Epidemiological Evidence for Possible Radiation Hormesis from Residential Radon Exposure: A Case-Control Study Conducted In Worcester County, MA.

Richard E. Thompson
Department of Biostatistics
Johns Hopkins Bloomberg School of Public Health

OUTLINE OF TALK

- Background on Dosimetry and Study Design

- Review of Overall Results

- Overview of Models Used to Analyze the Data

- Discussion of How these Results Compare to Other North American Studies

DOSIMETRY

Radon measured in yearlong exposure

- 'Blanks' and 'spikes' were in each batch

- Number determined by U.S. EPA's National Air and Radiation Environmental Lab in AL

- Correction factor was calibrated from spikes

1/10 homes had two detectors placed side-by-side

STUDY DESIGN

Case-Control Design (1 case : 2 controls)

- 200 cases / 397 controls

- All were members of same HMO

- All were residents of Worcester, Co

- Study protocol followed CT study

STUDY DESIGN

Cases

- ≥ 40 years of age
- Primary lung cancer histologically or cytologically confirmed
- Minimum of 10 year residency

Controls

- Randomly selected from same HMO
- Two controls matched to each case by gender and age (+/- 2.5 years).

STUDY DESIGN

Extensive interviews were conducted for each case and control – general demographics

A detailed smoking history was obtained on the type and number of cigarettes smoked / decade

Surrogate interviews were obtained due to death

- Spouse or offspring were used as surrogates
- 3.3% of controls and 21.5% of cases

STUDY DESIGN

Distribution of wakeful time spent in the living room, bedroom(s), and other levels of the home

- Occupancy distribution determined placement of detectors

-Estimated exposure weighted by this distribution of in-home occupancy

- Accounted for changes in ‘life-events’

STATISTICAL ANALYSIS

Conditional Logistic was used on binary outcome

-Multivariable model controlled for smoking, residency, education, income, and job exposure

-Smoking quantified with eight variables based on categories of pack-years (current smokers) and years since last smoked (former smokers)

RESULTS

	Controls	Cases	p-value
Residency (y)			
< 20	90 (22.7%)	62 (31.0%)	0.081
20–39	203 (51.1%)	94 (47.0%)	
≥ 40	104 (26.2%)	44 (22.0%)	

RESULTS

Unadjusted OR for Income and Education

	Cases/ Controls	Odds Ratio
< $ 30,000 / y	109/159	1.00
≥ $ 30,000 / y	58/190	0.37[c]
< High School	67/77	1.00
H.S. Graduate	90/149	0.66[a]
≥ Some College	40/165	0.22[c]

[a] $p \leq 0.10$ [b] $p \leq 0.05$ [c] $p \leq 0.001$

RESULTS

Unadjusted OR for Job Exposure

	Cases/ Controls	Odds Ratio
0 years	134/290	1.00
1-9 years	25/52	1.07
≥ 10 years	41/55	1.74[b]

[a] $p \leq 0.10$ [b] $p \leq 0.05$ [c] $p \leq 0.001$

RESULTS

Unadjusted OR for Current Smokers

	Cases/ Controls	Odds Ratio
Never Smoked	15/162	1.00
5–30 Pack-y	15/12	10.75[c]
30–50 Pack-y	40/12	50.23[c]
50–60 Pack-y	16/7	49.26[c]
> 60 Pack-y	34/8	68.39[c]

[a] $p \leq 0.10$ [b] $p \leq 0.05$ [c] $p \leq 0.001$

RESULTS

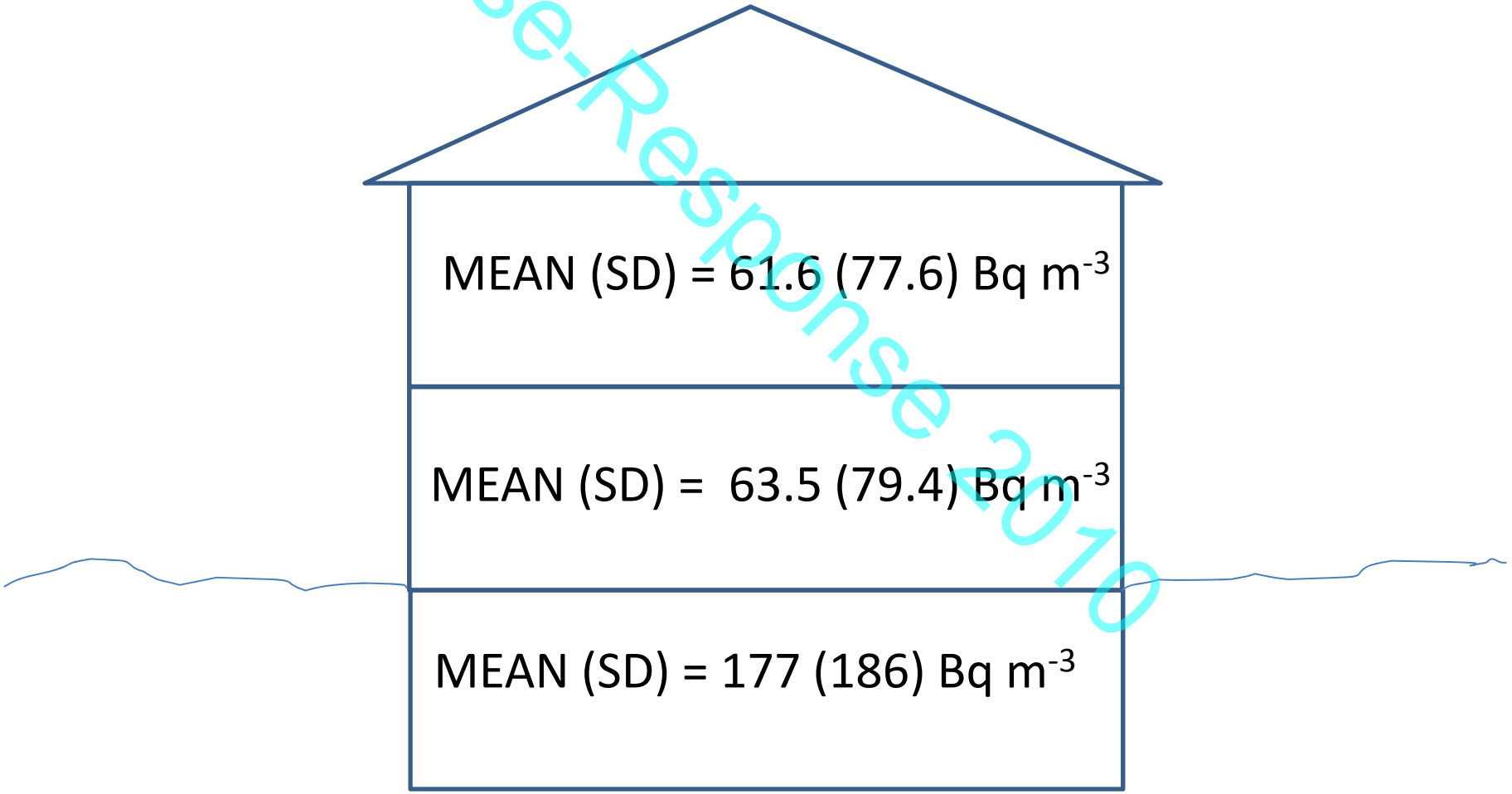
Unadjusted OR for Former Smokers

	Cases/ Controls	Odds Ratio
Never Smoked	15/162	1.00
3–5 y	20/13	17.66[c]
6–10 y	22/16	19.50[c]
11–15 y	15/31	6.12[c]
> 15 y	23/136	2.09[a]

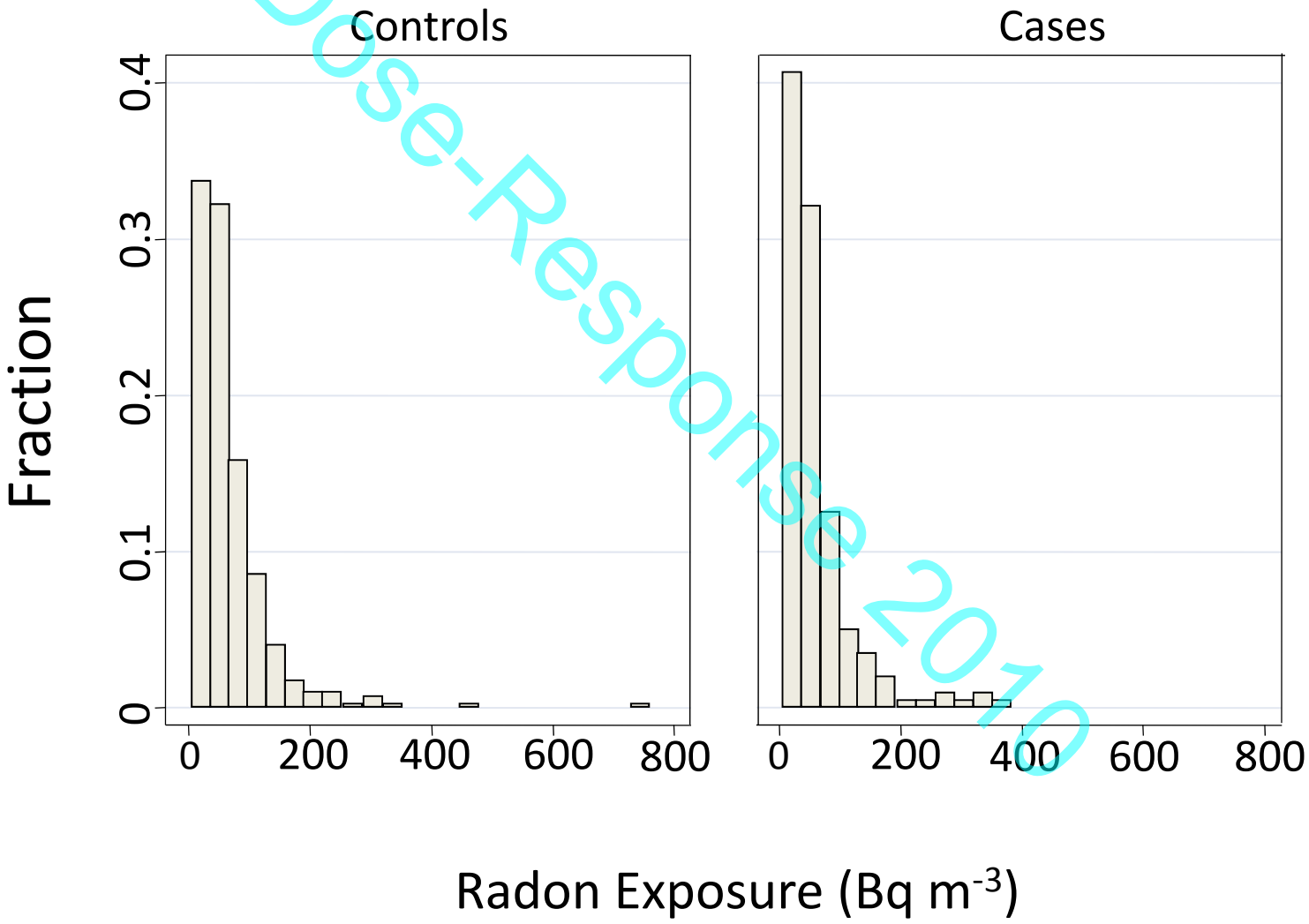
[a] $p \leq 0.10$ [b] $p \leq 0.05$ [c] $p \leq 0.001$

RESULTS

Observed Mean Rn Concentrations in Bedroom, Living Room, and Basement



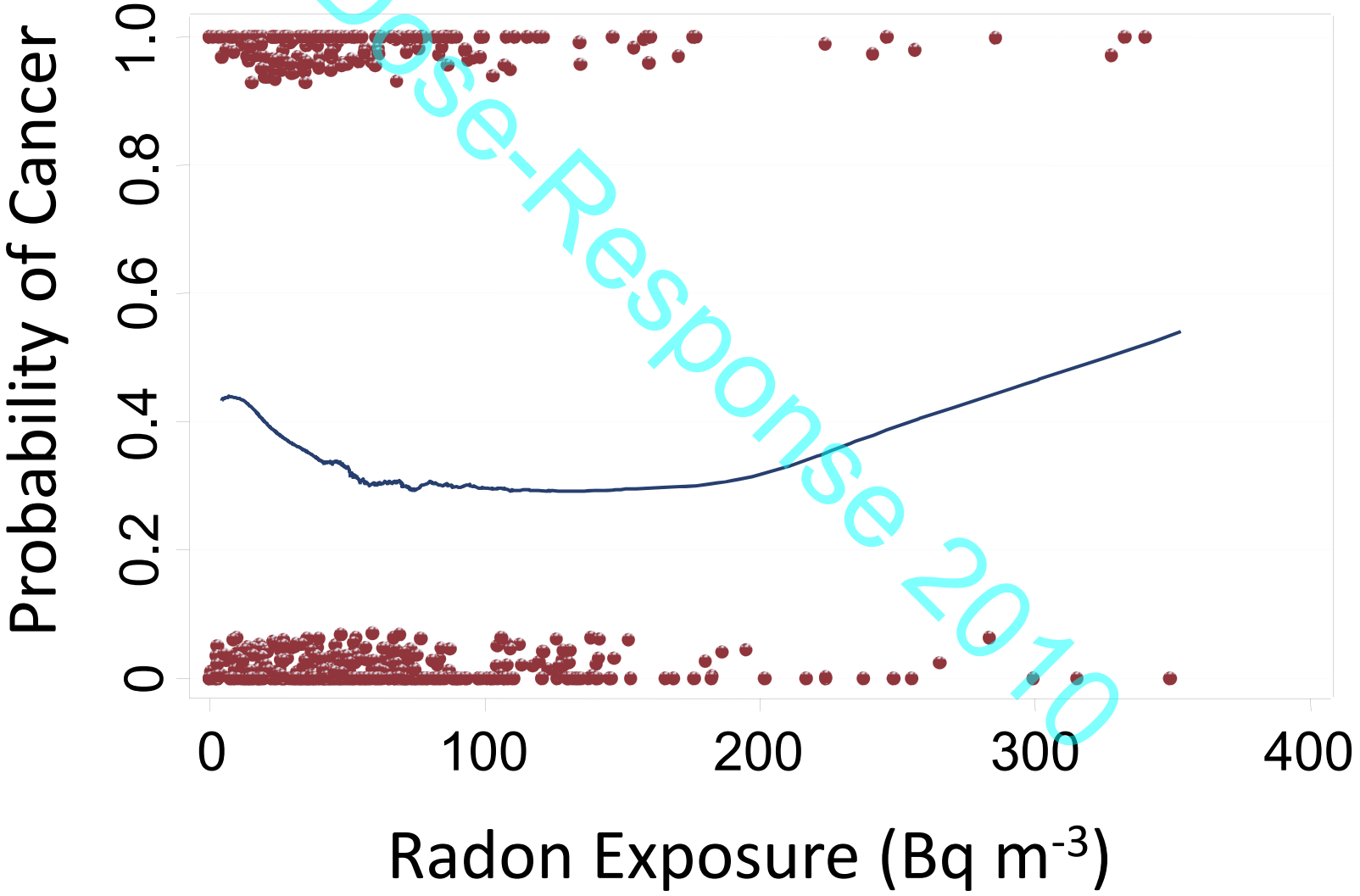
Distribution of Weighted Radon Exposure

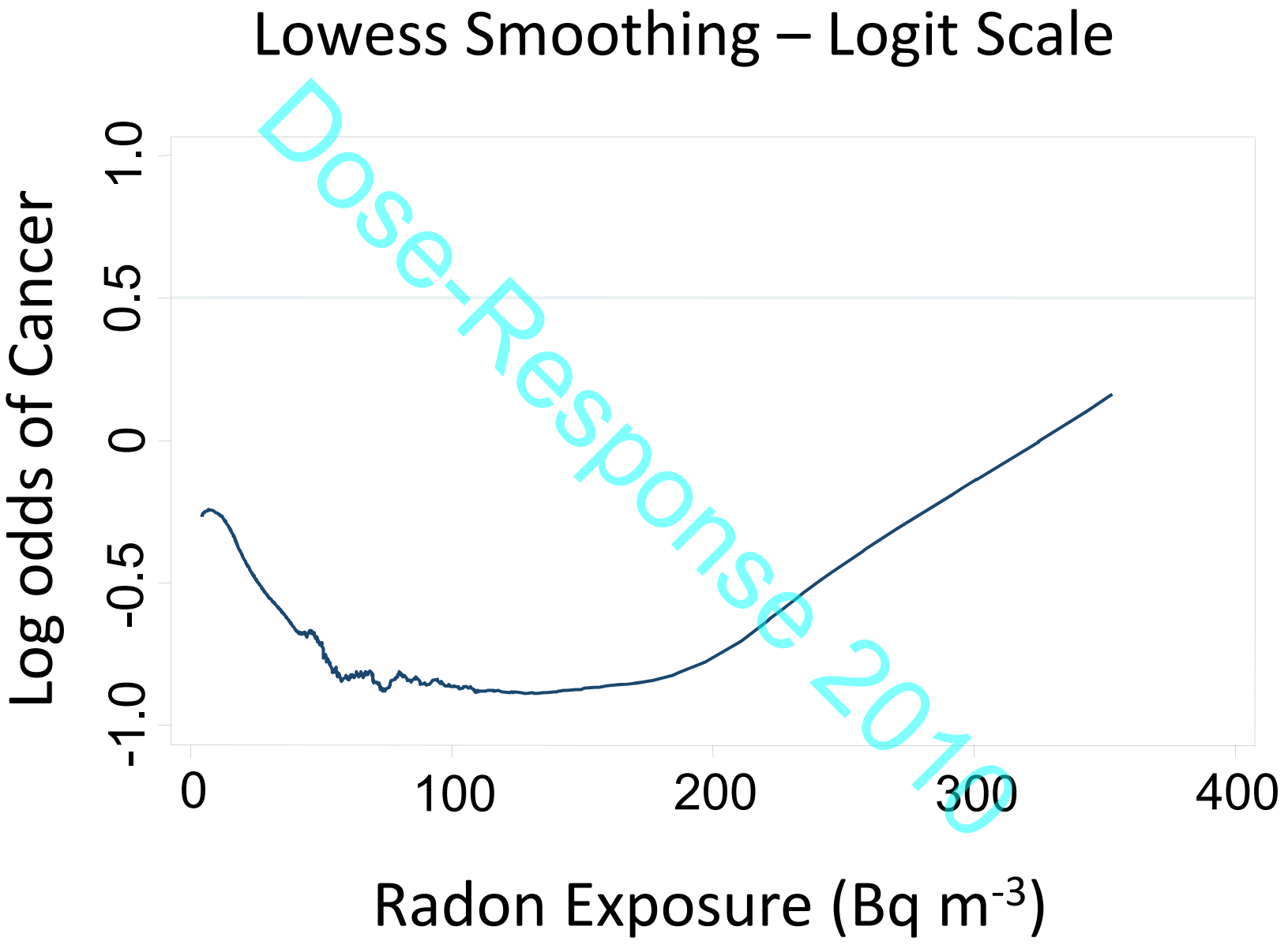


RESULTS

	Controls	Cases	p-value
Mean Rn exposure	66.3 (65.2)	67.5(118.5)	0.086
One outlier removed (~1511 Bq m^{-3})	66.3 (65.2)	60.2 (59.4)	0.047
Median Rn exposure	50.2	43.7	0.039
One outlier removed	50.2	43.6	0.030

Lowess Smoothing of Cancer on Radon Exposure




Lowess Smoothing – Logit Scale
Dose-Response 2018
Log odds of Cancer
1.0
0.5
0
-0.5
-1.0
0
100
200
300
400
Radon Exposure (Bq m-3)

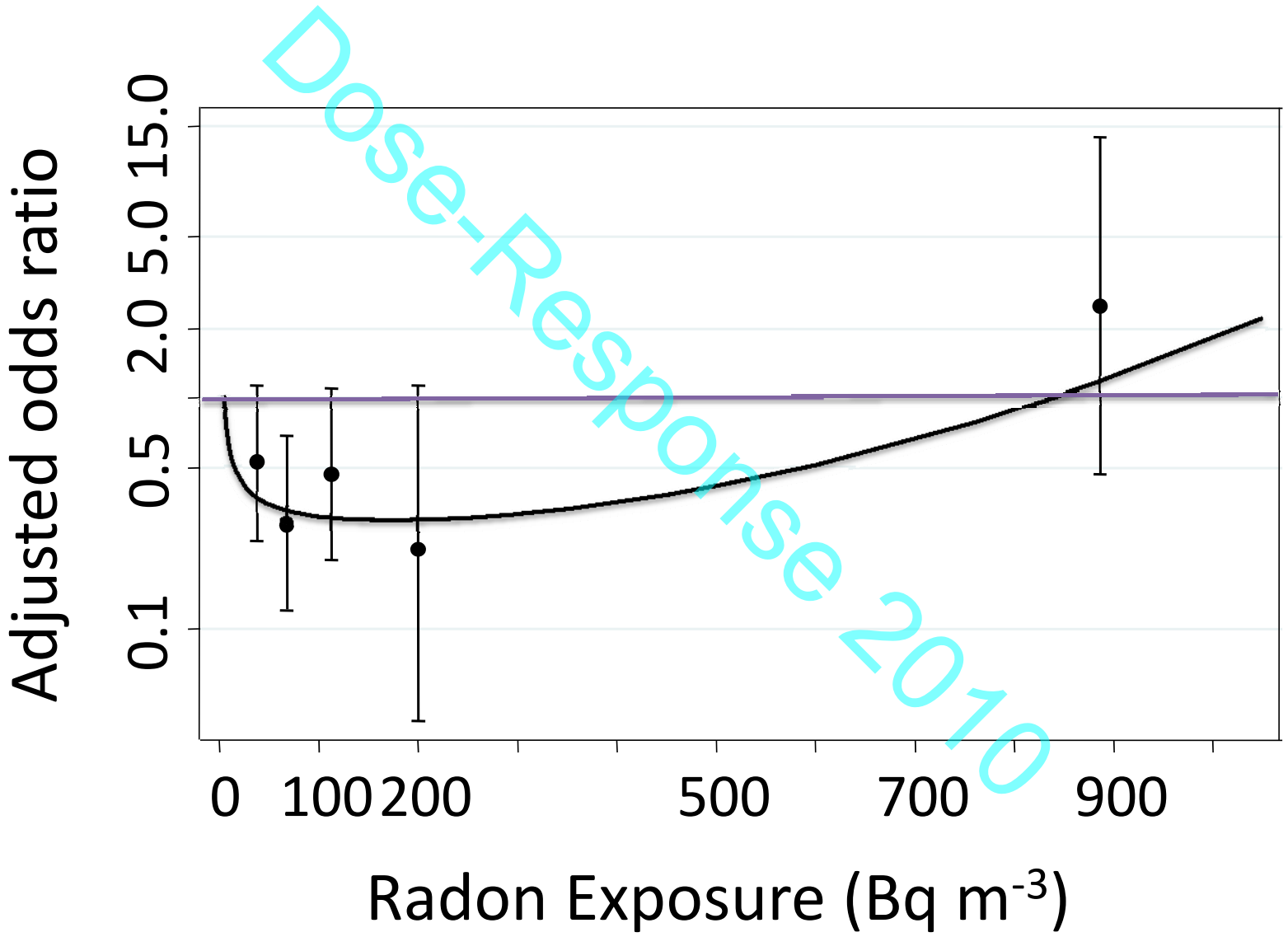
RESULTS

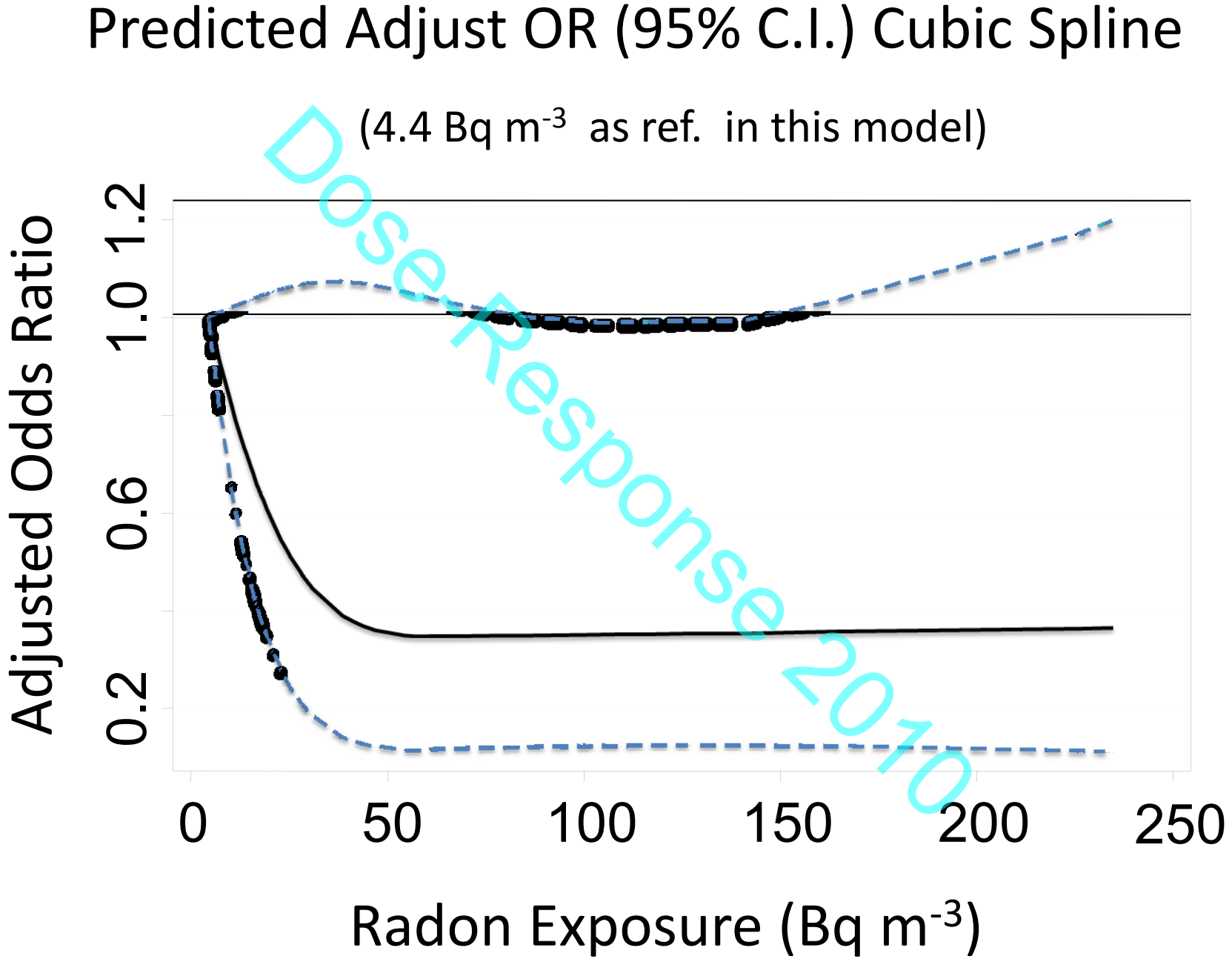
Unadjusted OR for Categories of Exposure

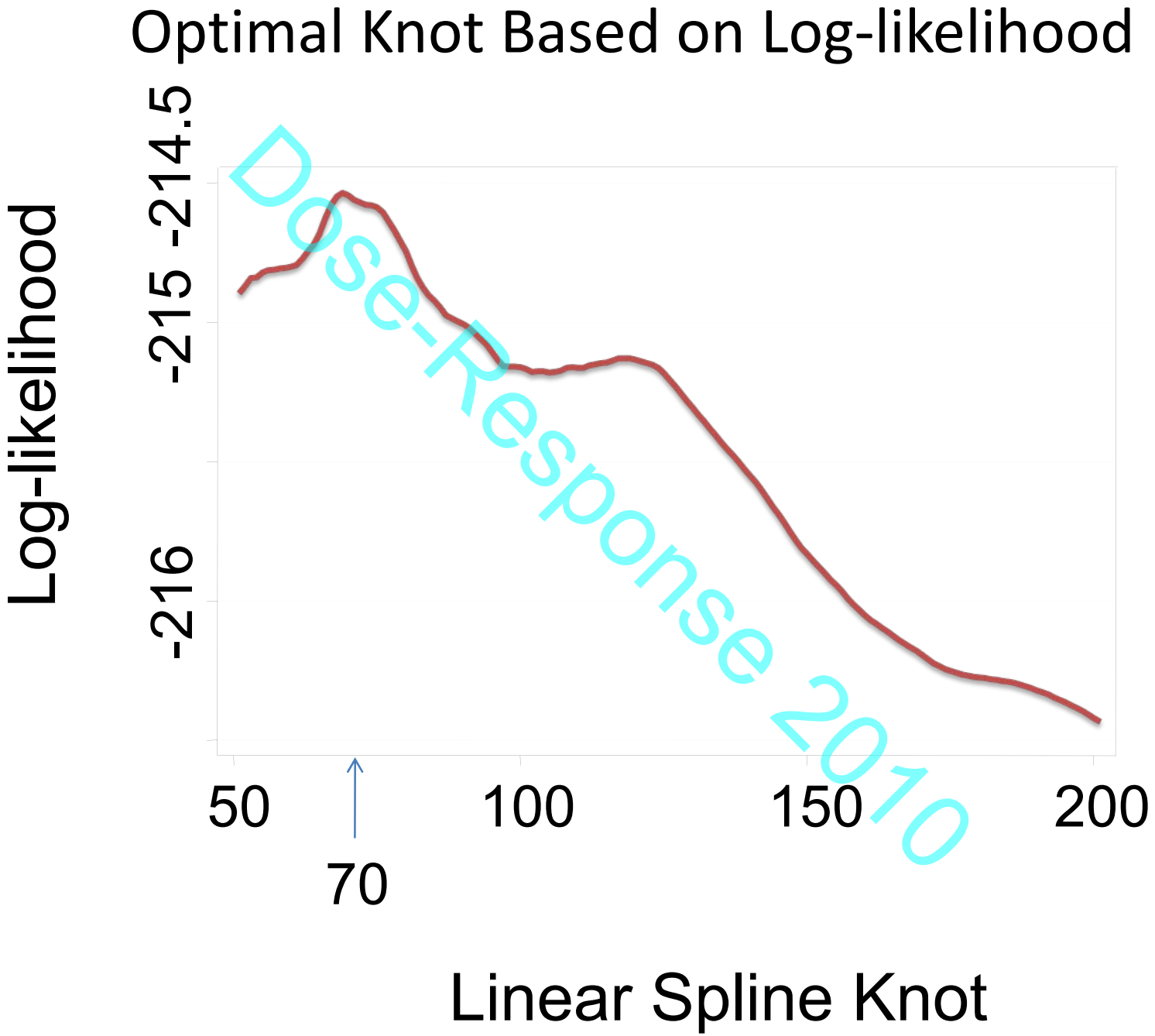
	Cases/ Controls	Odds Ratio
< 25 Bq m^{-3}	57/70	1.00
25–< 50 Bq m^{-3}	60/127	0.53[b]
50–< 75 Bq m^{-3}	34/89	0.45[b]
75–< 150 Bq m^{-3}	34/86	0.44[b]
150–< 250 Bq m^{-3}	8/18	0.49
≥ 250 Bq m^{-3}	7/7	1.20

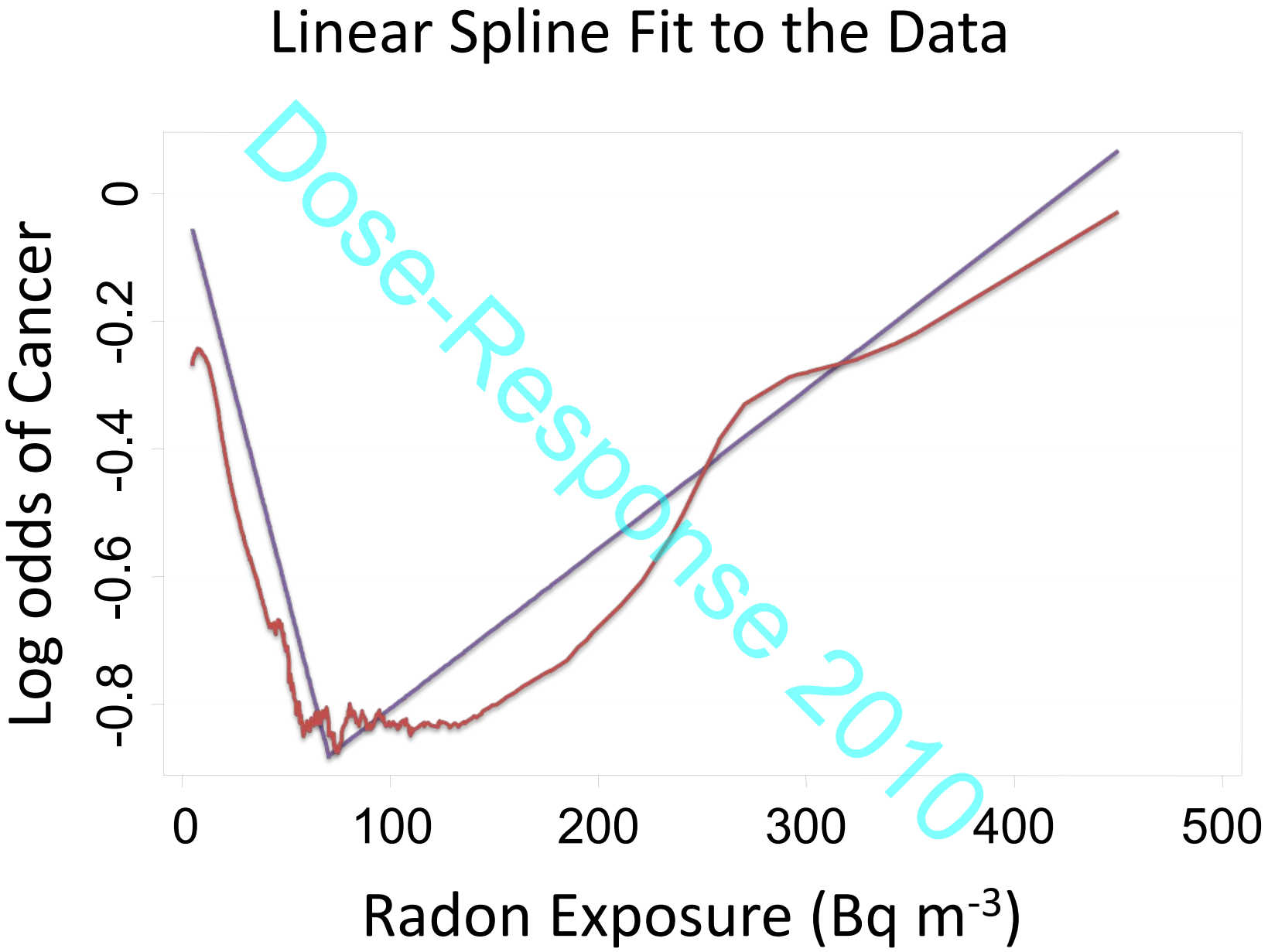
[a] $p \leq 0.10$ [b] $p \leq 0.05$ [c] $p \leq 0.001$

Adjust OR from Rn Categories – Cubic Spline Fit




Predicted Adjust OR (95% C.I.) Cubic Spline
(4.4 Bq m-3 as ref. in this model)
Dose-Response 2010
Adjusted Odds Ratio
0.2
0.6
1.0
1.2
0
50
100
150
200
250
Radon Exposure (Bq m-3)


Optimal Knot Based on Log-likelihood
Log-likelihood
-214.5
-215
-216
Dose-Response 2010
50
70
100
150
200
Linear Spline Knot


Linear Spline Fit to the Data
Dose-Response 2010
Log odds of Cancer
0
-0.2
-0.4
-0.6
-0.8
0
100
200
300
400
500
Radon Exposure (Bq m-3)

Results from Linear Spline Model

< 70 Bq m^{-3}

AOR [95% CI] = 0.984 [0.970, 0.998] (p = 0.021)

≥ 70 Bq m^{-3}

AOR [95% CI] per 100 Bq m^{-3} = 1.246 [0.877, 1.771]

Comparison with N. American Pooling Study:

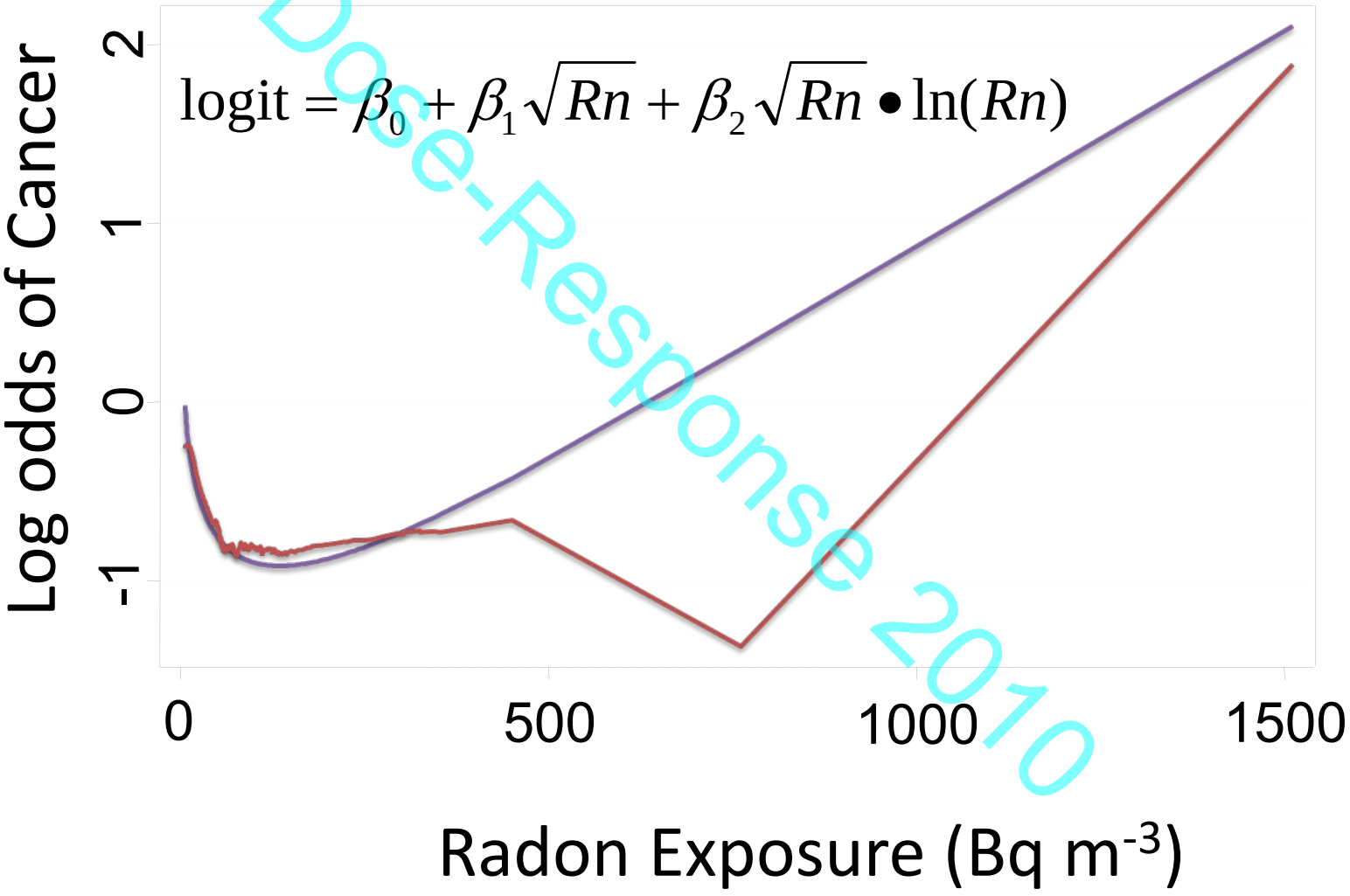
AOR [95% CI] per 100 Bq m $^{-3}$
= 1.18 [1.02, 1.43]

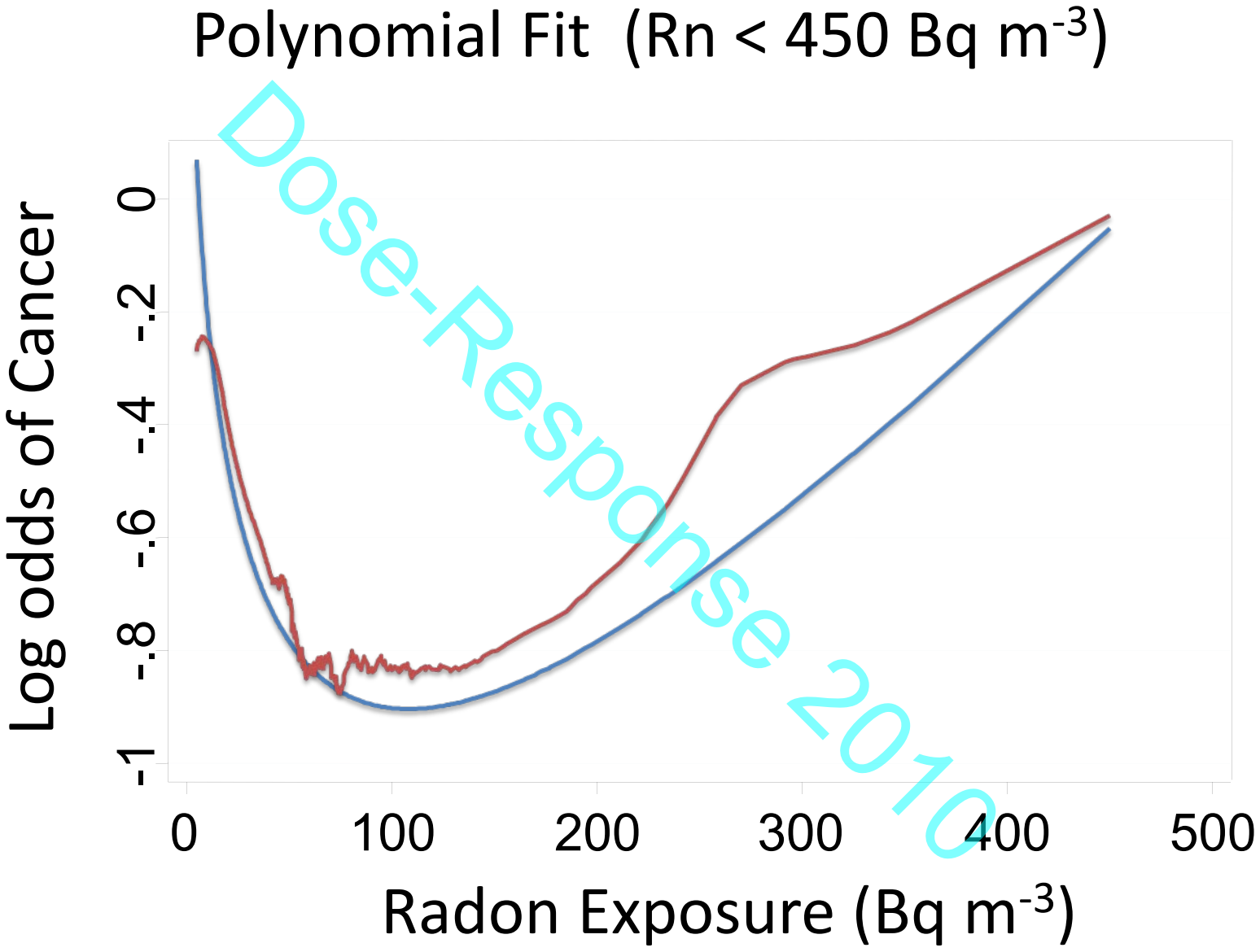
(≤ 2 residences / ≥ 20 years α-track Rn meas.)

AOR [95% CI] per 100 Bq m $^{-3}$
= 1.10 [-1.01, 1.26]

(all data / subjects)

Polynomial Fit to the Data




Polynomial Fit (Rn < 450 Bq m-3)
Dose-Response 2010
Log odds of Cancer
0
-.2
-.4
-.6
-.8
-1
0
100
200
300
400
500
Radon Exposure (Bq m-3)

62.5 Bq m^{-3} v. 4.4 Bq m^{-3}

	AOR	95% CI
Cubic Spline	0.35	[0.14, 1.07]
Linear Spline	0.39	[0.18, 0.87]
Polynomial Model	0.33	[0.12, 0.90]
Categorical Model [50 - <75 v. 25]	0.31	[0.13, 0.73]

112.5 Bq m^{-3} v. 4.4 Bq m^{-3}

	AOR	95% CI
Cubic Spline	0.35	[0.13, 0.99]
Linear Spline	0.38	[0.16, 0.91]
Polynomial Model	0.29	[0.09, 0.90]
Categorical Model [75 - <150 v. 25]	0.47	[0.20. 1.10]

200 Bq m^{-3} v. 4.4 Bq m^{-3}

	AOR	95% CI
Cubic Spline	0.36	[0.12, 1.10]
Linear Spline	0.46	[0.19, 1.12]
Polynomial Model	0.29	[0.08, 1.00]
Categorical Model [150 - <250 v. 25]	0.22	[0.04, 1.13]

880 Bq m^{-3} v. 4.4 Bq m^{-3}

	AOR	95% CI
Cubic Spline	0.47	[0.11, 2.04]
Linear Spline	2.07	[0.14, 31.7]
Polynomial Model	1.81	[0.11, 29.1]
Categorical Model [>= 250 v. 25]	2.50	[0.47, 13.46]

Comparison with N. American Pooling Study:

Krewski et al (2006):

AOR [95% CI] per 100 Bq m^{-3}
= 1.18 [1.02, 1.43]

L.S. (≥ 70 Bq m^{-3}):

AOR [95% CI] per 100 Bq m^{-3}
= 1.25 [0.88, 1.77]

LNT Model from Krewski et al 2006

$$OR(x) = 1 + 0.0018x$$

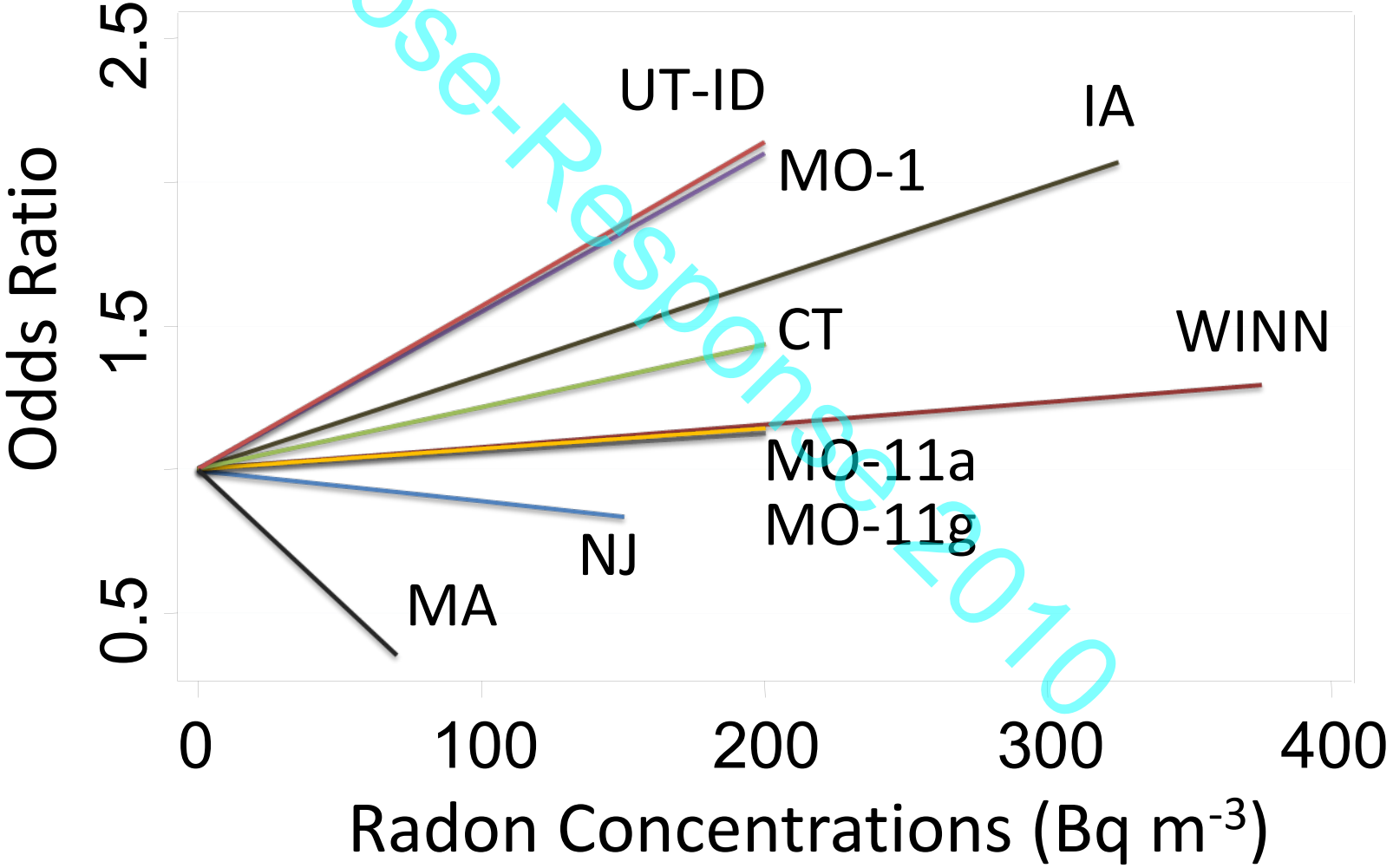
OR at 880 Bq m^{-3} = 2.58 [1.18, 4.79]

Cat. OR [95% CI] = 2.50 [0.47, 13.5]

L.S. OR [95% CI] = 2.07 [0.14, 31.7]

DISCUSSION

Results of N. American Studies (Krewski et al 2006)



DISCUSSION

Can Variability of Predicted Risk from All Studies be Due to Random Sampling Variability?

- All studies estimate the ‘true’ radon risk
- Deviance from ‘truth’ is random variability
- We can’t dismiss this possibility

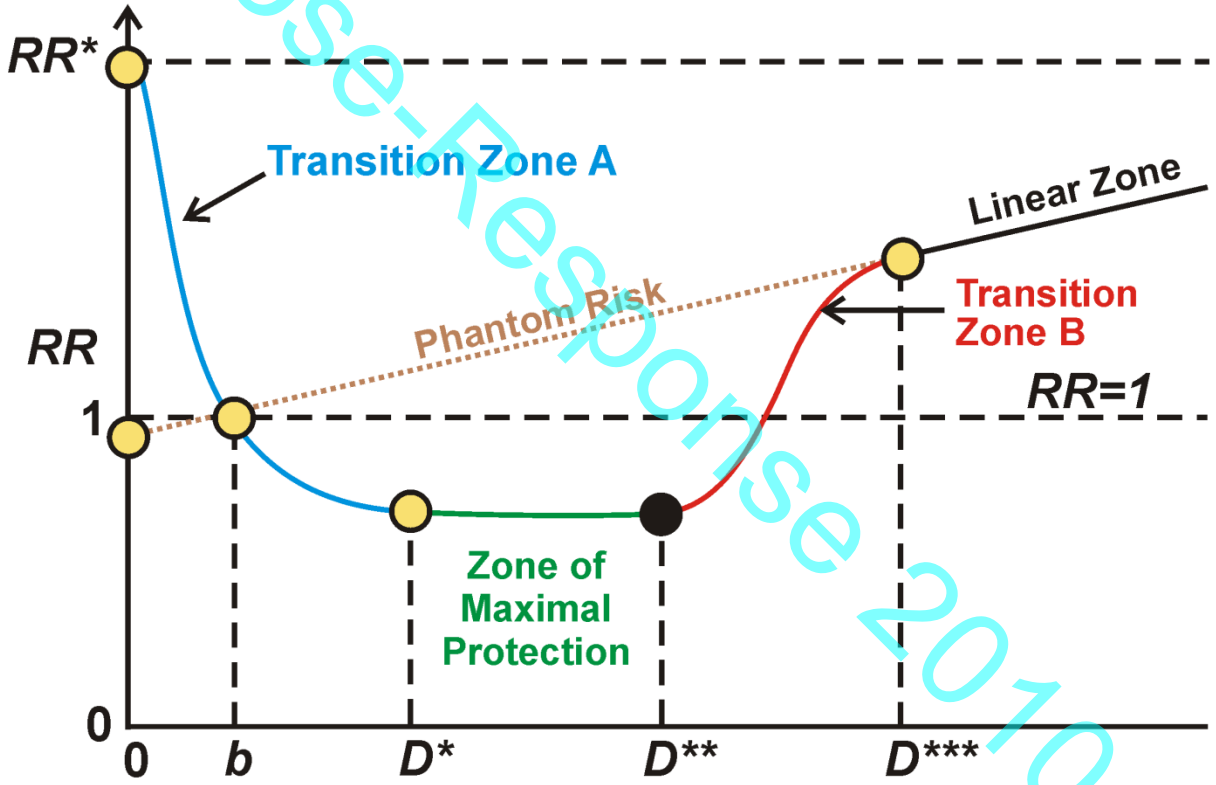
ALTERNATIVELY

Underlying and Unknown Mechanism(s) ?

- All studies estimate ‘regional’ radon risk?
- Site-specific dose-response relationships?
- Adaptive protection against high LET?
  - Activated by low LET at some Rn levels
  - Silenced by high LET at other Rn levels

DISCUSSION

Hormetic Relative Risk Model – Adapt. Prot. Resp.



Scott et al. (2009) Dose-Response 7:104-31

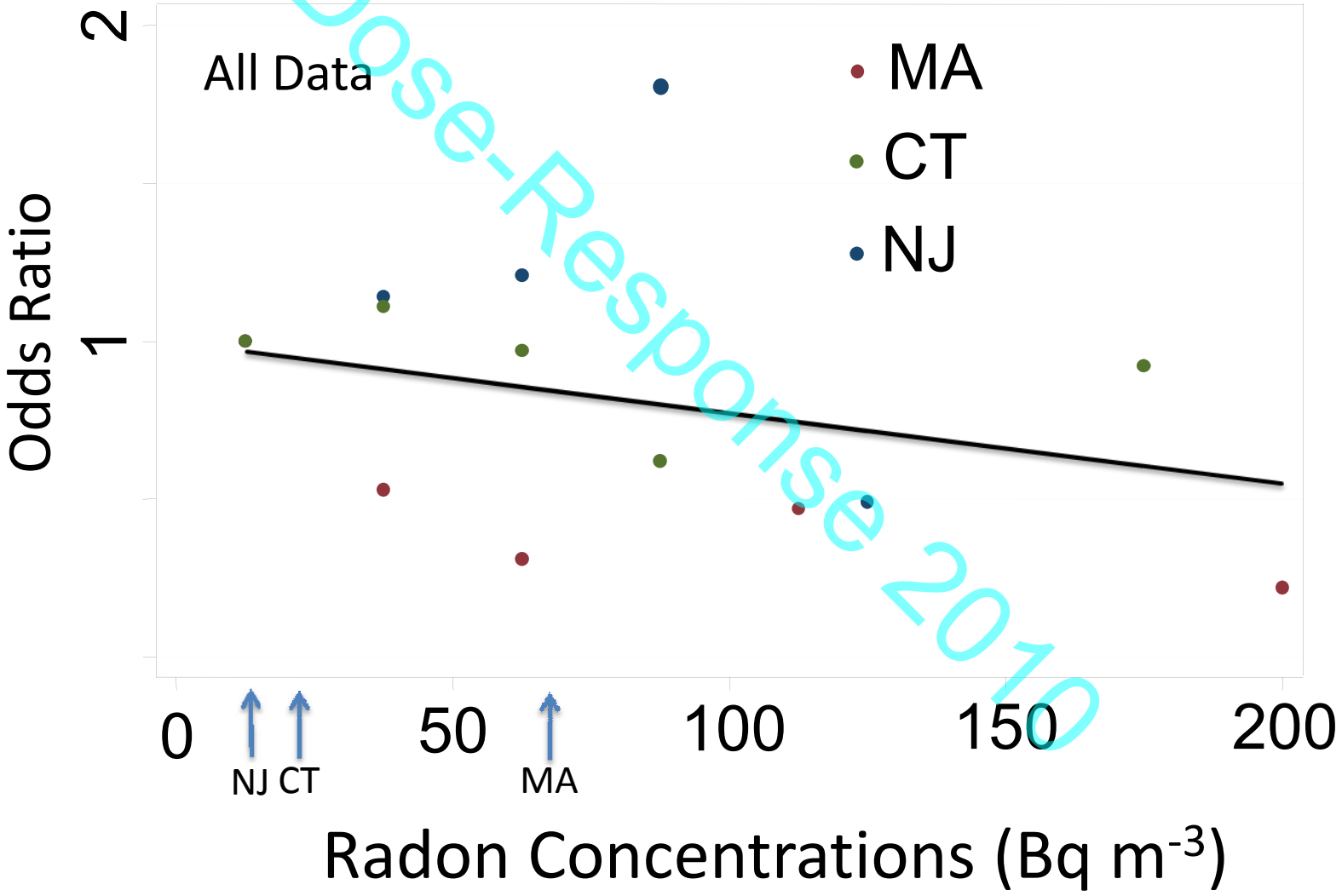
DISCUSSION

Hormetic Relative Risk Model

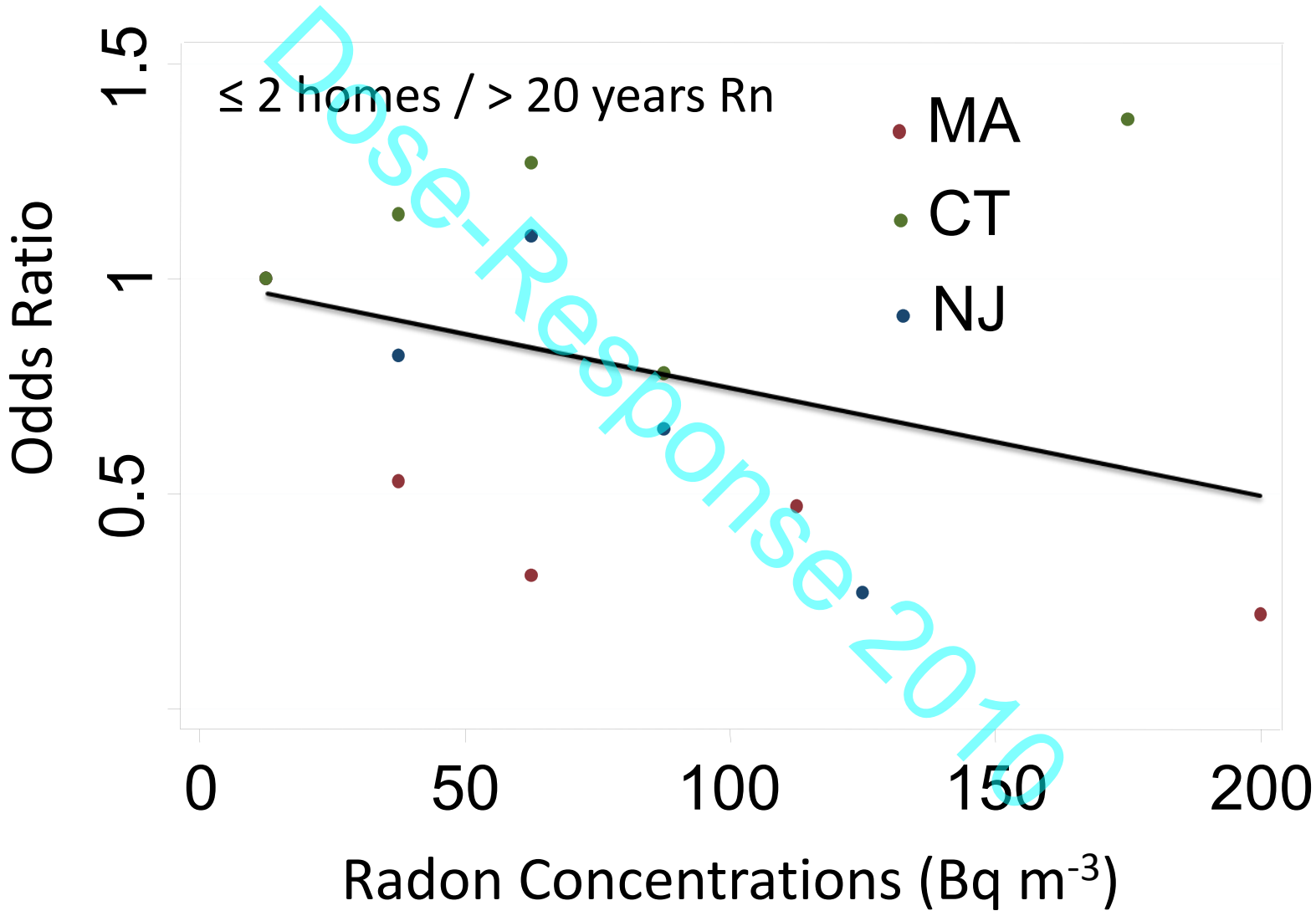
- Transition Zone A: Low LET stimulates APR
- Maximal Protection: Zone where everyone has APR
- Transition Zone B: Transition to silencing of APR
- Linear Zone: Everyone has APR silenced
- Stochastic: Thresholds person-specific

DISCUSSION

'Regional Results'



DISCUSSION

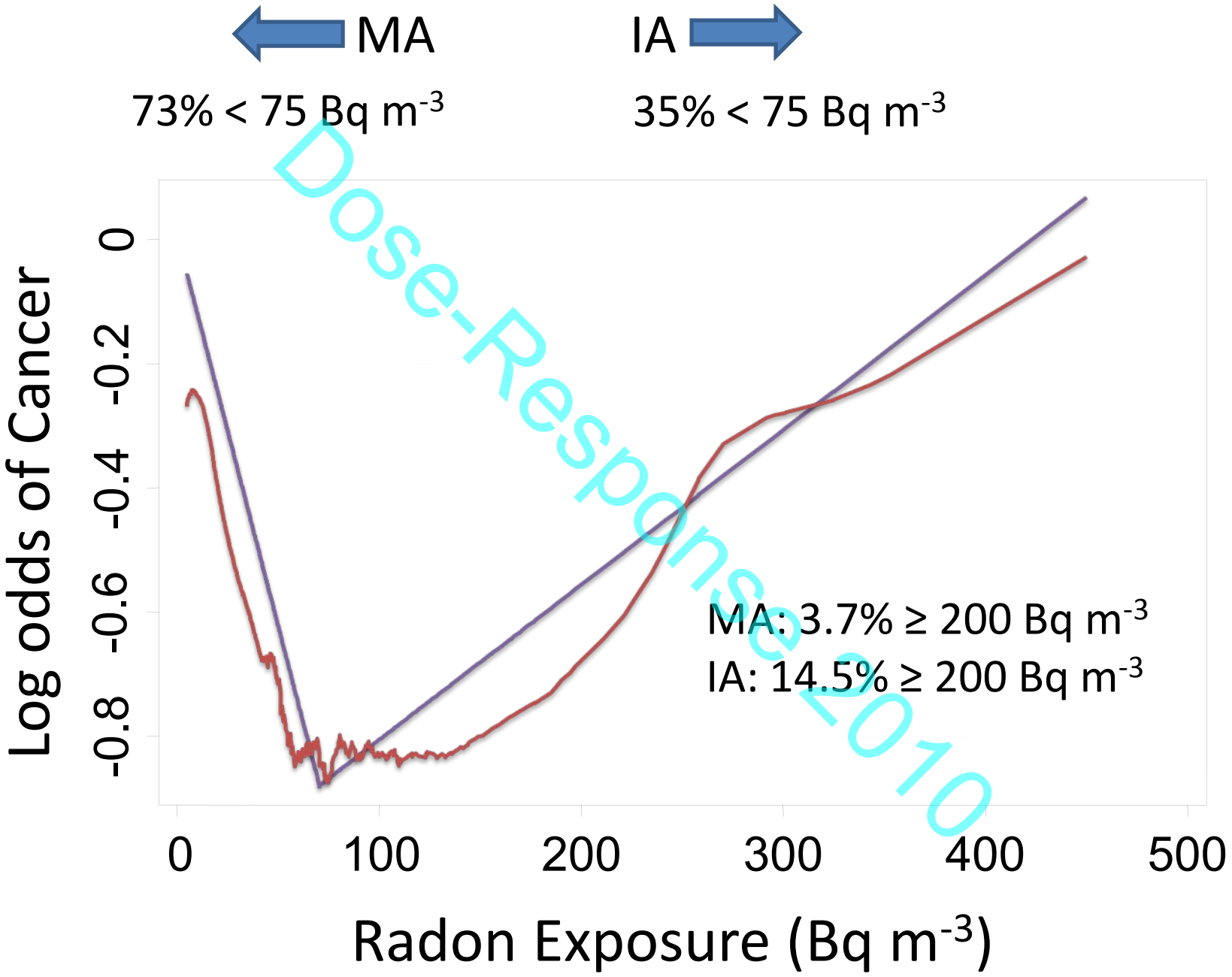

≤ 2 homes / > 20 years Rn
MA
CT
NJ
Odds Ratio
0.5
1
1.5
0
50
100
150
200
Radon Concentrations (Bq m-3)
Dose-Response 2016

DISCUSSION

What About the Sites with High Doses of Rn?

Consider IA Data:

- EOR [95% CI] = 0.44 [0.05, 1.59] / 100 Bq m^{-3}
- Mean Rn concentration = 127 Bq m^{-3}
- IA data 'drives' the Krewski et al results
- Does IA data contradict MA data?


MA
IA
73% < 75 Bq m-3
35% < 75 Bq m-3
Dose-Response 2010
Log odds of Cancer
0
-0.2
-0.4
-0.6
-0.8
MA: 3.7% ≥ 200 Bq m-3
IA: 14.5% ≥ 200 Bq m-3
0
100
200
300
400
500
Radon Exposure (Bq m-3)

DISCUSSION

Is it possible to perform case-control studies to test For APR at the human population / ecological level ?

- Measure ambient low LET from Rn decay and other radio-isotopes / high LET alpha Rn exposure
- Possible to measure 'sign' given 'noise of humans?
- Possible to quantify low LET given multiple sources?
- Data available to power such a study?

CONCLUSION

- Hormetic drip seen in the dose-response curve from Worcester County, MA data
- Good agreement with Krewski et al at high Rn levels
- Suggestions possible presence of low LET initiated APR that protects against high LET Rn exposure
- MA data provides 'inspiration' for other case-control studies to look at low LET in conjunction with high LET Radon Exposure

Acknowledgments

Co-authors

Donald F. Nelson

Joel H. Popkin

Zenaida Popkin

Colleague

Elizabeth Johnson Colantuoni

Lung Cancer Patients, their Families and, the Matched Controls