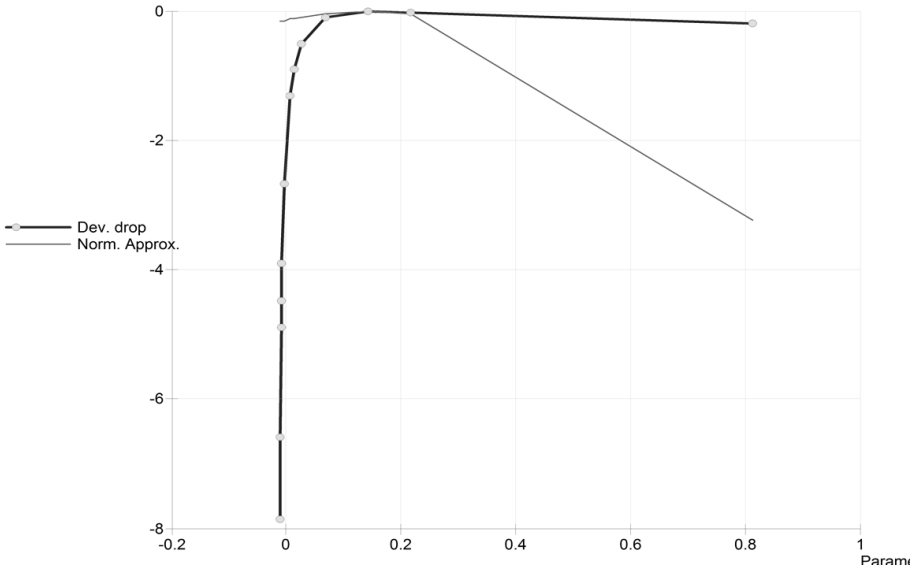
Cole et al. 2013

Example: Wald- vs. LR-based CI

- ERR=0.1422
  Standard error=0.3741

- Wald-based 95% CI:
  $[0.1422 - 1.96 * 0.3741, 0.1422 + 1.96 * 0.3741] = [-0.59, 0.88]$

- LR-based 95% CI:
  $[-0.006979, 15.22]$



Dose-response curve

Dose-response curve

- Linear ERR model: one particular shape of dose-response relationship
- Allow for departure from linearity
- Test whether goodness of fit improves
- Departure can be mild or wild

Different shapes

Linear	ERR=βD (i.e., RR=1+βD)
Linear-quadratic	ERR=$\beta D + \gamma D^2$
Quadratic	ERR=γD^2
Cubic spline	ERR=$\beta_1 D + \beta_2 D^2 + \beta_3 D^3$ $+\beta_4 \text{max}(D - d_1, 0)^3 + \beta_5 \text{max}(D - d_2, 0)^3 + \ldots$
Exponential curvature	ERR=$\beta D e^{\gamma D}$
Linear threshold	ERR=$\beta \text{max}(D - d_1, 0)$
Non-parametric (categorical)	ERR=δ_j for $d_j - 1 \leq D < d_j$

Exponential curvature

$$RR = 1 + \beta D e^{\gamma D}$$

- Test departure from linearity by likelihood ratio test of H_0: $\gamma = 0$

- If linearity rejected:
  - Downward curvature (concave, $\gamma < 0$)
  - Upward curvature (convex, $\gamma > 0$)

More flexible curves – splines

$$RR = 1 + \beta_1 D + \beta_2 D^2 + \beta_3 D^3 + \beta_4 \text{max}(D - d_1, 0)^3 + \beta_5 \text{max}(D - d_2, 0)^3 + \ldots$$

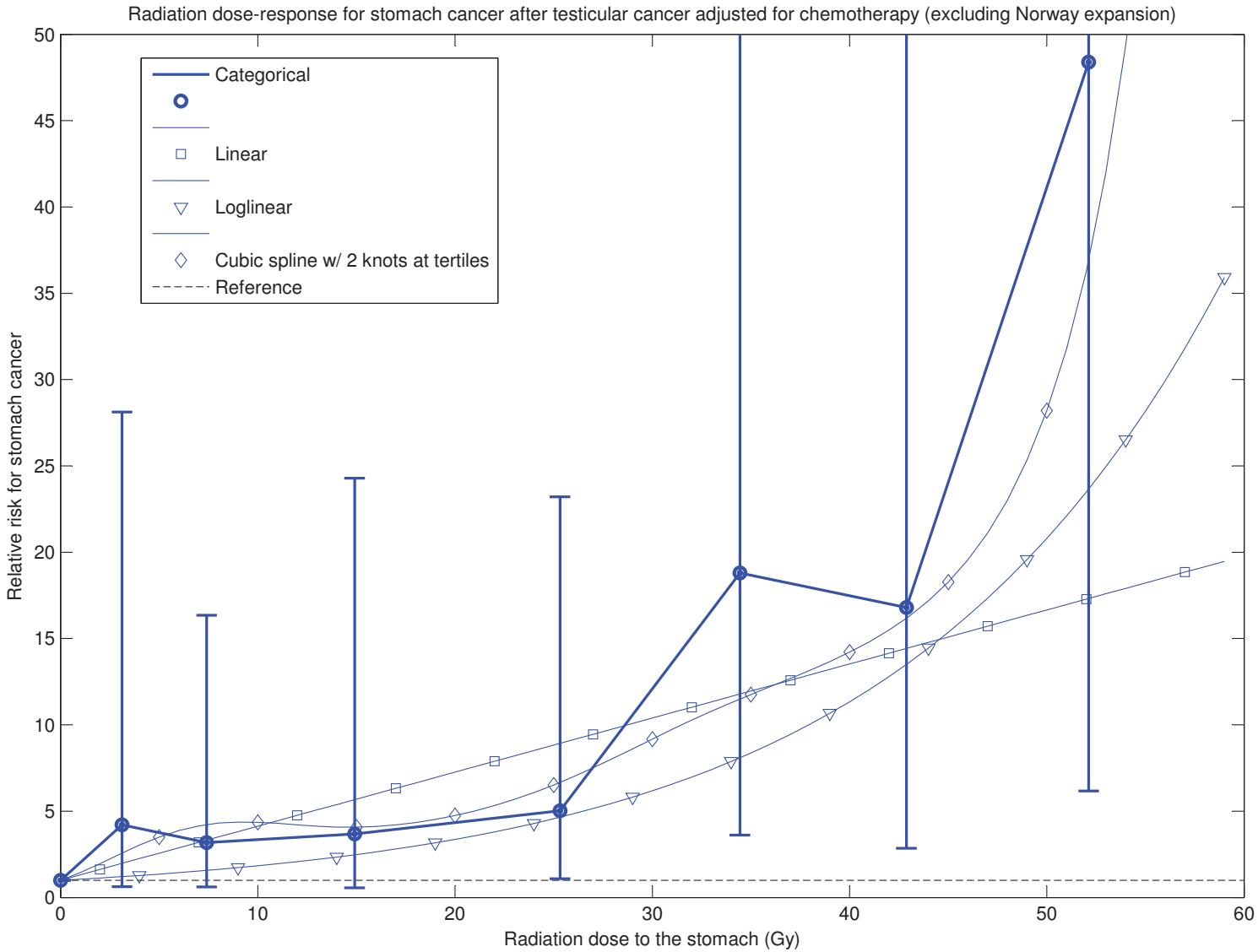
- Smooth piecewise polynomial with join points $d_1, d_2, \ldots$, to accommodate a local minimum or maximum
- Optimization for number and location of knots $d_1, d_2, \ldots$ difficult
  $\Rightarrow$ choose small number of knots at percentiles (e.g., tertiles)
- Linear model nested in spline model
- Cubic truncated power spline parametrization $\Rightarrow$ high correlation between spline covariates, erratic tail behavior
- More stable results with B-splines (orthogonal basis functions) or natural splines (restricted to linearity in the tails)

Example: Stomach cancer after testicular cancer

	# Cases	# Controls	OR	95% CI
Stomach radiation dose (Gy)				
0-9.9	15	49	1.0	Ref
10.0-19.9	7	16	2.0	0.5-8.7
20.0-29.9	17	43	2.5	0.8-7.9
30.0-39.9	28	39	7.2	2.1-24.9
40.0-49.9	11	21	6.7	1.7-27.1
>=50.0	8	6	20.5	3.7-114.3
Unknown	6	6		
p-trend			<0.001	

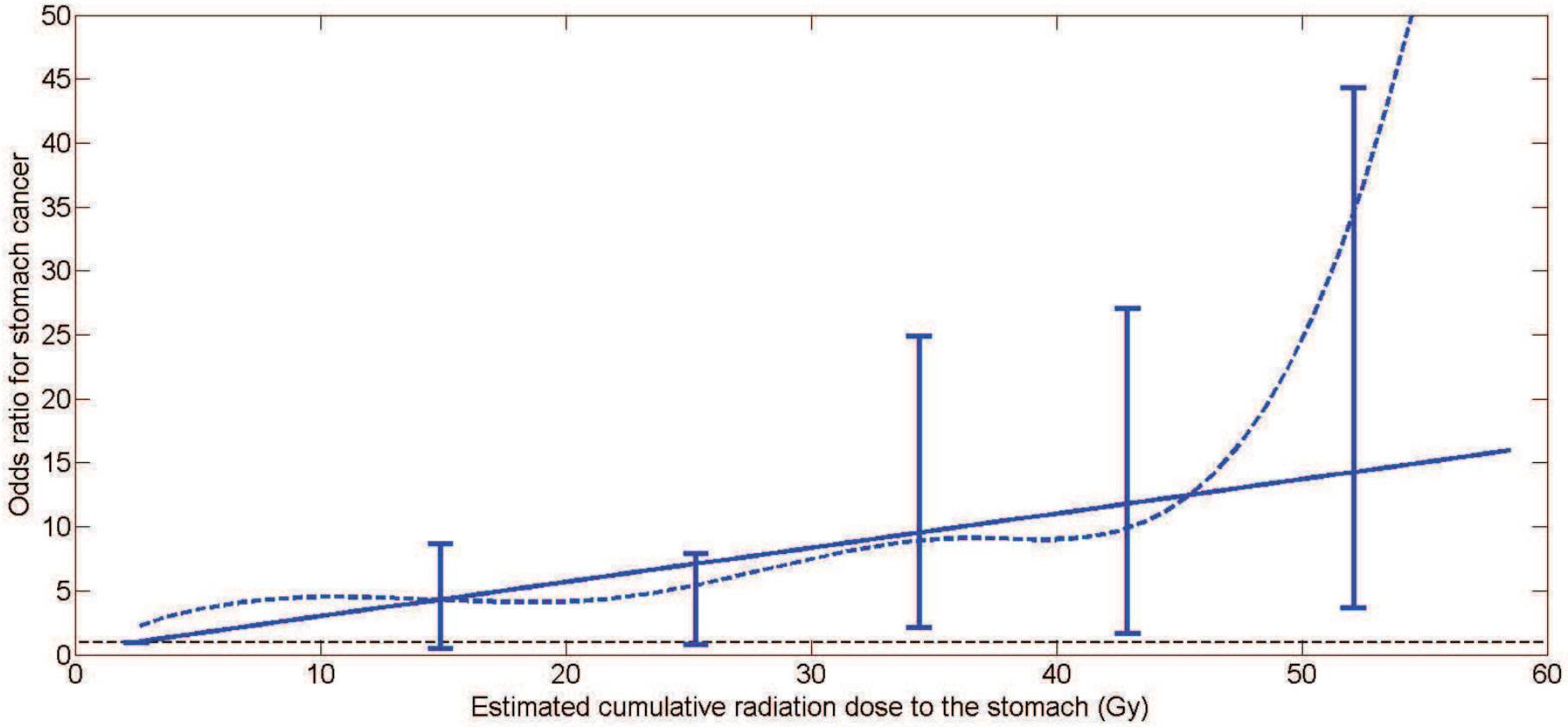
Hauptmann et al. 2014

Several non-linear models



Exponential curvature vs. linear p=0.567 (1 DF)

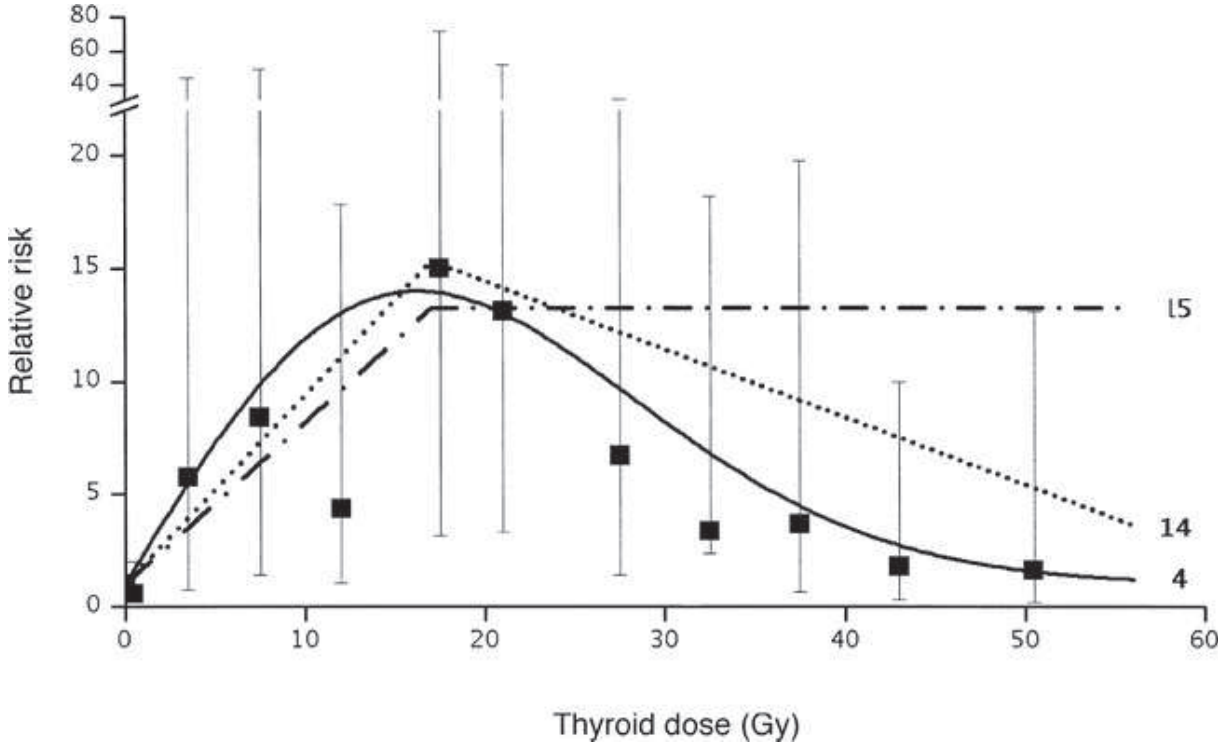
Linear fit and cubic spline



Cubic spline with 2 interior knots at dose tertiles among cases (22.1, 36.1)

Spline vs. linear p=0.456 (4 DF)

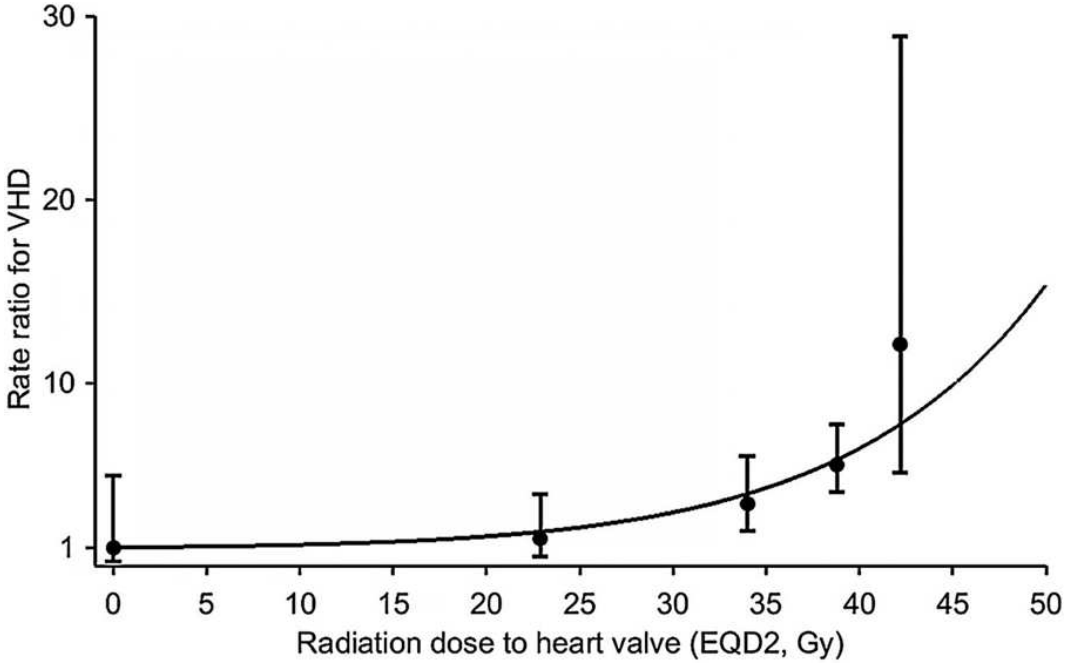
Thyroid cancer in the Childhood Cancer Survivor Study



No.	Model	Ref.	Deviance	p
1	$\mathrm{RR} = 1$	–	195.892	–
2	$\mathrm{RR} = 1 + 0.5117\,D$	1	164.919	<0.001
4	$\mathrm{RR} = 1 + 1.316\,D\,e^{-0.00189\,D^2}$	2	153.283	<0.001
14	$\mathrm{RR} = 1 + 0.8425\,D - 1.143\max(D-17, 0)$	2	154.566	0.0158
15	$\mathrm{RR} = 1 + 0.7211\min(D, 17)$	14	157.755	0.074

Ronckers et al., 2006

Valvular heart disease after treatment for Hodgkin lymphoma



$$\text{RR} = 1 + e^{\beta D} e^{\gamma D}$$

$$\beta = -5.015 \text{ (95\%CI } -9.867, -1.915)$$

$$\gamma = 0.07531 \text{ (95\%CI } 0.007243, 0.1774)$$

2-sided p-linearity=0.03

Cutter et al., 2015

Questions

- Is there an overall dose effect?
  Test $(\beta, \gamma) = (0, 0)$

- Can the results be summarized in one ERR estimate?
  No

- How can the results be summarized?
  In a figure

- What is the confidence of the dose-response?

~~Interaction~~ Joint effects

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- Effect of two factors together is greater (synergism) or less (antagonism) when they occur jointly than what would have been expected on the basis of their separate effects

- "Null" no-interaction model needed (expectation under independent joint action)

- "No interaction" based on additivity or multiplicativity?

Joint effect in radiation epidemiology

- Multiplicative model: $RR = e^{\alpha X}(1 + \beta D)$
- Multiplicative with departure term: $RR = e^{\alpha x}(1 + \beta D)e^{\delta(X*D)}$
- Additive model: $RR = 1 + \alpha X + \beta D$
- Additive with departure term:
  - $RR = 1 + (\alpha X + \beta D)e^{\delta(X*D)}$
  - $RR = 1 + \alpha X + \beta D + \delta(X * D)$

Additive or multiplicative "null" no-interaction model?

- Expectation under independent joint action of D & X

- Rare outcome, 2 causative factors acting through completely separate causal pathways $\Rightarrow$ expect additive joint effect

- However not always

Two hunters aiming at same duck

- Both good aim $\Rightarrow$ risk multiplicative in the complement
  each hunter hits duck w/ probability .6 $\Rightarrow$ risk for duck $= 1 - (1 - .6)^2$

- Both very bad aim $\Rightarrow$ risk for duck can be approximated by sum of 2 very small risks

- Probabilistically independent risks combine additively if they are small but not if they are large

- Continuous failure times: instantaneous risk (= hazard) small
  $\Rightarrow$ hazards additive

Weinberg 2012

Exceptions possible

- 2 factors acting independently at different stages of multistage carcinogenic process (initiator vs. promotor) $\Rightarrow$ combined effect multiplicative

- Example: initiator triples rate of formation of initiated cells, promotor doubles likelihood for each initiated cell to transform to cancerous cell $\Rightarrow$ 6-fold risk from exposure to both factors

Little difference multiplicative/additive for small risks

- Additive joint RR=RR(D)+RR(X)-1
- Multiplicative joint RR=RR(D)*RR(X)
- Multiplicative:additive

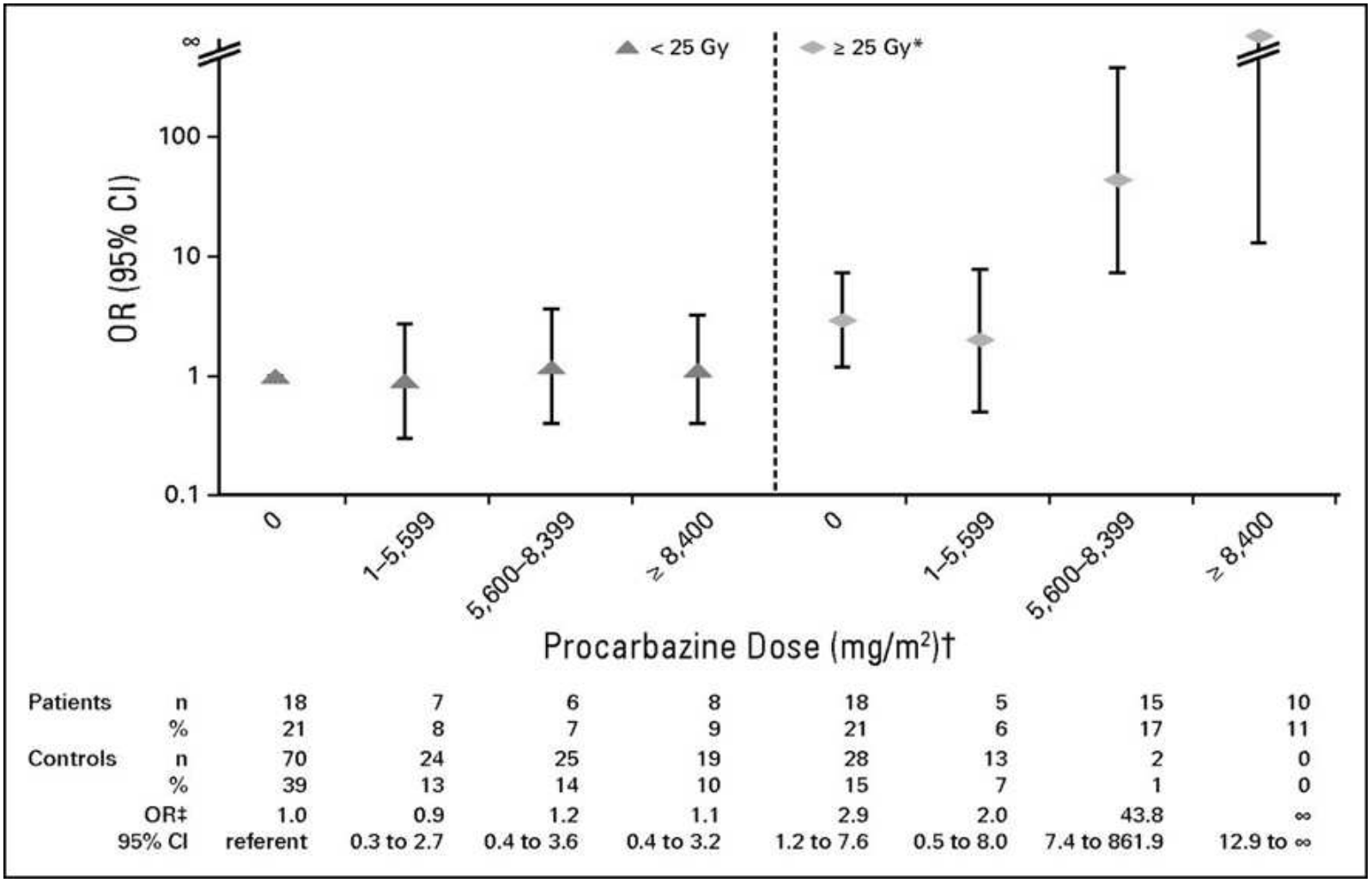
	RR(D)			
RR(X)	1.2	1.5	2.0	3.0
1.1	1.3:1.3	1.7:1.6	2.2:2.1	3.3:3.1
1.2	1.4:1.4	1.8:1.7	2.4:2.2	3.6:3.2
1.3	1.6:1.5	2.0:1.8	2.6:2.3	3.9:3.3
1.4	1.7:1.6	2.1:1.9	2.8:2.4	4.2:3.4
1.5	1.8:1.7	2.3:2.0	3.0:2.5	4.5:3.5

Synergy between radiotherapy and procarbazine among Hodgkin lymphoma survivors

Characteristic		Cases (n = 89)		Controls (n = 190)				
Radiation Dose (Gy)*	Procarbazine dose (mg/m^2)†	No.	%‡	No.	%‡	OR	95% CI‡	$P_{interaction}$§
All patients								< .001
< 25	< 5,600	25	29	94	52	1.0	Referent	
≥ 25	< 5,600	23	26	41	23	2.8	1.3 to 6.4	
< 25	≥ 5,600	14	16	44	24	1.2	0.5 to 2.7	
≥ 25	≥ 5,600	25	29	2	1	77.5	14.7 to 1,452	

Morton et al. 2013

Synergy between radiotherapy and procarbazine among Hodgkin lymphoma survivors



Patients	n	18	7	6	8	18	5	15	10
	%	21	8	7	9	21	6	17	11
Controls	n	70	24	25	19	28	13	2	0
	%	39	13	14	10	15	7	1	0
	OR‡	1.0	0.9	1.2	1.1	2.9	2.0	43.8	∞
	95% CI	referent	0.3 to 2.7	0.4 to 3.6	0.4 to 3.2	1.2 to 7.6	0.5 to 8.0	7.4 to 861.9	12.9 to ∞

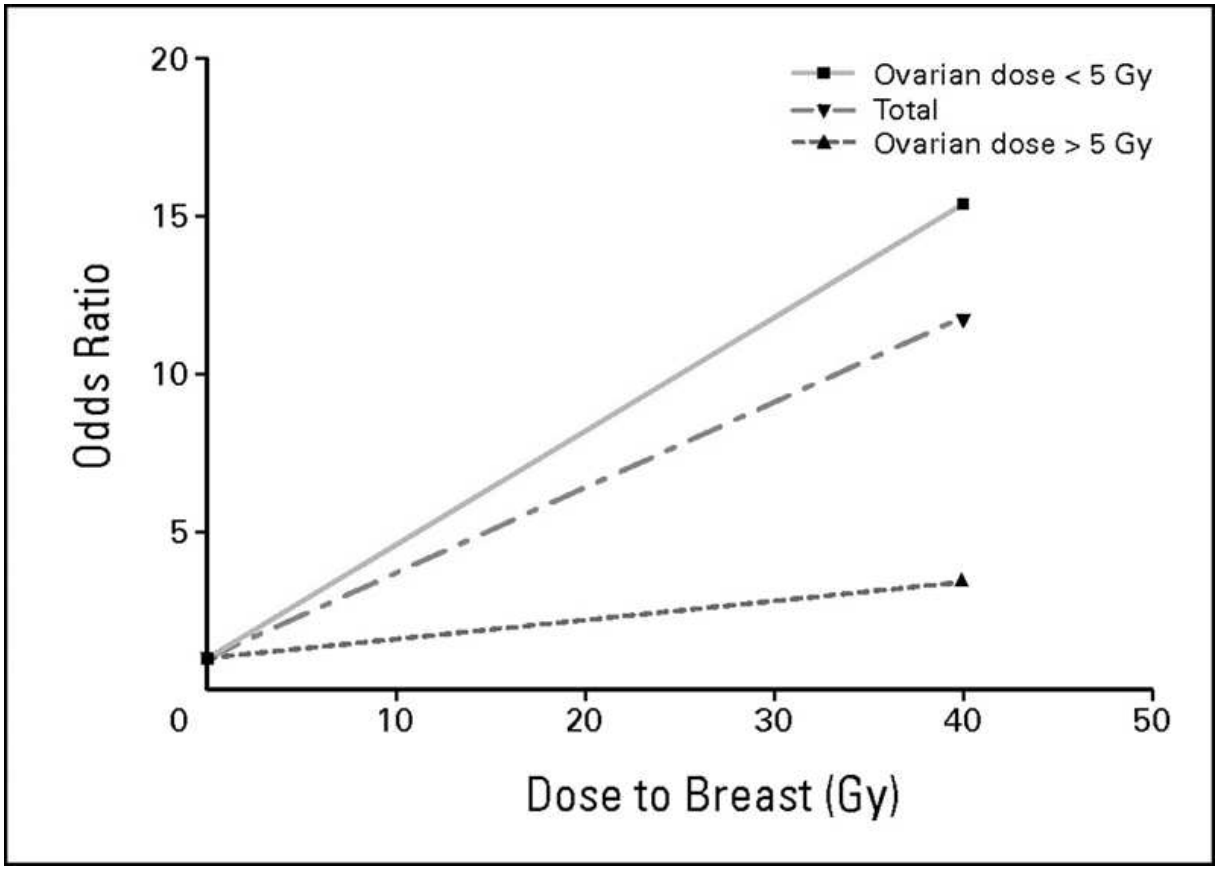
Morton et al. 2013

Antagonism between breast dose and ovary dose on breast cancer risk among childhood cancer survivors

Characteristic	No. of Patients	No. of Controls	Analysis		
			EOR/Gy	95% CI	*P**
Overall	107	389	0.27	0.10 to 0.67	< .0001
Age at initial cancer, years					.43
< 13	15	74	0.29	0.06 to 1.09	
13-15	37	125	0.44	0.14 to 1.36	
16-20	55	190	0.21	0.06 to 0.62	
Type of initial cancer†					
HL	67	145	Model fit failed‡		Unknown
All others	40	244	0.21	0.09 to 0.51	
Year of initial cancer					
1970-1974	53	175	0.33	0.12 to 0.90	.57
1975-1979	41	156	0.24	0.08 to 0.66	
1980-1986	13	86	0.19	−0.07 to 0.64	
Years since first cancer					.25
5.00-4.9	24	85	0.39	0.09 to 1.77	
15.0-19.9	32	115	0.35	−0.13 to 1.71§	
20.0-24.9	31	115	0.26	0.06 to 1.01	
25.0-32.0	20	74	0.13	−0.09 to 0.70§	
Attained age, years					.17
18-34	46	184	0.33	0.11 to 0.92	
35-39	41	134	0.56	0.15 to 1.93	
40-44	14	52	0.02	−0.06 to 0.09‖	
45-50	6	19	0.70	−1.56 to 2.95‖	
Radiation dose to ovaries, Gy					.002
< 5	99	342	0.36	0.14 to 0.93	
≥ 5	8	47	0.06	−0.06 to 0.27§	

Inskip et al. 2009

Antagonism between breast dose and ovary dose on breast cancer risk among childhood cancer survivors



Inskip et al. 2009

CVD in 10,000 breast cancer survivors

- Joint effect of radiotherapy to the internal mammary chain and anthracycline-containing chemotherapy

- Non-parametric model

IMC	Anthra	RR	95% CI
N	N	1.0	Ref
Y	N	1.5	1.4, 1.7
N	Y	1.5	1.1, 1.9
Y	Y	2.1	1.7, 2.7

Consistency with additive & multiplicative models

- Departure from additive joint effect (p>.5)

$$RR = 1 + .52\,IMC + .45\,Anthra + .16\,(IMC*Anthra)$$

- Departure from multiplicative joint effect (p>.5)

$$RR = EXP\{.42\,IMC + .37\,Anthra - .037\,(IMC*Anthra)\}$$

Dose metric

Uncertainty in selection of dose metric

- Exposed yes/no $\rightarrow$ Whole body dose $\rightarrow$ Organ dose $\rightarrow$ Dose to tumor location

- In prospective studies (cohorts): organ dose is best

- In retrospective studies (case-control): dose to tumor location

- Important since gradients of dose can be steep in medical radiation

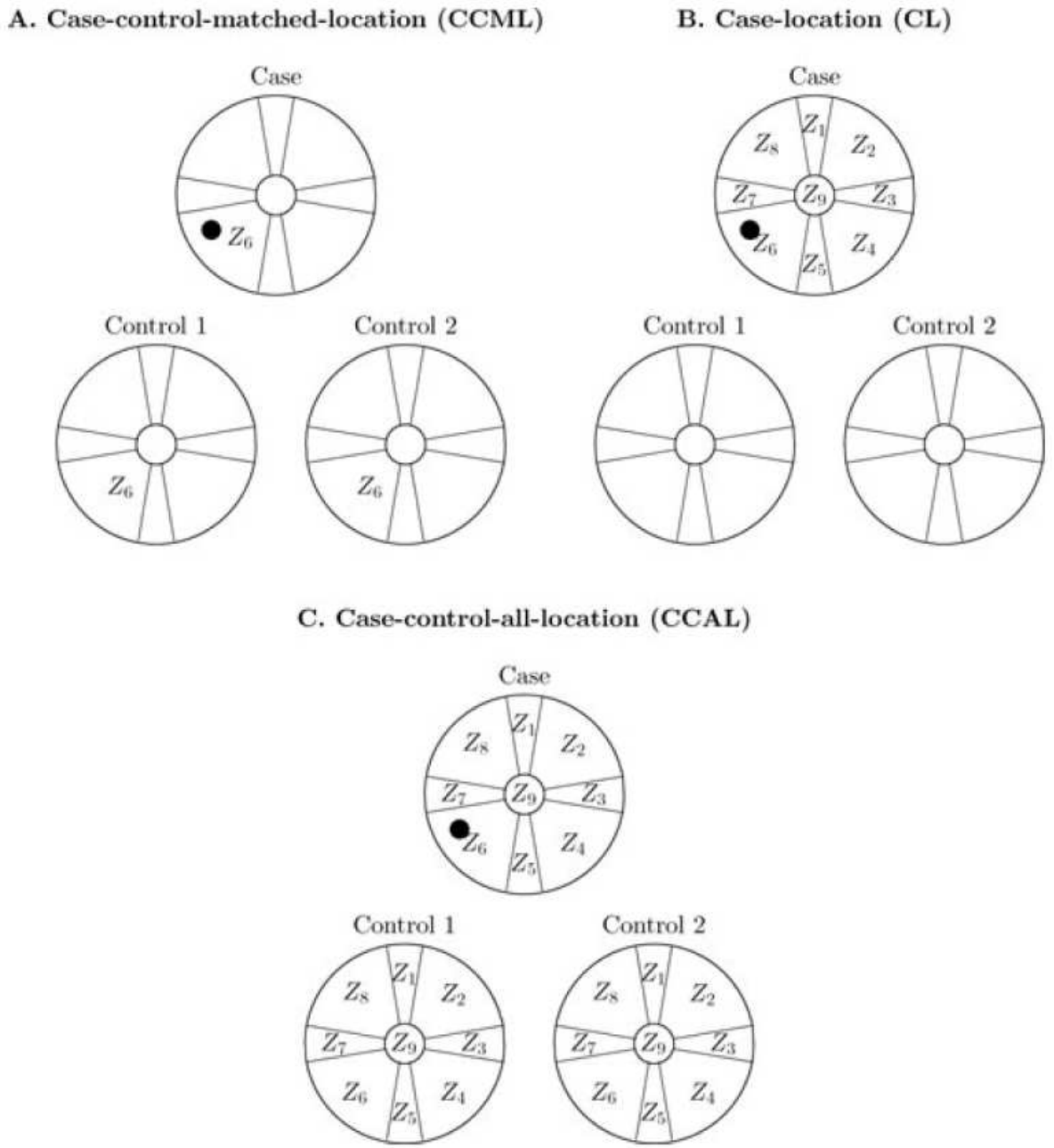
Case-control studies

- Dose to tumor location and corresponding location in matched controls
- Segmentation of target organ in subsites
- Subsite-specific dose estimation
- Often: average anatomy assumed

Example: Stomach cancer after testicular cancer

- For each testicular cancer treatment combination, dose estimated to 464 points in a stomach with typical anatomy
- Doses averaged within subsites cardia, fundus, body, antrum and pylorus
- For cases, used dose to tumor location, for controls dose to same location as matched case

Why use only dose to tumor location?



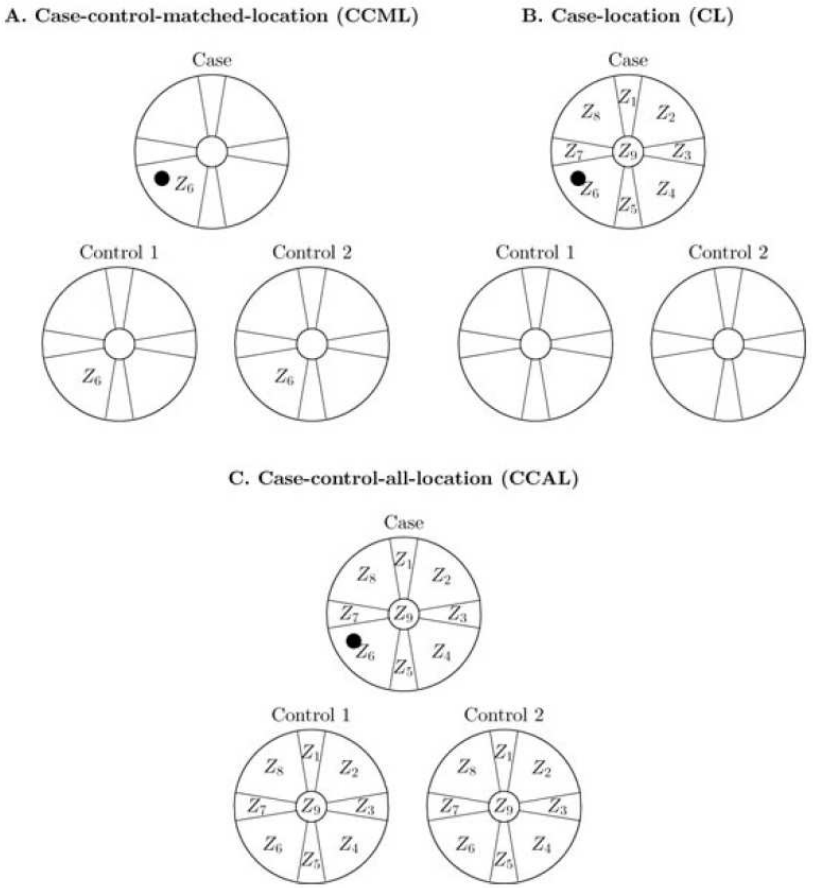
Langholz et al., 2009

Properties of different methods

- CCML
  1:2
  Wastes a lot of information

- CL
  1:8
  Immune against control selection bias
  Cost savings since no controls needed

- CCAL
  1:26
  Most efficient since all data used



Some complications

- Some cases with unknown tumor location
- Subsite-specific baseline cancer incidence needs to be modelled
- Unexposed cases are lost from CL
- Assumption: biologically relevant dose at a specific location is radiation dose at that location
- Ignores non-targeted or volume effects (stem cell repopulation, bystander effect)
- Not yet applied to real data

Combination of organs with individual organ dose estimates

- Imagine cohort study with organ dose estimates for >10 different organs
- Cancer at individual sites is rare so combination of sites is necessary
- Which dose should be used?

Joint analysis of site-specific cancer risk (Pierce & Preston 1993)

- Each subject contributes k observations, one for each organ
- Each organ in each subject has its own survival time & is associated with unique radiation dose
- Unit of observation = organ not individual
- Competing risk theory for censored survival data

Example: Solid cancer incidence in a-bomb survivors

- Stomach dose for cancers of the digestive tract
- Lung dose for the respiratory system
- Intestinal dose for other cancers

Source of variation	*df*	χ^2	*P* value
Type: main effect	2	0.48	0.79
Age at exposure by type	2	3.58	0.17
Sex by type	3	0.07	0.99

Pierce & Preston 1993

Wrap-up

- Nested case-control study
- Linear excess relative risk model
- Shape of dose-response relationship
- Interaction
- Choice of dose metric