THE UNIVERSITY OF TEXAS
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Prostate Cancer
Assorted Mortality Statistics

John W. Davis, MD, FACS

Annals of Internal Medicine | CLINICAL GUIDELINE

Screening for Prostate Cancer: U.S. Preventive Services Task Force Recommendation Statement

Ann Intern Med. 2012;157.

Virginia A. Moyer, MD, MPH, on behalf of the U.S. Preventive Services Task Force*

Annals of Internal Medicine

U.S. Preventive Services TASK FORCE
www.USPreventiveServicesTaskForce.org

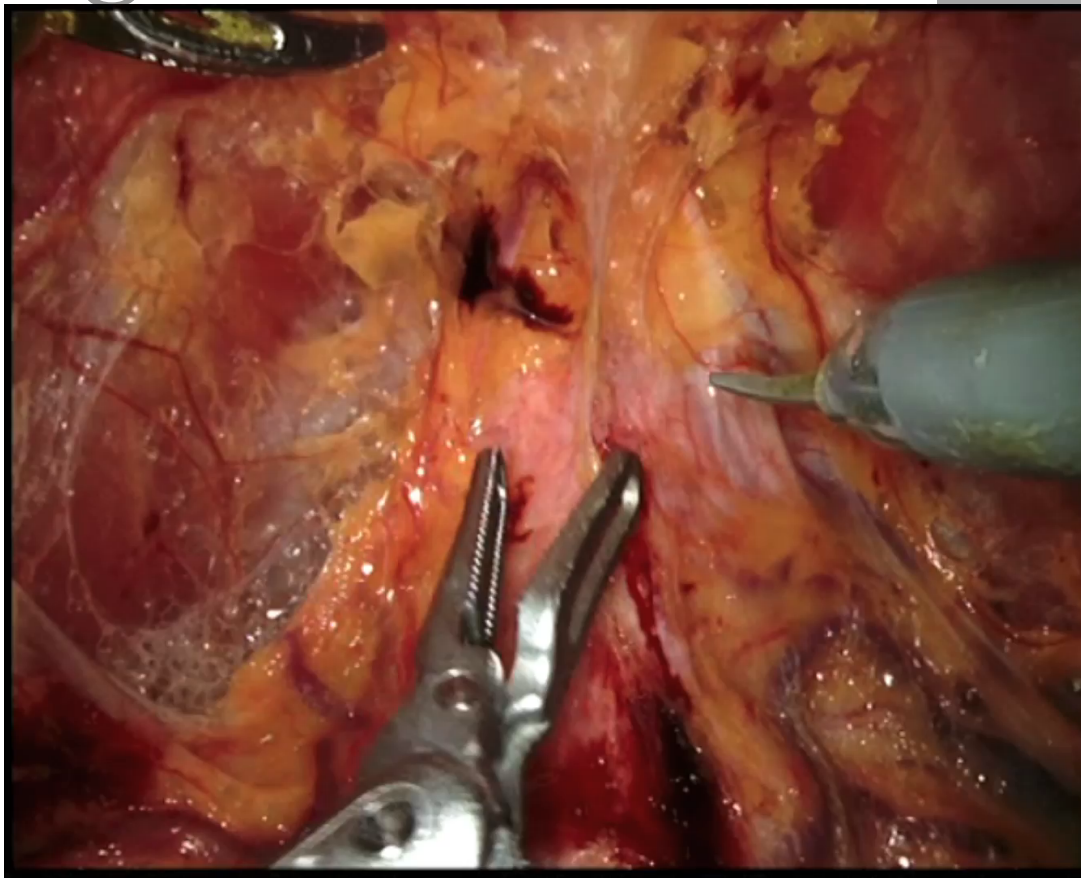
SCREENING FOR PROSTATE CANCER

CLINICAL SUMMARY OF U.S. PREVENTIVE SERVICES TASK FORCE RECOMMENDATION

Population	Adult Males
Recommendation	Do not use prostate-specific antigen (PSA)–based screening for prostate cancer.
	Grade: D

Up Close: Just Right

- 46 y/o with Family history of PCa
- Multi-core GS 3+4 and 3+3
- Favorable MRI
- Significant delay—fear of side effects, single/dating
- RARP: pT2 3+4, R0 Nx
- Immediately continent/ potent



Harms of treatment

- We knew this one:
  - ***Adequate evidence shows that nearly 90% of men with PSA-detected prostate cancer in the United States have early treatment with surgery, radiation, or androgen deprivation therapy***
- Not sure I knew/believed this one:
  - ***Adequate evidence shows that up to 5 in 1000 men will die within 1 month of prostate cancer surgery***

Simple Math

- 5 in 1000
- 1 in 200—what was reported in interviews
- 0.5%
- I do 200-220/year—this would be every year
  - I've had 1 in 2500—pt with known cardiac disease—infarcted stents while on asa intraop

Source Information

- Yao S-L, Lu-Yao G. Population-based study of relationships between hospital volume of prostatectomies, patient outcomes, and length of hospital stay. J Natl Cancer Inst 1999; **91:** 1950.
- Szabo L. Experts explain why PSA test is not worth risk. *USA Today* May 23, 2012, quoting Virginia Moyer on behalf of the U.S. Preventive Services Task Force. Available at: http://www.usatoday.com/news/health/story/2012-05-21/psa-test-questions-answers/55120916/1.
- Alibhai SMH, Leach M, Tomlinson G et al. 30-day mortality and major complications after radical prostatectomy: influence of age and comorbidity. J Natl Cancer Inst 2005; **97:** 1525.
- Begg CB, Riedel ER, Bach PB et al. Variations in morbidity after radical prostatectomy. N Engl J Med 2002; **346:** 1138.
- Walz J, Montorsi F, Jeldres C et al. The effect of surgical volume, age, and comorbidities on 30-day mortality after radical prostatectomy: a population-based analysis of 9208 consecutive cases. BJU Int 2008; **101:** 826.

What do you think?

Project—Modern Numbers, Techniques

- Premier Perspective Database—large, hospital-based data collection—aims for benchmarking, resource utilization
- Billing/diagnostic codes
- Can distinguish procedures
- Co-morbidity scores, perioperative outcomes
- Limitations in 2012—no pathology, no post discharge events

RP: Cohorts

Characteristic	ORP—All 43,964	ORP—RH 30,124	RARP 27,348	LRP 733	P val
# hospitals	347	142	142	53	
#surgeons	2995	1767	744	105	
Age	63.2	63	61	59	<0.001
Op Time-Hrs	3.3	3.4	4.4	3.9	<0.001
LOS	3.5	3.4	2.2	3.6	<0.001
Complications	16.5%	15.8%	10.6%	10.2%	<0.001

RP Cohorts

2004-2010 Totals	ORP-All	ORP-RH	RARP	LRP	P val
#discharges	43,964	30,124	27,348	733	0.0008
# Mortalities	46	27	9	2	0.0066
% Mortalities	0.10	0.09	0.03	0.27	0.0218
Mortality ratio	1 : 956	1:1,116	1: 3039	1 : 367	

Critique---Post discharge events not captured

2017 Update—Now with post discharge

2008-2016	Open All	Open RH	RARP	LRP
Patients	26,253	21,110	84,186	1,002
Hosp Mortality	62 (0.234%)	46 (0.220%)	36 (0.042%)	3 (0.300%)
Post Discharge	17 (0.065%)	17 (0.081%)	27 (0.032%)	0
Overall Periop Mortality	79 (0.301%)	63 (0.300%)	63 (0.070%)	3 (0.300%)
Ratio 1 in __	332	333	1428	333

Issues following prostate cancer treatment

Christopher J.D. Wallis

April 13, 2017

Issues following prostate cancer treatment

aka

Oncologic and competing causes of morbidity and mortality for patients following prostate cancer treatment

Christopher J.D. Wallis

April 13, 2017

Issues following prostate cancer treatment

Or, as John Davis suggested,
Clinically Significant Prostate Cancer: Biological and Epidemiological Observations to Improve Cancer-Free and Survival Metrics

Christopher J.D. Wallis

April 13, 2017

Overview

- Background
- Part 1: Identifying miRNA predictors of metastasis following RP
- Part 2: Assessing the role of ADT and primary Rx in non-PCSM
- Part 3: Quantifying the risk of secondary cancer after prostate RT
- Conclusions

Background

- The majority of newly diagnosed patients will receive treatment
  - Surgery, radiotherapy, or androgen deprivation therapy[1]
- Prostate cancer treatment is associated with significant complications
  - Erectile dysfunction
  - Urinary incontinence[2]
- Recent work has demonstrated other complications occur commonly
  - Urologic procedures
  - Rectal-anal procedures
  - Major surgeries
  - Secondary malignancies[3-5]

[1]Cooperberg and Carrol. *JAMA*. 2015;314:80.
[2]Resnick et al. *NEJM*. 2013;368:436.
[3]Wallis et al. *Brit J Cancer* 2015;112(6):977
[4]Wallis et al. *Urology* 2015;85(3):621
[5]Nam et al. *Lancet Oncol* 2014;15(2):223.

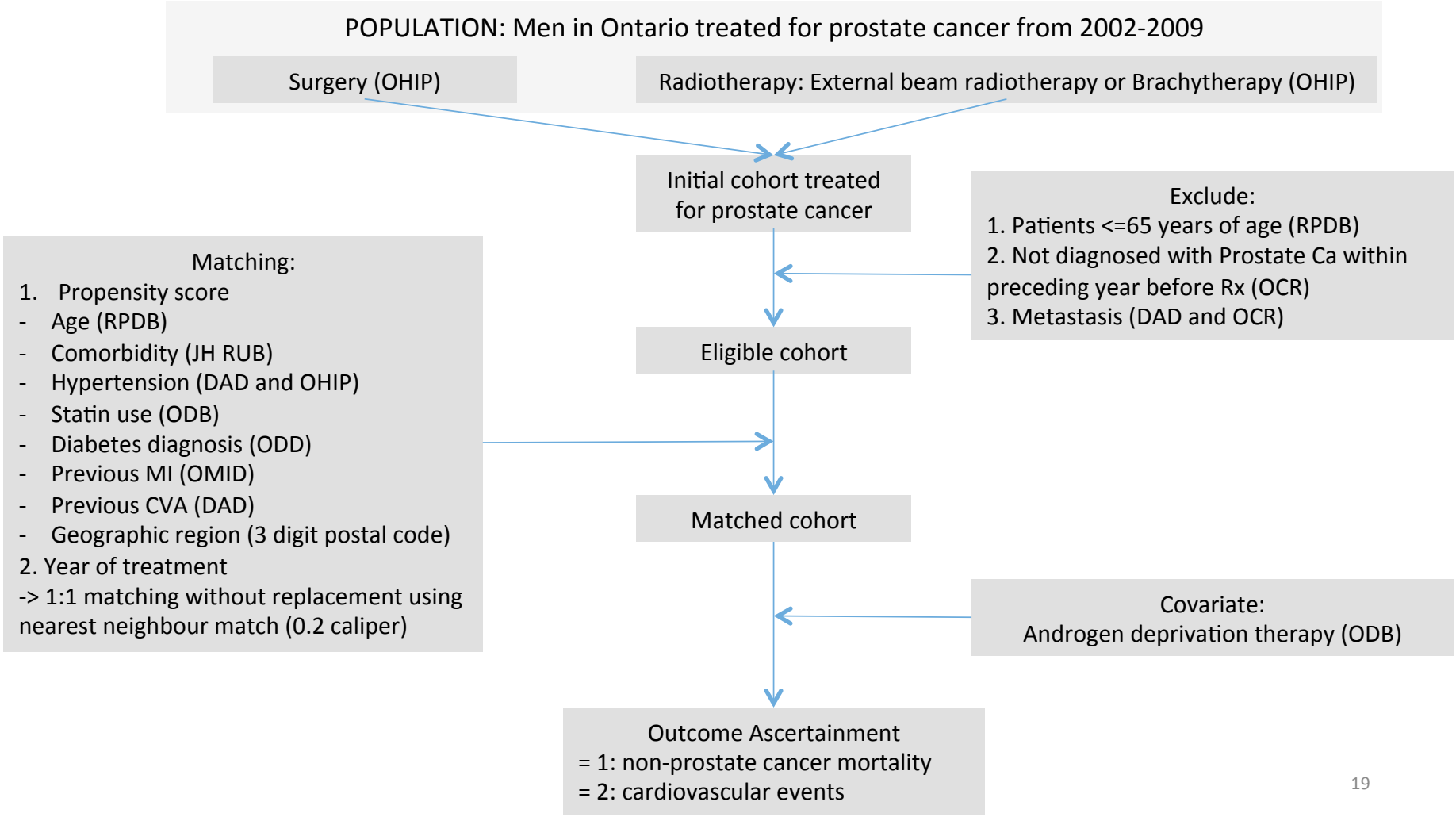
Part 1 Conclusions

- We have identified a panel of 5 miRNA which are associated with the development of metastasis following radical prostatectomy.

- Further work is underway to validate these results among independent cohorts.

Part 2:

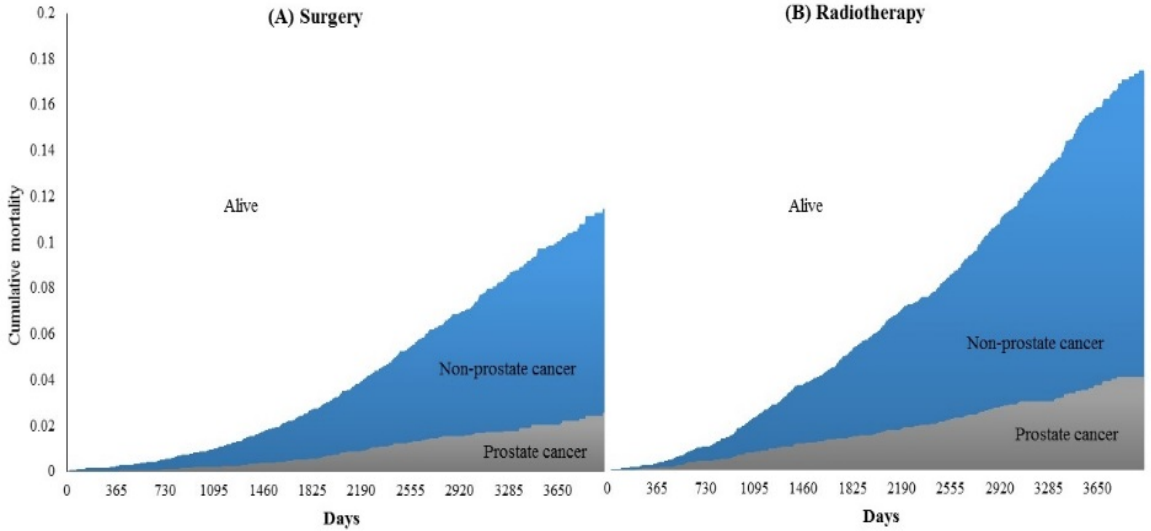
Long-term complications following prostate cancer treatment:
The role of primary treatment modality and androgen deprivation therapy


POPULATION: Men in Ontario treated for prostate cancer from 2002-2009
Surgery (OHIP)
Radiotherapy: External beam radiotherapy or Brachytherapy (OHIP)
Initial cohort treated for prostate cancer
Exclude:
1. Patients <=65 years of age (RPDB)
2. Not diagnosed with Prostate Ca within preceding year before Rx (OCR)
3. Metastasis (DAD and OCR)
Eligible cohort
Matching:
1. Propensity score
- Age (RPDB)
- Comorbidity (JH RUB)
- Hypertension (DAD and OHIP)
- Statin use (ODB)
- Diabetes diagnosis (ODD)
- Previous MI (OMID)
- Previous CVA (DAD)
- Geographic region (3 digit postal code)
2. Year of treatment
-> 1:1 matching without replacement using nearest neighbour match (0.2 caliper)
Matched cohort
Covariate:
Androgen deprivation therapy (ODB)
Outcome Ascertainment
= 1: non-prostate cancer mortality
= 2: cardiovascular events

Baseline characteristics

	Before propensity-score matching			After propensity-score matching		
VARIABLE	**Surgery**	**Radiotherapy**	**Std Diff**	**Surgery**	**Radiotherapy**	**Std Diff**
Sample size	N=6,851	N=13,800		N=5,393	N=5,393	
Age at diagnosis						
Mean ± SD	68.92 ± 2.63	72.99 ± 4.46	1.11	69.45 ± 2.68	69.46 ± 2.78	0
Median (IQR)	68 (67-70)	73 (70-76)	1.15	69 (67-71)	69 (67-71)	0.01
Hypertension (n,%)	5,149 (75.2%)	11,183 (81.0%)	0.14	4,166 (77.2%)	4,187 (77.6%)	0.01
Active statin use (n,%)	654 (9.5%)	3,256 (23.6%)	0.38	622 (11.5%)	636 (11.8%)	0.01
Diabetes (n,%)	1,176 (17.2%)	3,115 (22.6%)	0.14	1,003 (18.6%)	1,067 (19.8%)	0.03
History of MI (n,%)	68 (1.0%)	301 (2.2%)	0.1	65 (1.2%)	76 (1.4%)	0.02
History of stroke (n,%)	18 (0.3%)	135 (1.0%)	0.09	18 (0.3%)	15 (0.3%)	0.01
Year of treatment (n,%)						
2002	710 (10.4%)	1,542 (11.2%)	0.03	580 (10.8%)	571 (10.6%)	0.01
2003	717 (10.5%)	1,617 (11.7%)	0.04	587 (10.9%)	623 (11.6%)	0.02
2004	770 (11.2%)	1,648 (11.9%)	0.02	614 (11.4%)	610 (11.3%)	0
2005	839 (12.2%)	1,623 (11.8%)	0.01	648 (12.0%)	632 (11.7%)	0.01
2006	936 (13.7%)	1,754 (12.7%)	0.03	732 (13.6%)	707 (13.1%)	0.01
2007	988 (14.4%)	1,784 (12.9%)	0.04	770 (14.3%)	763 (14.1%)	0
2008	834 (12.2%)	1,682 (12.2%)	0	636 (11.8%)	644 (11.9%)	0
2009	795 (11.6%)	1,581 (11.5%)	0	614 (11.4%)	633 (11.7%)	0.01
2010	262 (3.8%)	569 (4.1%)	0.02	212 (3.9%)	210 (3.9%)	0
Comorbidity score (ADG sum)						
Mean ± SD	8.39 ± 2.98	9.12 ± 3.11	0.24	8.56 ± 3.00	8.62 ± 2.99	0.02
Median (IQR)	8 (6-10)	9 (7-11)	0.23	8 (6-11)	8 (6-11)	0.02

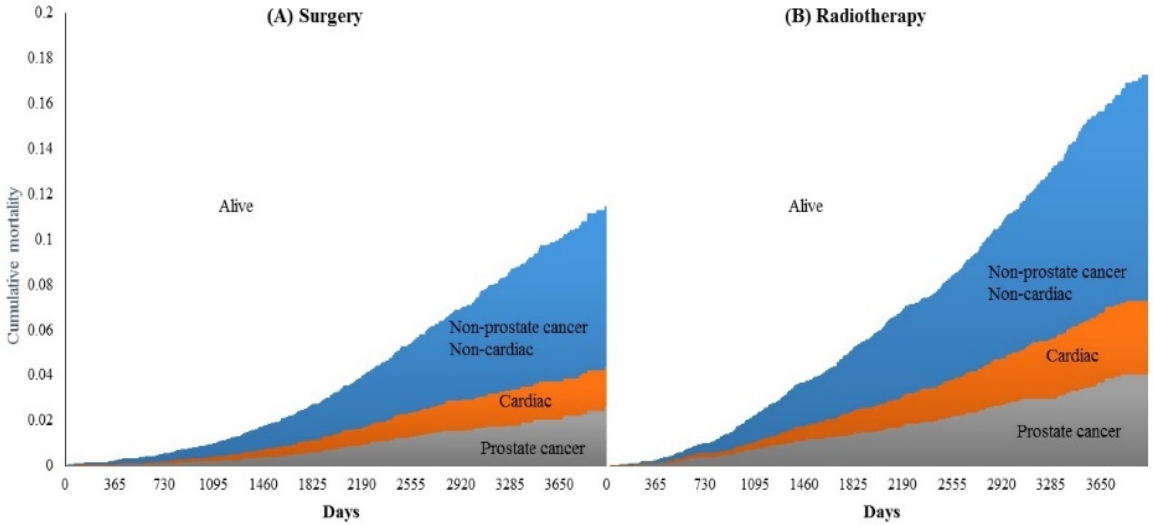
Non-prostate cancer mortality



	Non-prostate cancer death (sdHR, 95% CI)
Univariate competing risk model	
Surgery	Referent
Radiotherapy	1.57 (1.35-1.83)
Accounting for binary ADT exposure	
Surgery	Referent
Radiotherapy	1.57 (1.35-1.83)
Accounting for cumulative ADT exposure (3 categories)	
Surgery	Referent
Radiotherapy	1.56 (1.34-1.82)
Accounting for cumulative ADT exposure (6 categories)	
Surgery	Referent
Radiotherapy	1.57 (1.35-1.83)

ADT exposure not significantly associated with NPCM.

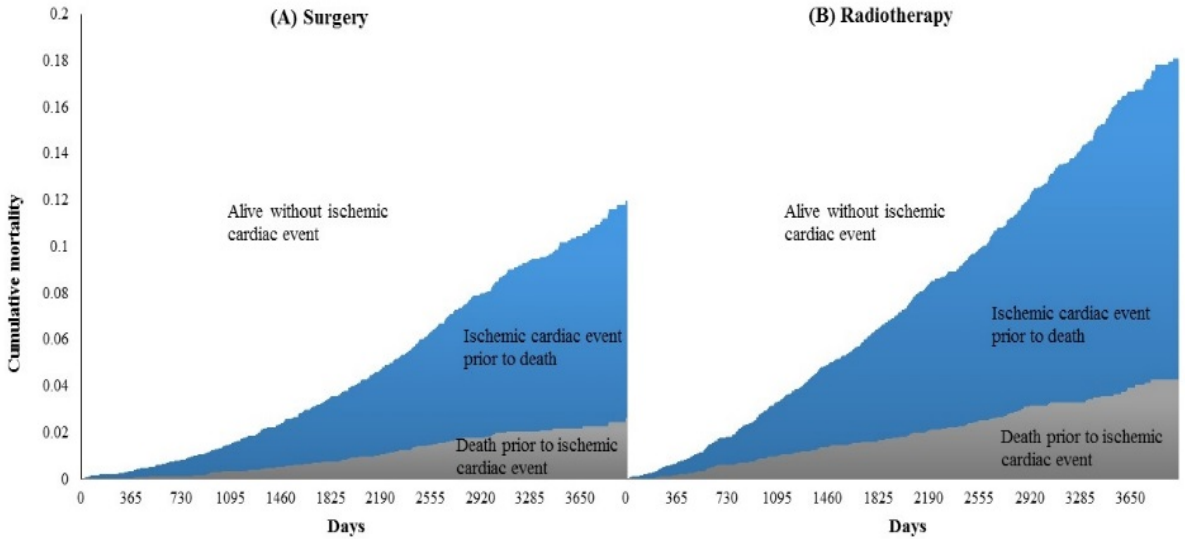
Cardiovascular mortality



	Cardiovascular death (sdHR, 95% CI)
Univariate competing risk model	
Surgery	Referent
Radiotherapy	1.74 (1.27-2.37)
Accounting for binary ADT exposure	
Surgery	Referent
Radiotherapy	1.74 (1.27-2.37)
Accounting for cumulative ADT exposure (3 categories)	
Surgery	Referent
Radiotherapy	1.78 (1.30-2.42)
Accounting for cumulative ADT exposure (6 categories)	
Surgery	Referent
Radiotherapy	1.75 (1.28-2.38)

ADT exposure not significantly associated with CVM.

Ischemic cardiovascular events



Cardiovascular Events (sdHR, 95% CI)	
Univariate competing risk model	
Surgery	Referent
Radiotherapy	1.13 (1.03-1.24)
Accounting for binary ADT exposure	
Surgery	Referent
Radiotherapy	1.13 (1.03-1.24)
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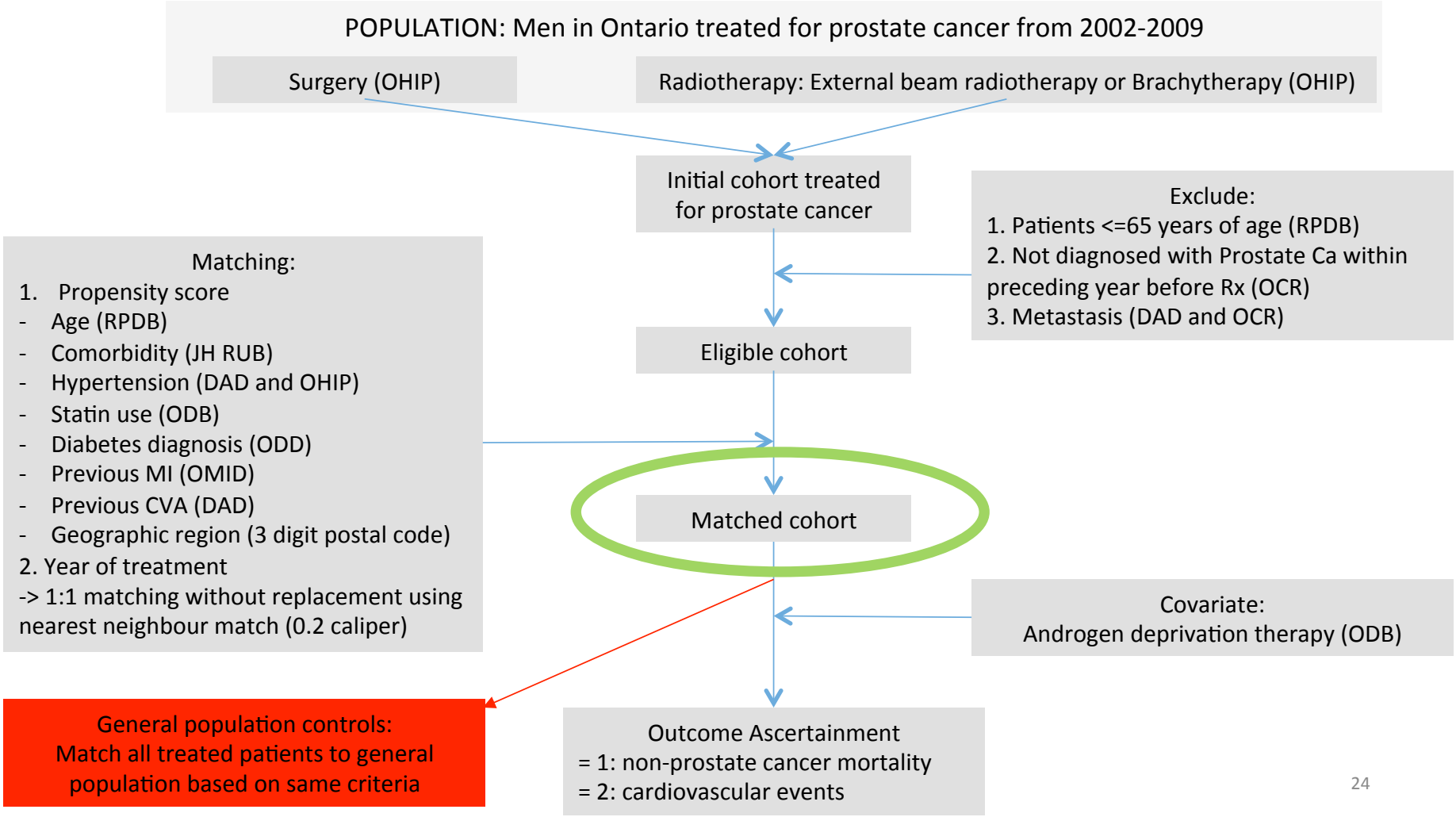
Surgery	Referent
Radiotherapy	1.13 (1.03-1.24)
Accounting for cumulative ADT exposure (6 categories)	
Surgery	Referent
Radiotherapy	1.13 (1.03-1.24)

ADT exposure not significantly associated with CV events.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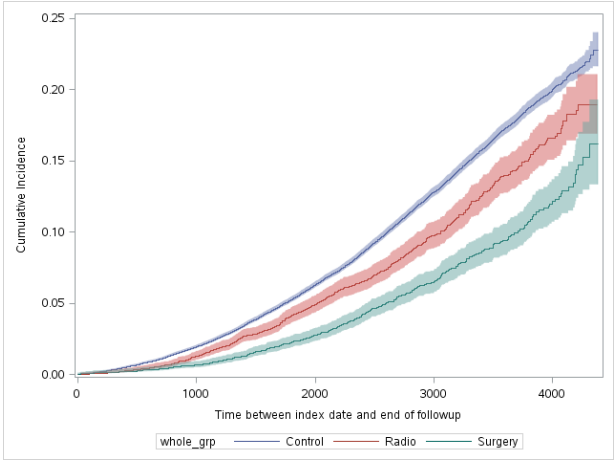
- Geographic region (3 digit postal code)
2. Year of treatment
-> 1:1 matching without replacement using nearest neighbour match (0.2 caliper)
Matched cohort
Covariate:
Androgen deprivation therapy (ODB)
General population controls:
Match all treated patients to general population based on same criteria
Outcome Ascertainment
= 1: non-prostate cancer mortality
= 2: cardiovascular events

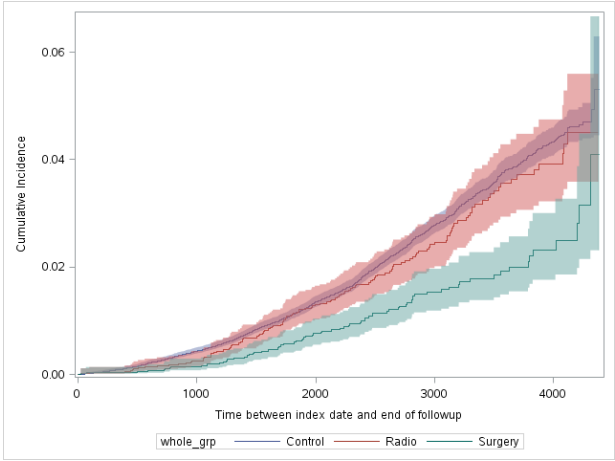
Outcomes

Non-prostate cancer mortality



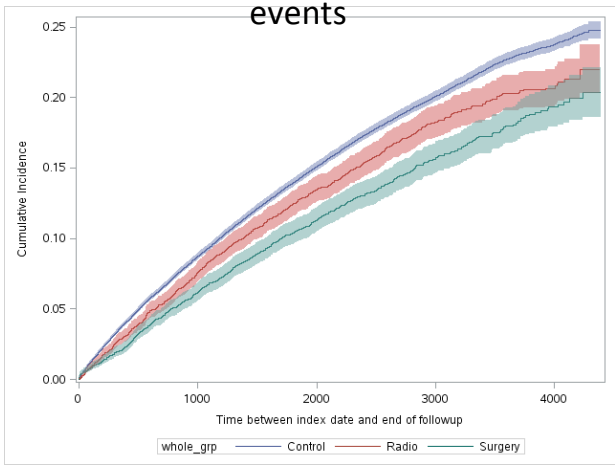
Control = referent
Surgery = sdHR 0.53 (0.47-0.59)
Radiotherapy = sdHR 0.79 (0.72-0.86)

Cardiovascular mortality



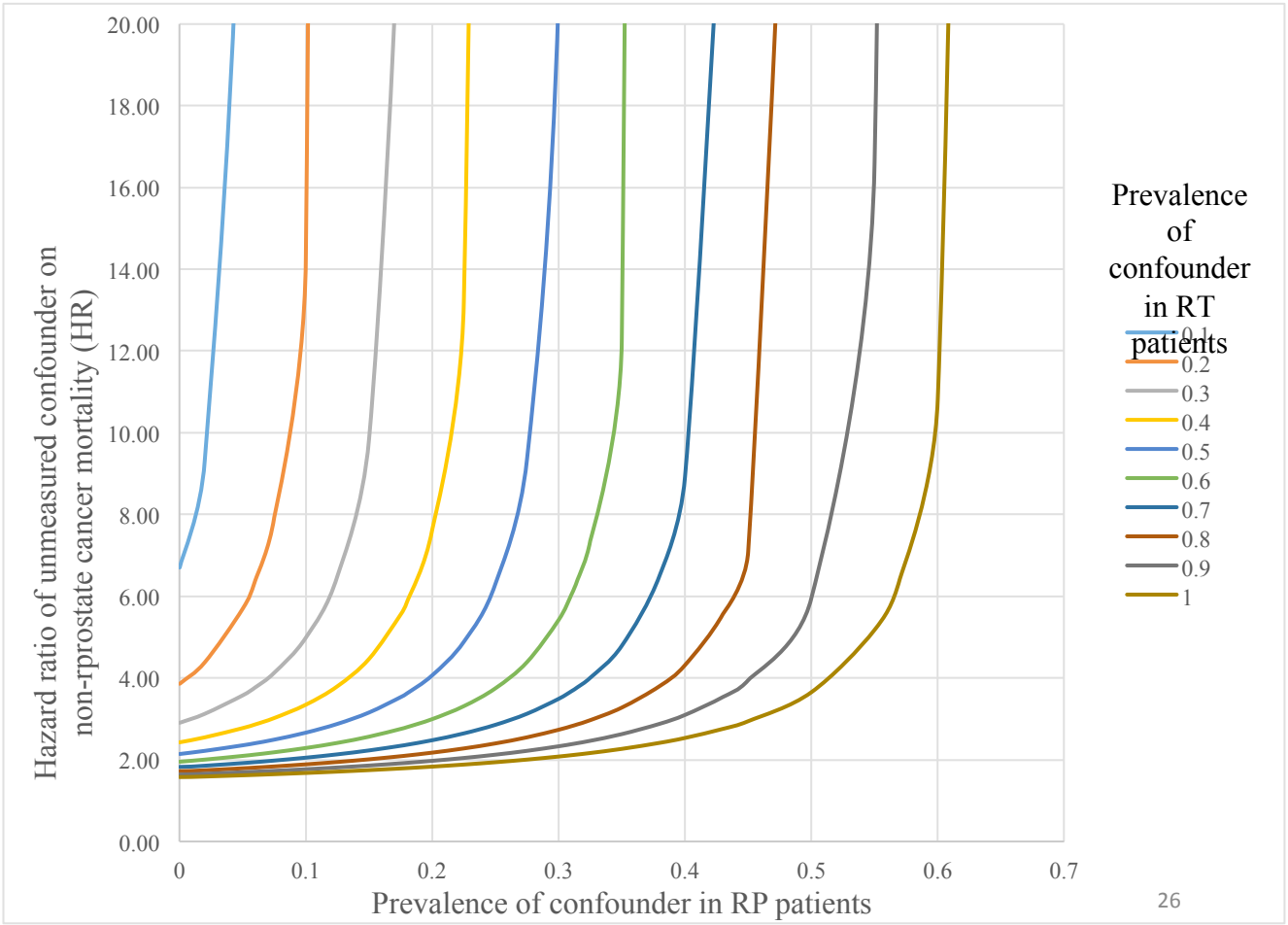
Control = referent
Surgery = sdHR 0.55 (0.44-0.69)
Radiotherapy = sdHR 0.93 (0.78-1.10)

Ischemic cardiovascular events



Control = referent
Surgery = sdHR 0.76 (0.70-0.81)
Radiotherapy = sdHR 0.88 (0.82-0.94)

Assessment of the effect of confounding



Part 2 Conclusions

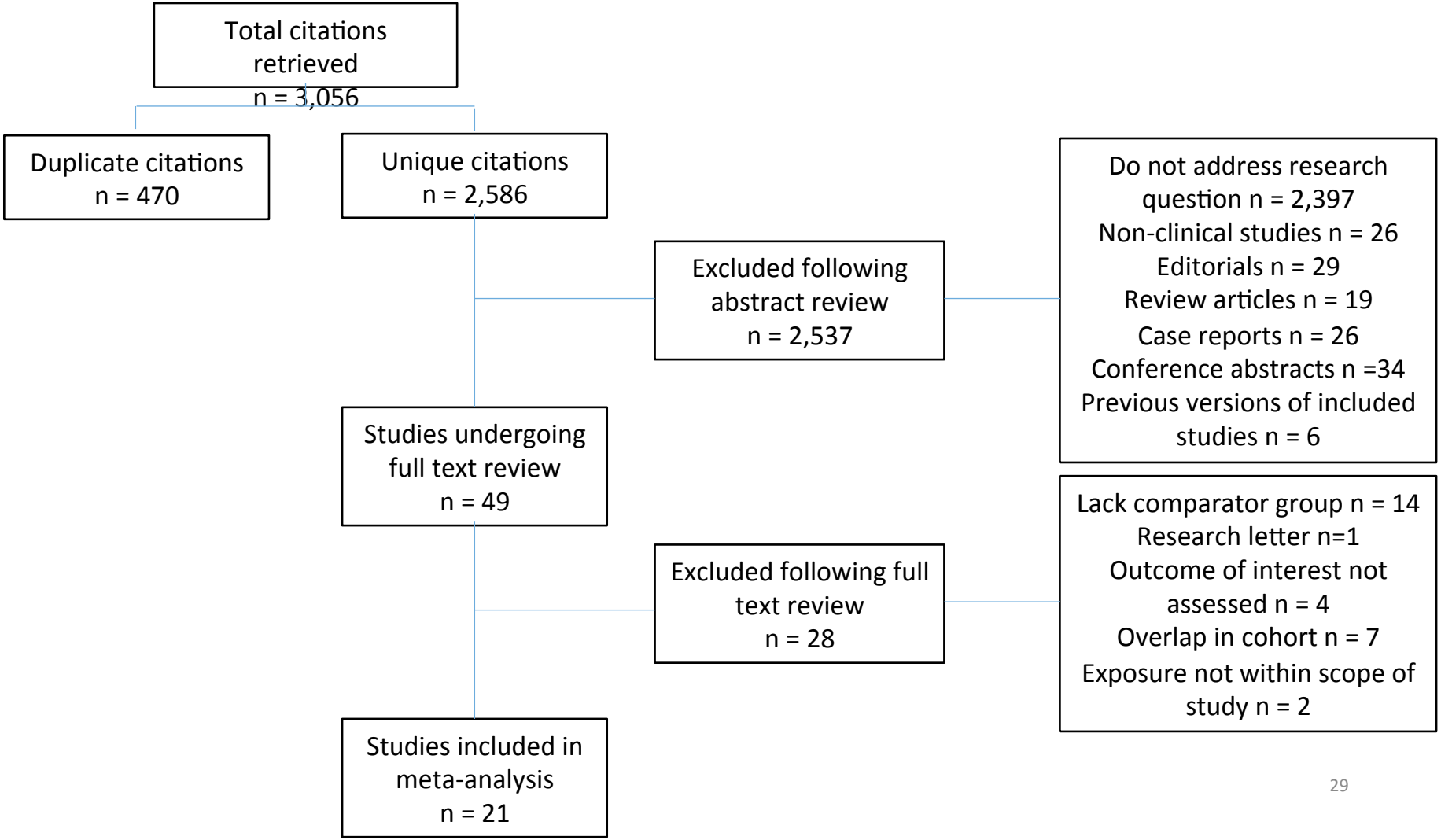
- Primary treatment modality is a significant predictor of NPCM.

- Explanations?
  - Selection bias
  - Biologic effect

- Based on this analysis, likely both!

Part 3:

Secondary malignancies following radiotherapy for prostate cancer: A systematic review and meta-analysis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Unique citations
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Do not address research question n = 2,397
Non-clinical studies n = 26
Editorials n = 29
Review articles n = 19
Case reports n = 26
Conference abstracts n =34
Previous versions of included studies n = 6
Studies undergoing full text review
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Excluded following full text review
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Lack comparator group n = 14
Research letter n=1
Outcome of interest not assessed n = 4
Overlap in cohort n = 7
Exposure not within scope of study n = 2
Studies included in meta-analysis
n = 21

Bladder cancer

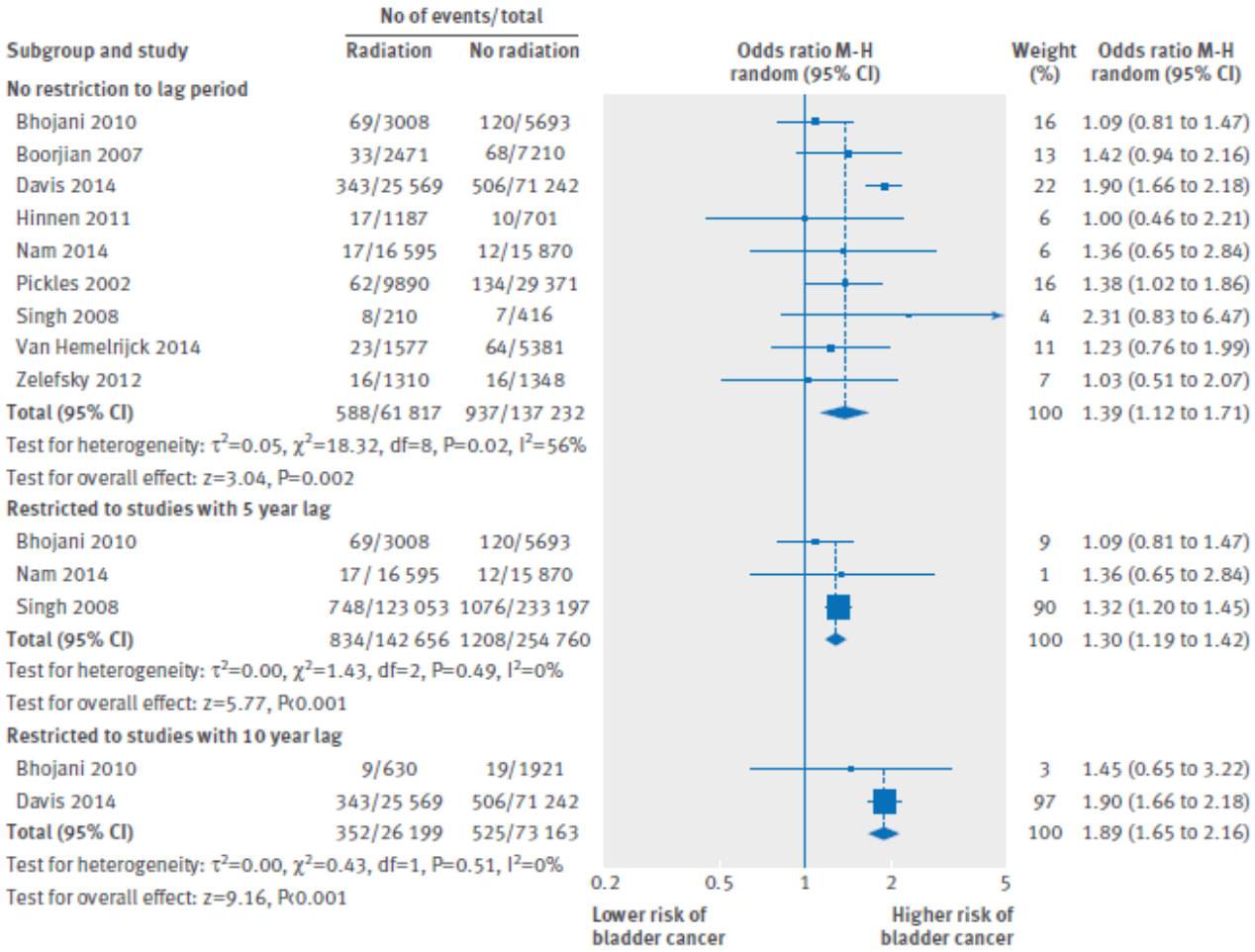
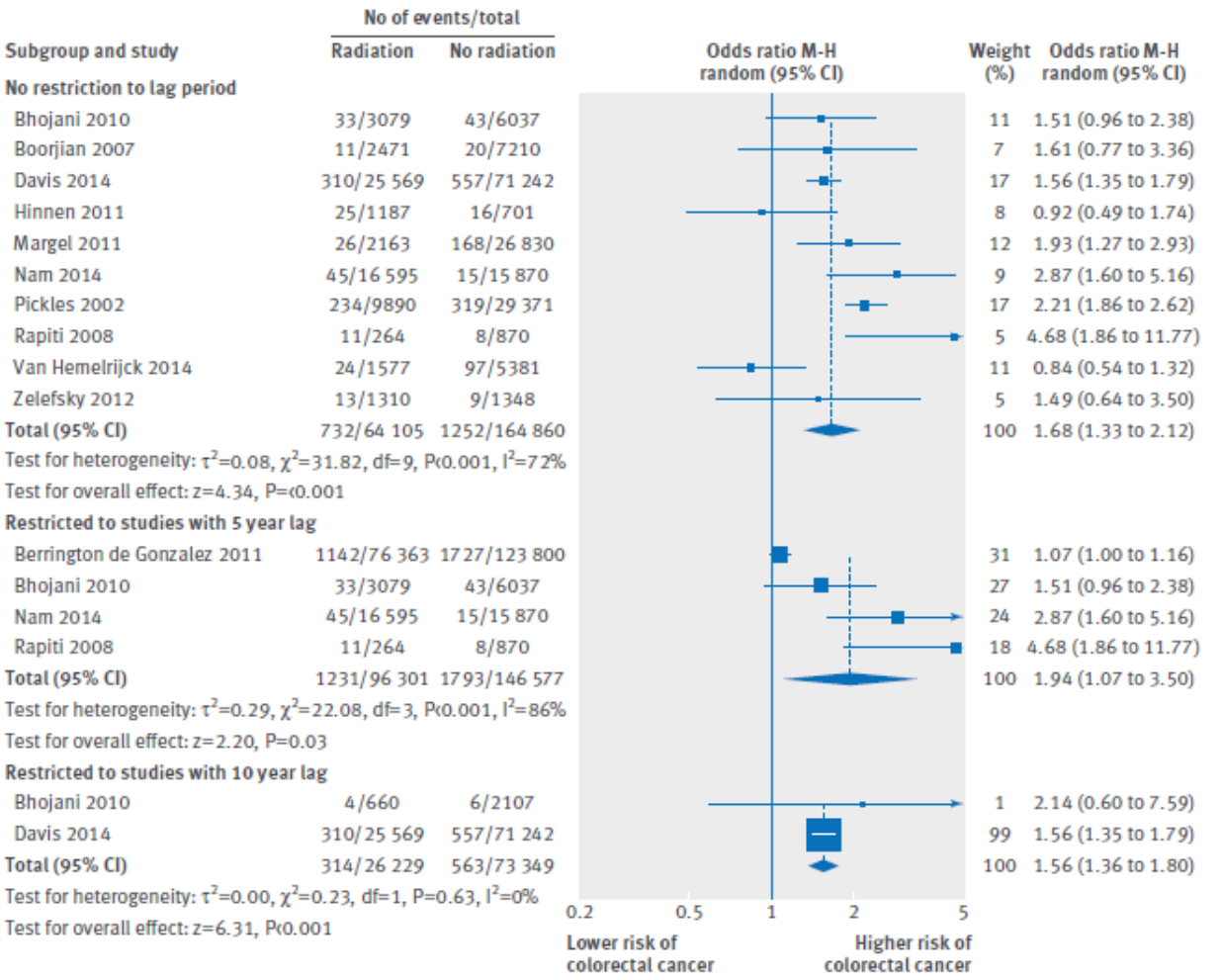


Fig 2 | Risk of bladder cancer after any radiotherapy compared with no radiation in studies with no restriction to lag period, studies with five year lag period, and studies with 10 year lag period

Colorectal cancer



Subgroup and study	No of events/total: Radiation	No of events/total: No radiation	Odds ratio M-H random (95% CI)	Weight (%)	Odds ratio M-H random (95% CI)
No restriction to lag period					
Bhojani 2010	33/3079	43/6037		11	1.51 (0.96 to 2.38)
Boorjian 2007	11/2471	20/7210		7	1.61 (0.77 to 3.36)
Davis 2014	310/25 569	557/71 242		17	1.56 (1.35 to 1.79)
Hinnen 2011	25/1187	16/701		8	0.92 (0.49 to 1.74)
Margel 2011	26/2163	168/26 830		12	1.93 (1.27 to 2.93)
Nam 2014	45/16 595	15/15 870		9	2.87 (1.60 to 5.16)
Pickles 2002	234/9890	319/29 371		17	2.21 (1.86 to 2.62)
Rapiti 2008	11/264	8/870		5	4.68 (1.86 to 11.77)
Van Hemelrijck 2014	24/1577	97/5381		11	0.84 (0.54 to 1.32)
Zelefsky 2012	13/1310	9/1348		5	1.49 (0.64 to 3.50)
Total (95% CI)	732/64 105	1252/164 860		100	1.68 (1.33 to 2.12)
Test for heterogeneity: τ^2=0.08, χ^2=31.82, df=9, P<0.001, I^2=72%					
Test for overall effect: z=4.34, P=<0.001					
Restricted to studies with 5 year lag					
Berrington de Gonzalez 2011	1142/76 363	1727/123 800		31	1.07 (1.00 to 1.16)
Bhojani 2010	33/3079	43/6037		27	1.51 (0.96 to 2.38)
Nam 2014	45/16 595	15/15 870		24	2.87 (1.60 to 5.16)
Rapiti 2008	11/264	8/870		18	4.68 (1.86 to 11.77)
Total (95% CI)	1231/96 301	1793/146 577		100	1.94 (1.07 to 3.50)
Test for heterogeneity: τ^2=0.29, χ^2=22.08, df=3, P<0.001, I^2=86%					
Test for overall effect: z=2.20, P=0.03					
Restricted to studies with 10 year lag					
Bhojani 2010	4/660	6/2107		1	2.14 (0.60 to 7.59)
Davis 2014	310/25 569	557/71 242		99	1.56 (1.35 to 1.79)
Total (95% CI)	314/26 229	563/73 349		100	1.56 (1.36 to 1.80)
Test for heterogeneity: τ^2=0.00, χ^2=0.23, df=1, P=0.63, I^2=0%					
Test for overall effect: z=6.31, P<0.001					

Fig 4 | Risk of colorectal cancer after any radiotherapy compared with no radiation in studies with no restriction to lag period, studies with five year lag period, and studies with 10 year lag period

Rectal cancer

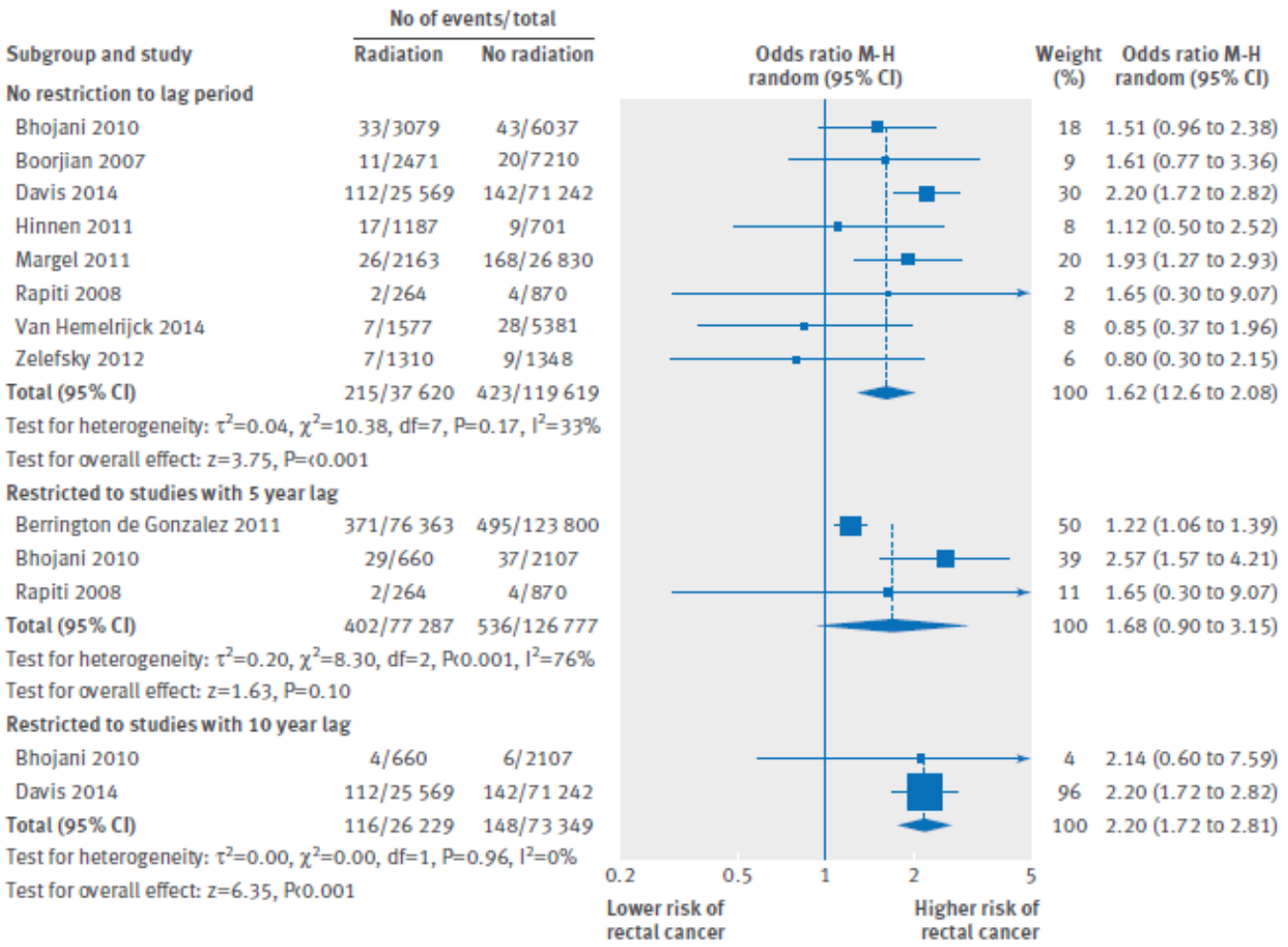


Fig 5 | Risk of rectal cancer after any radiotherapy compared with no radiation in studies with no restriction to lag period, studies with five year lag period, and studies with 10 year lag period

Part 3 Conclusions

- Radiotherapy for prostate cancer increases the risk of secondary malignancies within the radiotherapy field but not outside the field

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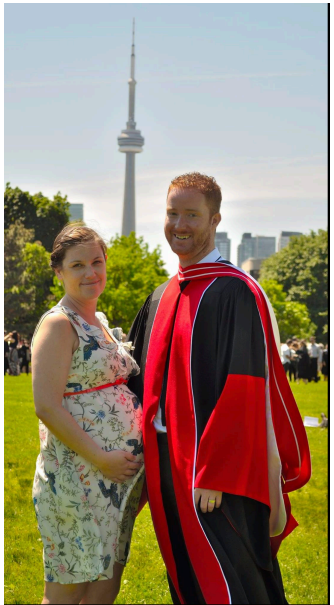
Bimal Bhindi @BBhindi



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Or…Hungry for more



FIRST OPINION

The new recommendations for prostate cancer screenings are a bad deal

By VINAY PRASAD / APRIL 11, 2017

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That popping sound you may have heard on Tuesday was made by urologists opening the champagne bottles they had chilled in anticipation of the United States Preventive Services Task Force (USPSTF) upgrading its recommendation about PSA screening for prostate cancer from a D (the harms outweigh the benefits) to a C (it's an individual decision).

Much like a teacher changing a dissatisfied student's grade from a D to a C — and only after much complaining — the new guidelines should hardly be construed as a ringing endorsement. PSA screening remains a difficult decision for healthy men and their doctors.

The data on which the USPSTF based its new recommendation for PSA screening is similar to the data it used for its prior recommendation in 2012. No study has shown that the test saves lives or improves the quality of life. It does not reduce mortality or extend survival in any randomized trial to date, nor when all studies are combined together. Let me say that again: There is no proof that PSA screening extends your life, improves the years you have, or reduces your risk of dying.

In my mind, the greatest misconception about the test is that we say it "saves lives" when that is uncertain. PSA testing reduces the risk of dying of prostate cancer, but there is no evidence it reduces the risk of dying.

There is a big difference between the phrase "reduces the risk of dying from prostate cancer" and the phrase "reduces the risk of dying." Men must understand the difference to make an informed choice.

Conclusions

- 30 day mortality after RP is better in the 2010's than 1990's
- Lowest 30 day mortality is RARP
- Post-discharge mortality less common but not trivial
- Radiation therapy might increase non-prostate ca mortality rates and secondary cancers
- Non PCa mortality incidence can "undo" some of the PCA mortality reductions we have proven with PSA screening and surgery