BCS Margins and Residual Cancer

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Some Reminders

- “Data” without logic is misleading
- “Data” without understanding is meaningless
- Sometimes even with understanding, it’s still meaningless !

Why are we talking about this?

- Recent (2016) DCIS margin guidelines, in part, seem to have no biological basis
- I want to present some (bio)**logical** (mathematical) considerations
- I want to emphasize the **residual cancer**

2 mm vs. > 0 mm Margin for DCIS?

- Data is only one piece of evidence
- Logic (mathematical model) seems to support this
- DCIS is not cancer
- Recurrence is 50% non-invasive
- RT (± boost) is probably sufficient adjuvant
- Lower threshold (focally microscopically positive*) *may even be acceptable*, if **residual cancer** is expected to be “minimal”

*Breast Cancer Res Treat 2017;164:157-67
*ASBS Guidelines, 2013

Some Topics

- Metaanalyses & guidelines
- Limitations (data & statistical analyses)
- Logic (biology & mathematical models)
- Other evidence (residual cancer)
- Personal experience

Meta-analyses & Guidelines

- SSO, ASTRO, ASCO, CAP, ASBrS, …
- Early stage (I – II) invasive breast cancer, 2014
  - No ink on tumor/ink free; > 0 mm
  - Includes DCIS + IDC (macroinvasive)
- Non-invasive cancer (DCIS), 2016
  - Optimum margin 2 mm
  - Includes DCIS + microinvasion

Houssami, et al. Ann Surg Oncol 2014;21:717-30
Moran, et al. Ann Surg Oncol 2014;21:704-16
Wang, et al. J Natl Cancer Inst 2012;104:507-16
Marinovich, et al. Ann Surg Oncol 2016;23:3811-21
Morrow, et al. J Clin Oncol 2016;34:4040-6

Meta-analyses

- Wang meta-analysis (DCIS), 2012
- Marinovich meta-analysis (DCIS), 2016
- Houssami meta-analysis (IDC), 2014

Wang, et al. J Natl Cancer Inst 2012;104:507-16
Houssami, et al. Ann Surg Oncol 2014;21:717-30
Marinovich, et al. Ann Surg Oncol 2016;23:3811-21

Limitations

- Nature of the data
- How are margins measured?
- How are various cutoffs defined by each author?
- There is so much heterogeneity that combining these studies is an act of questionable validity
- Are we even using the same definitions when applying the results of these studies to patients?

Wang, 2012 vs Marinovich, 2016

- Update of included studies: 6,264 vs. 7,883
- Differing exclusion criteria
  - Overlapping studies (Wang)
  - Less than 100 pts (Wang)
  - FU time < 48 months (Marinovich)
  - No summary age data (Marinovich)
  - Margins not clearly defined (Marinovich)
- One influential study in Wang, 2012, for margin > 10 mm (?)

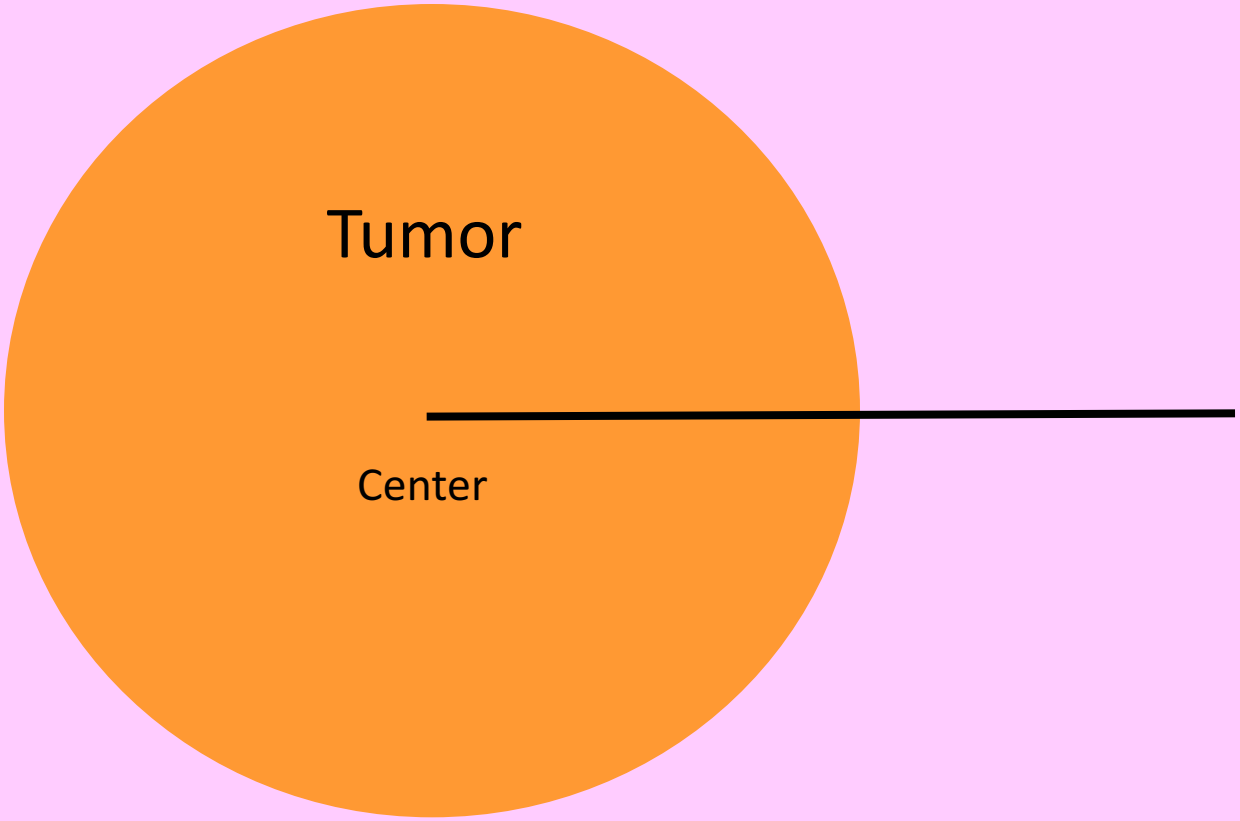
How Margins are Measured

- "…there is no standard method for margin evaluation, and this process is highly prone to sampling error"

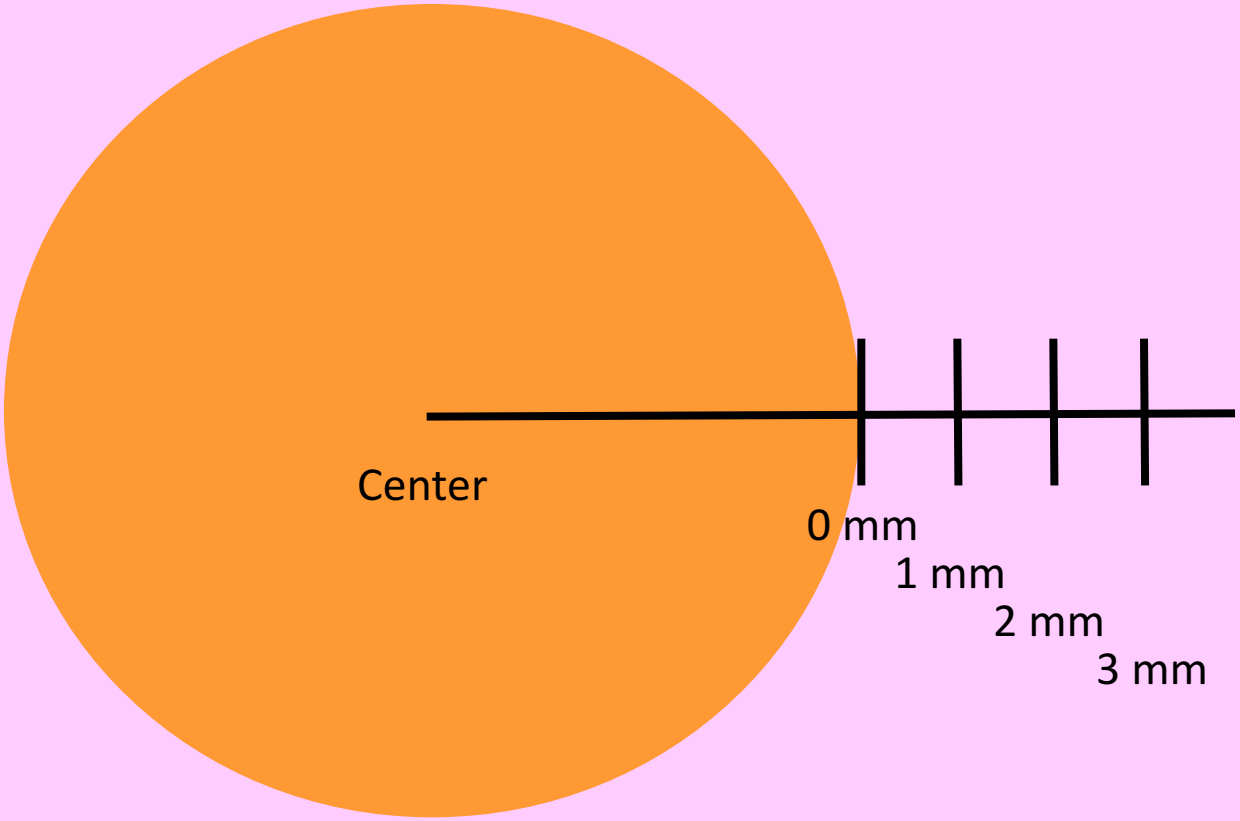
Ann Surg Oncol 2014;21:704-16

Definitions of OR's and Cutoffs

- **Margins** are defined to be **open-ended** and/or **closed-ended** depending on the study
- Odds Ratios can be defined for open-ended margin cutoffs, e.g. as a ratio of odds of recurrence for $\geq$ 2 mm vs. < 2 mm
- Or for multiple margins with a common control group, e.g. an open-ended "positive margin" of $\leq$ 0 mm vs. > 0 mm, $\geq$ 1 mm, $\geq$ 2 mm, etc.
- Or for some closed margins, e.g., < 0 mm margins vs. **1 - 2 mm**, $\geq$ **2 mm - 5 mm**, $\geq$ 5 mm, $\geq$ 10 mm

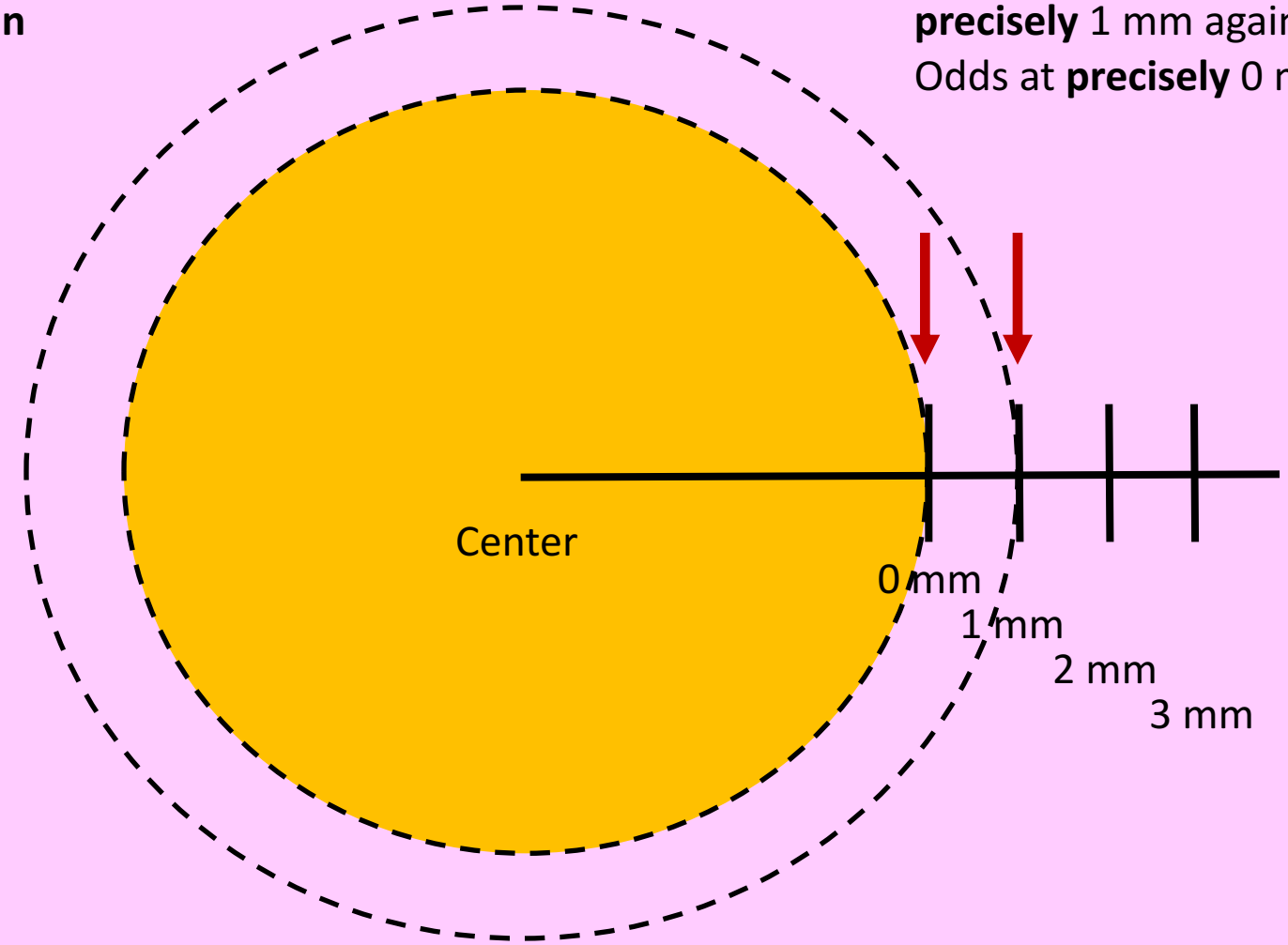

Tumor
Center

Odds Ratio of **Negative Margin 1 mm against Positive Margin**



Odds Ratio of **Negative Margin 1 mm against Positive Margin**

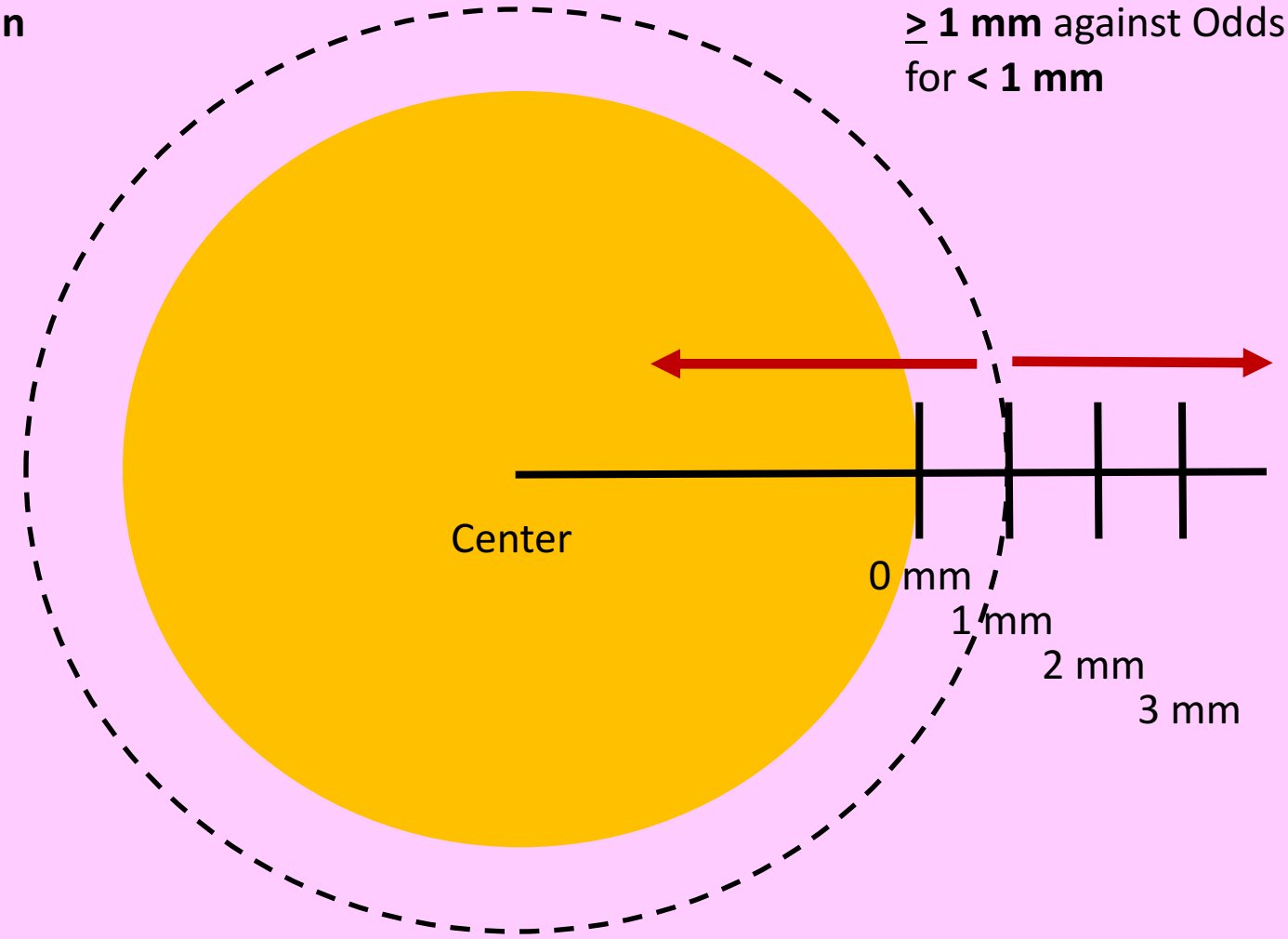
Odds Ratio defined as Odds of recurrence at **precisely** 1 mm against Odds at **precisely** 0 mm



"**Precise**" definition of OR's

Odds Ratio of **Negative Margin 1 mm against Positive Margin**

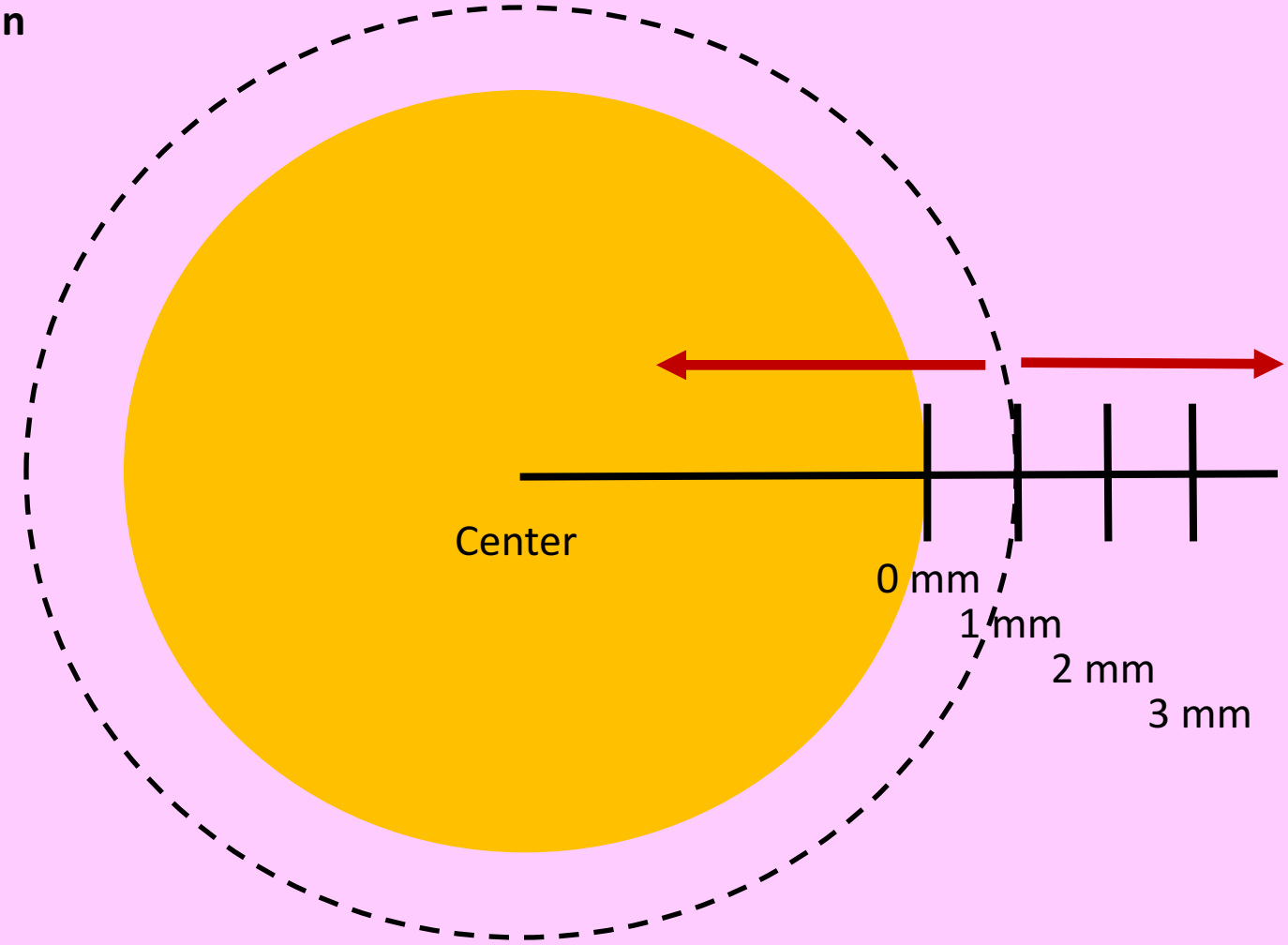
Odds Ratio defined as Odds of recurrence for **≥ 1 mm** against Odds for **< 1 mm**



"**Cut-off**" definition of OR's: Odds **open-ended, no common control**

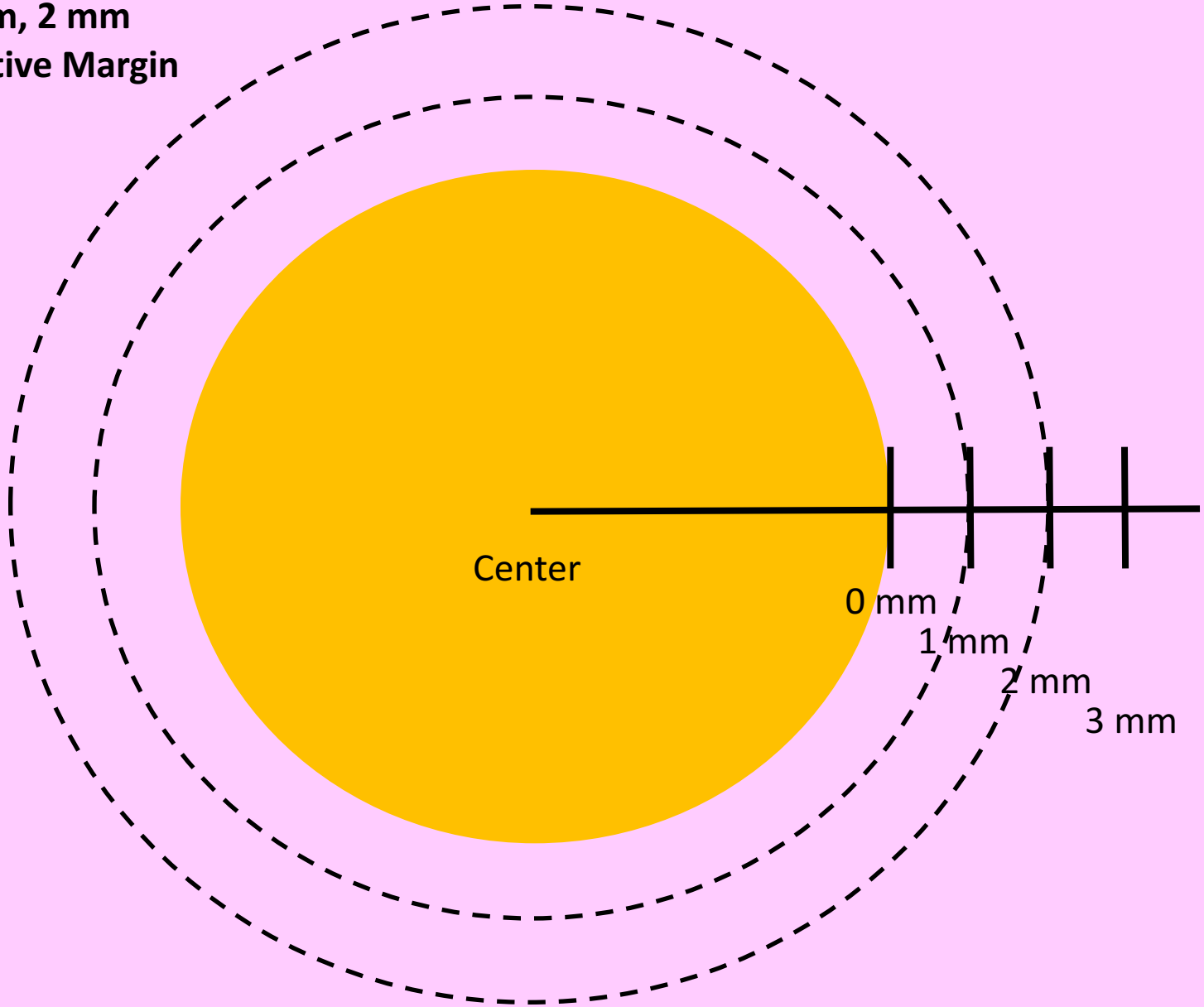
Odds Ratio of **Negative Margin 1 mm against Positive Margin**

Used in the **Frequentist Meta-analysis** of **Houssami, 2014 & Marinovich, 2016**



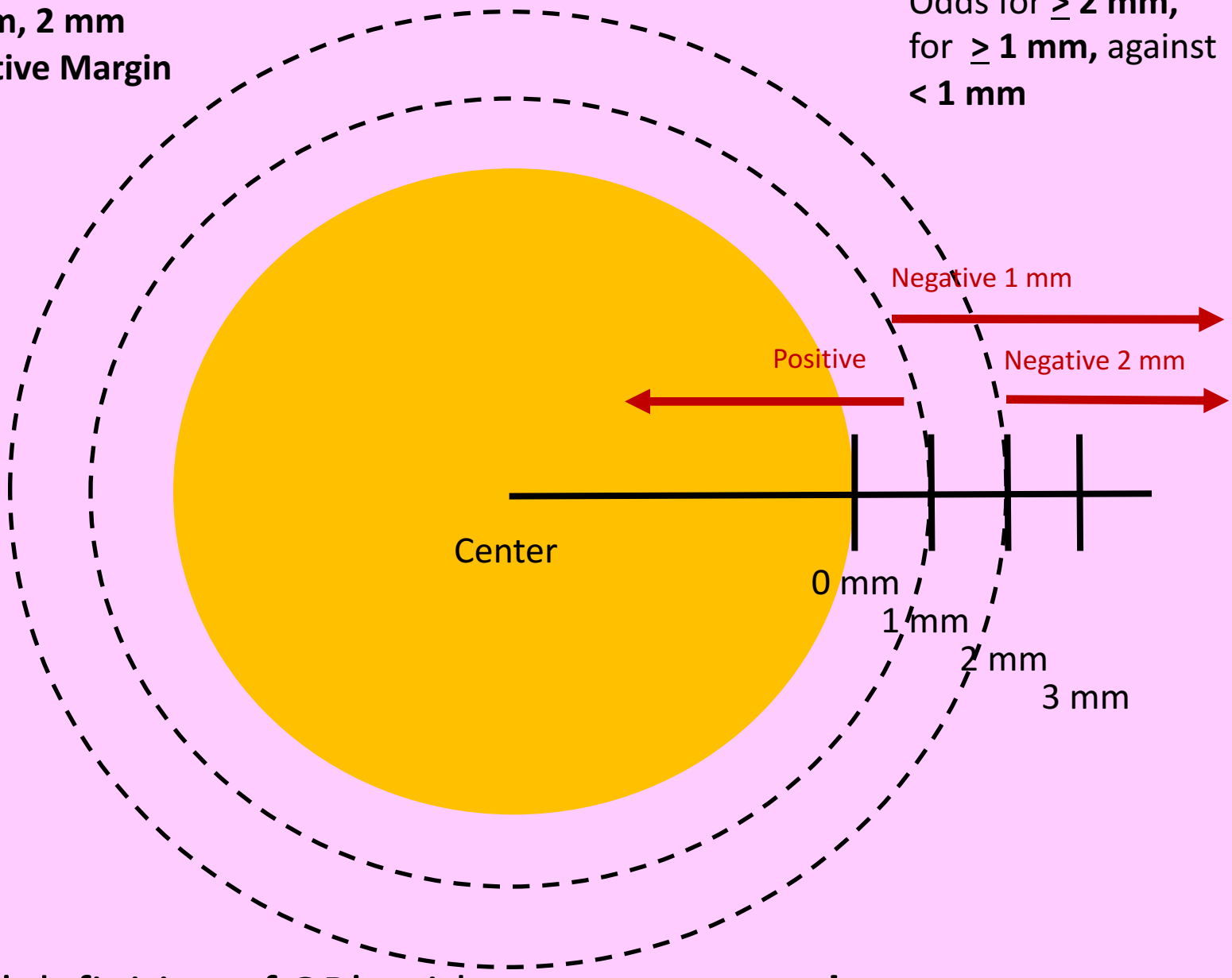
"**Cut-off**" definition of OR's: Odds **open-ended, no common control**

Odds Ratio of **Negative Margin 1 mm, 2 mm against Positive Margin**



Odds Ratio of **Negative Margin 1 mm, 2 mm against Positive Margin**

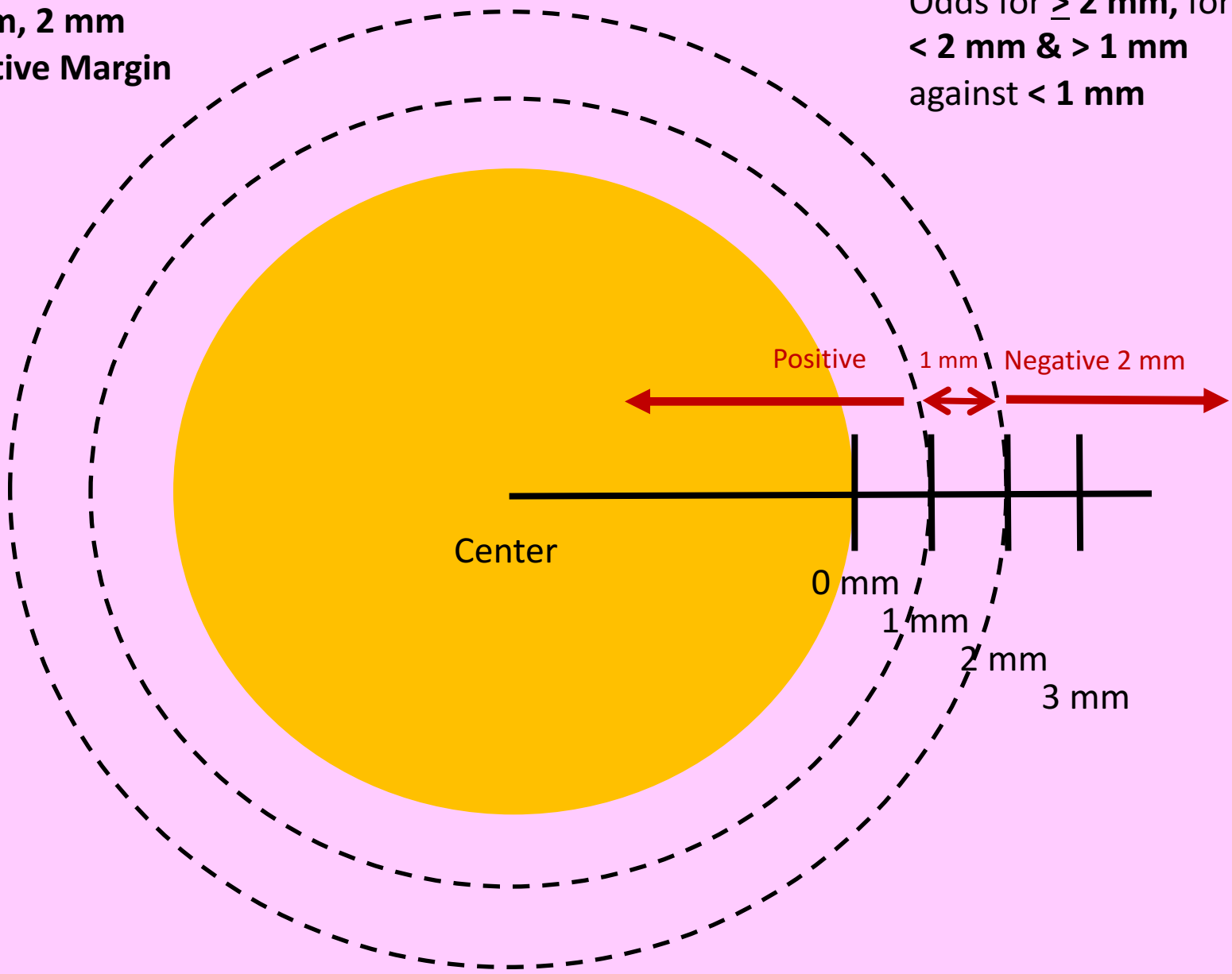
Odds for ≥ **2 mm,** for ≥ **1 mm,** against **< 1 mm**



"**Cut-off**" definition of OR's with **common control**

Odds Ratio of **Negative Margin 1 mm, 2 mm against Positive Margin**

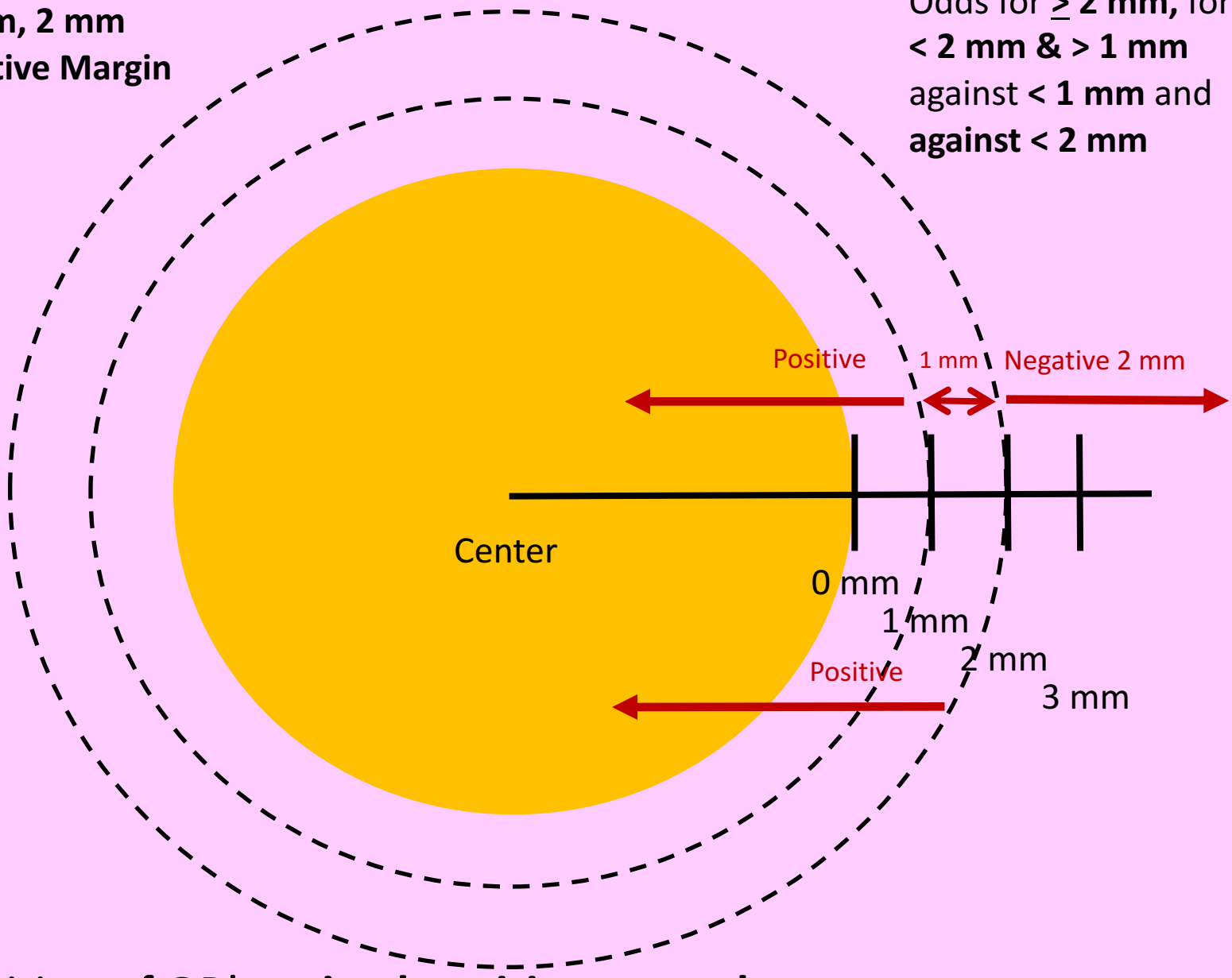
Odds for ≥ **2 mm,** for **< 2 mm & > 1 mm** against **< 1 mm**



"**Mixed**" definition of OR's: **Open** and **close-ended**, common control

Odds Ratio of **Negative Margin 1 mm, 2 mm against Positive Margin**

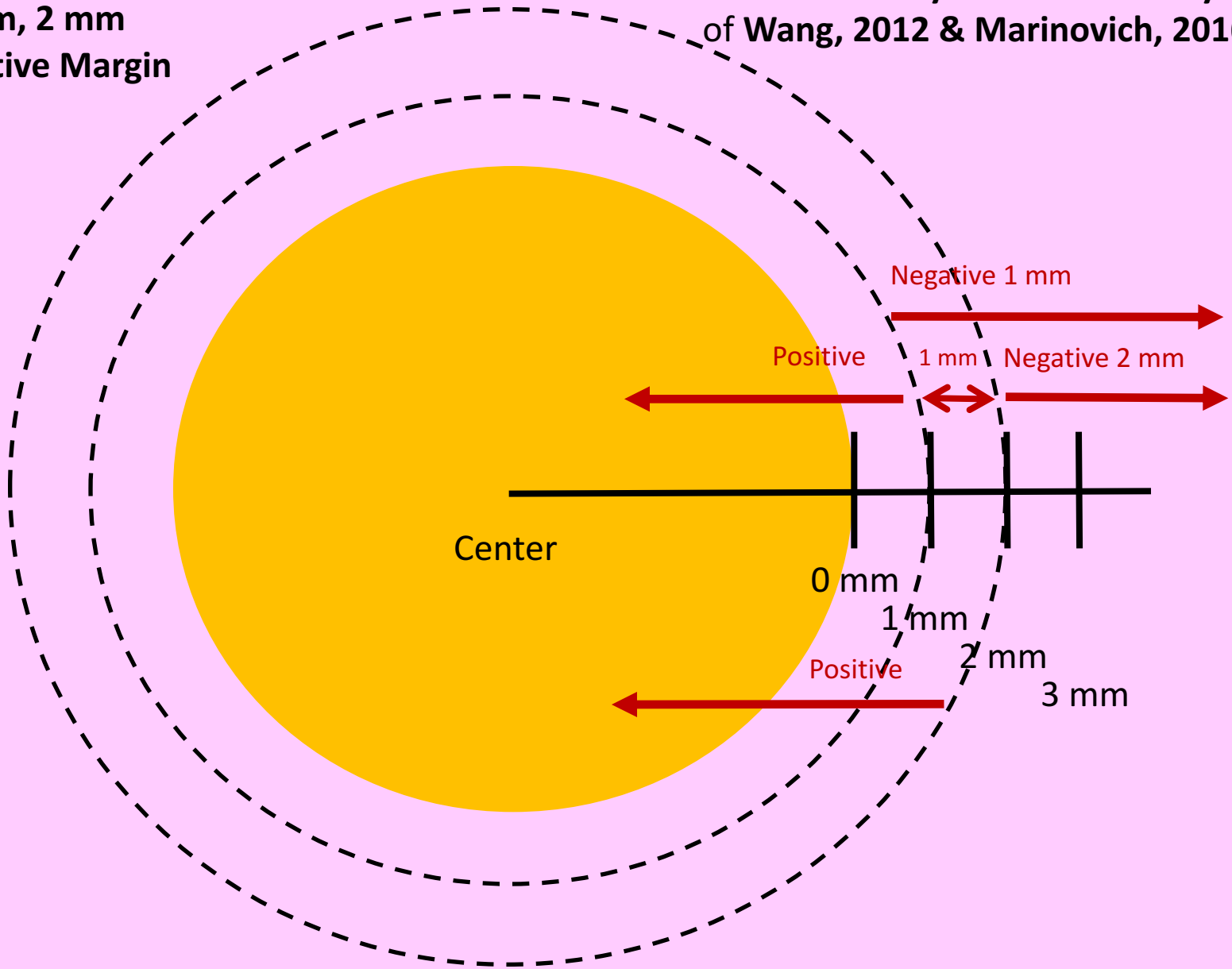
Odds for ≥ **2 mm,** for **< 2 mm & > 1 mm** against **< 1 mm** and **against < 2 mm**



"**?**" definition of OR's: **mixed positive control**

Odds Ratio of **Negative Margin 1 mm, 2 mm against Positive Margin**

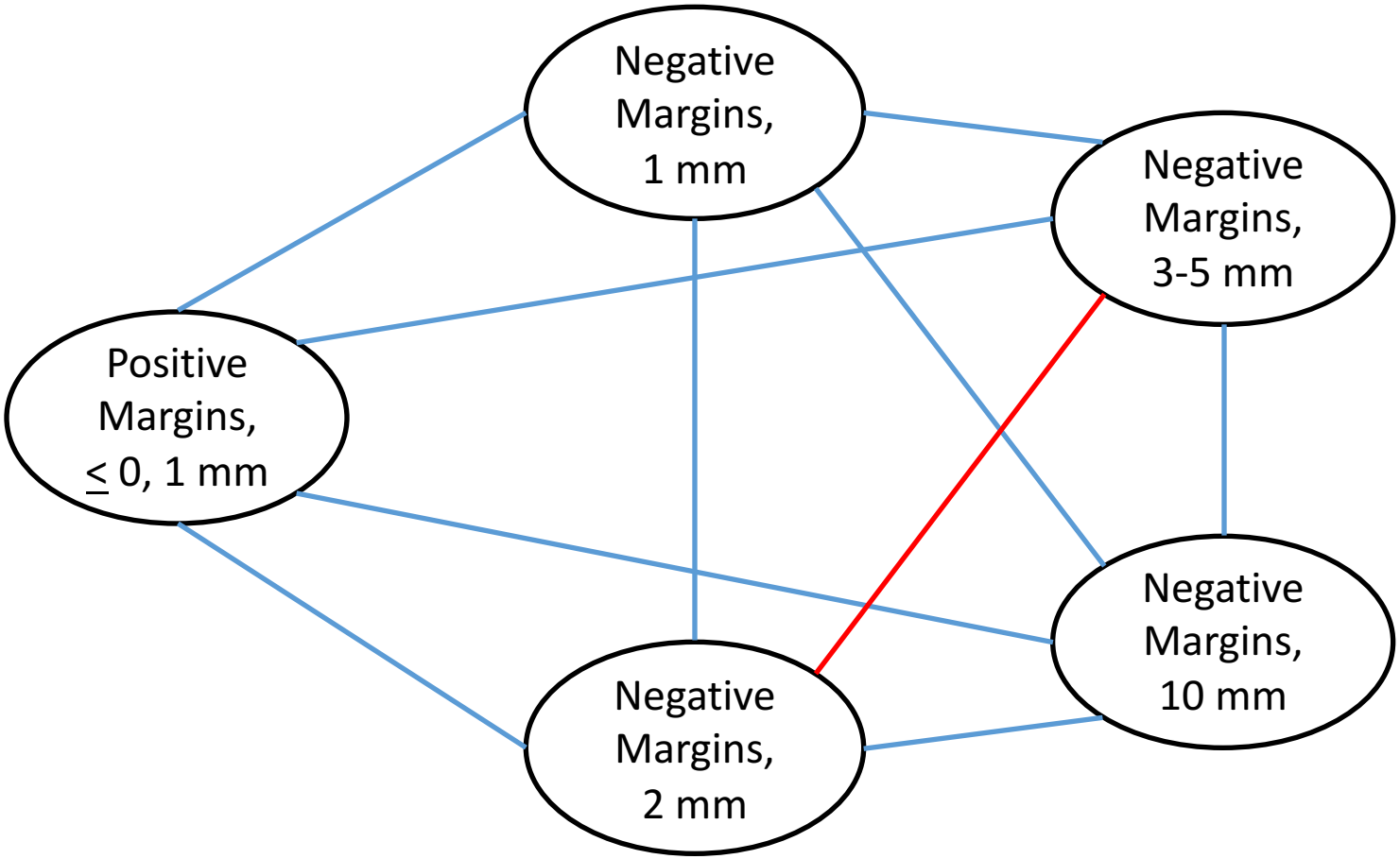
Used in the **Bayesian Meta-analysis** of **Wang, 2012 & Marinovich, 2016**



Statistical Models

- Frequentist random-effects logistic regression
  - Comparing open-ended cutoffs
  - OR's of recurrence, e.g., $\geq$ 1mm **vs.** < 1 mm
- Bayesian "network meta-analysis"
  - Comparing closed or open-ended margins with **common control** (open-ended)
  - OR's of recurrence, e.g., $\geq$ 1 mm & < 3 mm **vs.** $\leq$ 0 mm

Why is it called a “Network”?



Model

Bayesian Hierarchical Model;
Exchangeability assumption*

$$r_c \sim bin(p_c, n_c)$$
$$r_{t_j} \sim bin\left(p_{t_j}, n_{t_j}\right)$$
$$logit(p_{ci}) = \mu_i + \beta \times futime_i$$
$$logit\left(p_{t_j i}\right) = \mu_i + \theta_j + \beta \times futime_i$$
$$\mu_i \sim N(\mu_a, \sigma_a^2)$$

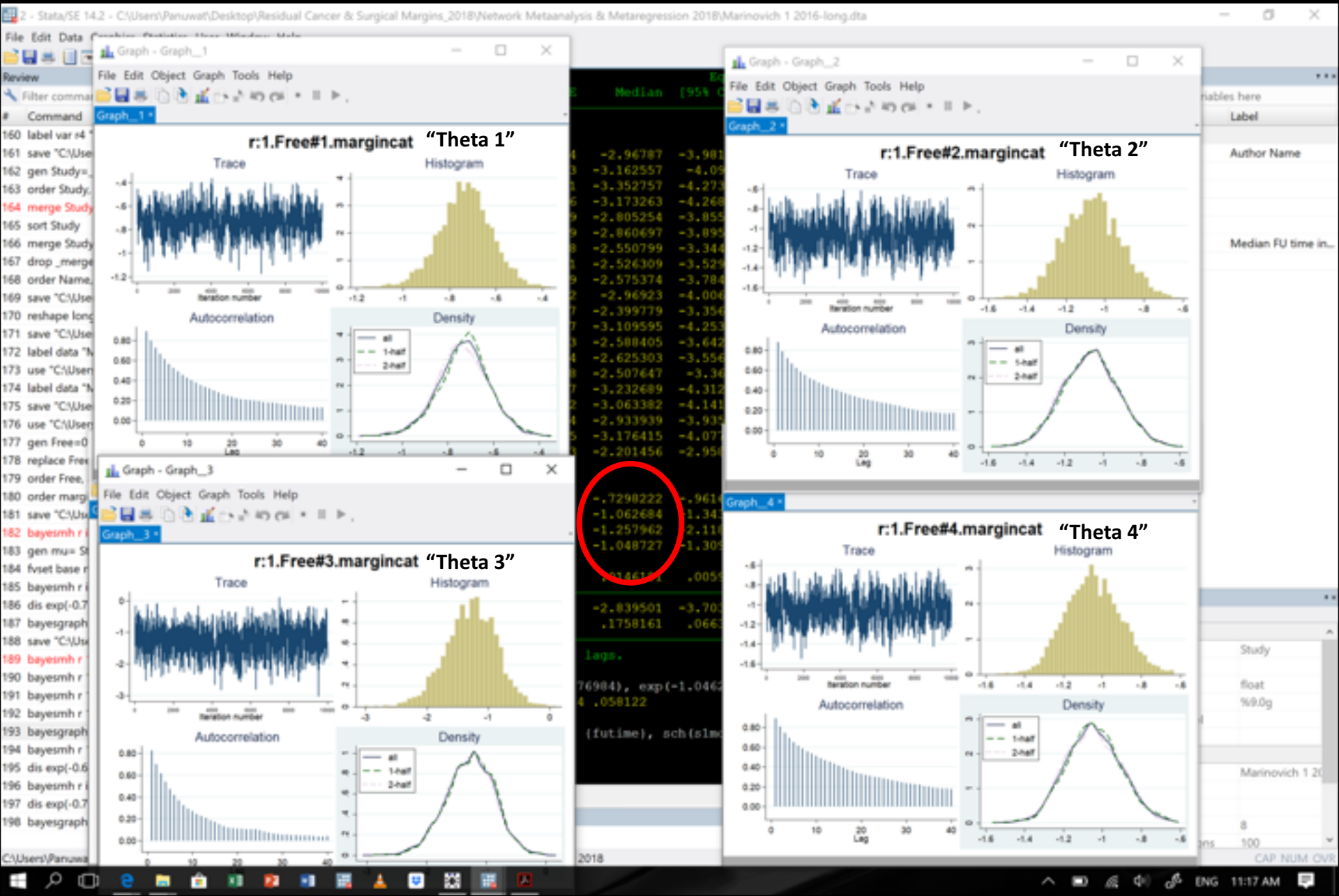
i $\in \{1, .., 20\}$
20 studies;
$j \in \{1, \ldots, 4\}$
4 "treatments"

$$\mu_a \sim N(0, 10^6)$$
$$1/\sigma_a^2 \sim gamma(0.001, 0.001)$$
$$\beta \sim N(0, 10^6)$$
$$\theta_i \sim N(0, 10^6)$$

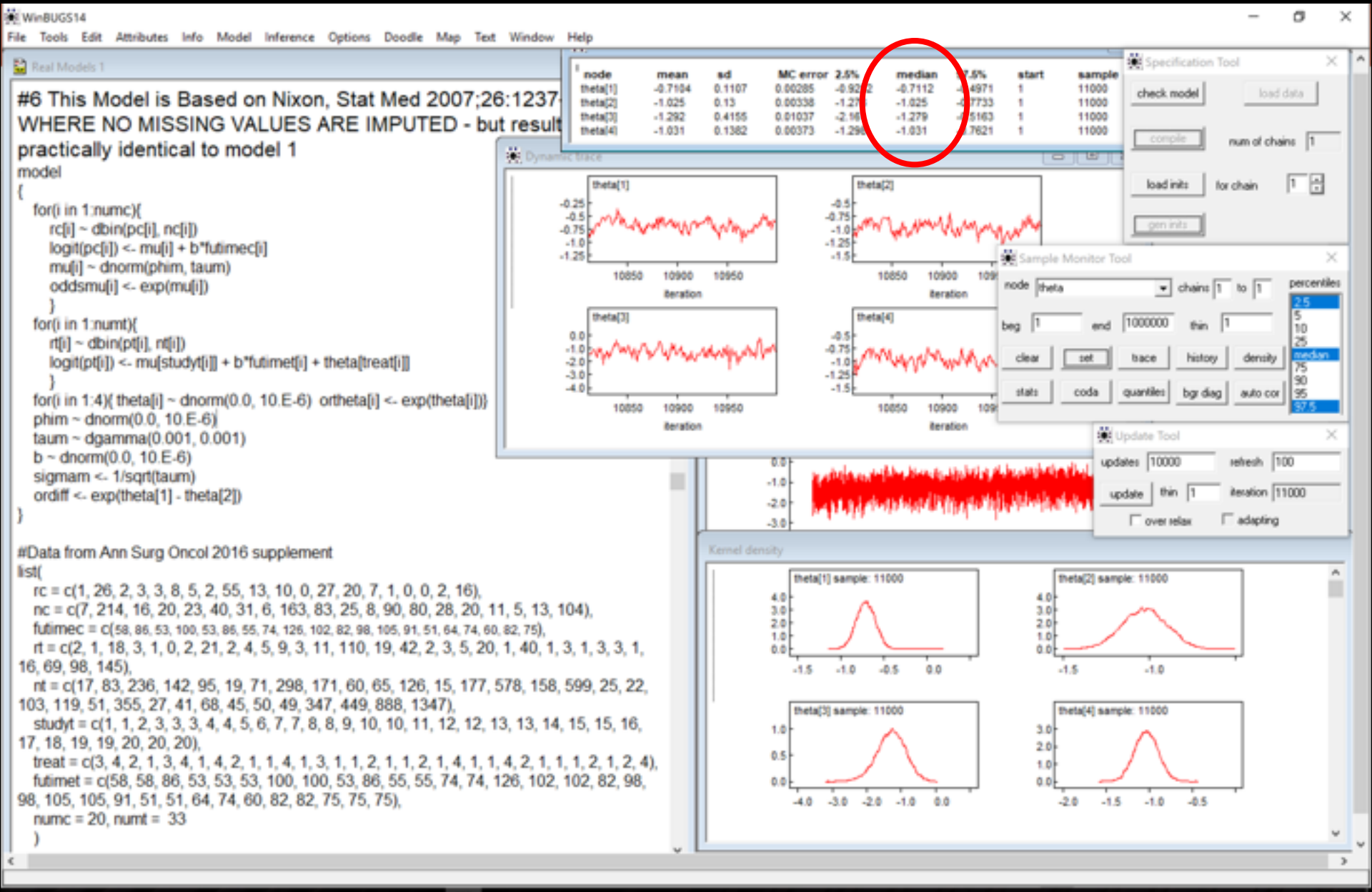
"Diffuse" or non-informative prior distributions

*see, for example: Congdon PD. Applied Bayesian Hierarchical Methods. CRC Press, 2010

Marinovich Data Analyzed Using Stata v.14



Marinovich Data Analyzed Using WinBUGS v.1.4.3



Results

Based on the re-analysis (OR = Odds Ratio):

- Results similar between different software
- Results differ somewhat from published study*

Treatment	Published OR = exp(θ)	Stata 14 OR	WinBUGS OR
1 mm (θ1)	0.45	0.48	0.49
2 mm (θ2)	0.32	0.35	0.36
3-5 mm (θ3)	0.30	0.28	0.28
10 mm (θ4)	0.32	0.35	0.36

*Marinovich, *et al*. Ann Surg Oncol 2016;23:3811-21

Some Contradictory Statements?

- "…a negative margin is best regarded as one indicating that *the residual tumor burden in the breast is low enough* that it is **likely to be controlled with radiotherapy**" Cancer 2018;124:1335-41
- "A positive margin … is associated with a significant increase in IBTR. This *increase* is **not nullified by the use of WBRT**" J Clin Oncol 2016;34:4040-6

(***Emphasis*** all mine)

Statistical vs. Mathematical Modelling

- Statistics models the probability process underlying data generation, empirically, without any specific biological-mechanistic hypothesis (although there may be biological interpretation of these processes)
- Mathematical modelling is based on simplified biological assumptions, with specified mechanisms producing the observed phenomenon of which the data is just a part

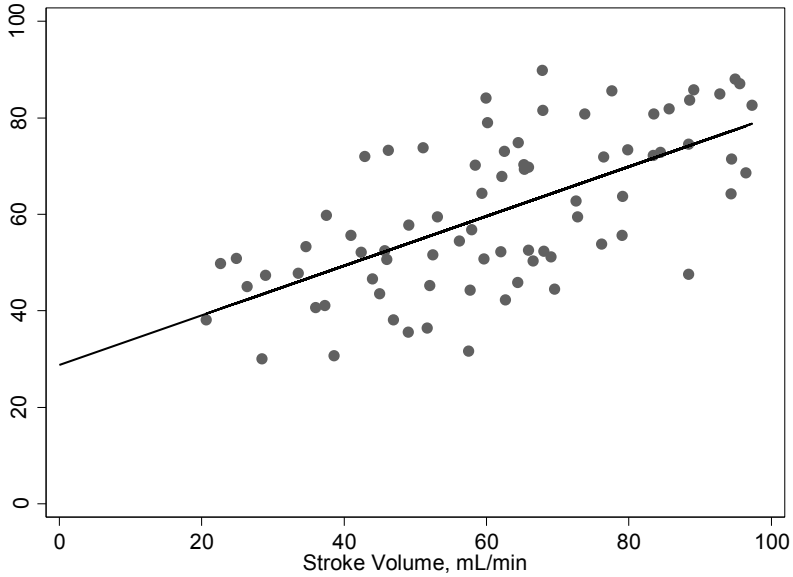
Logic

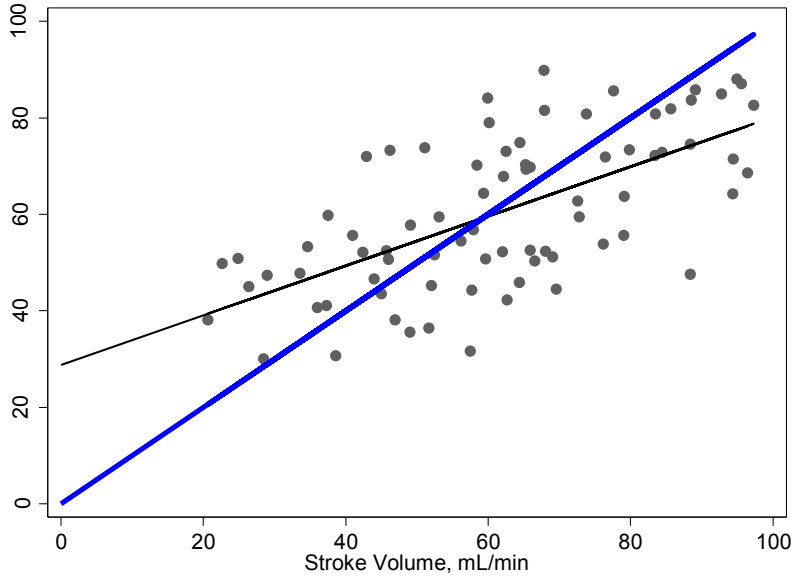
- Logic taken to the extreme is mathematization
- The assumptions upon which logical deductions are based are crucial

Example: SV vs. PP

Pulse Pressure = 29 mmHg;
although Stroke Volume = 0

Theory corrects for this





Mastectomy vs BCS

- Logically, mastectomy will always be associated with a lower risk of cancer recurrence than BCS
- What clinical studies tell us is that a significant difference will not be detectable/not clinically relevant **during a typical patient's remaining lifetime**

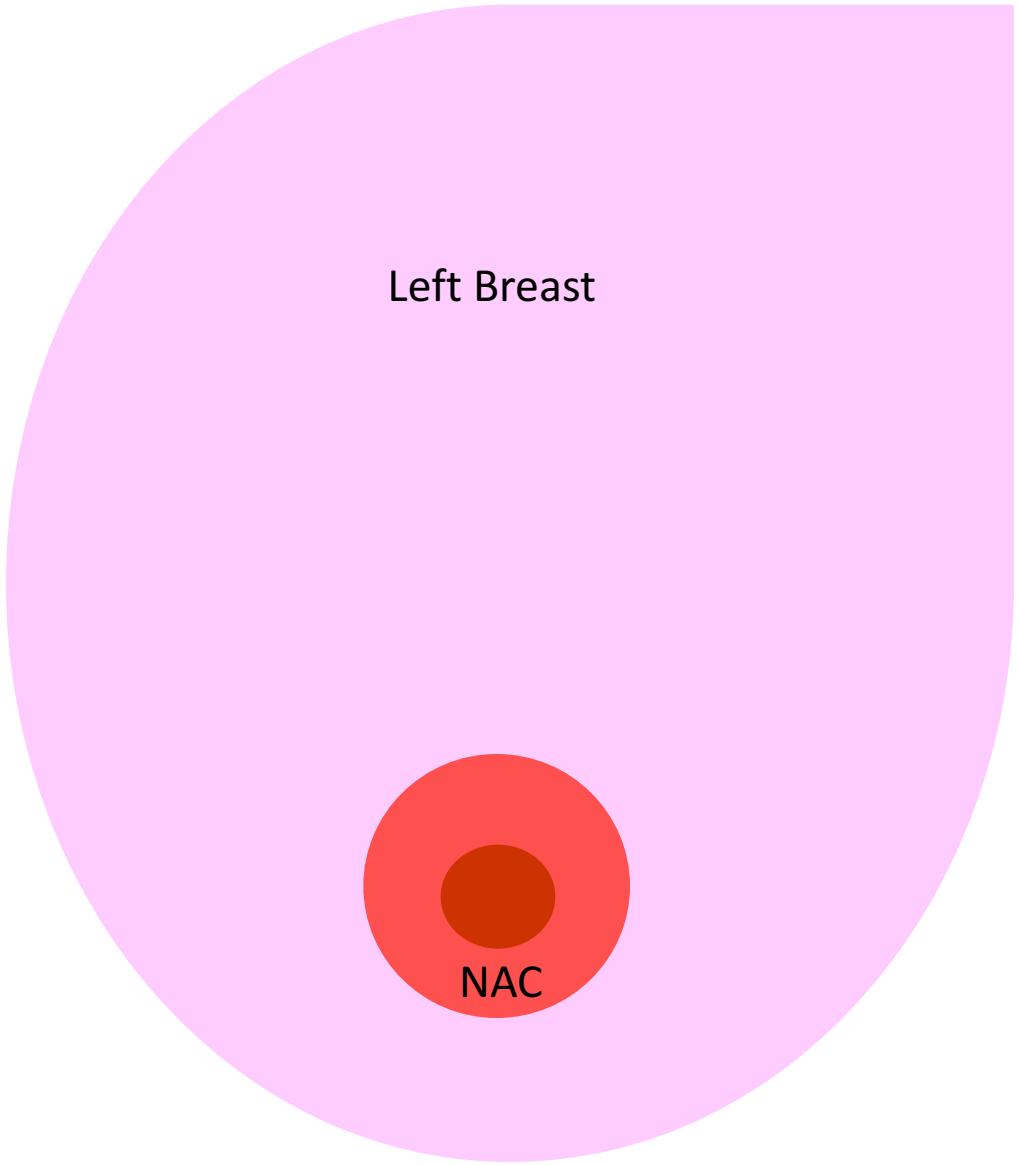
Basic Model Assumptions

Our assumptions include

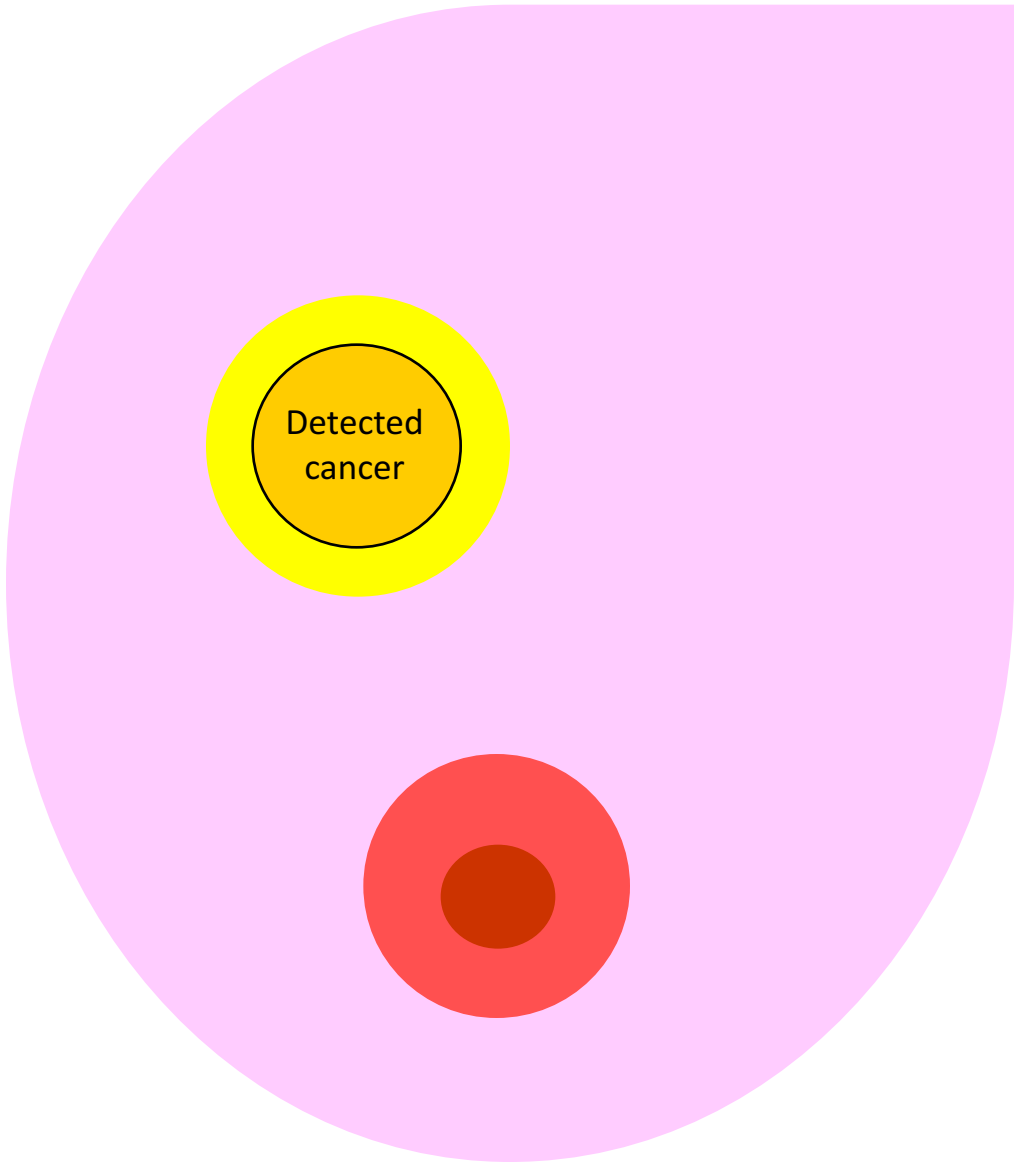
- Two sources of local recurrence: residual tumor and “background risk”
- Close margin resection will (almost) always leave some residual tumor
- So even if all primary tumor is removed, recurrences can still occur because of background risk

Detailed Model Assumptions

- The tumor/cancer is **spherical** (& unicentric)
- The **detected tumor** is **not all** existing tumor
- Excision is a spherically symmetric “coring out” of the tumor/cancer area
- The locoregional recurrence **hazard is proportional to** the **residual tumor**, and **time since surgery**
- **FU time** is the same for all patients
- **Independent censorship**
- The **surgeon’s ability to excise cancer** is expressed as a simple probability distribution function
- Mathematical functions representing these assumptions should be as simple as possible


Left Breast
NAC

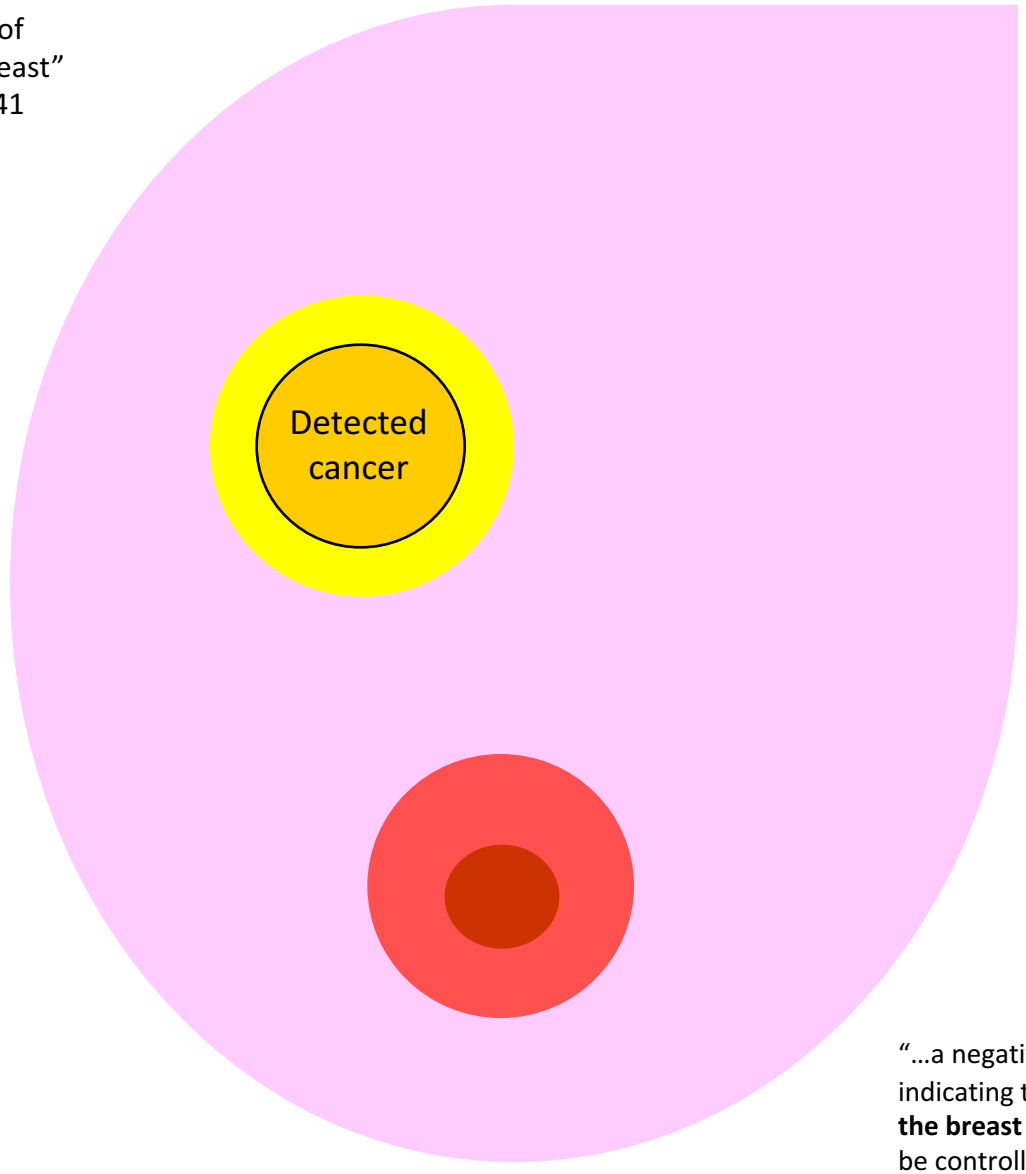
Primary Tumor: 3 cm



Detected cancer (orange) and peripheral **undetected cancer** (yellow)

Primary Tumor

"…a negative margin **does not guarantee the absence** of residual tumor in the breast"
Cancer 2018;124:1335-41



Detected cancer (orange) and peripheral **undetected cancer** (yellow)

"…a negative margin is best regarded as one indicating that **the residual tumor burden in the breast is low enough** that it is likely to be controlled with radiotherapy"
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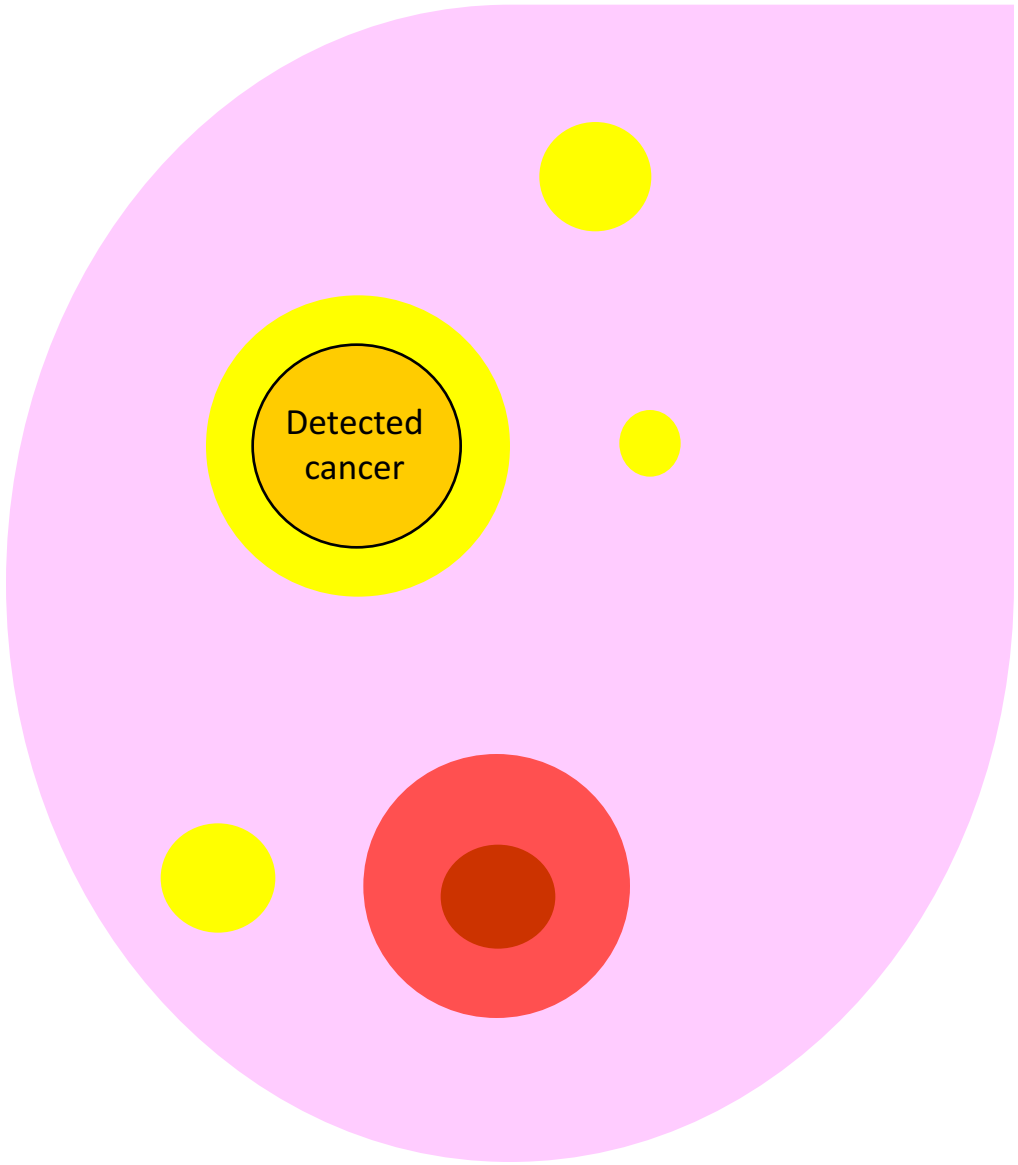
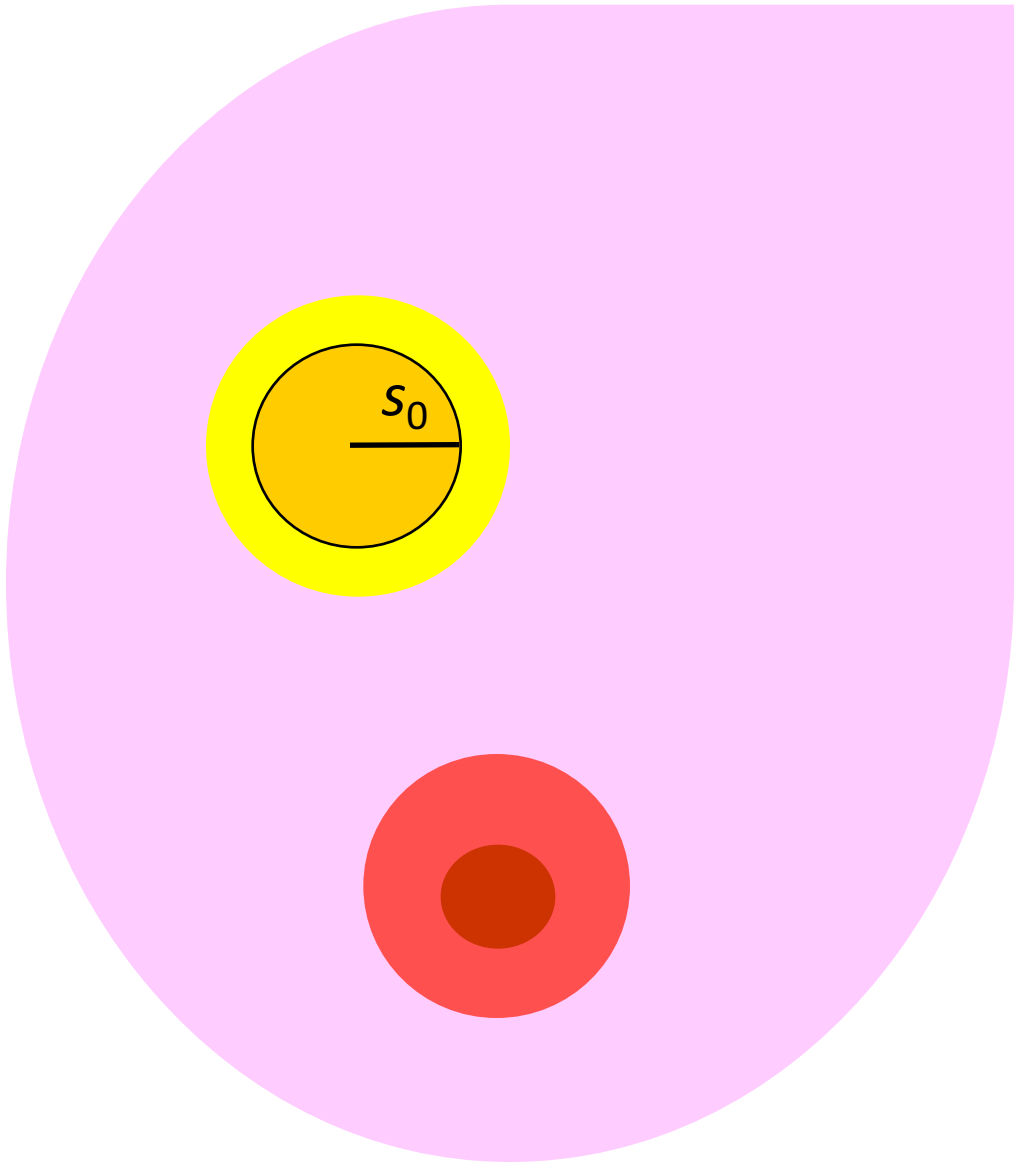
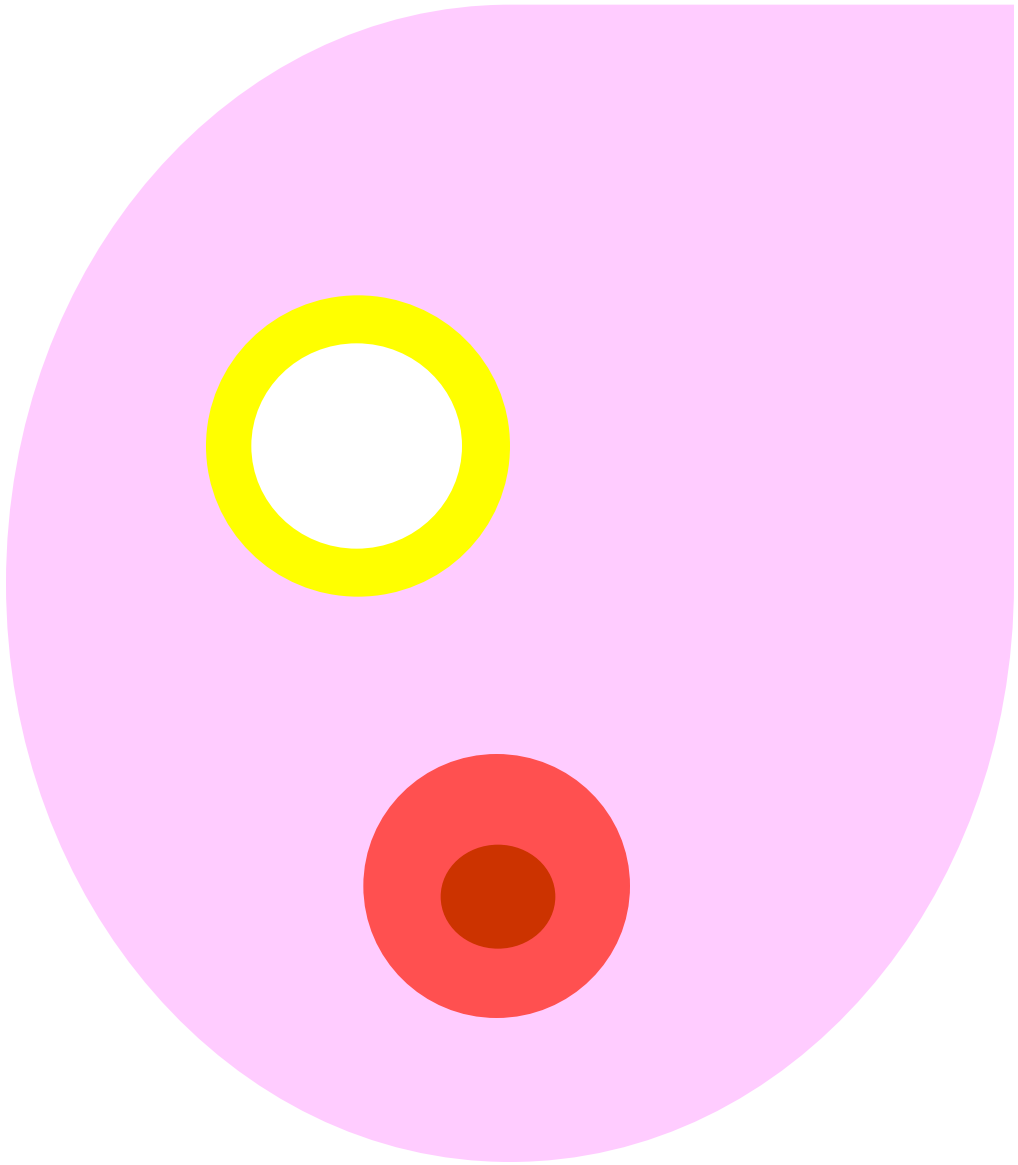
Background Risk



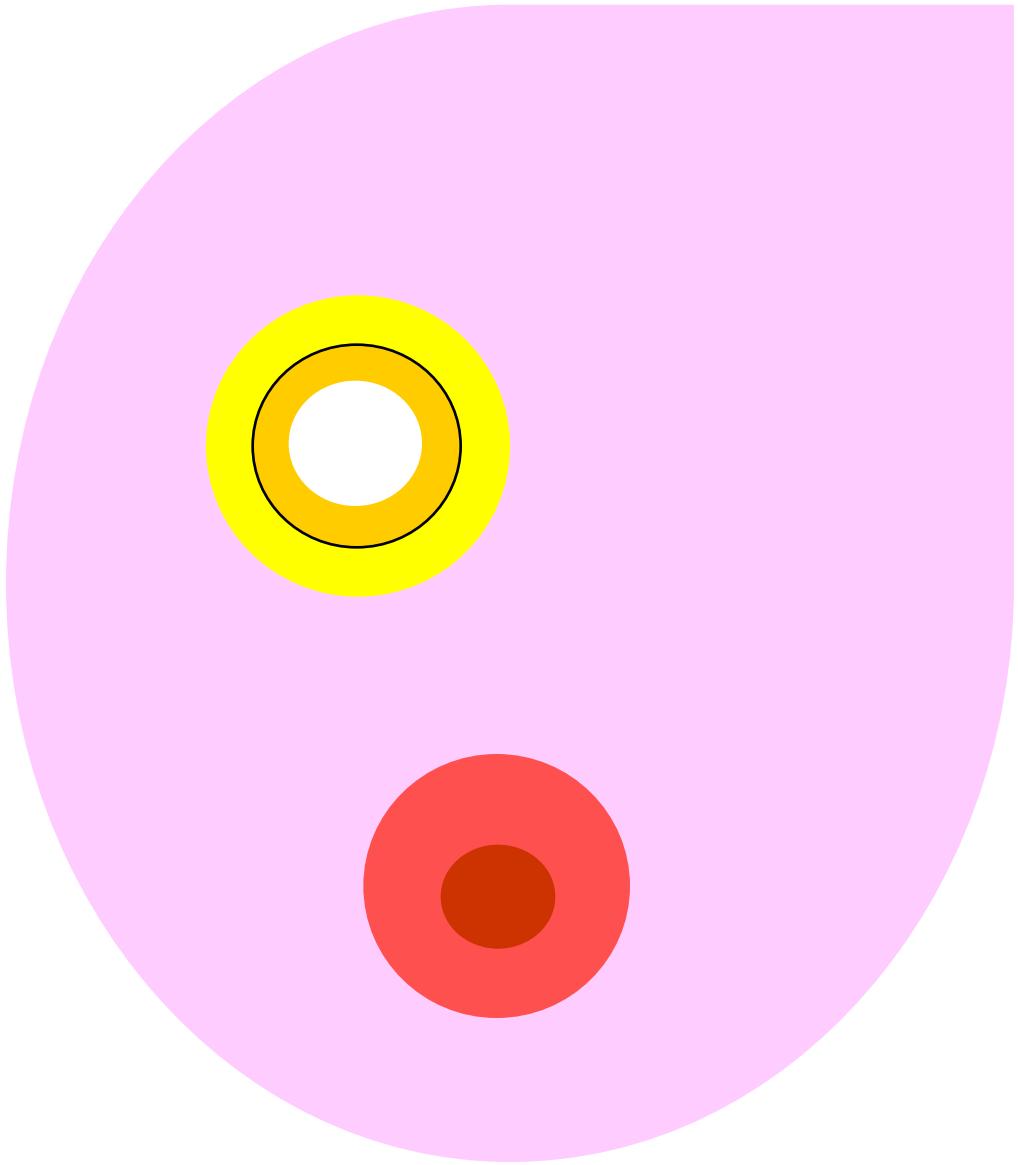
The **background risk** may be **interpreted as** undetected cancer at other centers/foci or other underlying risks **not related to the primary tumor**



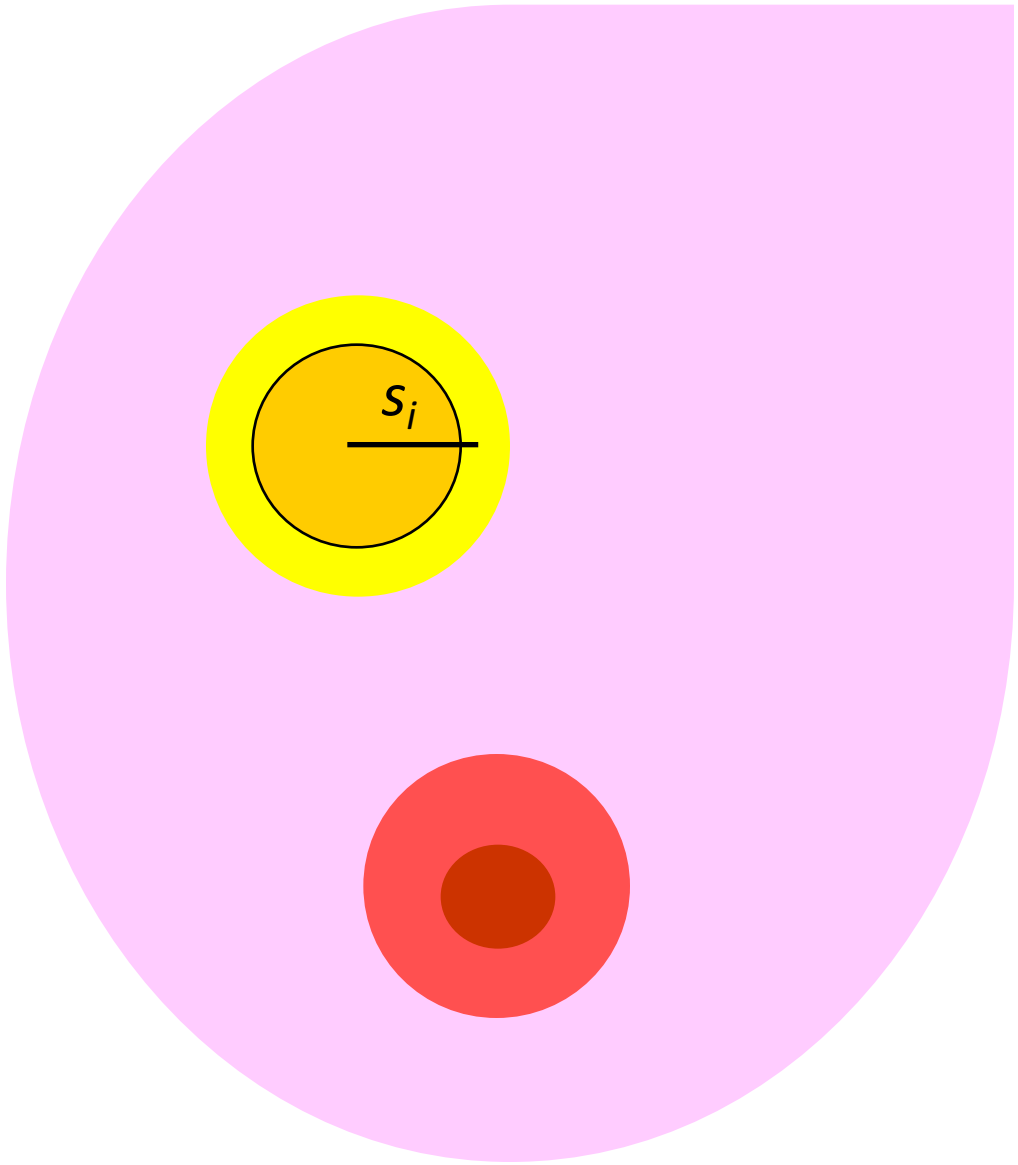
s_0 is the detected tumor size



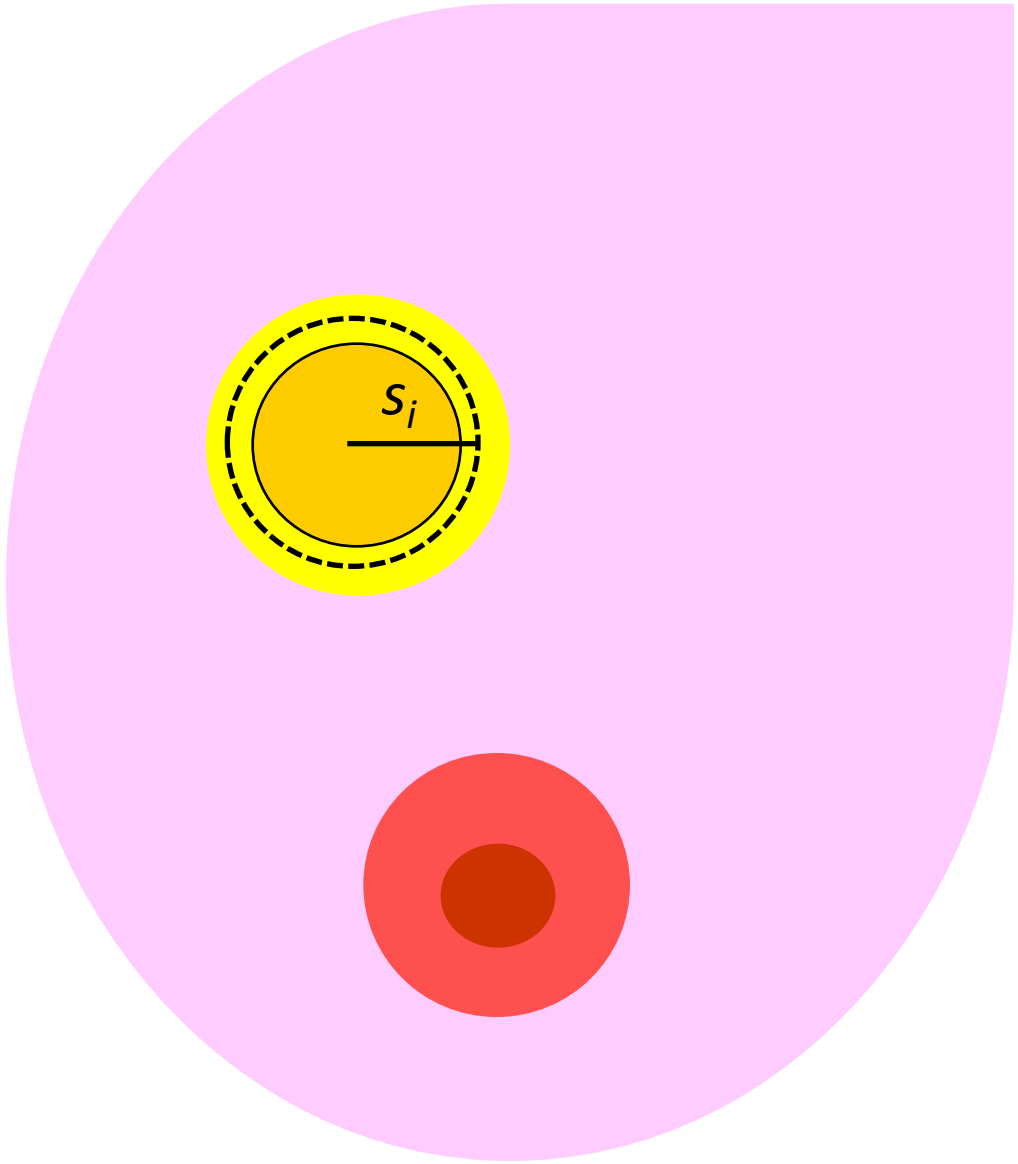
No ink on tumor, or > 0, or > s_0 resection

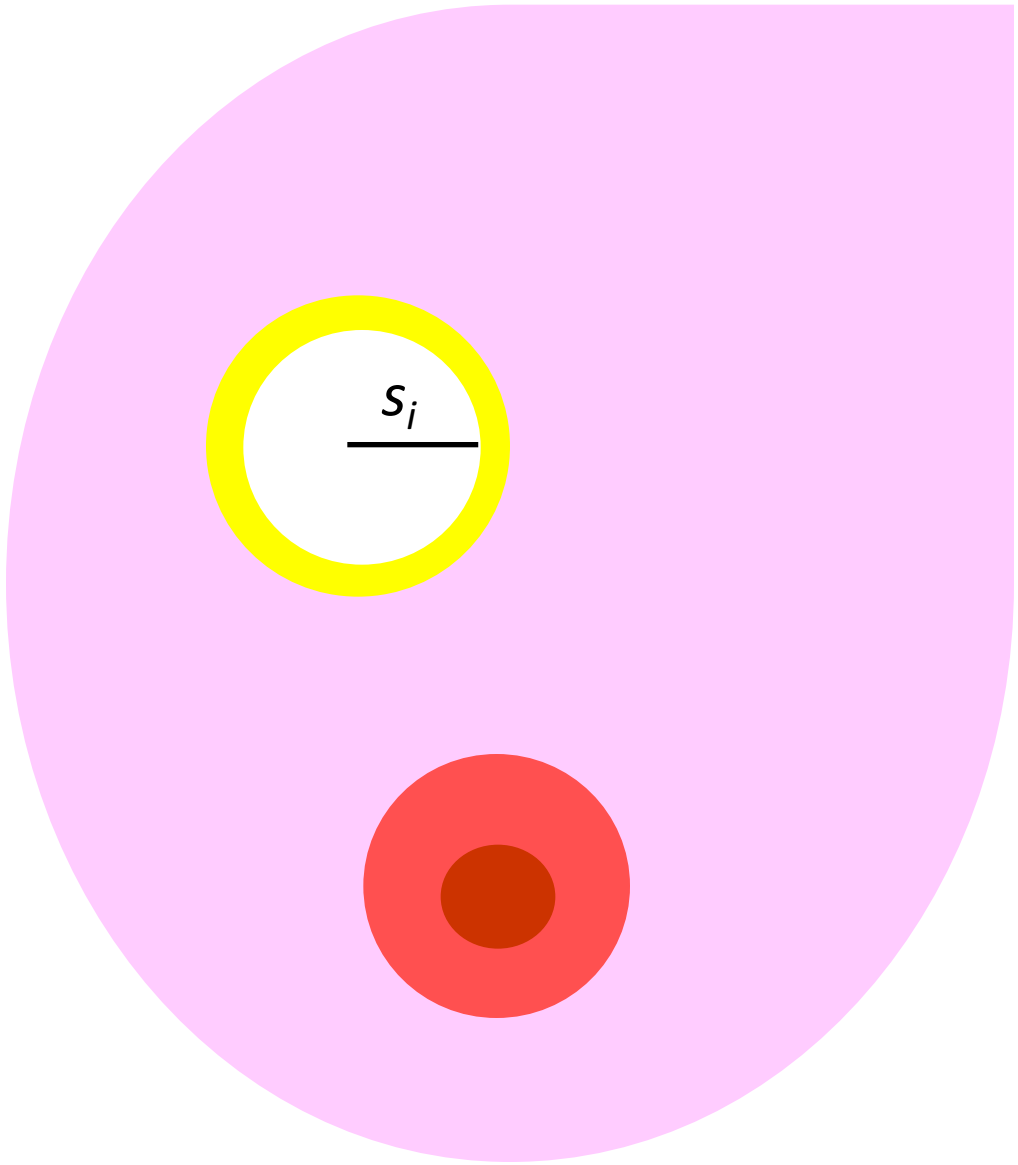


Positive margin resection

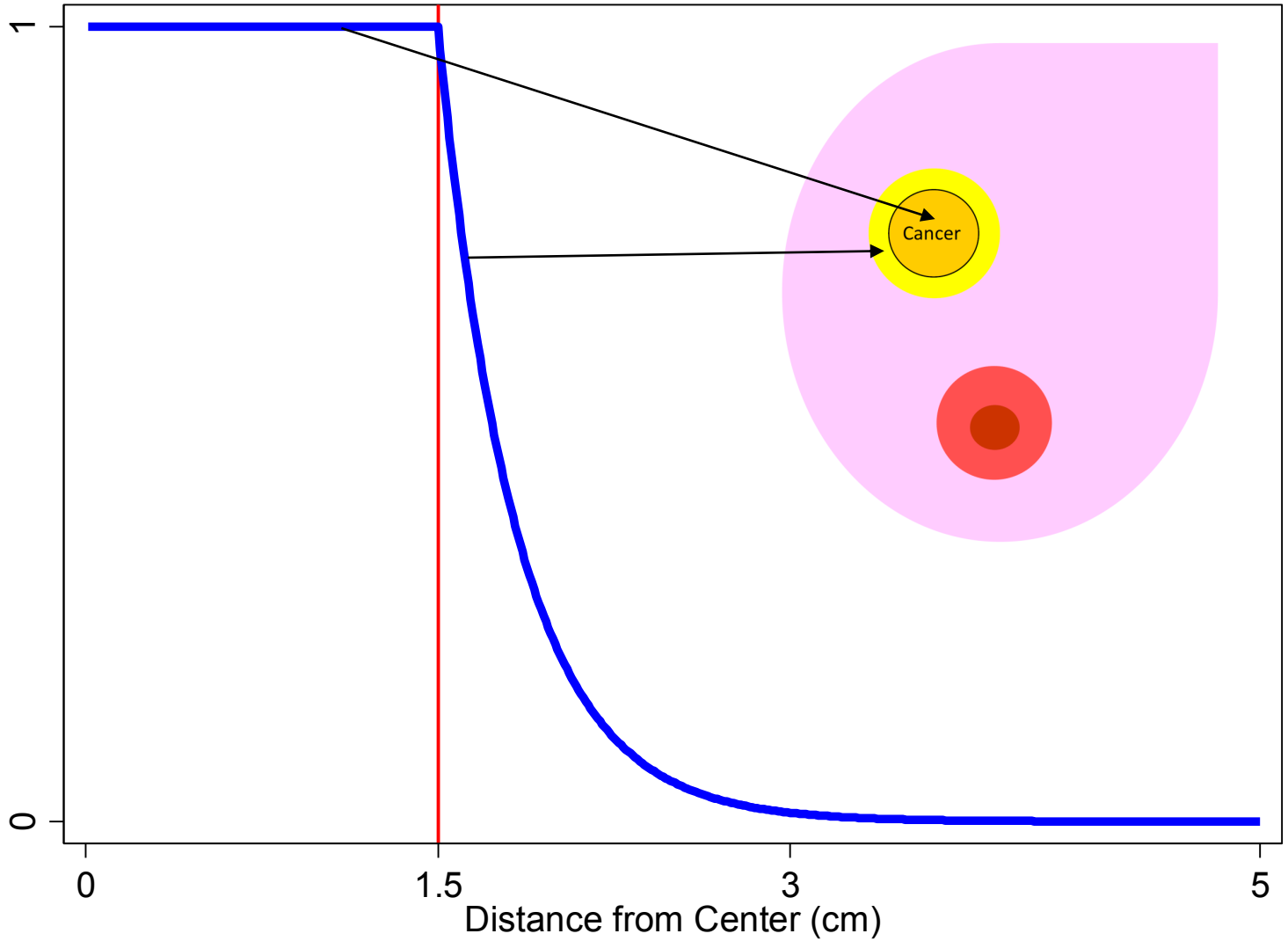


s_i is the resection size with margin *i*


s_i

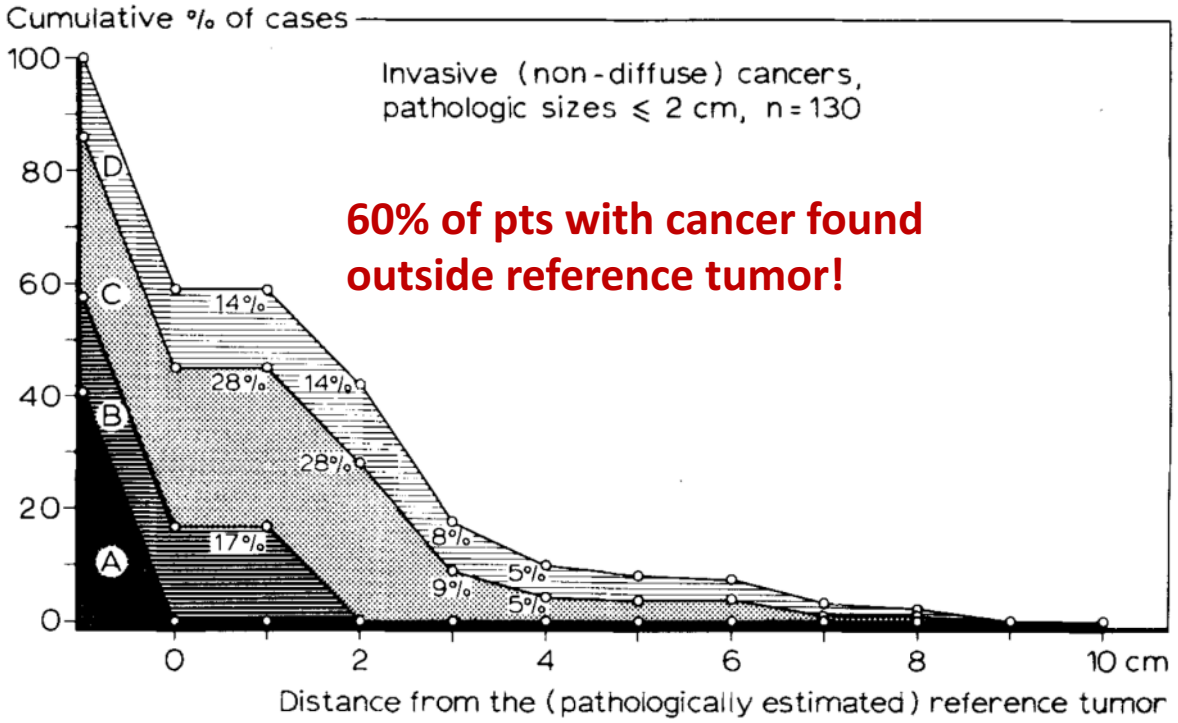


Negative margin or s_i resection


Probability of Cancer Detection as a Function of Distance (3-cm Tumor)
1
0
Cancer
0
1.5
3
5
Distance from Center (cm)

Holland Data

FIG. 2. Distribution of tumor foci at different distances from the reference tumor and proportions of cases with and without tumor foci around the reference tumor. The pathologic size served as reference size. For Figs. 2–7, the cases are divided into four groups—A: Cases without tumor foci outside of the reference tumor. B: Cases with tumor foci within 2 cm of the reference tumor. The exact distance of these foci and their invasive or noninvasive character was not further specified. C: Cases with noninvasive tumor foci at a distance greater than 2 cm from the reference tumor. D: Cases with invasive tumor foci, at a distance greater than 2 cm from the reference tumor. The values of percentages within the groups indicate the proportion of cases with tumor foci located at or beyond the point given on the abscissa (distance from reference tumor).



60% of pts with cancer found outside reference tumor!

Holland R. Cancer 1985;56:979-90

The Tumor: Model Details

- Detectable tumor size (radius) $\equiv s_0$
- Density of the detected tumor $\equiv \rho(s) = \rho_0$ if $s \leq s_0$
- Density of the undetected tumor $\rho(s) \cong \rho_0 e^{-\epsilon(s-s_0)}$ ("exponential") if $s > s_0$
- Where s is the distance from the tumor center and ϵ and ρ_0 are constants

Tumor Burden

Amount of tumor at any distance s from the tumor center:

$$T(s) = \int_0^s \rho(r) 4\pi\, r^2 dr$$

- $T(s) = 4\pi\rho_0 s^3/3$ if $s \leq s_0$
- $T(s) = 4\pi\rho_0 \left(\frac{s_0^3}{3} + \frac{s_0^2}{\epsilon} - e^{-\epsilon(s-s_0)}\frac{s^2}{\epsilon}\right)$ if $s > s_0$
- **Total amount** of tumor is $\omega = 4\pi\rho_0 \left(\frac{s_0^3}{3} + \frac{s_0^2}{\epsilon}\right)$
- Note that the function $\rho(s)$ for $s > s_0$ is *not* exponential if the above expression is strictly true – but is exponential if above is approximately true, for $\epsilon \gg s_0$

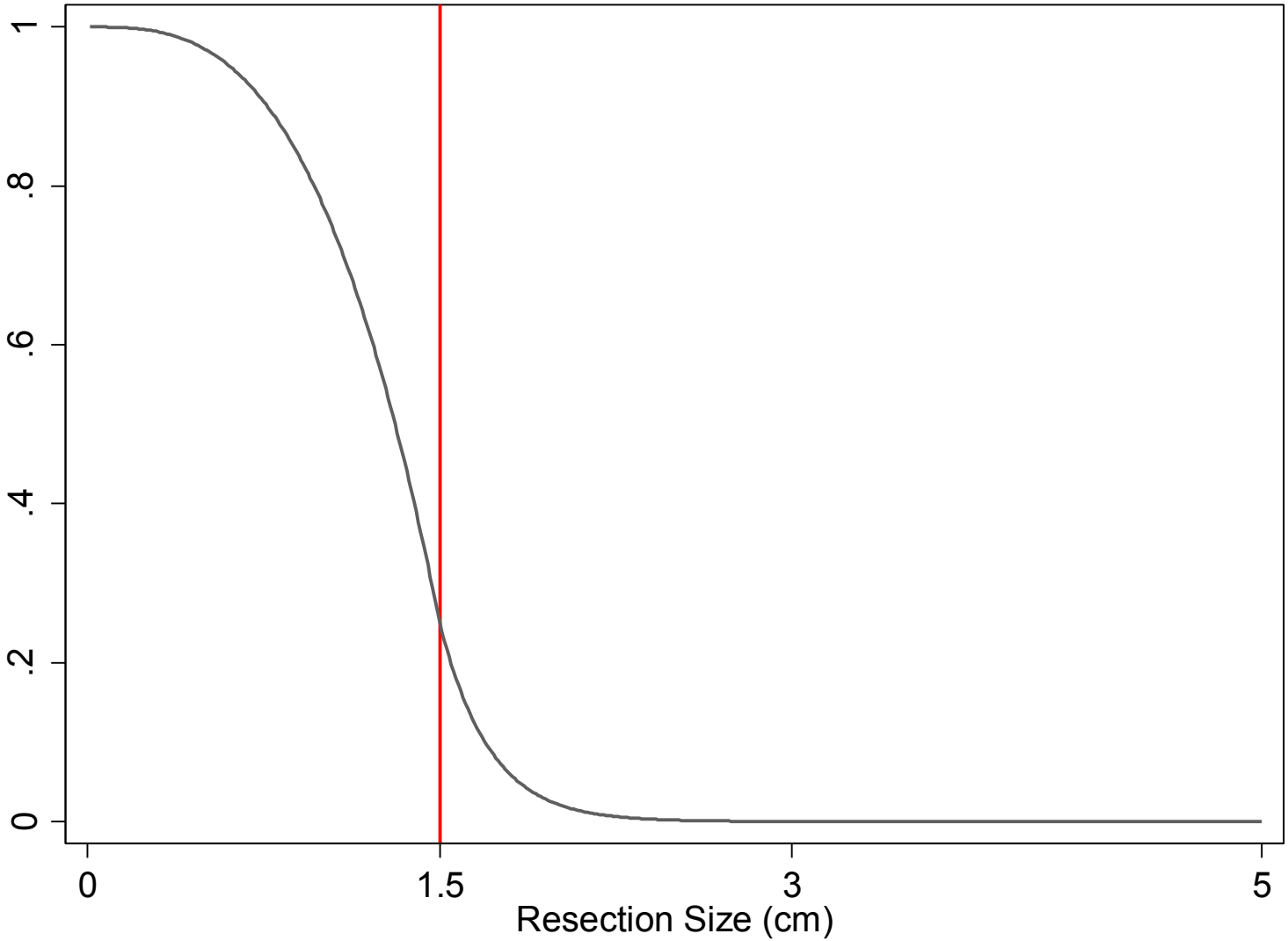
Residual Cancer

If the cancer is resected at any "core-out" distance s ("**resection size/distance**"), then the remaining, or residual, tumor would be

$$\omega - T(s) = R(s)$$

- $R(s) = 4\pi\rho_0 \left(\frac{s_0^3 - s^3}{3} + \frac{s_0^2}{\epsilon}\right)$ if $s \leq s_0$
- $R(s) = 4\pi\rho_0 e^{-\epsilon(s-s_0)} s^2/\epsilon$ if $s > s_0$

Proportion of Residual Tumor at various resection sizes:
assuming 25% residual cancer after *exact* resection of detected tumor



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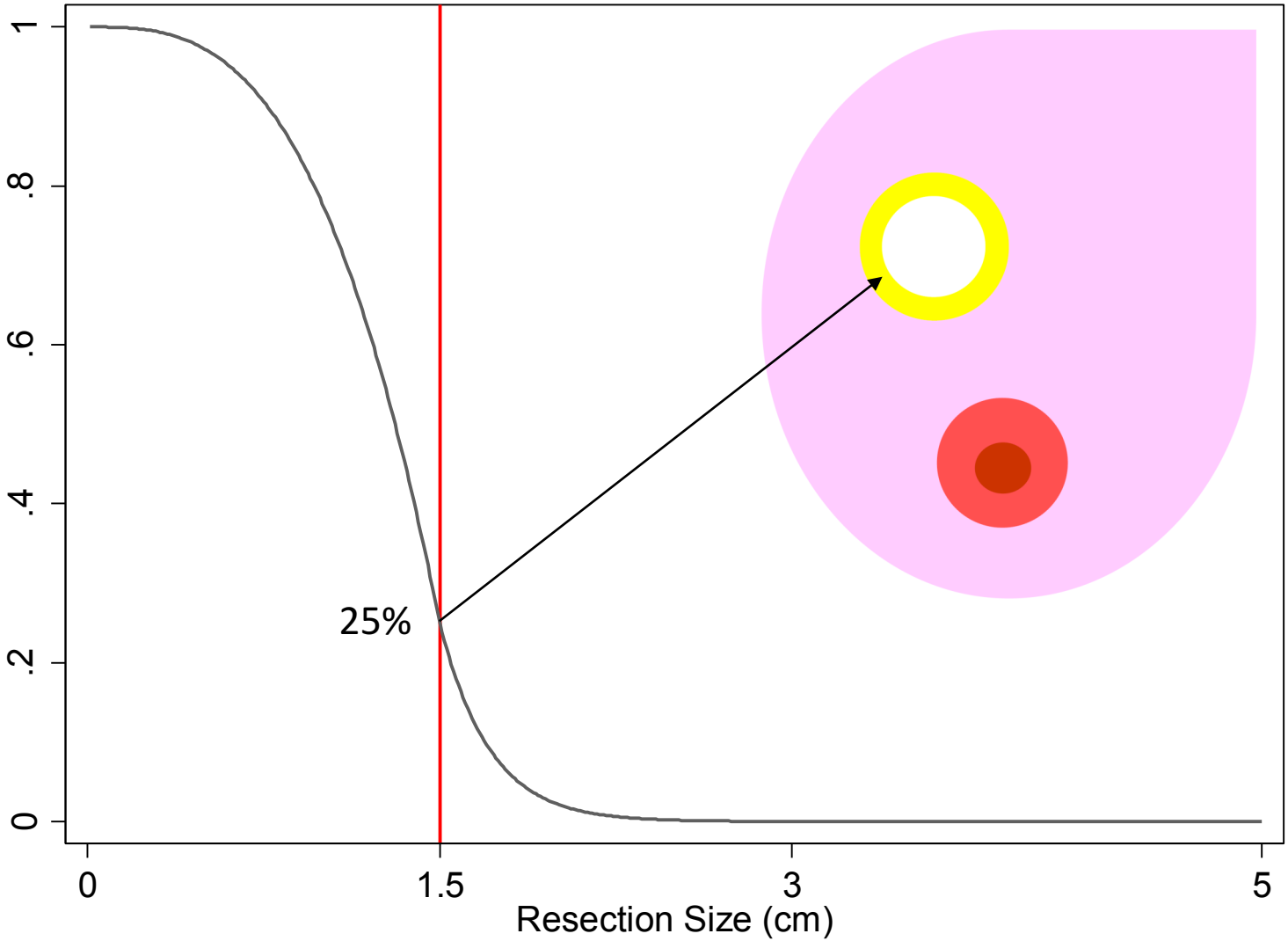


Recurrence Hazard

- The **hazard** (as in "Survival Analysis") of disease recurrence **at the primary site** at time t after surgery, is formulated as $h(t) = \lambda R(s)t$ with λ a proportionality constant
- Let's add a **background risk** of in-breast recurrence, unrelated to "residual tumor", to the hazard:

$$h(t) = \lambda R(s)t + \eta_0(t)$$

Recurrence Probability

- The **recurrence-free probability** is

$$S_t = S(t) = e^{-\lambda R(s) t^2/2 - \nu_0(t)}$$

- And hence the **recurrence probability** at time t is

$$F(t) = 1 - e^{-\lambda R(s) t^2/2 - \nu_0(t)}$$

Recurrence Probability, Open-ended

- But if the resection size is **open-ended**, and each s has a *probability distribution* (density) $g(s)$, then the probability of recurrence given $s \geq s_i$ will be

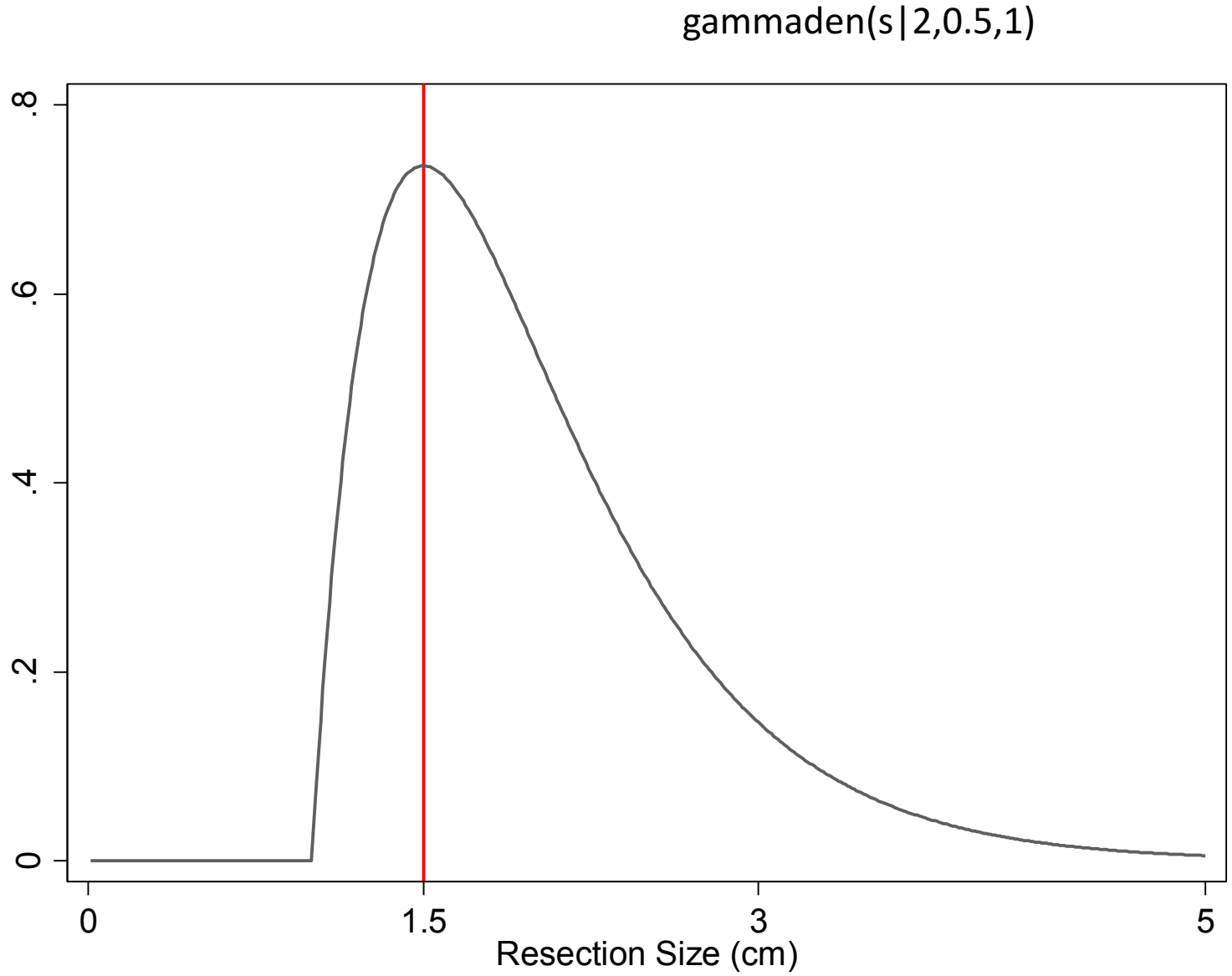
$$\Pr(\geq s_i) = \frac{\int_{s_i}^{\infty} \left(1 - e^{-\lambda R(r) t^2/2 - \nu_0(t)}\right) g(r) dr}{\int_{s_i}^{\infty} g(r) dr}$$

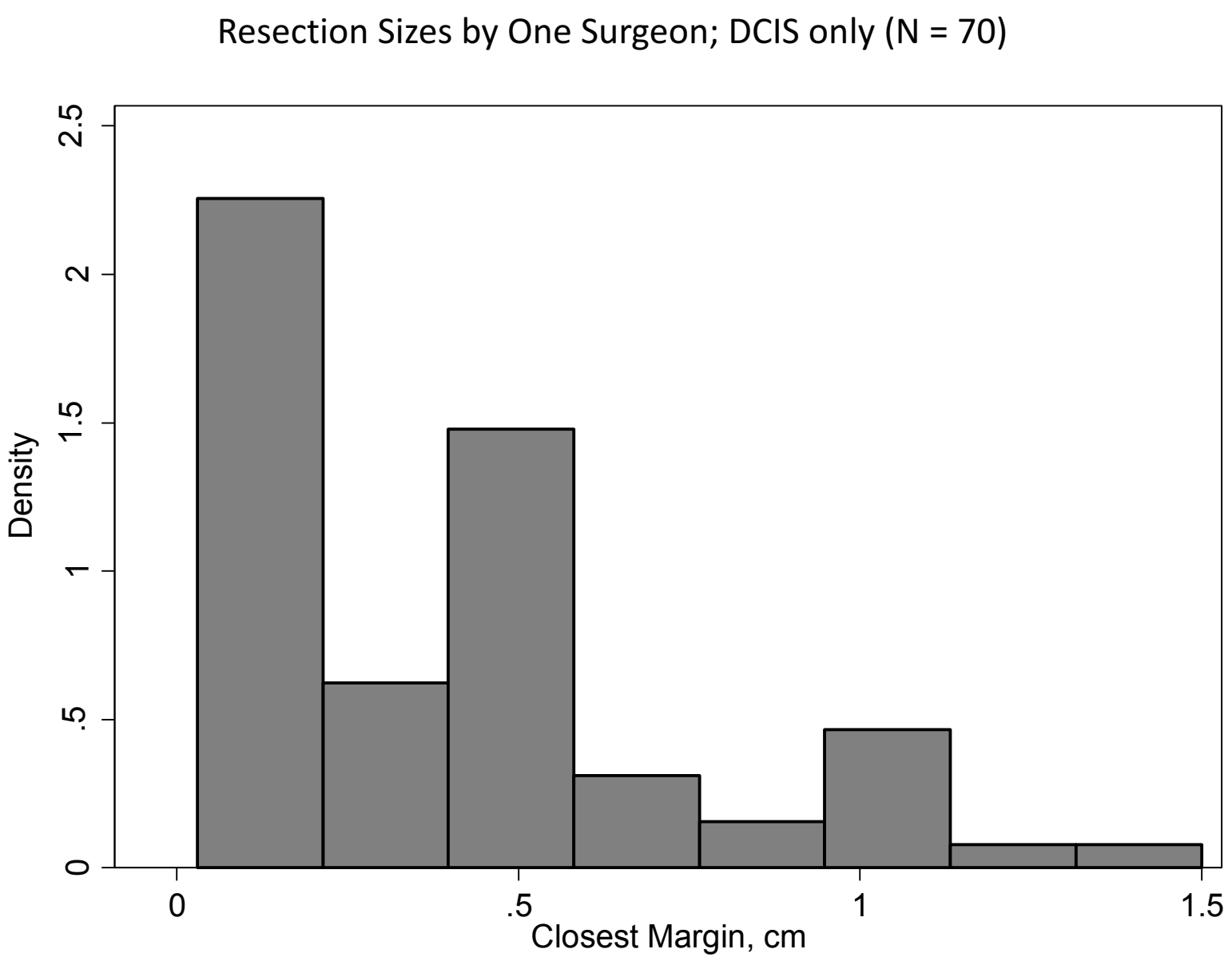
The Resection Size Probability

Modeled here as a Gamma density:

- $g(s) \equiv ga(s|a,b,c) = \frac{b^{-a}}{\Gamma(a)}(s-c)^{a-1}e^{-(s-c)/b}$
- Where $\Gamma(a)$ is the Gamma Function and a, b, c are shape, scale & location parameters resp.
- Denote

$$g(s_1, s_2) = \int_{s_1}^{s_2} g(r)dr$$


gammaden(s|2,0.5,1)
.8
.6
.4
.2
0
0
1.5
3
5
Resection Size (cm)


Resection Sizes by One Surgeon; DCIS only (N = 70)
Density
0
.5
1
1.5
2
2.5
0
.5
1
1.5
Closest Margin, cm

Full Recurrence Probability, Open-ended

The recurrence probability will be, **for $s_i \geq s_0$**

- $\Pr(\geq s_i) = \left[\int_{s_i}^{\infty} \left(1 - \exp\left(-\frac{\phi}{\epsilon} e^{-\epsilon(r-s_0)} r^2 - \nu_0\right)\right) g(r) dr\right] / g(s_i, \infty)$
- $\Pr(< s_i) = \left[\int_{s_0}^{s_i} \left(1 - \exp\left(-\frac{\phi}{\epsilon} e^{-\epsilon(r-s_0)} r^2 - \nu_0\right)\right) g(r) dr + \int_0^{s_0} \left\{1 - \exp\left(-\phi\left(\frac{s_0^3 - r^3}{3} + \frac{s_0^2}{\epsilon}\right) - \nu_0\right)\right\} g(r) dr\right] / g(0, s_i)$

- Where $\nu_0 \equiv \int \eta_0(t) dt$ (any ν_0 with no s dependence will do)
- With $\phi \equiv 2\pi\rho_0\lambda t_0^2$ for some fixed $t = t_0$
- And similarly for $s_i < s_0$

Notes on Parameters

- If we set the peripheral component of the tumor to be a proportion z_0 of the *whole tumor* (both detectable and undetectable):

$$\frac{\frac{s_0^2}{\epsilon}}{\left(\frac{s_0^3}{3}+\frac{s_0^2}{\epsilon}\right)} = z_0$$

- Then $\epsilon = \frac{3}{s_0}\left(\frac{1}{z_0}-1\right)$

Notes on Parameters

- Let's assume that the background hazard is **a fraction** υ of that of the residual tumor at a fixed t_0, e.g. when the recurrence-free probability is 0.9 = S_{t_0}, with resection at s_0 as before, thus

$$-\log\left(S_{t_0}\right) = \frac{\lambda R(s_0) t_0^2}{2} + \nu_0$$

- **So let** $\nu_0 = \upsilon \lambda R(s_0) t_0^2/2$
- And as before set $\phi \equiv 2\pi\rho_0\lambda t_0^2$

Notes on Parameters

We find

$$\phi = \frac{-3\log(S_{t_0})}{s_0^3(1+2v)}\left(\frac{1}{z_0}-1\right)$$

$$\nu_0 = \frac{-2v\log(S_{t_0})}{(1+2v)}$$

- So we must now plug in **4 numbers**: s_0, z_0, S_{t_0}, v to determine ϕ, ϵ, ν_0

Adjustable Parameters

Four numbers are used for model fitting

- Tumor size (radius): **fixed** at 3 cm
- *Proportion of tumor which is undetected at the primary site (all cancer beyond 0-mm margin)*
- *Disease free probability at some given time*
- *Contribution of background hazard at that time, as a fraction of the 0-mm margin residual cancer hazard*

One probability density (**fixed** in what follows)

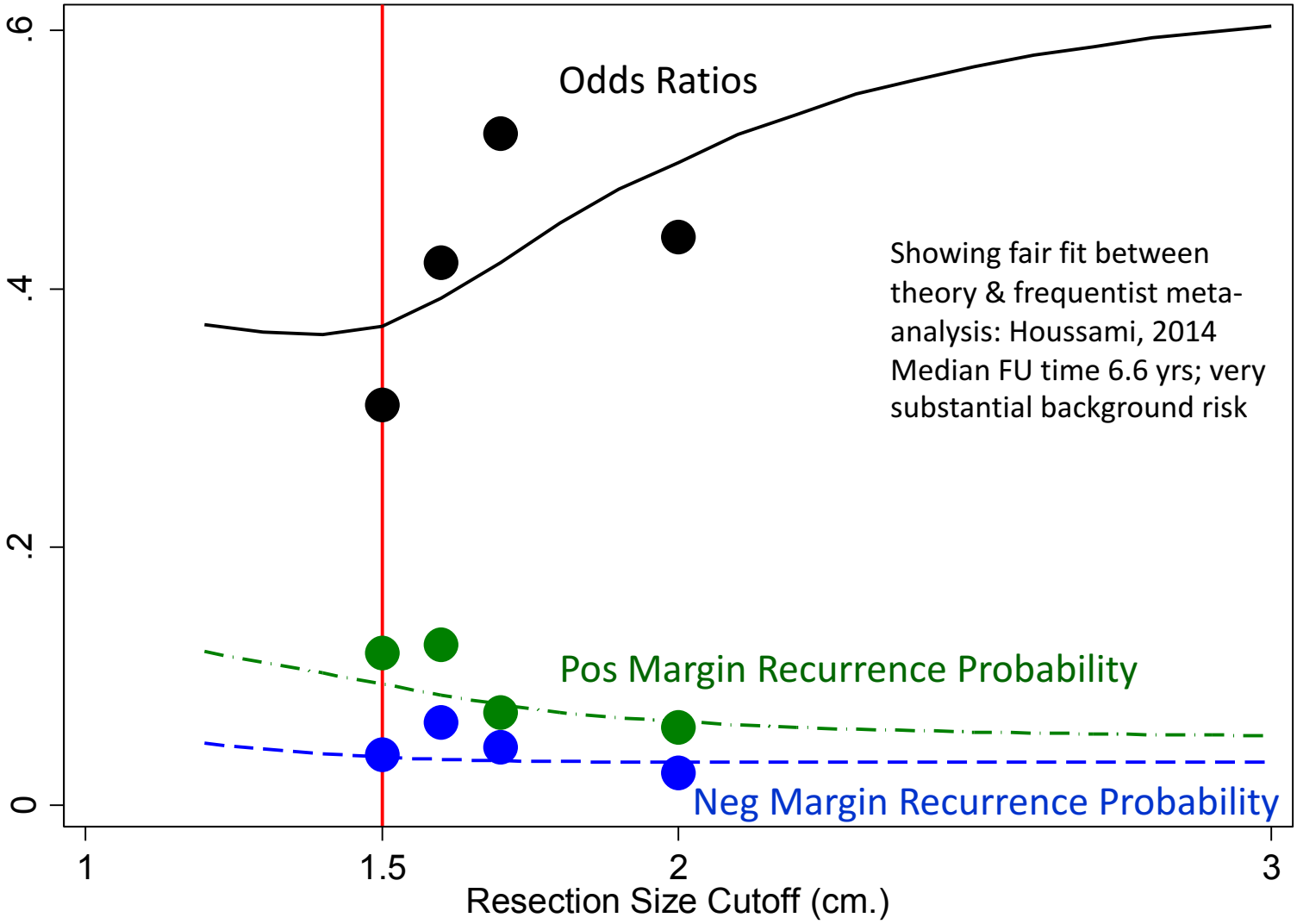
- Resection size probability

Model “Fitting”

- We attempt to “fit” a model, with appropriate parameters, to the **Houssami, 2014 data**
- **Odds Ratios are open-ended, no common control**
- There are 4 negative margins: > 0 (no ink on tumor), 1, 2, and 5 mm
- Using the Houssami data, we estimated the **pooled OR** and **recurrence rate** for each margin using the DerSimonian & Laird random effects model
- **The pooled OR’s & rates are used as data for model “fitting”**

Houssami, et al. Ann Surg Oncol 2014;21:717-30

Houssami Data: **0.94** dis free; **20%** undetected CA; **0.6** background



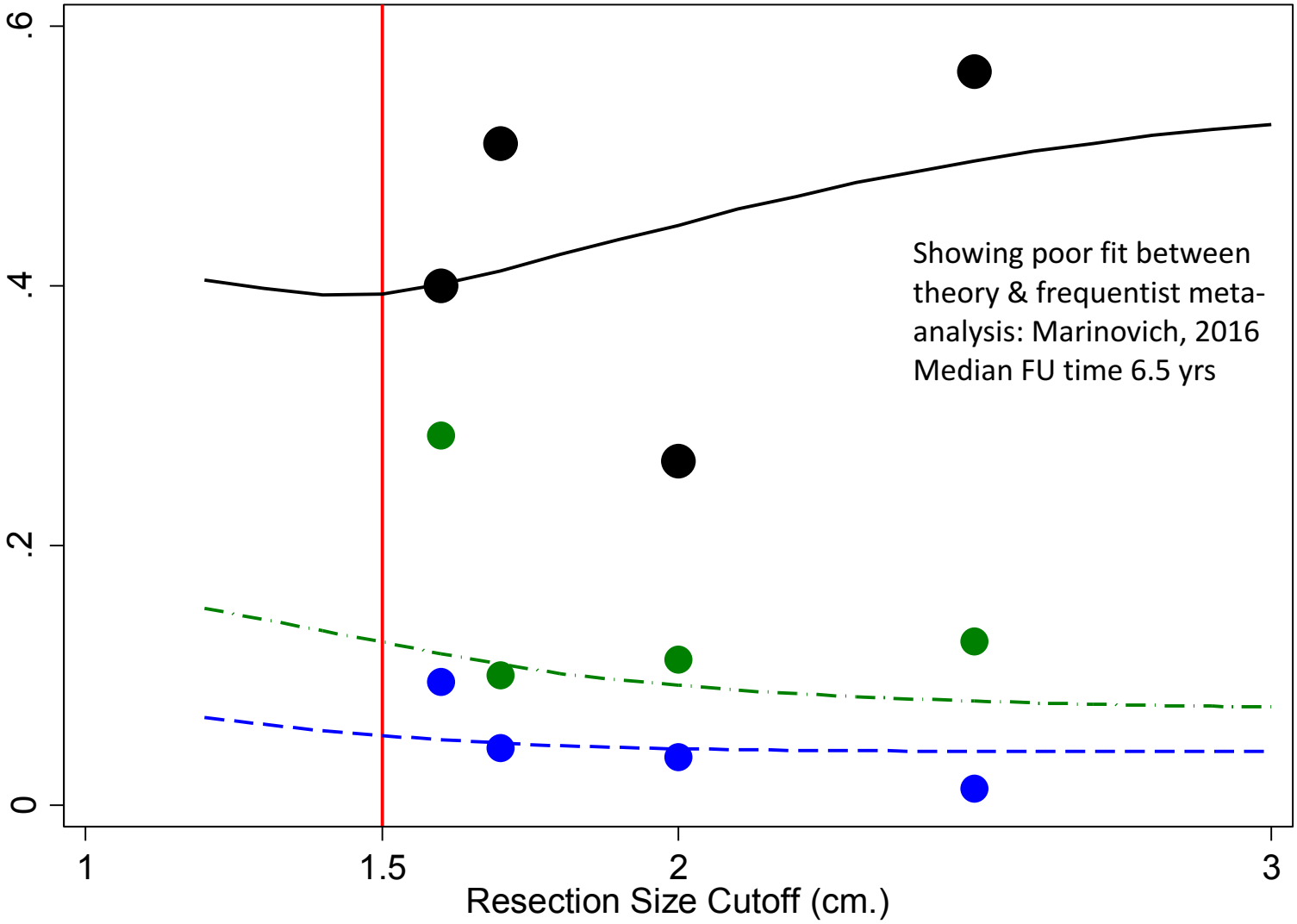
Open-ended margin OR's with **no common control**

More Model “Fitting”

Similar to what we did for the Houssami data, for the **Marinovich, 2016 & Wang, 2012 data**:

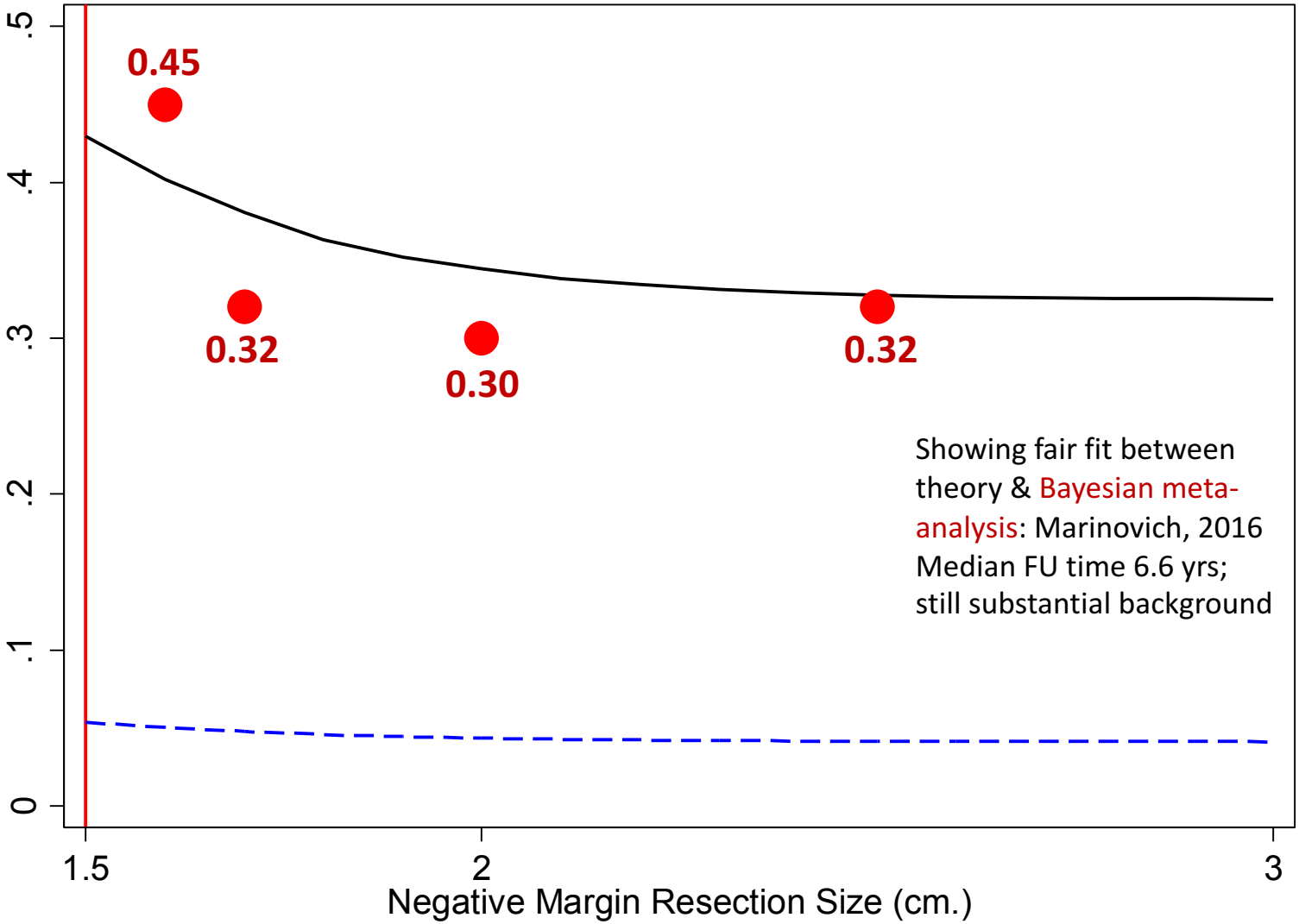
- We used DerSimonian & Laird random effects model to estimate frequentist OR’s & recurrence rates and used these as data for “fitting” models with open-ended cutoffs (Marinovich only)
- But we also have **Bayesian estimates**; these were used for fitting models with common controls, for both Marinovich & Wang data

Marinovich Data: **0.91** dis free; **30%** undetected CA; **0.4** background



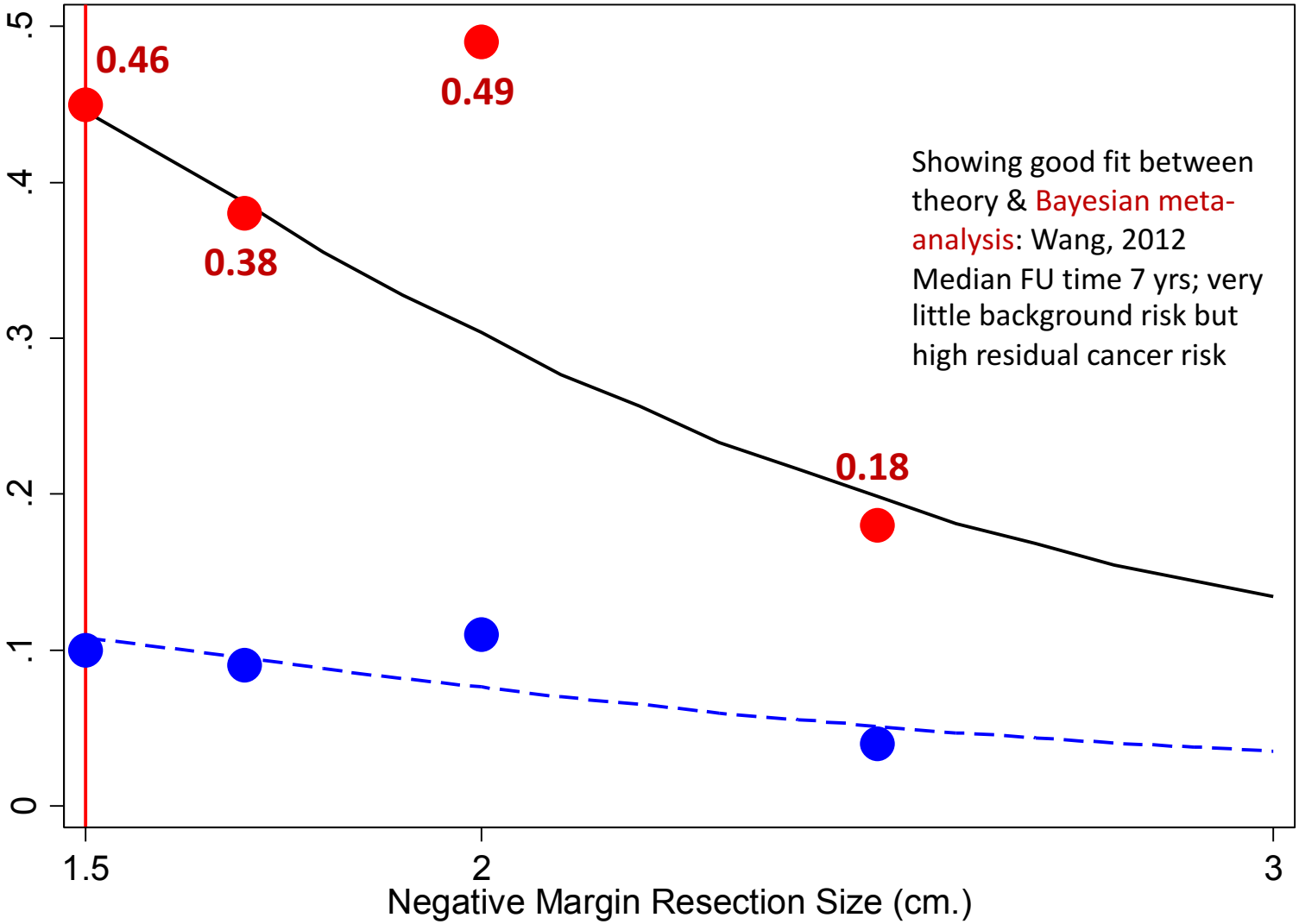
Open-ended margin OR's with **no common control**

Marinovich Data: **0.91** dis free; **30%** undetected CA; **0.4** background



Open-ended margin OR's with < 1 mm-positive, **common control**

Wang Data: **0.83** dis free; **50%** undetected CA; **0.05** background



Open-ended margin OR's with < 0 mm-positive, **common control**

The OR of Real Interest

- The OR's of real interest, as was also noted in all metaanalyses, are ones contrasting the various cutoffs, or technically the comparison among Recurrence Probabilities of $s \geq s_0, s \geq s_1, s \geq s_2, s \geq s_3$ and so on
- For example in Houssami (2014), the contrast was between $s \geq s_1$ and the rest (0, 2, 5 mm), and in Marinovich (2016) it was 0-1 against 2, 3-5, 10 mm
- We will do theoretical calculations for these

The OR of Real Interest

- In the metaanalyses, the OR's were obtained *indirectly* by way of statistical modeling: as estimated coefficient-parameter values of a covariate in the GLMM, or via "analogous" Bayesian models
- Here, we will calculate in our usual, direct way
- Then we will compare theoretical values with statistical estimates from metaanalyses

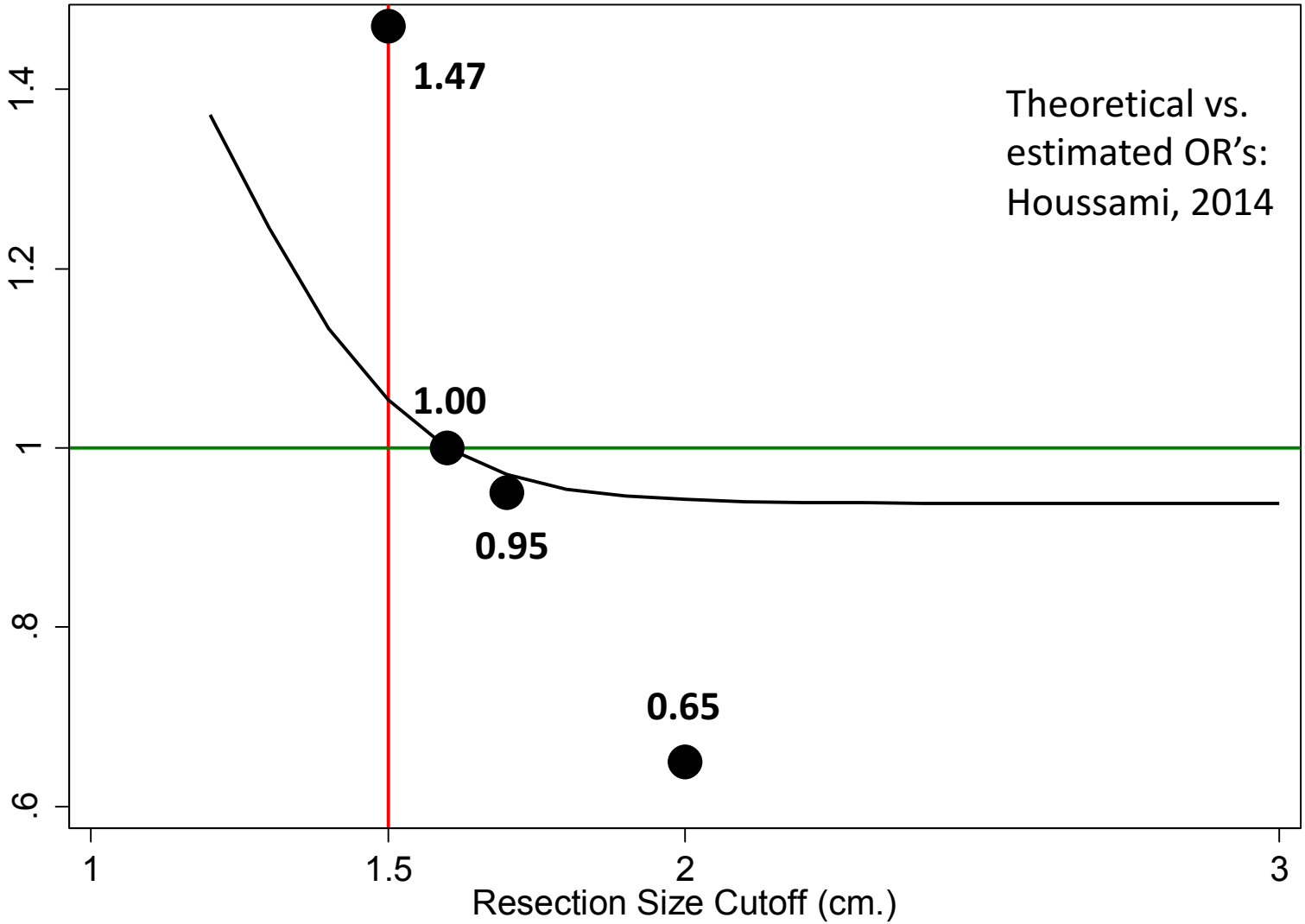
Recurrence Probabilities

We contrast recurrence probabilities of cutoff 1 mm with all others (background risk assumed)

- $\Pr(\geq s_1) = \left[\int_{s_i}^{\infty} \left(1 - \exp\left(-\frac{\phi}{\epsilon} e^{-\epsilon(r-s_0)} r^2 - \nu_0\right)\right) g(r) dr\right] / g(s_1, \infty)$
- $\Pr(\geq s_k) = \left[\int_{s_k}^{\infty} \left(1 - \exp\left(-\frac{\phi}{\epsilon} e^{-\epsilon(r-s_0)} r^2 - \nu_0\right)\right) g(r) dr\right] / g(s_k, \infty)$

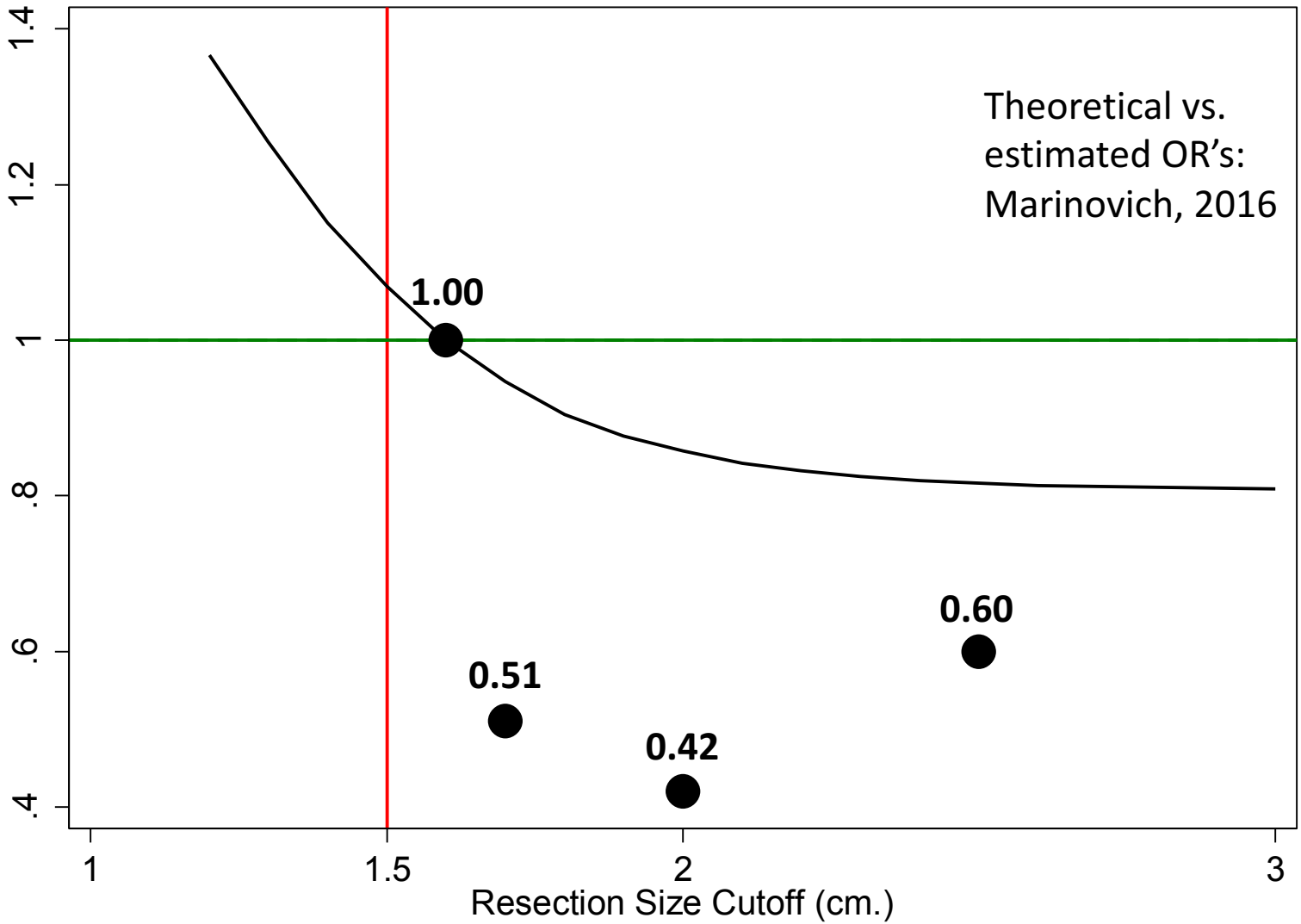
- Where k is 0 or 2, 3, 5, 10 mm, etc.

Houssami Data: **0.94** dis free; **20%** undetected CA; **0.6** background



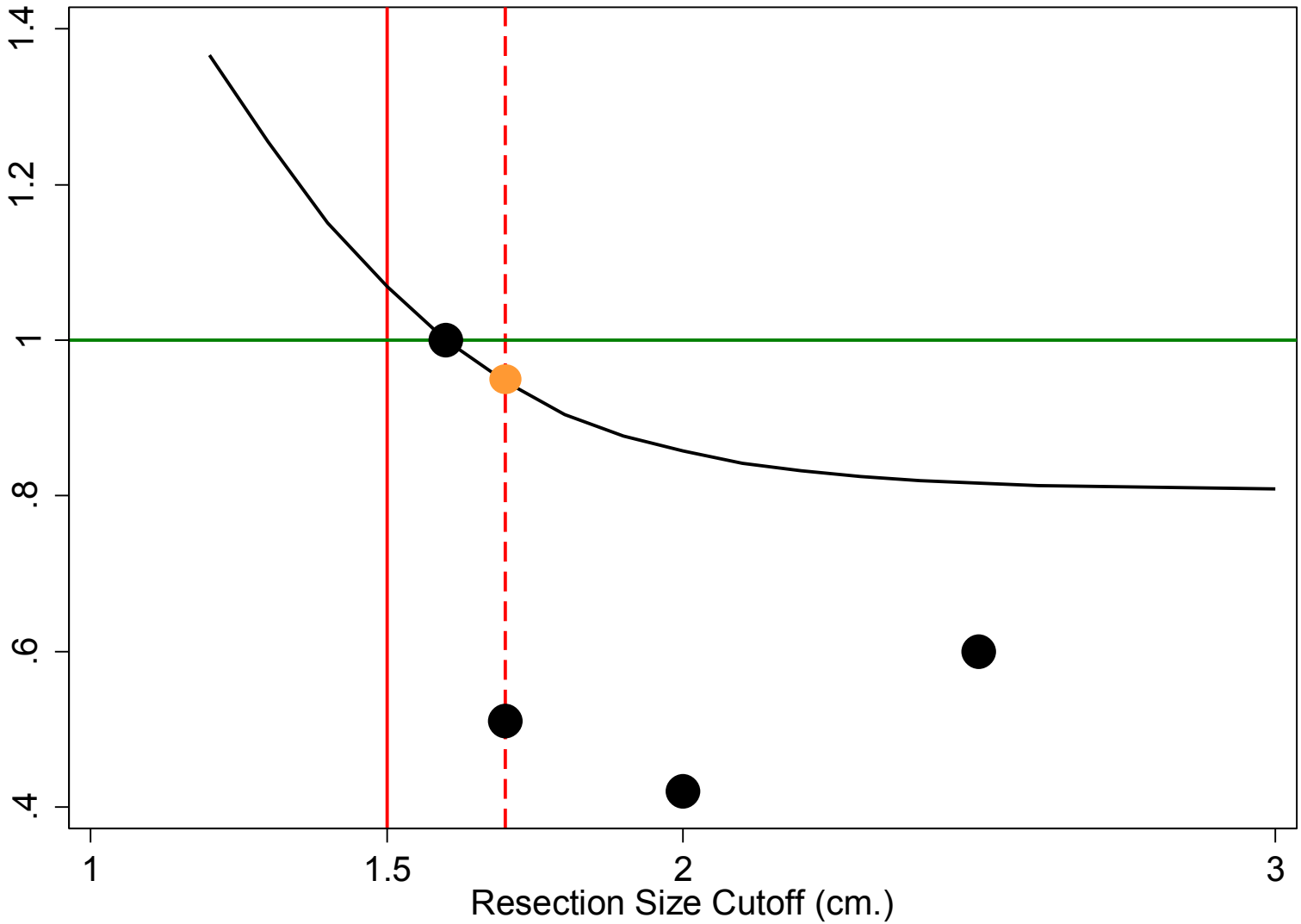
Open-ended margin OR's with **1 mm neg margin as common control**

Marinovich Data: **0.91** dis free; **30%** undetected CA; **0.4** background



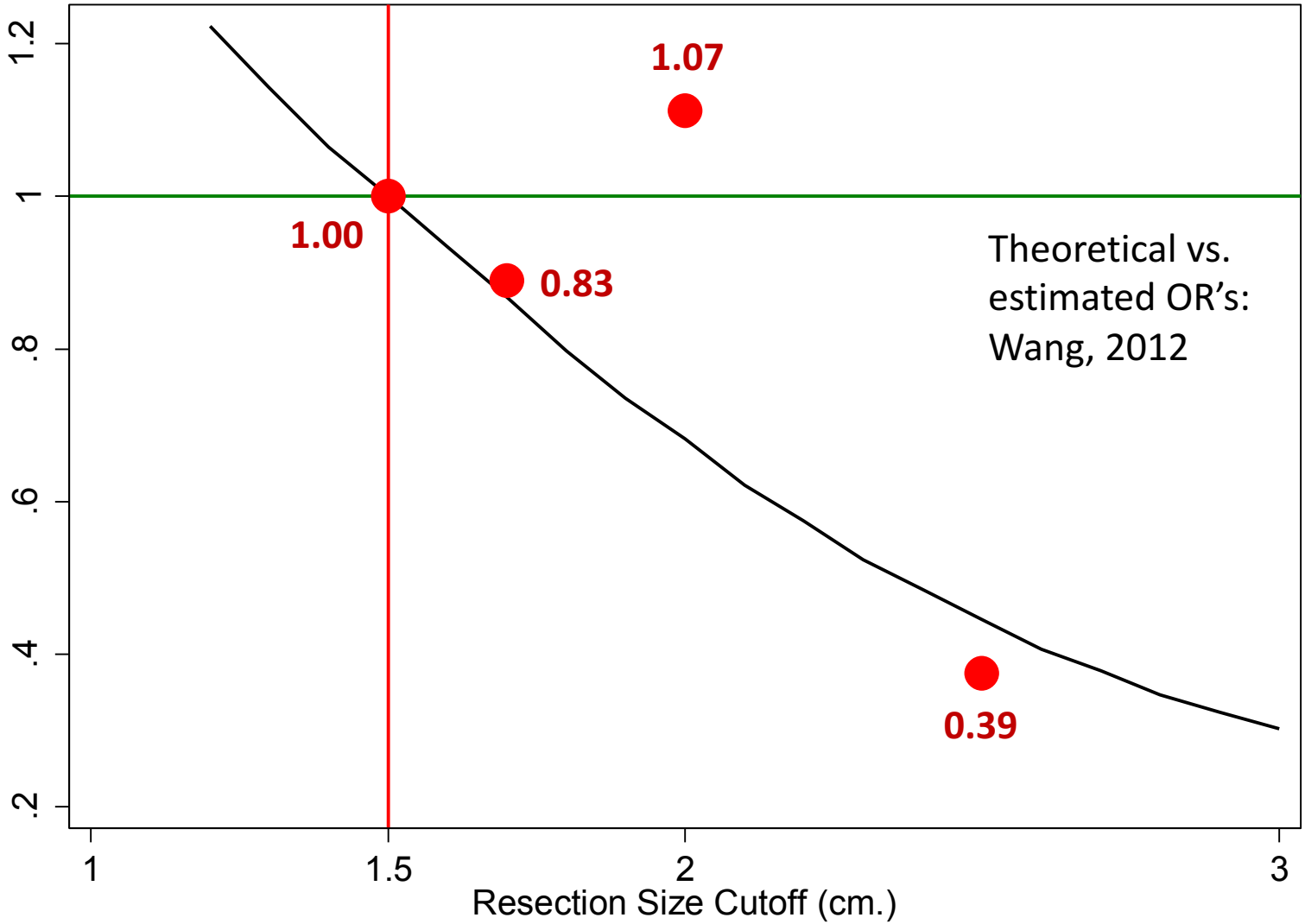
Open-ended margin OR's with **1 mm neg margin as common control**

Marinovich Data: **0.91** dis free; **30%** undetected CA; **0.4** background



Open-ended margin OR's with **1 mm neg margin as common control**

Wang Data: **0.83** dis free; **50%** undetected CA; **0.05** background



Open-ended margin OR's with **1 mm neg margin as common control**

Comments

- **Houssami data & fitted** theoretical values suggest no great differences among > 0, 1, 2 mm margins, and also an early leveling of OR values
- **Marinovich fitted values** suggest similarly that > 0, 1, 2 mm margins are not so different as *the data seem to say*; but there is later leveling
- **Wang data & fitted** values suggest something else entirely: large differences among all cutoffs of interest and no leveling

Comparing Precise Margins

- As a theoretical exercise, we can compare recurrence probabilities between each *precise* margin, e.g. comparing 1 mm precisely with 2 mm precisely (not ≥ 1 mm with ≥ 2 mm)
- This is probably the **ideal comparison**
- But this can be difficult to do in reality, since it would require a **large number of patients** with very precisely defined margin of resection for each and every margin

Comparing Precise Margins

- However, this is very easy to do theoretically
- We can then contrast how the OR's differ between different ways of defining margins: between precise and open ended definitions (as was done previously)

Comparing Precise Margins

The Recurrence Probabilities are, for $s > s_0$,

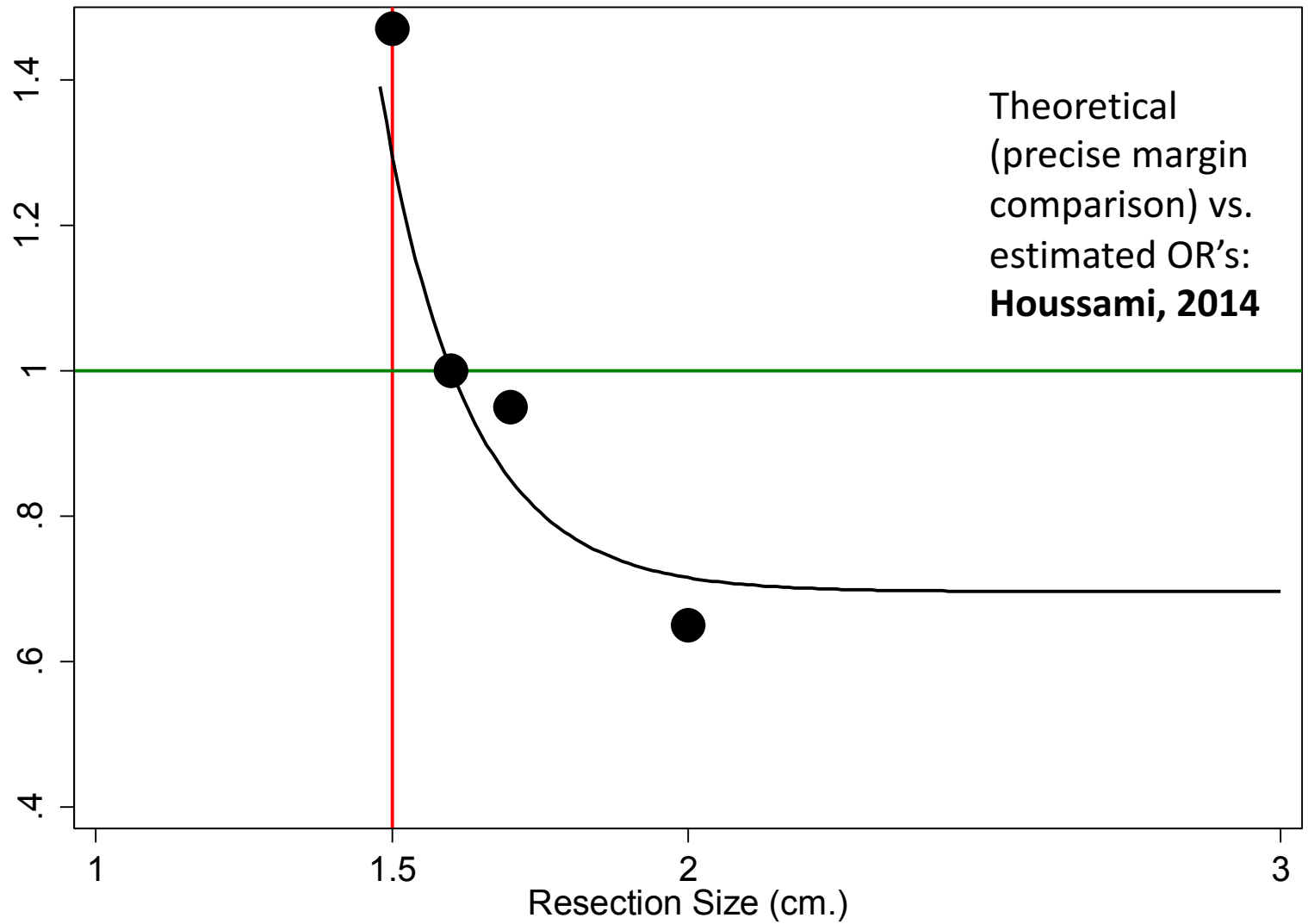
$$\Pr(=s_1) = \left\{1 - \exp\left(-\frac{\phi}{\epsilon}e^{-\epsilon(s_1 - s_0)}s_1^2 - \nu_0\right)\right\}$$

$$\Pr(=s_i) = \left\{1 - \exp\left(-\frac{\phi}{\epsilon}e^{-\epsilon(s_i - s_0)}s_i^2 - \nu_0\right)\right\}$$

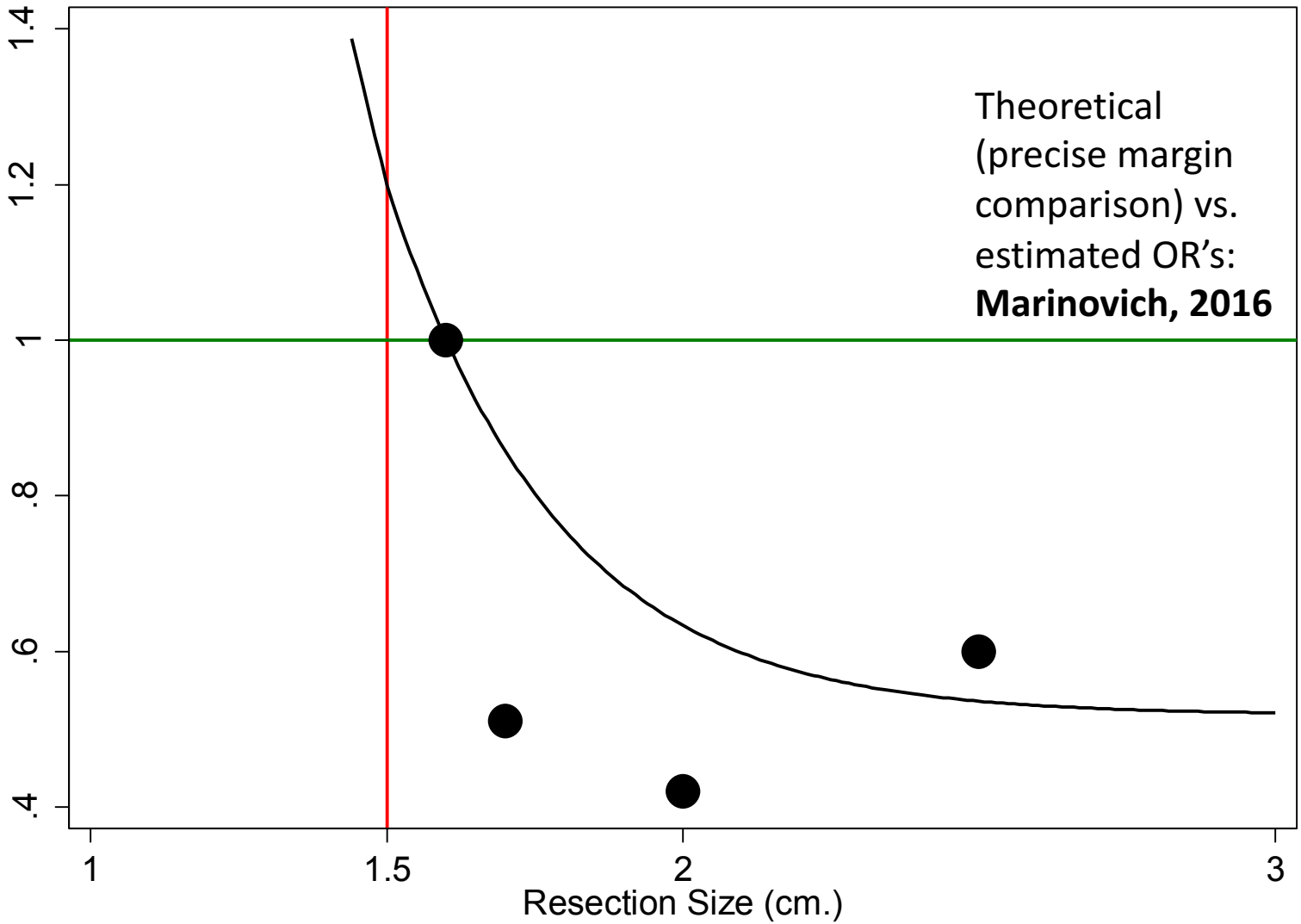
The Odds Ratio of margin i compared with 1 is, **asymptotically** as $s_i \to \infty$,

$$OR = \frac{e^{-\frac{\phi}{\epsilon}e^{-\epsilon(s_1 - s_0)}s_1^2}(1 - e^{-\nu_0})}{1 - e^{-\frac{\phi}{\epsilon}e^{-\epsilon(s_1 - s_0)}s_1^2 - \nu_0}}$$

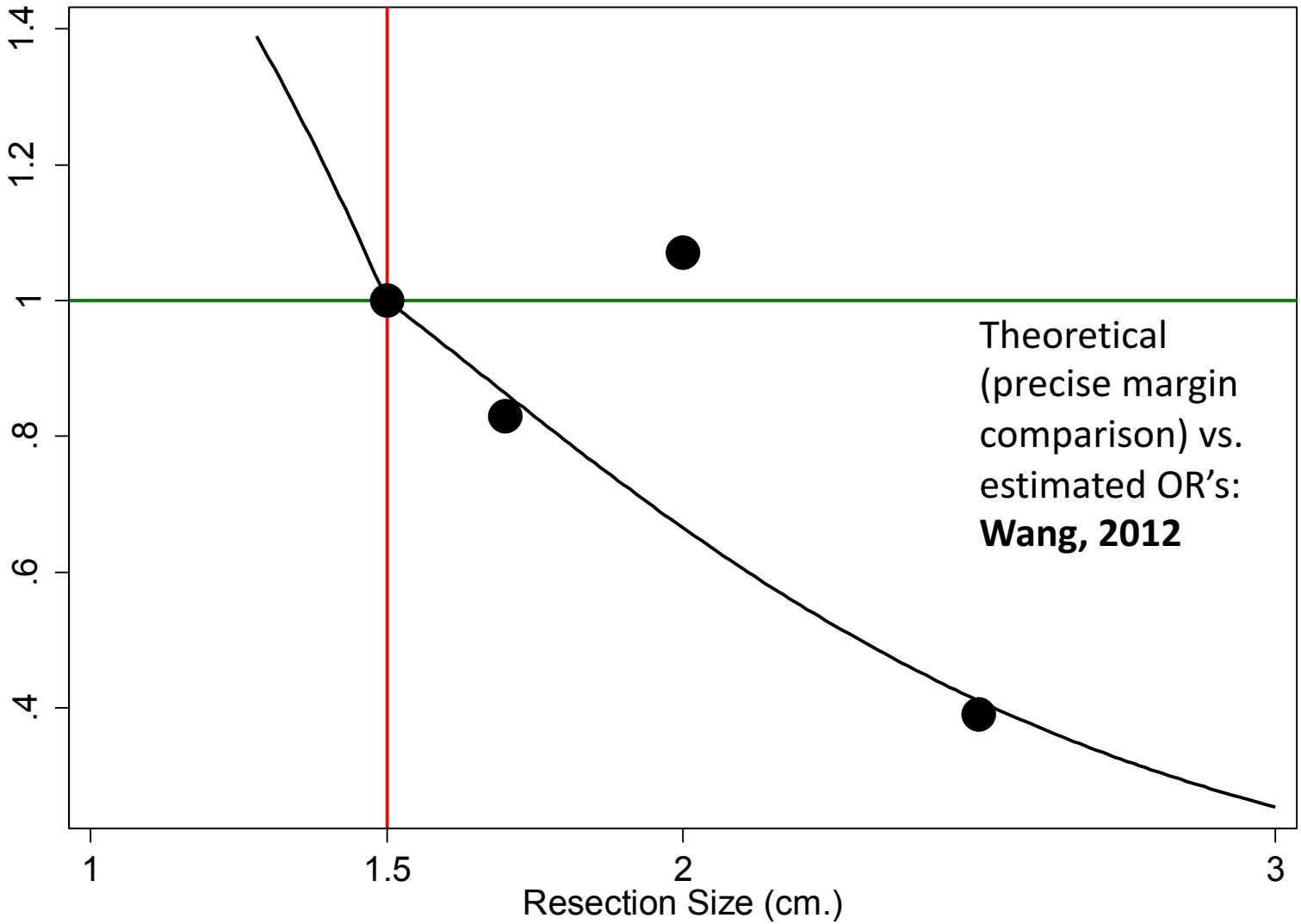
Which goes to 0 if there is no background risk ($\nu_0 = 0$)



Precise margin OR's with **1 mm neg margin as common control**



Precise margin OR's with **1 mm neg margin as common control**



Precise margin OR's with **1 mm neg margin as common control**

Comments

- **Precise margin comparisons** fit the data **much better** than the **open-ended margin comparisons**
- I am not really sure why
- Models for Houssami & Marinovich have a similar pattern though the model for Marinovich has deeper fall in OR's and later leveling
- And there is considerable attenuation of the OR between 1mm & 2 mm margins
- Whatever we do, theory always fit Wang's data!

The Margin Problem

- It’s a problem when postoperative pathological examination reveals “close/positive” margins
- Usually pre- & intraoperative margins are planned and expected to be widely free

Margins?

- We’re talking around the edges of the tumor!
- It’s all about how much residual cancer we are willing to accept, such that RT/systemic therapy can help control the disease
- So that the pt can live free of symptoms & with acceptable life expectancy & QoL
- Margins can be **positive**
- Margins can **vary with biology & treatment**

DCIS with Margins < 1 mm

- If ER/PR +ve, with RT & Hormonal therapy: no further resection?
- If very small size, e.g. < 1 cm? < 0.5 cm?
- If low grade (nuclear grade I/II)
- If focally, microscopically positive?
- If patient is able to accept higher risk?

Some Data on Residual Cancer

One study*

- 0 mm: 40% 0-1 mm: 38% 1-2 mm: 33%
- No relation between residual cancer and histology, ER, LVI, triple neg, no. of close margins (borderline)

Another study**

- No relation between residual cancer and margin width

*The Breast 2015;24:413-7 **J Surg Oncol 2014;109:426-30

Some Data on Residual Cancer

- From May 2010 – May 2016: 720 attempted BCS
- 154 **margin shavings**/re-excisions/mastectomies for whatever reason; 143 with sufficient data

	Free Margins > 1 mm (n=25)	Close Margins ≤ 1 mm (n=54)	Positive Margins (n=64)
Residual Cancer	3 (12%)	20 (37%)	36 (56%)
Size (cm): Median (range)	0.4 [n=1]	0.3 (0.05 – 1.3) [n=15]	0.4 (0.05 – 7.5) [n=29]
Residual < 1 cm	1/1	14/15 (93%)	21/29 (72%)

Some Data on Residual Cancer

- Of the 104 patients with primary invasive cancer
- 45 (43%) have residual cancer
- Of these 21 (**47%**) are **non-invasive** residuals

- Of the 46 patients with primary invasive cancer and **positive margins**
- 27 (59%) have residual cancer
- Of these 11 (**41%**) are **non-invasive** residuals

Residual Cancer

- The majority (if small enough) do not become clinical recurrences for many years, or throughout the patient's remaining lifetime
- Under current treatment guidelines
- Residual cancers in close & positive margins seem not too dissimilar in frequency & extent
- It might be reasonable to offer no further surgery for **highly selected patients** with **positive margins**
- But we must first & foremost **reliably identify** such patients
- **e.g. size**, **excision for diagnosis**

Some Personal Experience

- BCS margins for DCIS ± microinvasion
- General policy is no secondary surgery if > 0 mm margins (since 2012)
- For some selected patients with DCIS
- Data from 2010 to 2017: **79** non-invasive cancers of 266 (30%)
- Of these, **72** were DCIS ± microinvasion
- Microinvasion in 10/72 (14%)

Some Personal Experience

Characteristics	Summary (n ≤ 72)
Age (years): mean (sd) [range]	55.1 (12.9) [26 – 87]
Size (cm): median (range)	**0.7** (0.2 to 3.5) {n = 63}
Multifocality	24/72 (33%)
HR +ve	65/71 (92%)
Closest Margin (mm): median (range)	**3 (0.3 – 15)** {n = 64}
Margin not inc. parenchymal boundary	5 (0.3 – 16)
Multiple (≥ 2) close margins	7/72 (10%)
Proportion Margins < 1 mm	8/64 (13%)
Proportion Margins < 2 mm	**20/64 (31%)**
Hormonal Therapy	65/71 (92%)
RT	60/71 (85%)
FU time (months): median (range)	**22.5 (1 – 88.5) {n = 71}**
Number of locoregional recurrences	**0**

Conclusion

- Clinical Data can be best available but may not be best possible
- Logic and mathematical modeling may be useful in this context
- Surprising fit between simple models & data
- Suggesting the importance of background risk in in-breast cancer recurrence
- With the acceptance of some minimal degree of residual cancer, with good biology, absolute negative margin criteria are less important