Vitamin D, Calcium and Prostate Cancer: The Good, the Bad, and the Dairy

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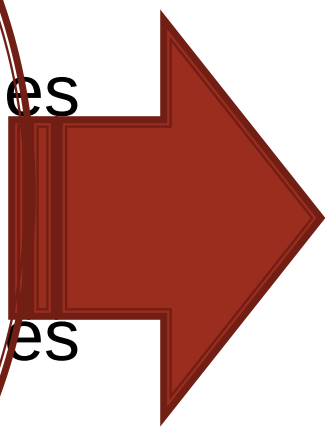
Outline

- Prostate cancer
- Biologic mechanisms
- Dairy and calcium intakes
  - Previous epidemiologic studies
  - PCaP methods and results
- Vitamin D status
  - Previous epidemiologic studies
  - PCaP results
- Summary/Conclusions
- Future Directions



Racial Disparities

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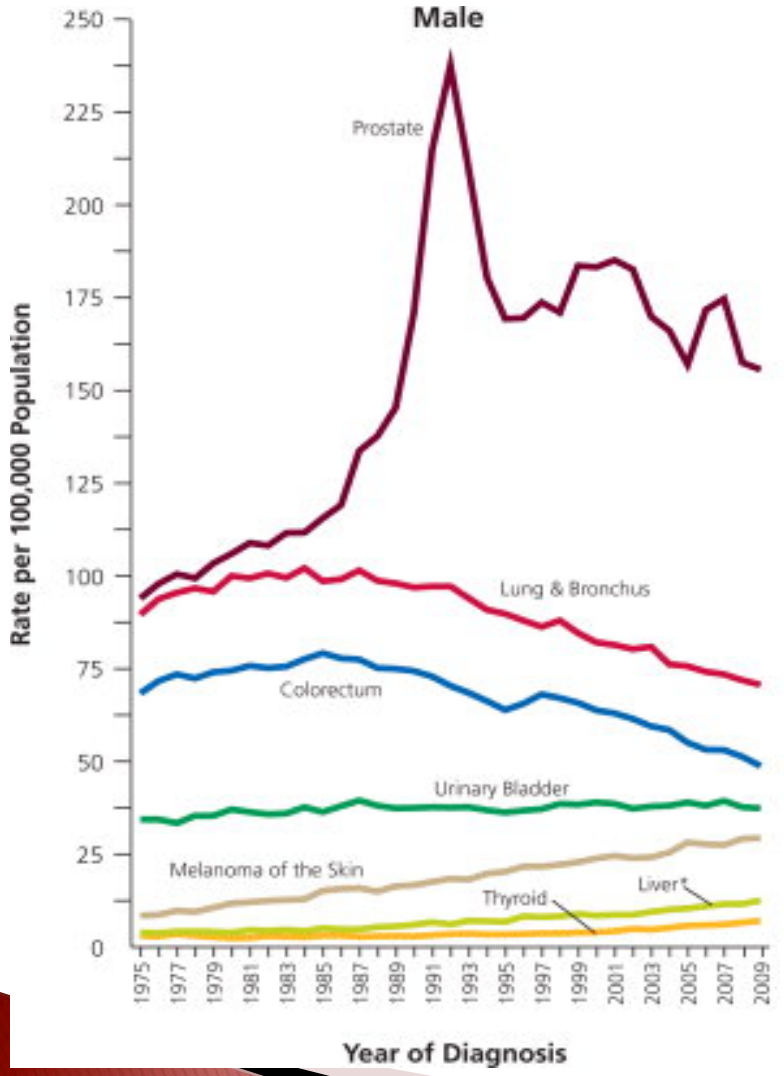
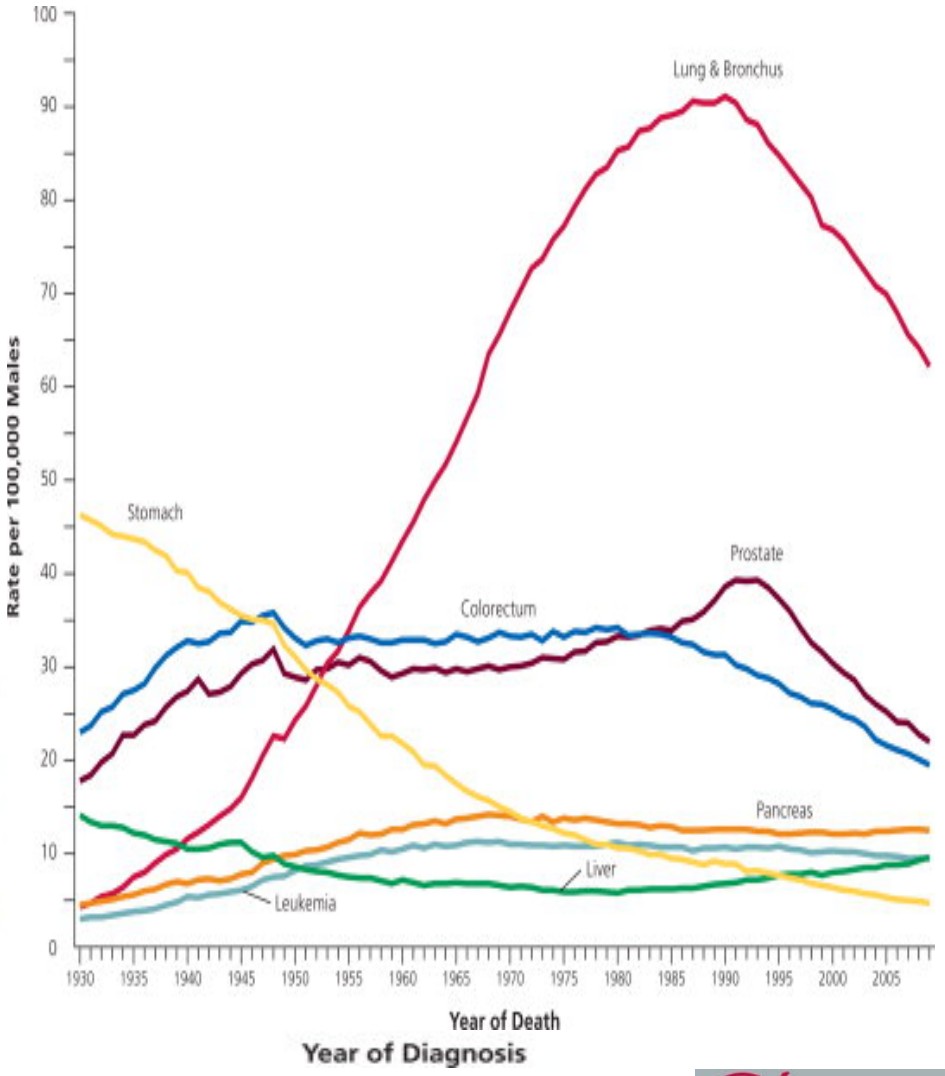
Annual Age-Adjusted Cancer Incidence Rates* for Selected Cancers by Sex, United States, 1975 to 2009



Annual Age-Adjusted Cancer Death Rates*Among Males for Selected Cancers, United States, 1930 to 2009

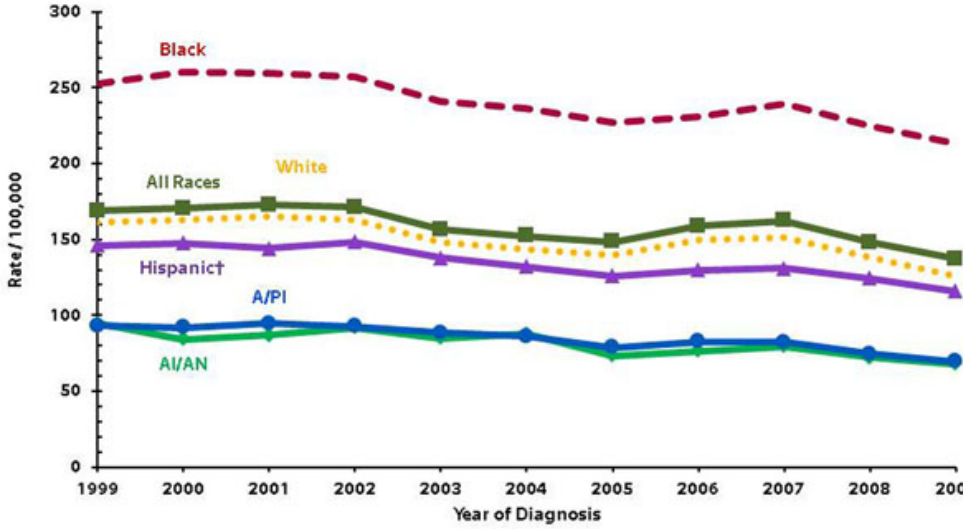


From Siegel, R., Naishadham, D. and Jemal, A. (2013), Cancer statistics, 2013. CA: A Cancer Journal for Clinicians, 63: 11–30. doi: 10.3322/caac.21166

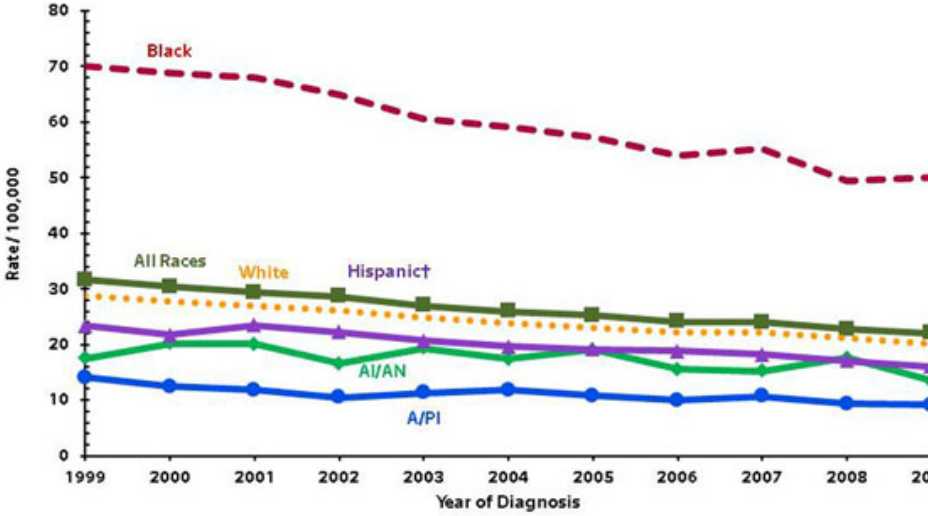
CA A Cancer Journal for Clinicians

Prostate cancer incidence and mortality by race and ethnicity, U.S. 1999-2009

Incidence



Mortality



CDC, National Program of Cancer Registries and NCI, SEER
CDC National Center for Health Statistics

Risk Factors for Prostate Cancer

- Age
- Race
- Family history of prostate cancer

- …possibly dairy products and/or calcium intake?

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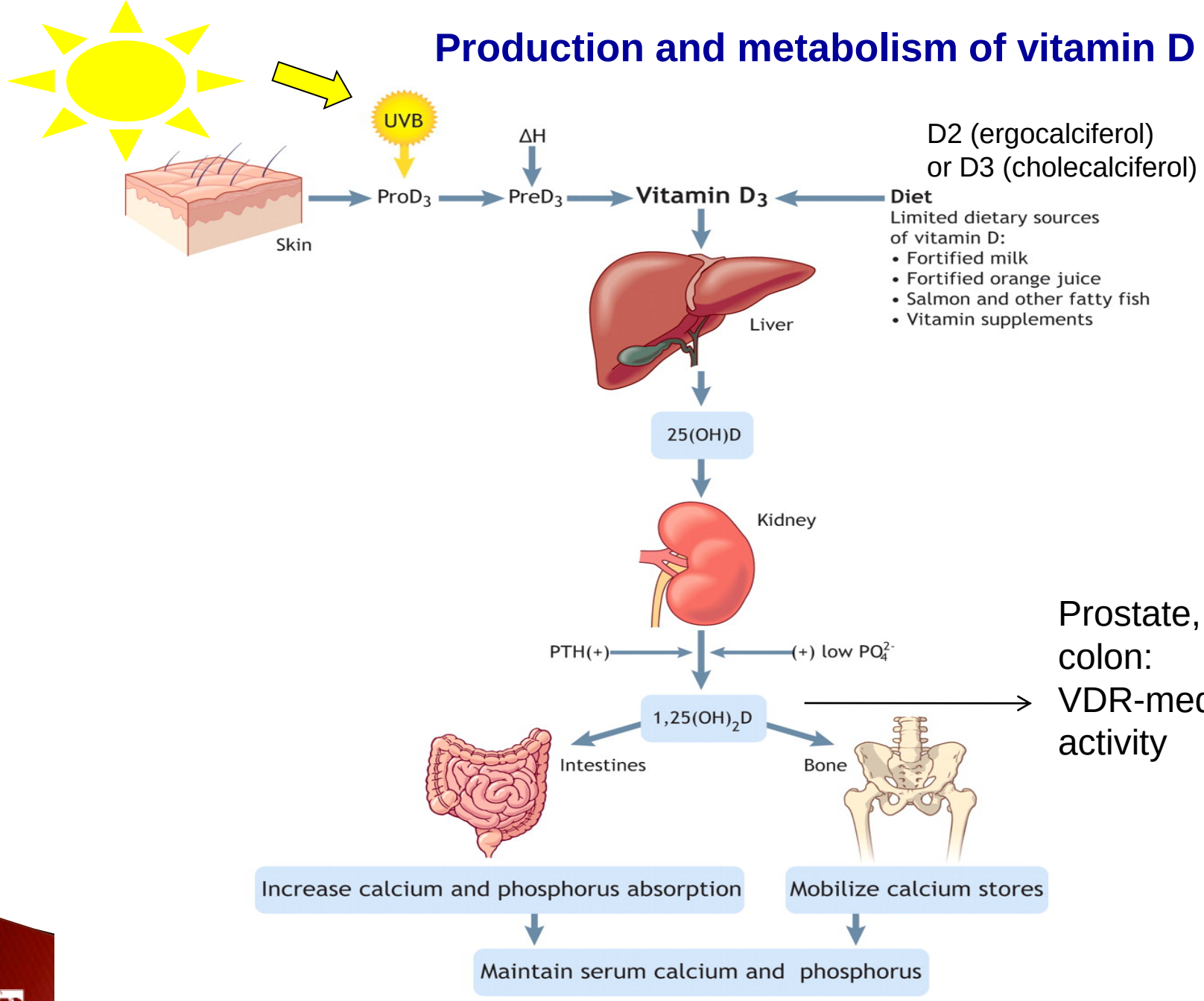
Production and metabolism of vitamin D



D2 (ergocalciferol)
or D3 (cholecalciferol)

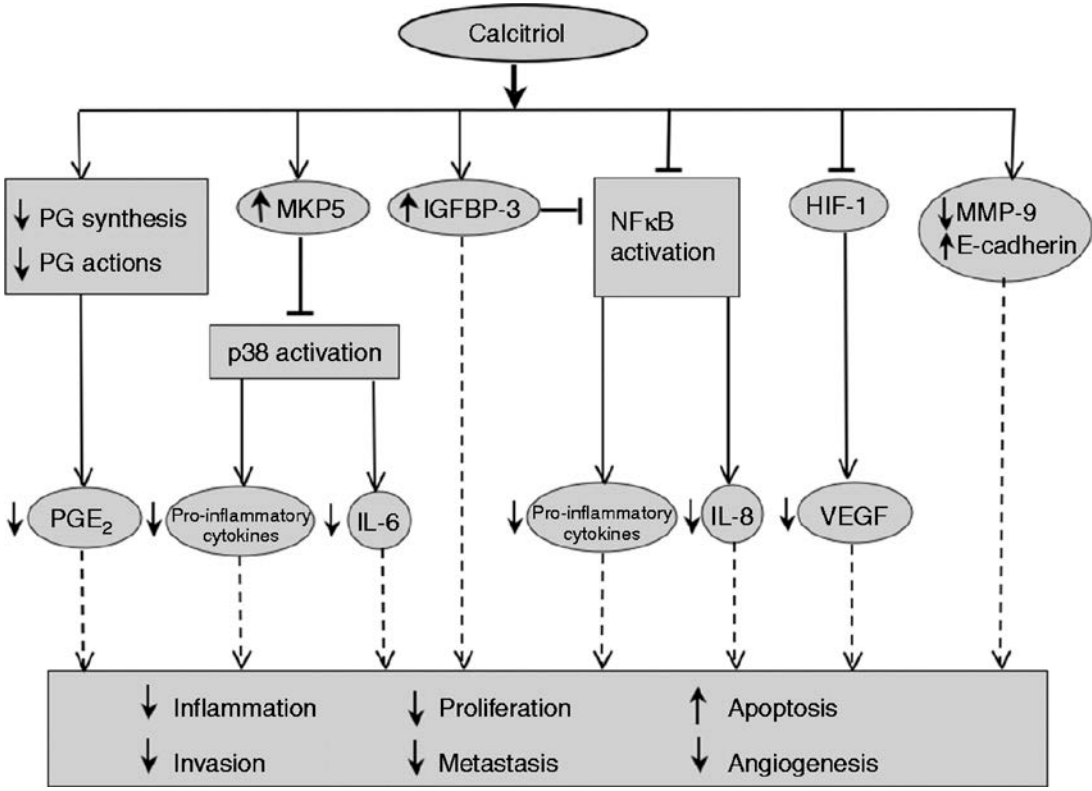
Prostate, breast, colon:
VDR-mediated activity

Adapted from Hollis, B. W. et al. CMAJ 2006;174:1287-1290

CMAJ·JAMC

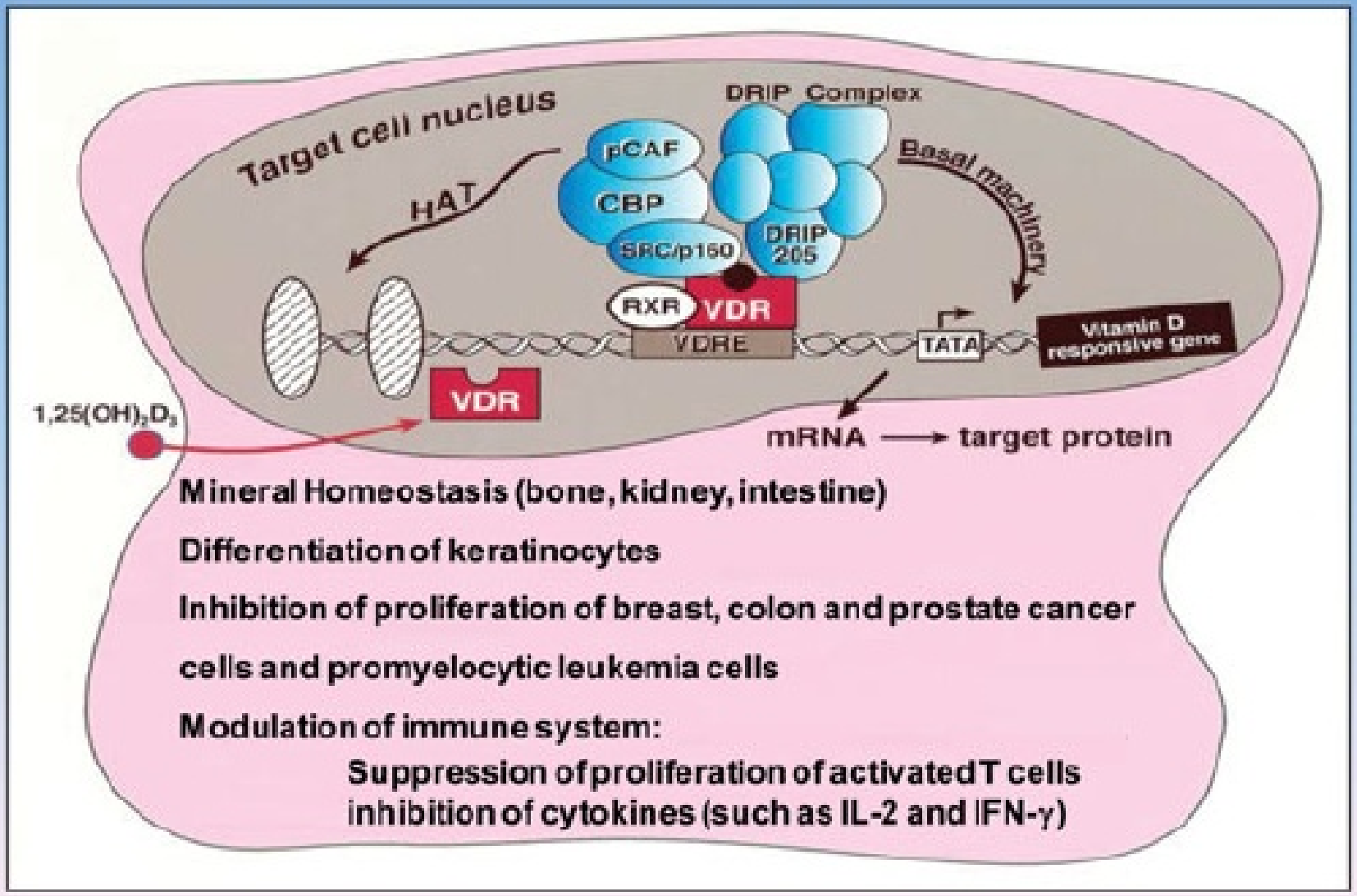
Potential mechanisms for dairy/calcium association with increased risk of PrCA

- Marker of high fat diet
- Estrogen in milk
- Increased levels of insulin-like growth factor
- Suppression of production of $1,25(OH)_2D$
- Increased inflammation



Krishnan and Feldman, Endocr Relat Cancer. 2010 Jan;17(1):R19-R38

Genomic mechanism of vitamin D activity



Christakos 2013 Ann NY Acad Sci

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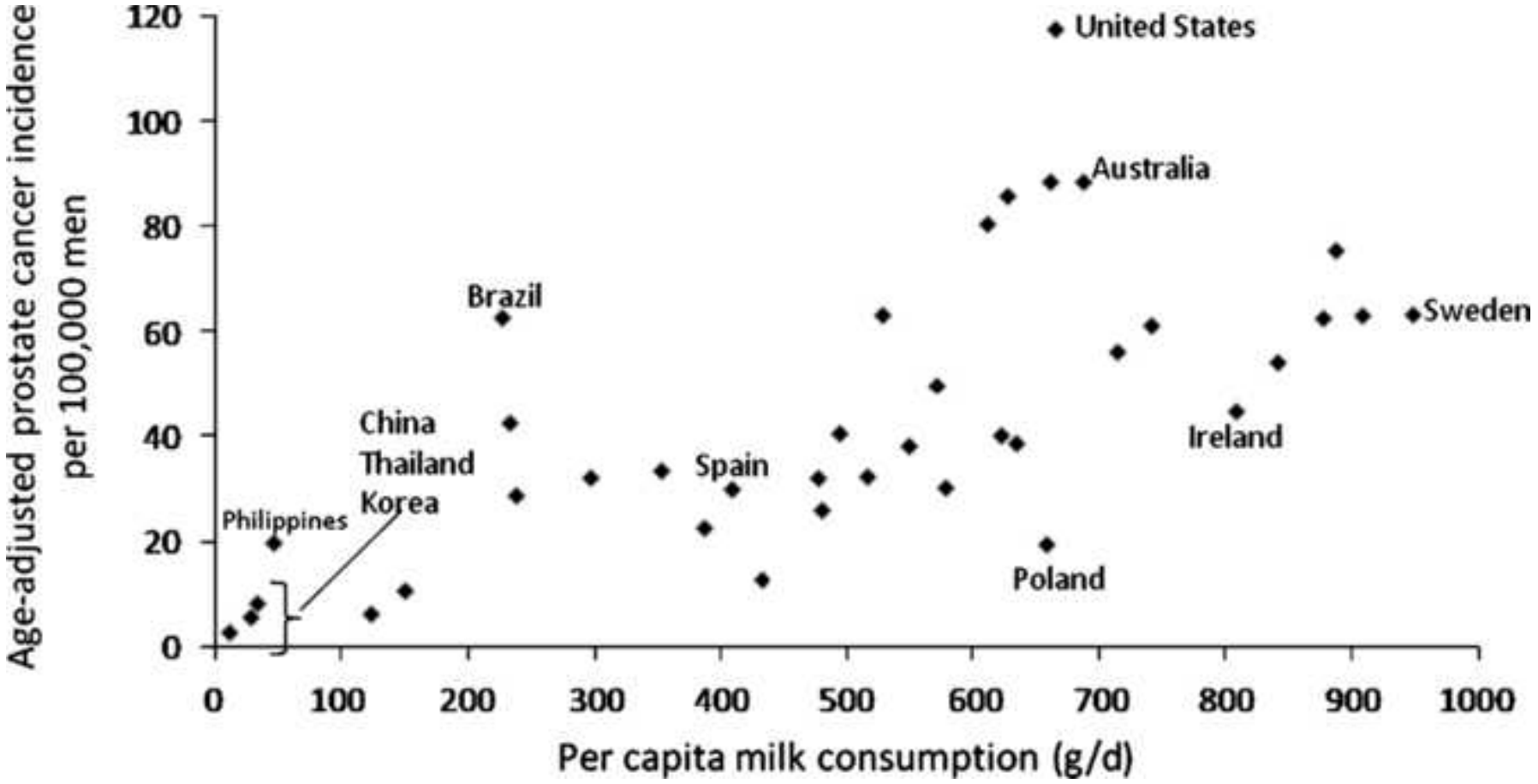
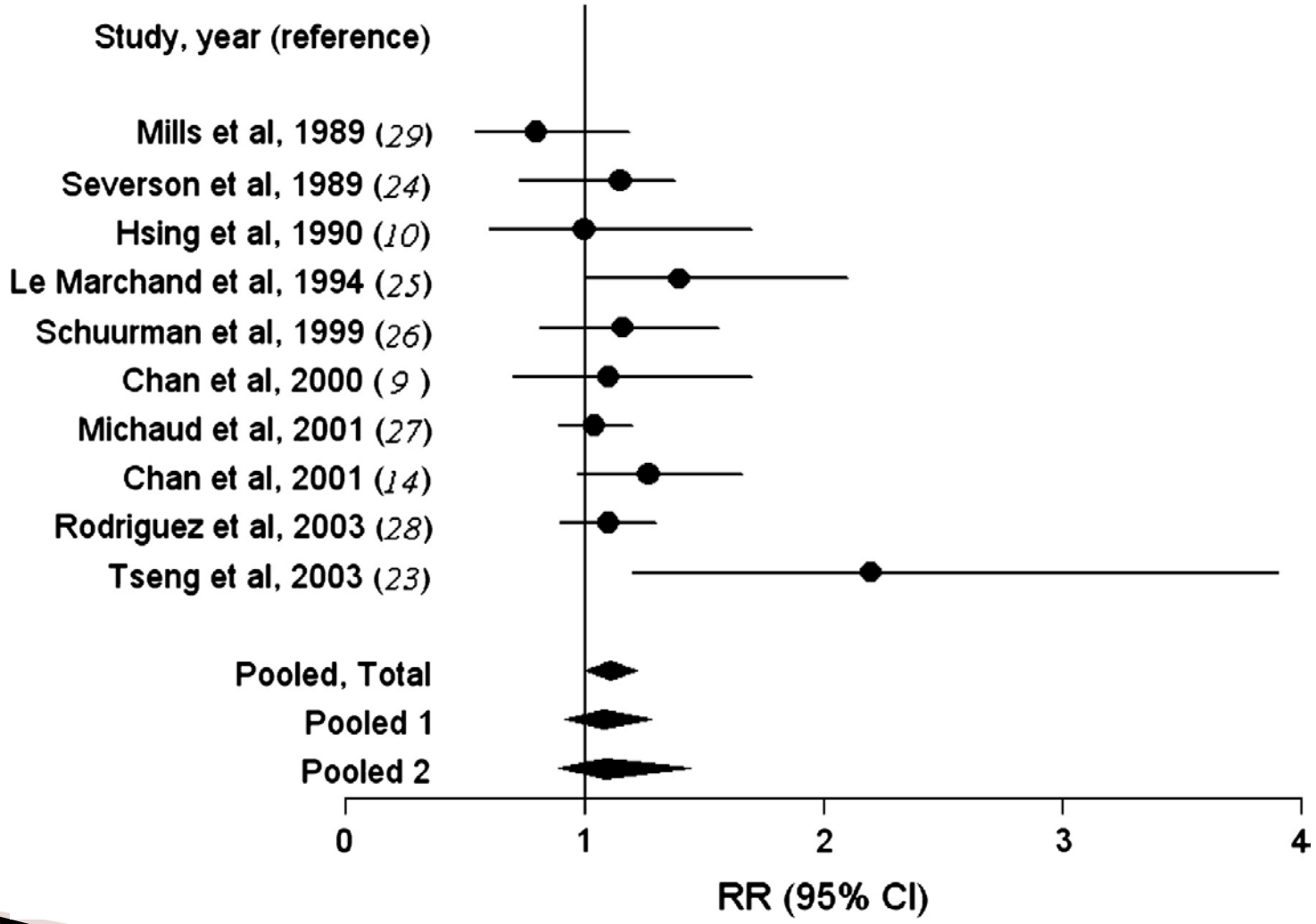
Prostate cancer incidence rates versus per capita milk intake among 38 countries



Butler et al. Cancer Res; 70(12) June 15, 2010
[adapted from Zhang and Kesteloot]

Meta-analysis: Relative risks of prostate cancer comparing the highest with the lowest **dairy product intake** categories



JNCI

Gao X et al. JNCI J Natl Cancer Inst 2005;97:1768-1777

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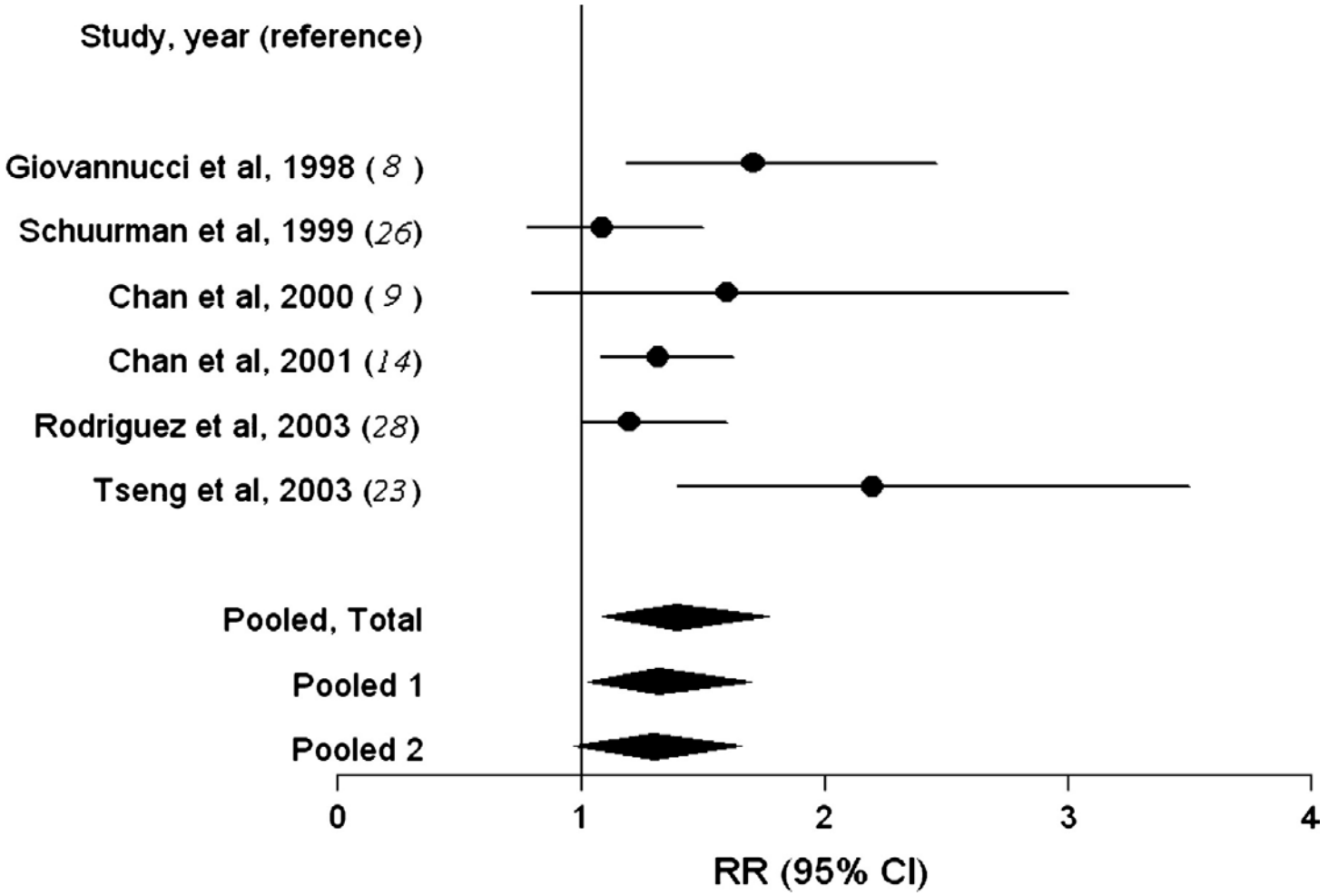


JNCI

Gao X et al. JNCI J Natl Cancer Inst 2005;97:1768-1777

Decreased cancer survival with high whole fat milk/dairy intake

- Health Professional Follow-up Study (HPFS)
  - Increased risk of lethal prostate cancer for those consuming whole milk >4 times/week compared to 0-3 times/month
  - Decreased risk of lethal prostate cancer for those consuming skim/low fat milk greater than once/day compared to 0-3 times/month
    - Pettersson et al. CEBP 2012
- Life After Cancer Epidemiology (LACE)
  - Higher risk of mortality after breast cancer diagnosis with high intake of high-fat dairy (but not low-fat dairy)
    - Kroenke et al. JNCI 2013

Objectives

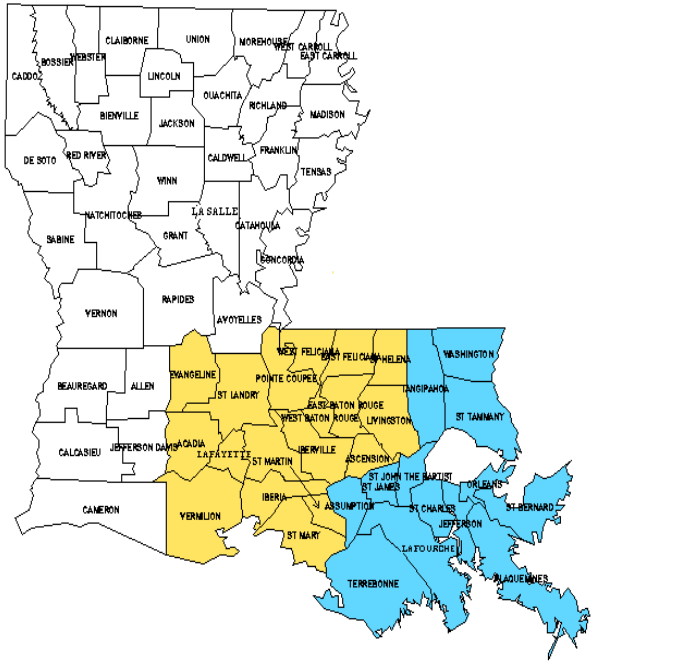
- To examine the association between **dairy product** and **calcium** intake and **prostate cancer aggressiveness** among **African American** and **European American** men diagnosed with prostate cancer

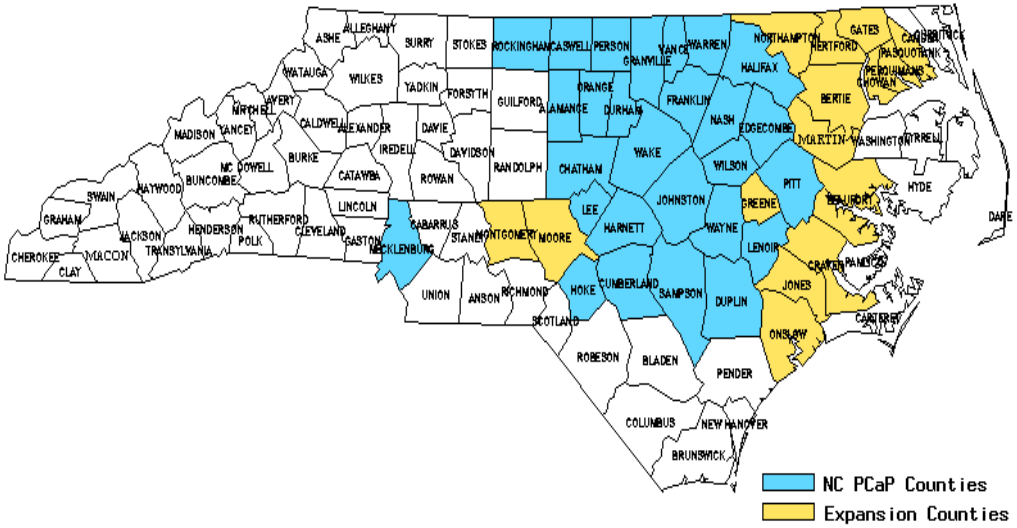
- To examine effect modification by **NSAIDs** use

North Carolina-Louisiana Prostate Cancer Project (PCaP)

PI: Dr. James Mohler

Case-only study of prostate cancer among African American and European American men





Methods: PCaP

- Eligibility criteria:
  - Residents of NC and LA study areas with a first diagnosis of histologically confirmed adenocarcinoma of the prostate
  - Between 40 and 80 years of age
  - English-speaking
  - Not institutionalized (nursing home)
  - Not cognitively impaired or in a severely debilitated physical state
  - Not under the influence of alcohol, severely medicated or apparently psychotic at the time of interview
  - Could self-identify as either African American or Caucasian American

Methods (continued)

- In-person interviews by registered nurse
  - NCI Diet History Questionnaire
    - modified for use in Southern population
    - assessed diet in year prior to diagnosis
    - excluded participants with unreasonable energy intakes (<500 or >6000 kcals/d)
  - Other demographic and lifestyle questionnaires
- Blood draw at interview
- Medical record abstraction
- High aggressive cases:
  - Gleason sum ≥8, or PSA>20ng/ml, or Gleason sum=7 AND stage cT3-cT4
- Low aggressive cases:
  - Gleason sum <7 AND clinical stage cT1-cT2 AND PSA <10 ng/ml
- Intermediate aggressive cases:
  - All others

Methods (continued)

- Statistical Analyses:
  - Descriptive statistics
  - Logistic regression comparing low/intermediate to high aggressive
  - Potential confounders and effect modifiers:
    - Age
    - Race
    - Education
    - Marital status
    - Body mass index
    - Diabetes
    - Smoking status
    - PSA screening history
    - Energy intake
    - Alcohol intake
    - Physical activity
    - Family history of PrCA
    - NSAIDs

Table 1. Descriptive Statistics

	Low/Intermediate Aggressive (n=1732)	High Aggressive (n=370)
Age, yrs (mean ± SD)	63 ± 8	65 ± 8
Dairy, servings/d (mean ± SD)	1.4 ±1.2	1.5 ±1.2
Calcium, mg/d (mean ± SD)	872 ± 457	915 ± 480
Race	**n(%)**	**n(%)**
African American	817 (47%)	206 (56%)
European American	915 (53%)	164 (44%)
Education		
Some/Less than high school	324 (19%)	112 (30%)
High school grad/vo/tec	535 (31%)	102 (28%)
Some college/College grad	616 (36%)	121 (33%)
Grad school/prof. degree	256 (15%)	35 (9%)

Table 1. (continued)

	Low/Intermediate Aggressive (n=1732)	High Aggressive (n=370)
Body mass index (kg/m^2)	**n(%)**	**n(%)**
Normal weight < 25	330 (19%)	60 (17%)
Overweight ≥25 - 30	750 (44%)	139 (39%)
Obese ≥30	641 (37%)	161 (45%)
Smoking status		
Never smoker	606 (35%)	99 (27%)
Former smoker	891 (51%)	194 (52%)
Current smoker	235 (14%)	77 (21%)
NSAIDs use (Yes)	1054 (61%)	228 (62%)
1st degree relative w/ prostate cancer	430 (27%)	77 (22%)

Table 2. Adjusted* ORs and 95%CIs for prostate cancer aggressiveness for dairy and calcium intake

	Low/Int Agg (n)	High Agg (n)	OR	95%CI
Dairy intake (servings/d)				
≤ 1	794	162	1.0	Referent
1 - ≤ 2	592	112	0.9	0.7, 1.2
>2	334	86	1.1	0.8, 1.6
Calcium from food (mg/d)				
≤ 500	341	63	1.0	Referent
500 - ≤ 1000	854	167	1.0	0.8, 1.8
1000 - ≤ 1500	383	87	1.2	0.7, 1.8
>1500	142	43	1.5	0.8, 2.6

*Adjusted for age, race, education, PSA screening history, body mass index, smoking status, and energy intake

Table 3. Adjusted ORs and 95%CI for prostate cancer aggressiveness for **calcium intake** stratified by NSAIDs use

	Low/Int Agg (n)	High Agg (n)	OR	95%CI
NSAIDs = Yes				
Calcium intake (mg/d)				
≤ 600	293	68	1.0	Referent
600 - ≤ 1000	409	79	0.9	0.5, 1.3
>1000	352	81	0.8	0.4, 1.3
NSAIDs = No				
Calcium intake (mg/d)				
≤ 600	242	36	1.0	Referent
600 - ≤ 1000	253	55	1.8	1.0, 3.2
>1000	174	49	2.3	1.1, 4.9

P<0.05 for interaction

Table 4. Adjusted ORs and 95%CI for prostate cancer aggressiveness for **dairy intake** stratified by NSAIDs use

	Low/Int Agg (n)	High Agg (n)	OR	95%CI
NSAIDs = Yes				
Dairy (servings/d)				
≤ 1	440	104	1.0	Referent
1 - ≤ 2	388	65	0.7	0.5, 1.0
>2	220	55	0.9	0.6, 1.4
NSAIDs = No				
Dairy (servings/d)				
≤ 1	350	56	1.0	Referent
1 - ≤ 2	201	47	1.7	1.1, 2.7
>2	113	31	1.7	0.9, 3.0

P<0.05 for interaction

No effect of other related dietary factors or supplements:

- Calcium supplements
- Vitamin D intake
- Vitamin D supplements
- Milk intake

Strengths/Weaknesses

- Case-only study so cannot evaluate incidence of disease, only aggressiveness

- Strengths:
  - Large, population-based study, half of enrolled participants are African American
  - Extensive questionnaires for evaluating potential confounders

- Weaknesses:
  - Association does not prove causation, cannot rule out the role of chance in findings
  - Did not consider dose or type of NSAIDs

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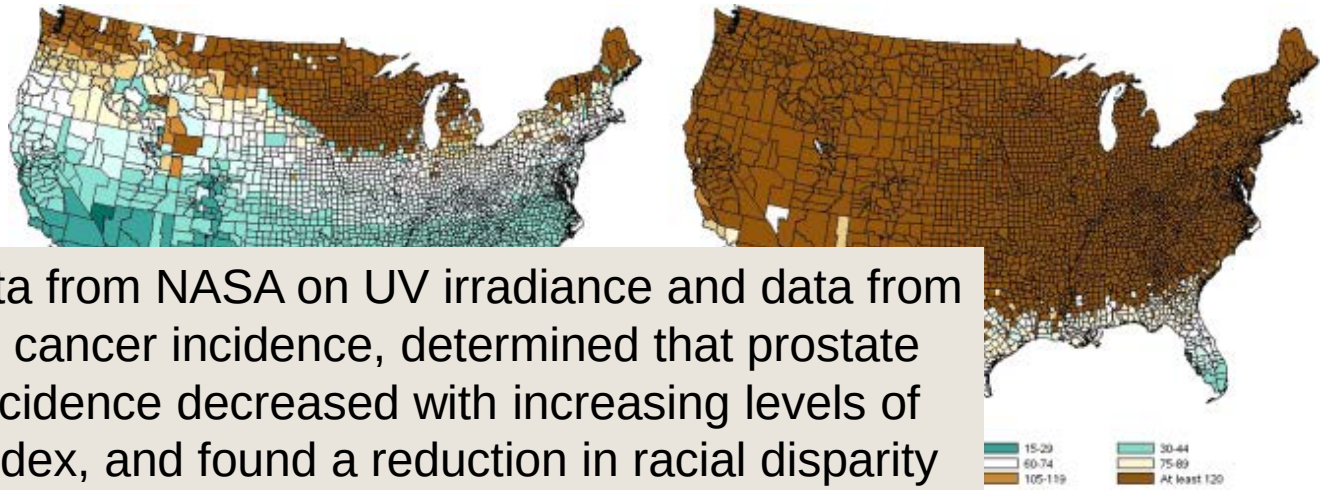
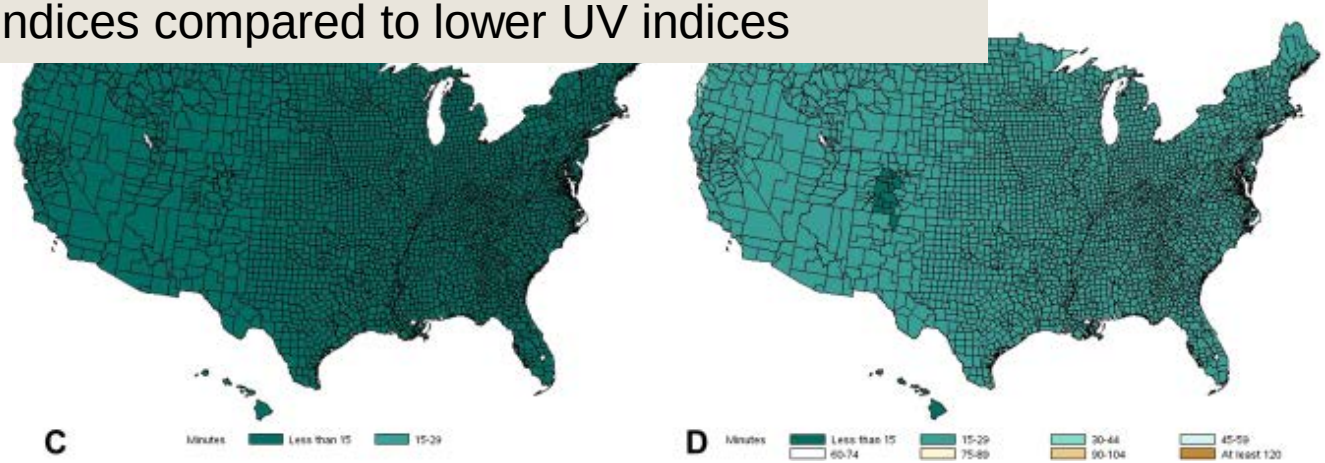
Estimated number of minutes required to synthesize 600IU vitamin D from sunlight



Using data from NASA on UV irradiance and data from SEER on cancer incidence, determined that prostate cancer incidence decreased with increasing levels of the UV index, and found a reduction in racial disparity in prostate cancer incidence in areas with moderately high UV indices compared to lower UV indices

est skin in January



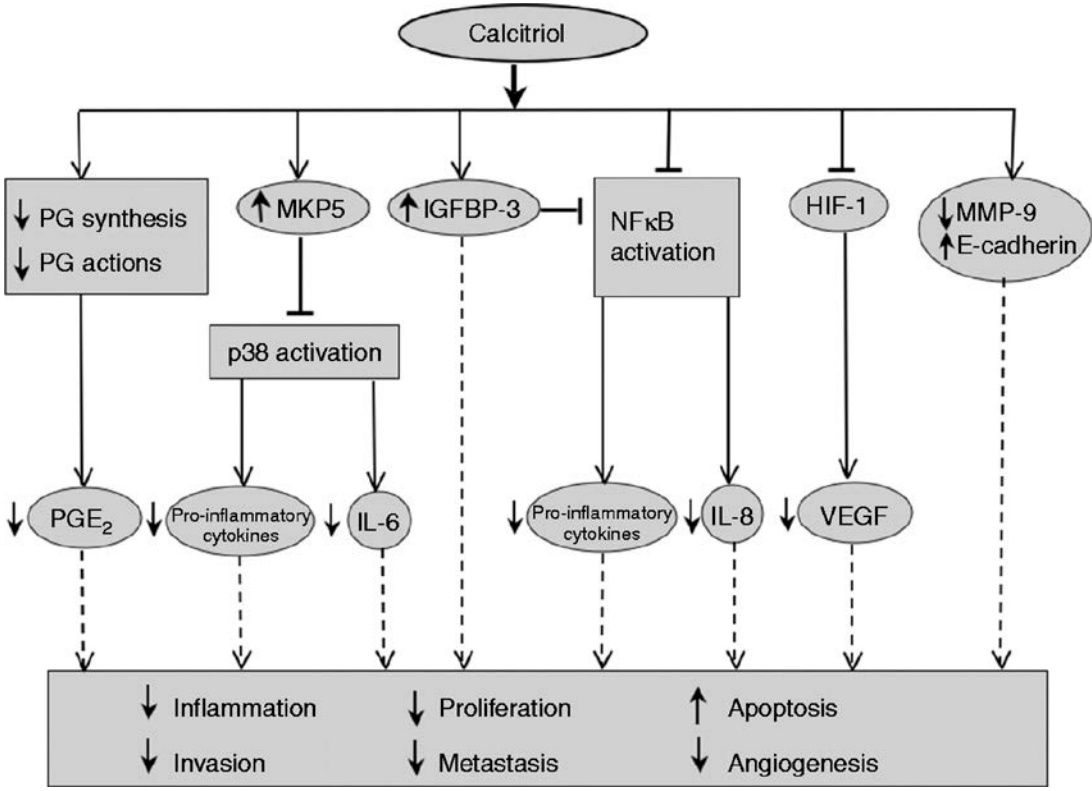
White, fairest skin in July

Black, darkest skin in July

Cancer
6 JUN 2013 DOI: 10.1002/cncr.28127
http://onlinelibrary.wiley.com/doi/10.1002/cncr.28127/full#cncr28127-fig-0001

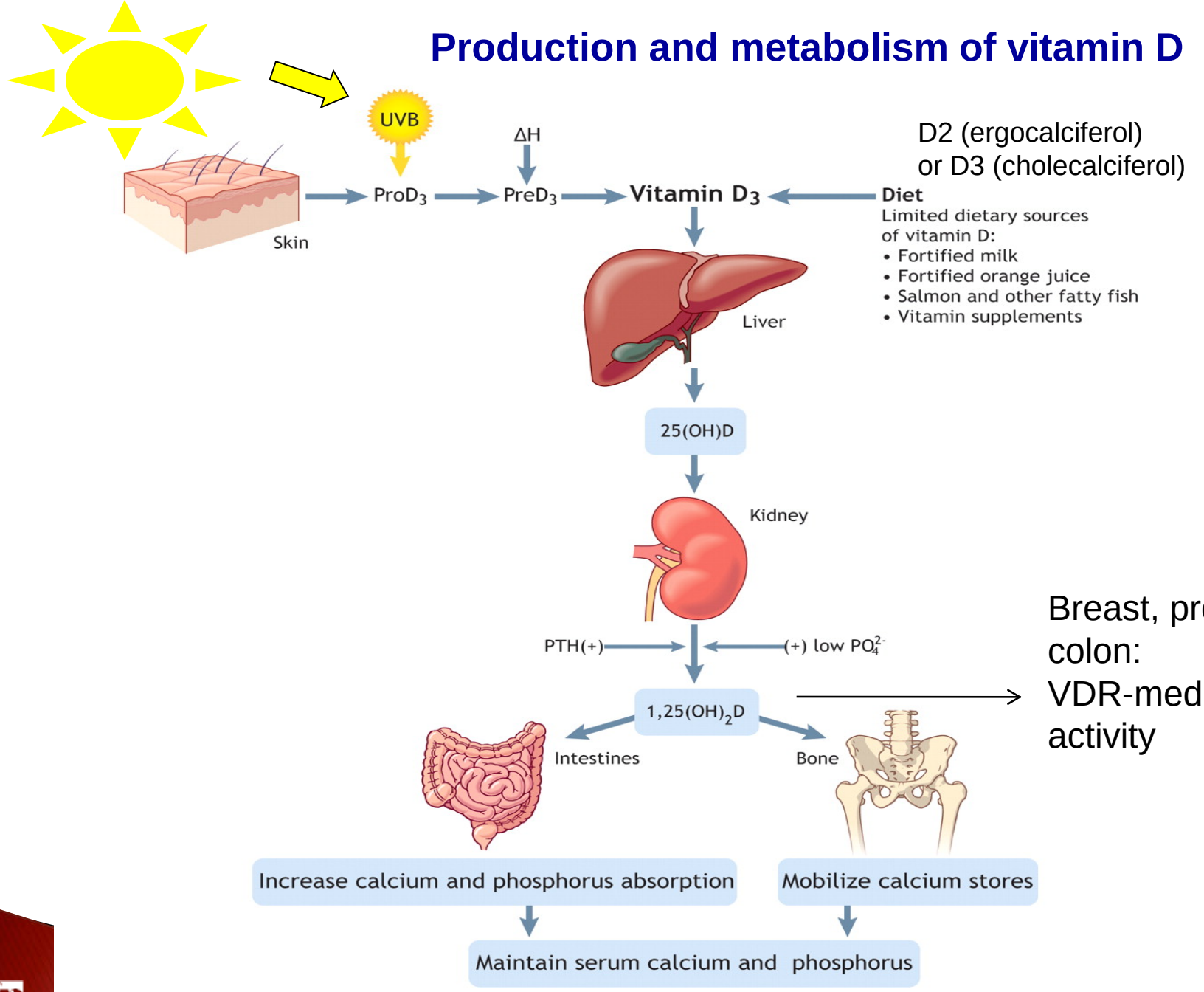
Potential mechanisms for dairy/calcium association with increased risk of PrCA

- Marker of high fat diet
- Estrogen in milk
- Increased levels of insulin-like growth factor
- **Suppression of production of $1,25(OH)_2D$**
- Increased inflammation



Krishnan and Feldman, Endocr Relat Cancer. 2010 Jan;17(1):R19-R38

Production and metabolism of vitamin D



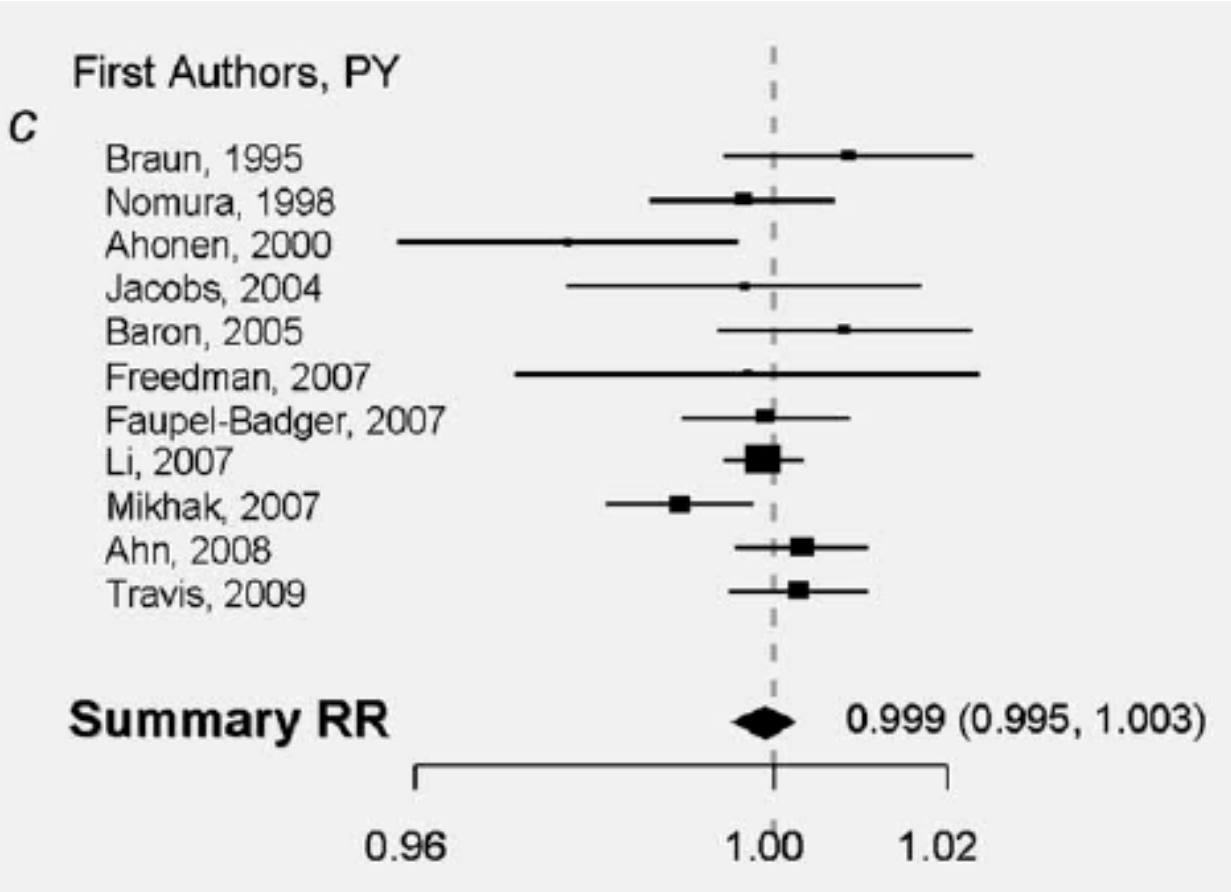
D2 (ergocalciferol)
or D3 (cholecalciferol)

Breast, prostate, colon:
VDR-mediated activity

Adapted from Hollis, B. W. et al. CMAJ 2006;174:1287-1290

CMAJ·JAMC

Meta-analysis of observational studies of 25(OH)D and prostate cancer



Gandini et al 2011 Int J Cancer

Suggested cutpoints for circulating 25(OH)D

- Measured in ng/ml or nmol/L
- Conversion: 1 ng/ml = 2.5 nmol/L

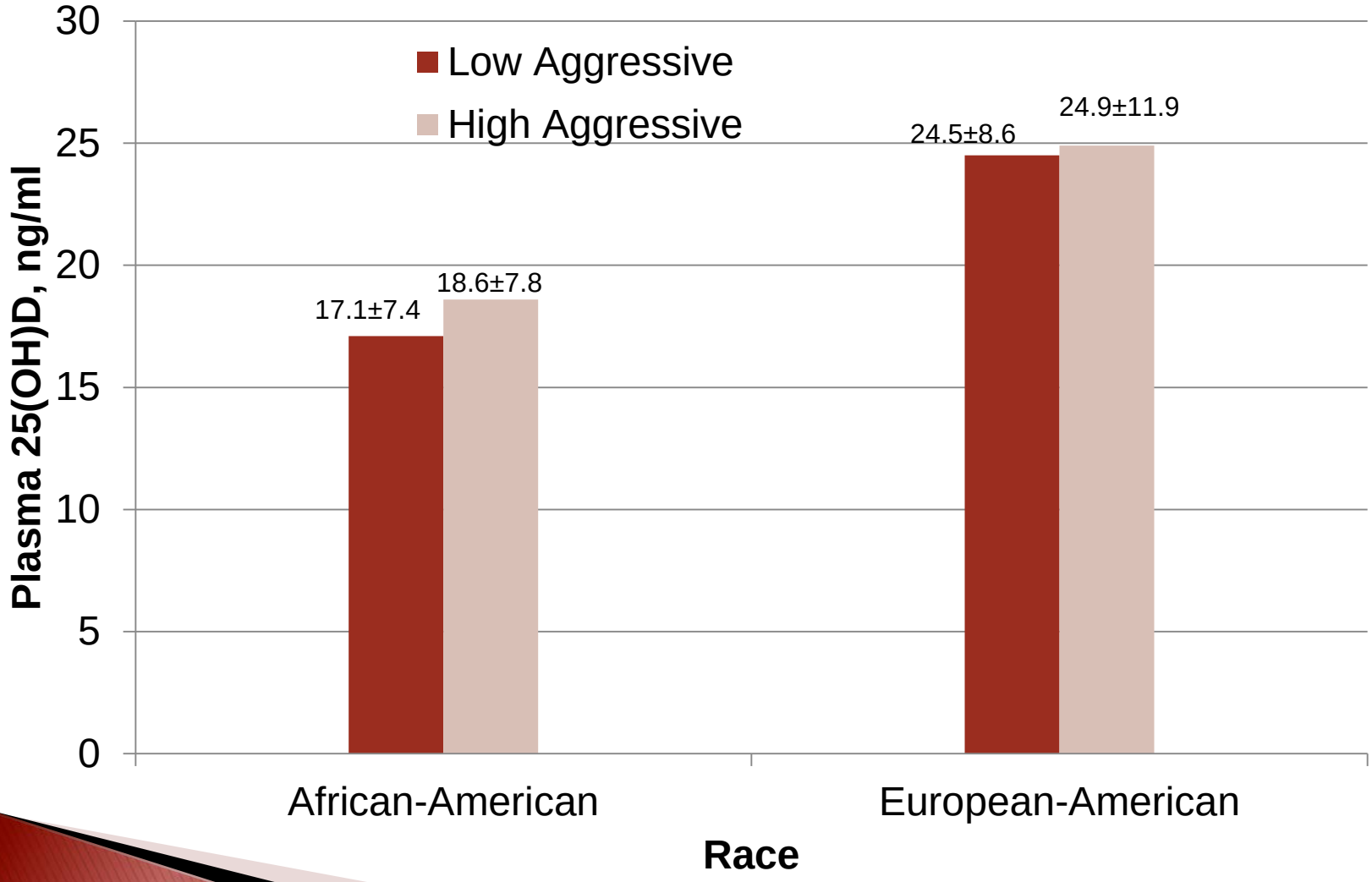
	ng/ml	nmol/L
Deficiency	< 8 - 20	< 20 - 50
Insufficiency	20 - 30	50 - 75
Toxicity	> 100 - 200	>250 - 500

Objectives & Methods

- To examine the association between **plasma 25(OH)D** and **prostate cancer aggressiveness** among **African American** and **European American** men diagnosed with prostate cancer

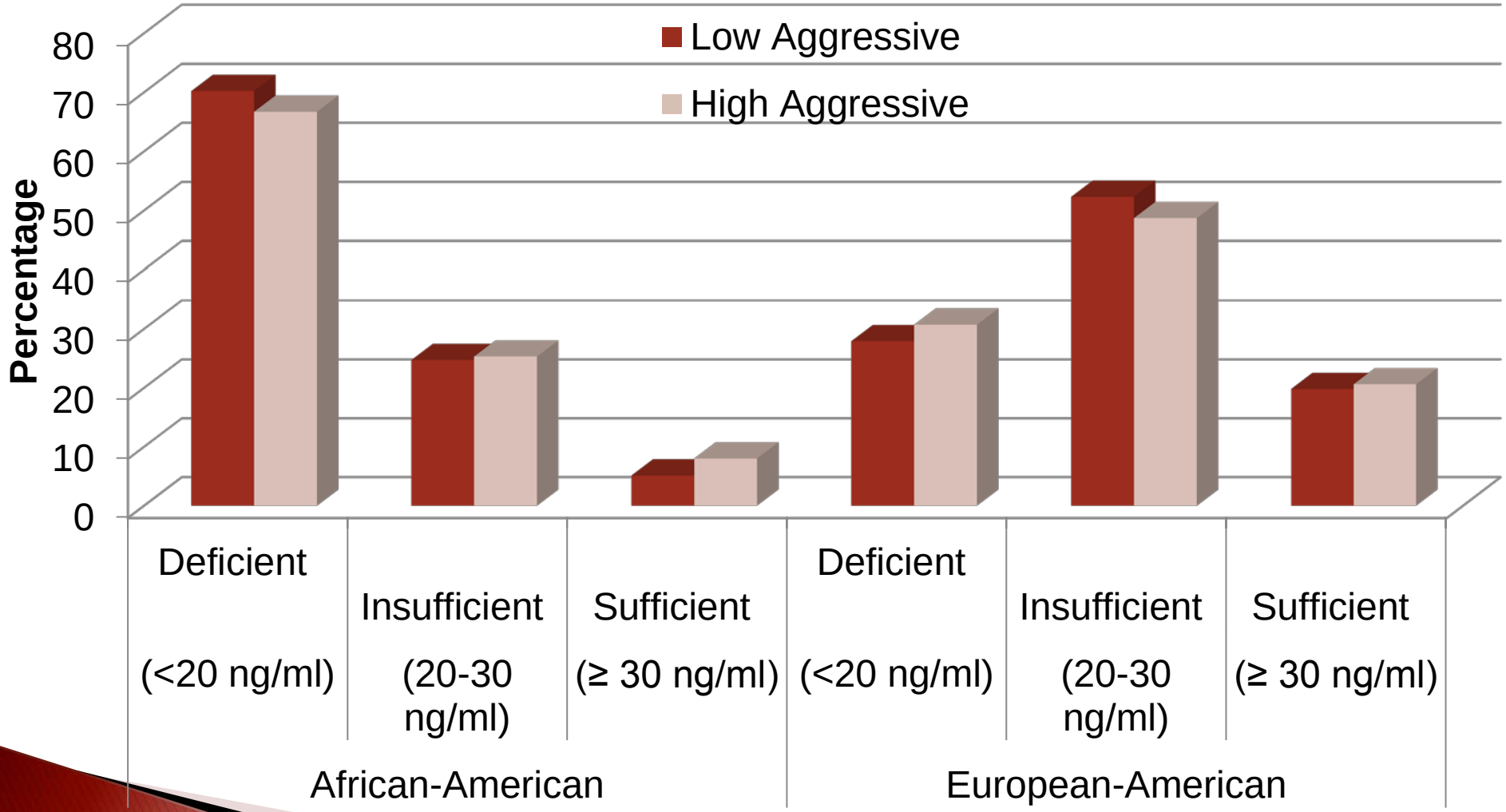
- Measured plasma 25(OH)D by LC/MS/MS in 1200 PCaP participants
- High aggressive cases (n=414):
  - Gleason sum ≥8, or PSA>20ng/ml, or Gleason sum=7 AND stage cT3-cT4, or Gleason sum=7 with primary pattern 4
- Low aggressive cases (n=786):
  - Gleason sum <7 AND clinical stage cT1-cT2 AND PSA <9 ng/ml

Figure 1. Plasma 25(OH)D by race and aggressiveness



Woloszynska-Read et al., presented at AACR 2013 Annual Meeting

Figure 2. Vitamin D sufficiency status by race and aggressiveness



Woloszynska-Read et al., presented at AACR 2013 Annual Meeting

Table 5. Adjusted* ORs and 95%CIs for prostate cancer aggressiveness for plasma 25(OH)D (ng/ml) by race

	Low Agg (n)	High Agg (n)	OR	95%CI
African Americans				
< 13.3	103	59	1.0	Referent
13.3 - < 18.9	105	79	1.8	1.1, 3.0
≥ 18.9	104	87	1.6	1.0, 2.6
European Americans				
< 21.1	158	69	1.0	Referent
21.1 - < 26.7	158	59	0.9	0.6, 1.4
≥ 26.7	158	61	0.9	0.6, 1.4

* Adjusted for age, BMI, education, smoking status, season of blood draw, PSA screening history, physical activity, energy intake, alcohol intake, NSAIDs use

Woloszynska-Read et al., presented at AACR 2013 Annual Meeting

Sensitivity Analyses

- No change in results or interpretation with:
  - Adjusting for weight change
  - Adjusting for time to blood processing
  - Excluding intermediate aggressive cases
  - Changing cutpoints for plasma 25(OH)D quantiles

Table 6. Adjusted* ORs and 95%CIs for prostate cancer aggressiveness for ratio of plasma 25(OH)D/1,25(OH)2D among African Americans

	Low Agg (n)	High Agg (n)	OR	95%CI
Ratio of plasma 25(OH)D/1,25(OH)2D				
1	63	35	1.0	Referent
2	65	27	0.9	0.5, 1.7
3	65	39	1.1	0.6, 2.1
4	64	69	2.2	1.2, 4.0

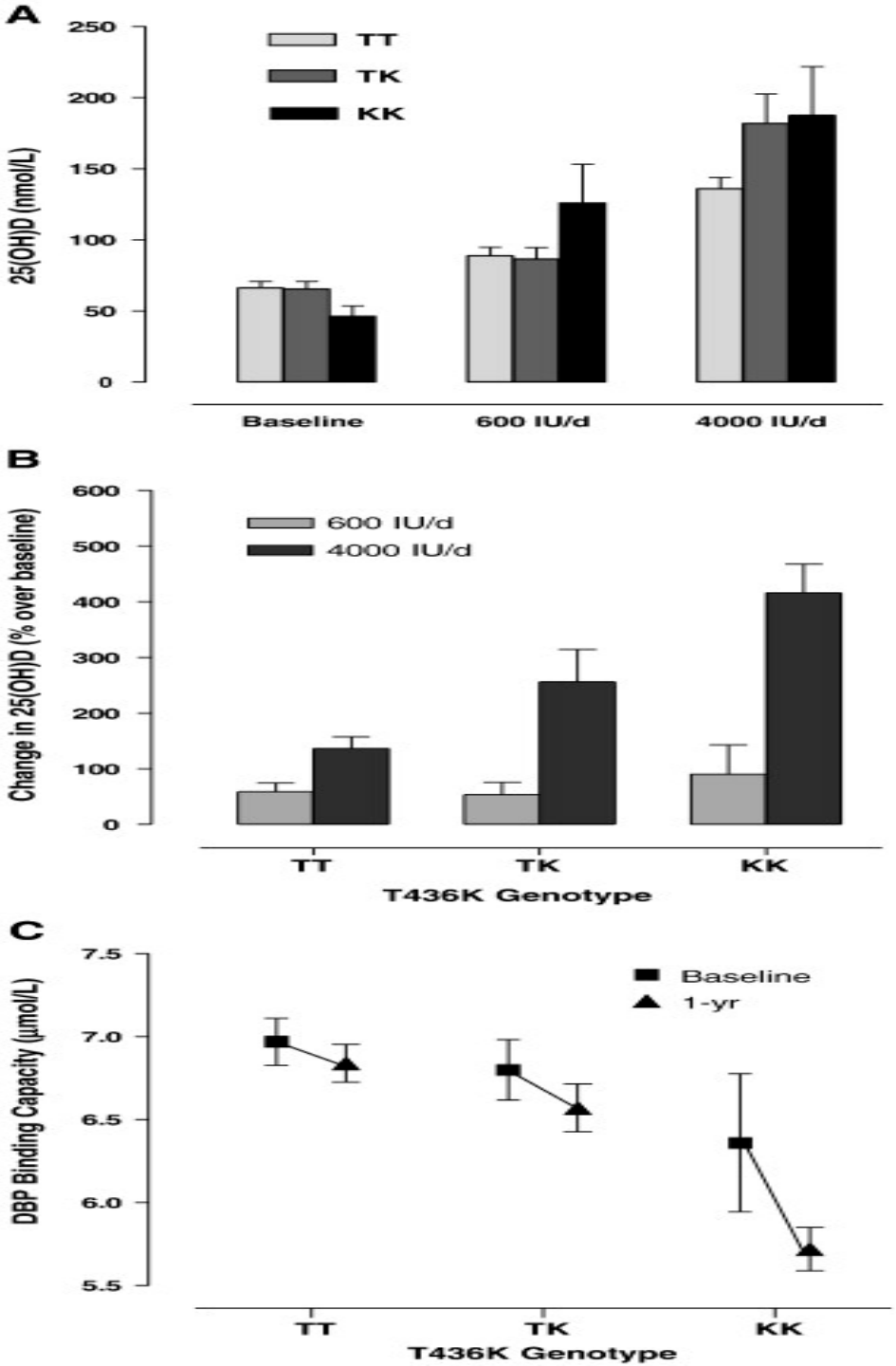
* Adjusted for age, BMI, education, smoking status, season of blood draw, PSA screening history, physical activity, energy intake, alcohol intake, NSAIDs use, study site

Issues to Consider

- Case-only study so cannot evaluate incidence of disease, only aggressiveness
- Temporality: Blood samples collected after diagnosis and at one point in time
  - Weight change?
  - Effects of therapy?
- Genetic differences in vitamin D binding protein affinity, vitamin D metabolism or VDR activity

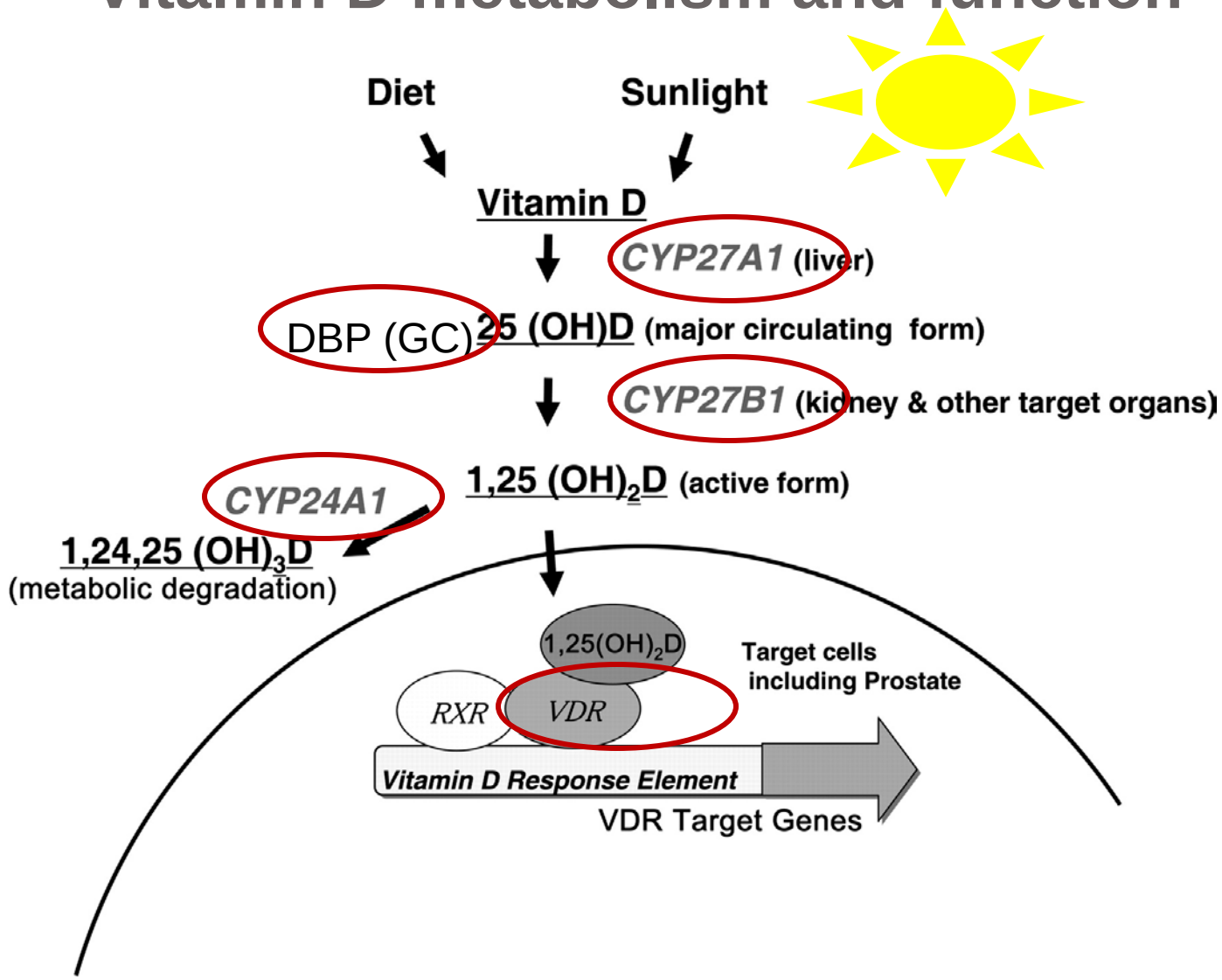
DBP polymorphism predicts differences in response to vitamin D supplementation

Fig. 1. Response of 25(OH)D to supplementation by T436K genotype. (A) Association of serum 25(OH)D concentrations with genotypes at baseline and after 1 year vitamin D loading in low-dose (600 IU/d) and high-dose (4000 IU/d) groups. (B) Association between genotypes and percentage increase in 25(OH)D at one year. (C) Specific DBP binding capacity by genotype at baseline and after 1 year vitamin D loading. Error bars show mean ± SE.



Fu L, et al. Clin Biochem 2009;42(10-11):1174-7.

Vitamin D metabolism and function



Adapted from Ahn, J. et al. Carcinogenesis 2009 30:769-776; doi:10.1093/carcin/bgp055

Carcinogenesis

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Summary/Conclusions

- Observed significant interaction between calcium/dairy intakes and NSAIDs use
  - high calcium and dairy intakes among non-regular users of NSAIDs was positively associated with aggressive prostate cancer
- Suggests moderation in dairy/calcium intake particularly among men not regularly using NSAIDs.

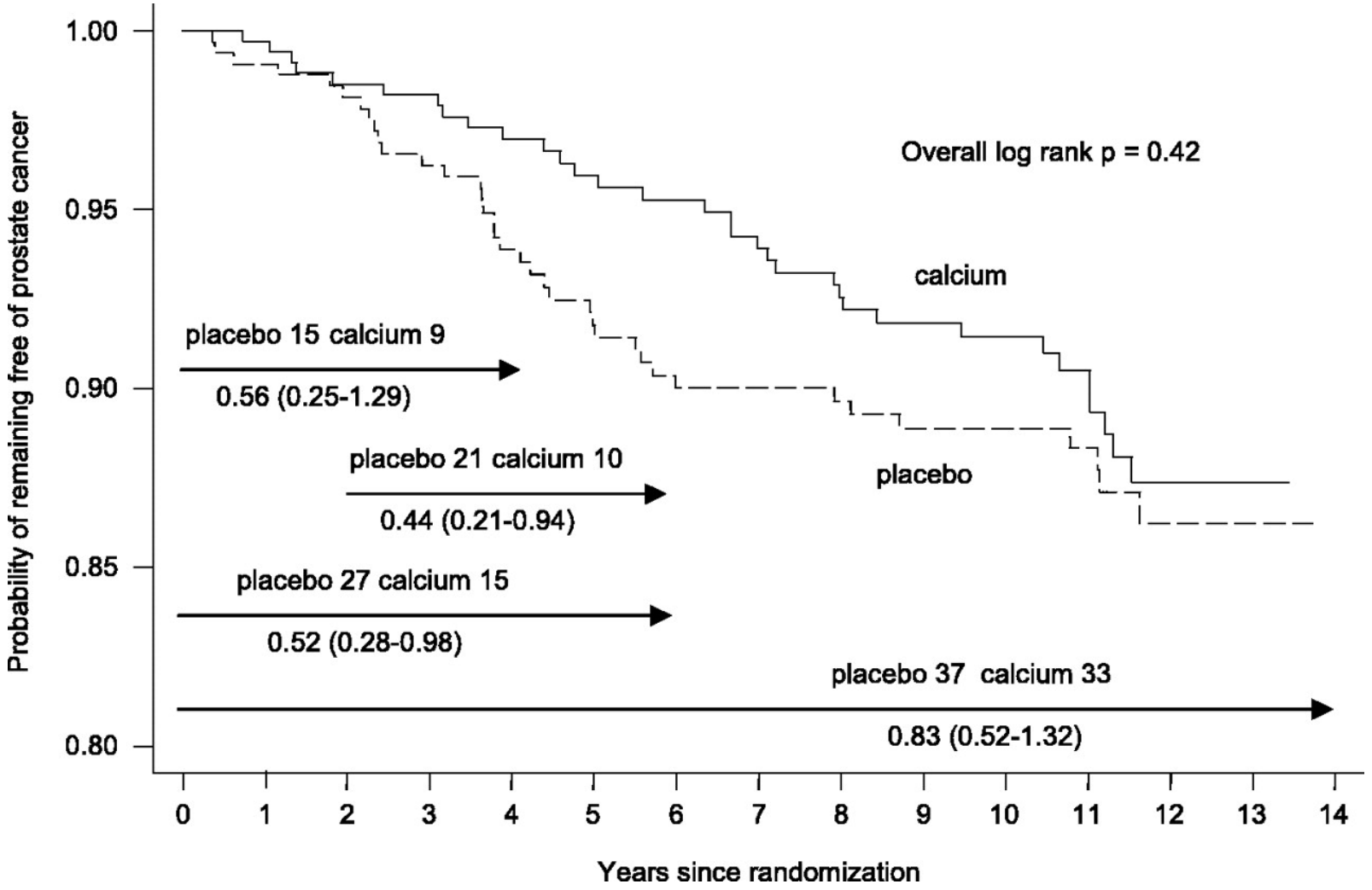
Summary/Conclusions

- Higher plasma 25(OH)D was associated with increased odds of high aggressive prostate cancer among African Americans only
- Preliminary results suggest high 25(OH)D and low 1,25(OH)2D have highest odds of high aggressive prostate cancer

Future Directions

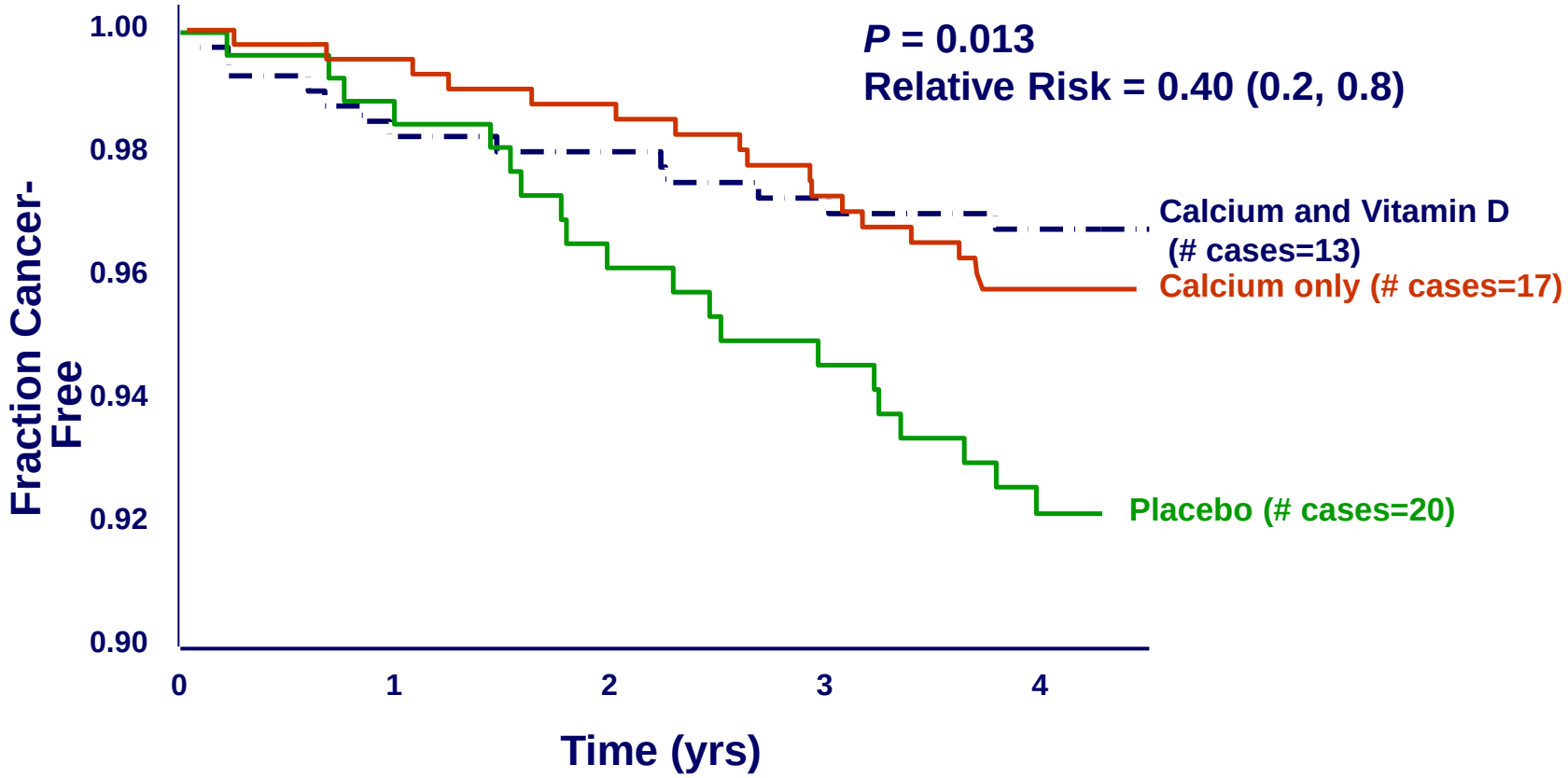
- Vitamin D associations with cancer may vary by specific genotypes (e.g.,*VDR, CYP24A1, CYP27A1, CYP27B1, CYP2R1*, and/or *GC*) and these associations may differ by race
- Measurement of free 25(OH)D may help to explain racial differences observed
- Analyses of whole fat milk vs. lowfat/skim milk, serum calcium, phosphorus, and PTH

Kaplan-Meier plot of the prostate cancer-free status over time of men in the calcium and placebo groups.



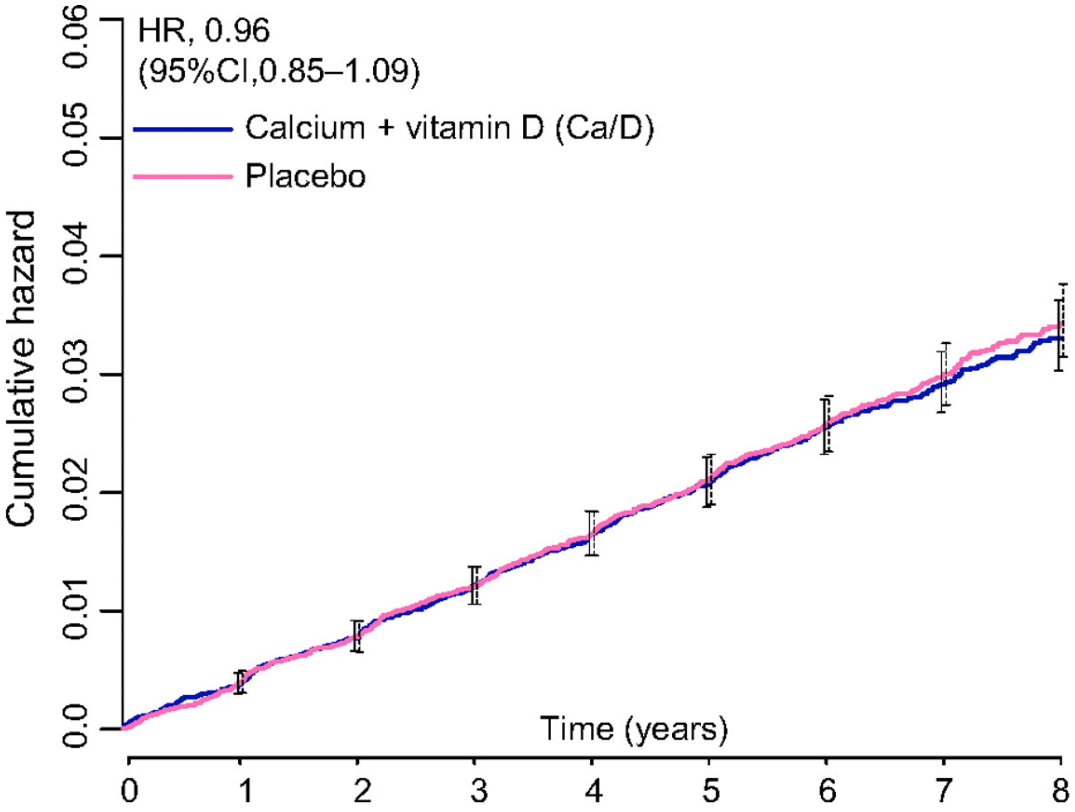
Baron J A et al. Cancer Epidemiol Biomarkers Prev 2005;14:586-589

Randomized Controlled Trial: Vitamin D (1,100 IU) plus calcium (1400-1500mg) in 1,180 women in Nebraska



Source: Lappe et al. Am J Clin Nutr 2007

Kaplan-Meier estimates of the cumulative hazard ratio for invasive breast cancer with supplemental calcium (1000mg) plus vitamin D (400IU) as compared with placebo (WHI)



Events									
(Ca/D)		69	70	79	78	76	78	45	28
Placebo		71	69	77	77	80	77	51	31
Number at risk									
(Ca/D)	18176	18004	17838	17624	17389	16980	14403	8953	4300
Placebo	18106	17922	17732	17505	17254	16814	14235	8842	4236

Chlebowski, R. T. et al. J. Natl. Cancer Inst. 2008 100:1581-1591

JNCI

Effect Modification by Vitamin D Intake or by Personal Supplement Use: Calcium + Vitamin D and WHI Breast Cancer Outcome

Baseline vitamin D intake	RR (95%CI)
<200IU	0.79 (0.65, 0.97)
200-<400IU	0.97 (0.74, 1.26)
400-<600IU	0.98 (0.77, 1.24)
600+IU	1.34 (1.01, 1.78)

Chlebowski et al. JNCI 2008

Personal supplement use	RR (95%CI)
No supplement use	0.82 (0.70, 0.97)
Supplement use	1.08 (0.94, 1.24)

Bolland et al. AJCN 2011

THE VITAMIN D AND OMEGA-3 TRIAL (VITAL)

What is the VITAL study?

The ***VIT***amin D and Omeg***A***-3 Tria***L*** (VITAL) is a research study in 20,000 U.S. men and women investigating whether taking daily dietary supplements of vitamin D (about 2000 IU) or fish oil (about 1 gram of omega-3 fatty acids) reduces the risk of developing cancer, heart disease, and stroke in people who do not have a prior history of these illnesses. Recruitment for the study began in January 2010.

Who is running the VITAL study?

The study is funded by the National Institutes of Health and is being run by Harvard Medical School and the Brigham and Women's Hospital in Boston, MA. But you don't have to travel to Boston to participate. All of the study materials—the study pills and the study forms—will be mailed directly to you and we are recruiting participants from every state in the country. Participation in the study does not require any clinic visits.

Who is eligible to participate in the VITAL study?

Both women and men can join the study. If you are a woman aged 65 or older or a man aged 60 or older and you have not previously had a heart attack, stroke or cancer (other than skin cancer), you may be eligible to participate in the VITAL study.

Acknowledgments

Funding source

- Department of Defense:
- PCaP: DAMD 17-03-2-0052
- Vitamin D Ancillary Study: DAMD 11-1-0568 (Prostate Cancer Health Disparity Research Award)

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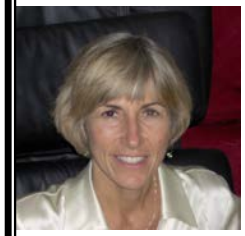
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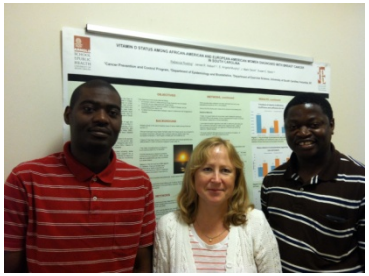
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