Localized Prostate Cancer: A Primer for Herbalists

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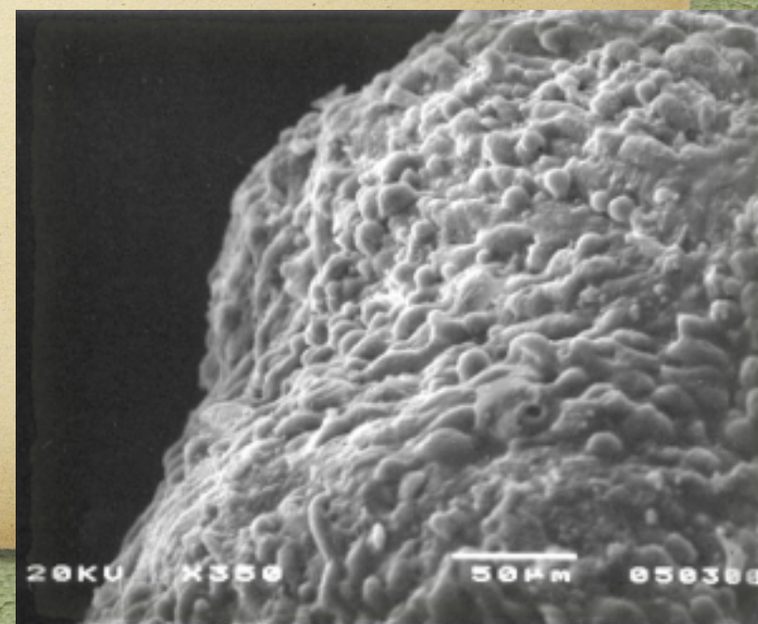
2015



The Problem

Multiple Prostate Cancers

- Every tumor is heterogeneous
- Every tumor is monoclonal, frequently spread to multiple areas within prostate (Boyd 2012)
- Every tumor is unique (very likely)
- Genetic similarities and differences between each patient's tumors

Epidemiology

- Most (70–80%) prostate cancer is localized and low-grade, non-metastatic, non-lethal (Eggener 2011)
- Put another way, only 20–30% of men with prostate cancer have aggressive disease that spreads, causes symptoms, and/or causes death

Definition of Low-Grade

- Gleason score 3+3 or 3+4 (possibly a single small focus of 4+3 that doesn't change) <—low grade
- At most 4 positive biopsy cores<—localized
- <20% of cores are positive for cancer<—localized
- No change over several years' time
- PSA rises slowly (PSADT >2 yr, PSAV <1 ng/ml/yr)

Etiology

Background environmental factors

Diet and lifestyle

Genetic mutations

Genetics

Cancer

Overdiagnosis and Overtreatment

- Much low-grade pr ca is being diagnosed due to PSA screening = over diagnosed
- Many of these men are treated aggressively (surgery, radiation)
- This doesn't extend life or improve quality of life = over treated
- Our job is actually to provide alternatives to ineffective, harmful conventional therapy in men with low-grade disease

PSA Debacle

- Richard Ablin, MD discovered PSA in 1970.
- By 2010 he said, in the New York Times, "PSA has been a hugely expensive public health disaster."
- False positives very high, resulting in a LOT of unnecessary surgery and radiation
- False negatives are also sufficiently common to be a problem

Sensitivity: 67–80%
Specificity: 69–93%
PPV: 31–54%
NPV: 81–96%
NNS: >1,410
NNT: 48

References:
Schröder 2009;
Brawer 1999

tPSA Screening Studies

Trial	Population	Method	Follow-Up	Result
Andriole 2009 PLCO	US, n=76,693	DBR	7 yr	No benefit
Kjellman 2009 Stockholm	Sweden, n=1,782	DBR	12.9 yr	No benefit
Schröder 2009 ERSPC	Europe, n=182,160	DBR	9 yr	20% pr ca mortality decr
Labrie 2004 Quebec	Canada, n=46,486	R	15 yr	No benefit (also Ilic 2006)
Sandblom 2004 Norrköping	Sweden, n=9,026	R	11 yr	No benefit

Lifespan Issue

- How much time does this patient likely have left? (livingto100.com is one tool to decide)
- 50-yr-old man with 35 year life expectancy: that's a long time for cancer to progress
- 75-year-old man with 10 year life expectancy: not much time for cancer to progress

What to Do

First Do Nothing

- Excellent site: http://www.prostatepointers.org/ww/wwopt.htm
- CT Tumor Registry: no need for aggressive tx for localized (Gleason <7) pr ca (Albertsen 2005)
- VACURG trial: RP vs placebo no difference (Iversen 1995)
- Modern tPSA screened patients with low-grade dz have very low pr ca mortality (Lu-Yao 2009)
- Scandinavian PCG-4 trial: most rigorous and unbiased; at 10 yr slightly improved pr ca and overall survival in RP vs WW group (Bill-Axelson 2005)

More Watchful Waiting

- No benefit for patient over 70 from aggressive tx; indeed, some indications of harm (Fleming 1993)

- 10-yr survival of British men with Gleason <7 and tPSA < 5 over 90% (Cuzick 2006)

- Meta-analysis--screen-detected pr ca pt with Gleason <7 and tPSA <10, no benefit of RP over WW (Alibhai 2004)

Is Killing the Only Option?

Medicinal mushrooms	Immune support	Re-differentiation	*Mahonia aquifolium*
Convolvulus arvensis	Angiogenesis inhibition	Energy deprivation	Reduce choline
Redox modulators	Prevent new mutations	Metastasis inhibition	Modified citrus pectin

Ornish Approach Original Trial

- n=93 (with T1c pr ca, Gleason 7 or less) (Ornish 2005)
- Baseline tPSA 4–10 ng/ml; decline 4% on average
- Randomized to Ornish approach (pescovegan, stress reduction, exercise), vs watchful waiting
- No Ornish patient required invasive treatment after 6 mon of treatment (6 controls did)

Ornish Approach Trial 2

- n=14, all T1c prostate cancer (Nguyen 2006)
- 6 mon duration
- All on vegan diet, tai chi for stress reduction
- PSADT change: 12 mon to 112 mon (average)
- tPSA: fell in 9 of 10 evaluable patients

Additional Trials

- Two-year follow-up: 2 of 43 (5%) of Ornish group vs 13 of 49 (27%) of controls had definitive therapy; no differences in PSA kinetics between groups (Frattaroli 2008)
- Beneficial changes in risk factors with Ornish diet (Dewell 2008)
- Beneficial changes in gene expression with Ornish diet (Ornish 2008)

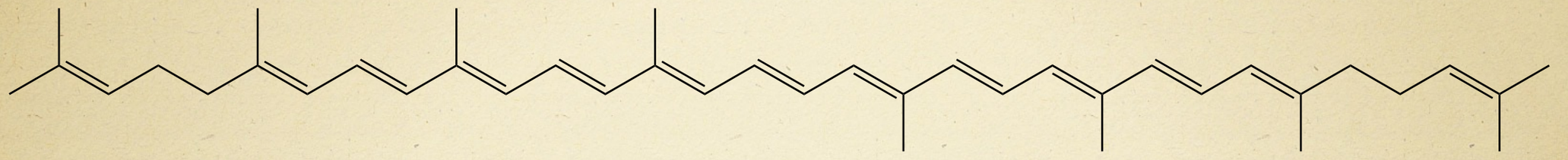
Vegan Diet Enhancements

- All organic food
- Include some fish (Ornish even says to do this now)
- Insulin sensitizing spices (cinnamon, cloves)
- Omega 3 fatty acids sources--hemp, walnut, fish
- Reduce omega 6 fatty acid intake
- It's vegetarian not grainitarian: avoid sugar & starch
- Exercise, stress reduction

Camellia sinensis (green tea)

- Meta-analysis of epidemiologic studies shows it is protective (Zheng 2011)
- In particular protects against aggressive dz (Kurahashi 2007)
- Multiple mechanisms likely
- Clinical trial: n=60 men with HGPIN, green tea catechins 600 mg qd vs placebo x 1 yr, decreased progression to prostate cancer w/ treatment (Bettuzzi 2006)

Tomatoes

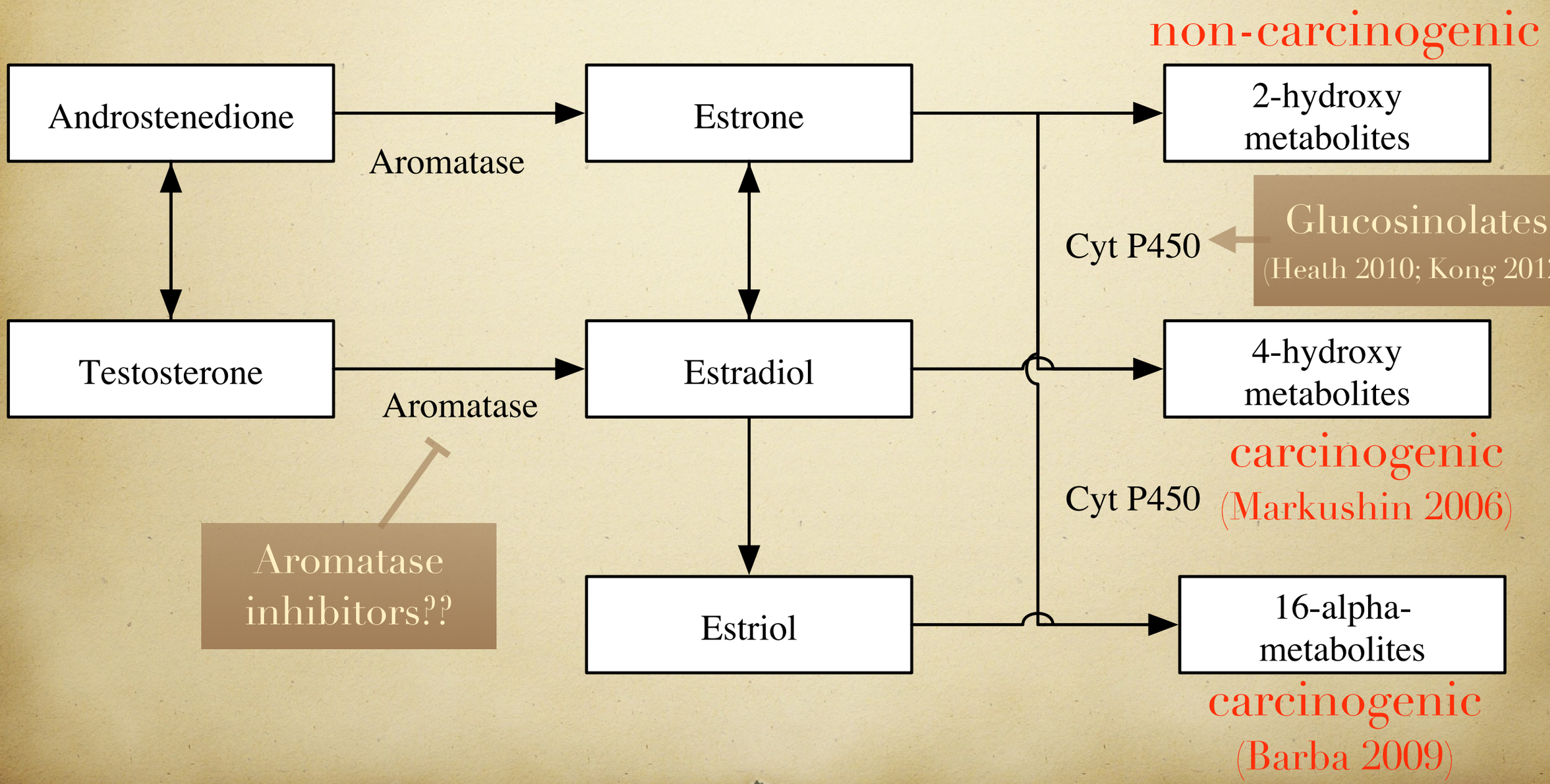


- Meta-analysis finds high-level intake protective (Etminan 2004)

- Is it really just a lycopene delivery vehicle?

Estrogen Catabolism

Cruciferous veggies preventative (Liu 2012)



Urine 2/16α Ratio and Soy

- Higher urine 2/16α-hydroxyestrone ratio protective against prostate cancer in at least two studies (Barba 2009; Muti 2002)
- Each point higher tPSA equates to 14% decrease in 2-hydroxyestrone in urine (Teas 2005)
- Soy protein raises 2/16α-hydroxyestrone ratio in men at risk of pr ca (Hamilton-Reeves 2007)
- Soy foods: meta-analysis found intake protective (Hwang 2009)

The Totality of Soy

Isoflavones

Protein

Glycine max
(**soy**)

Bowman-Birk protease

Inositol hexaphosphate (phytic acid)

Legumes and Isoflavones

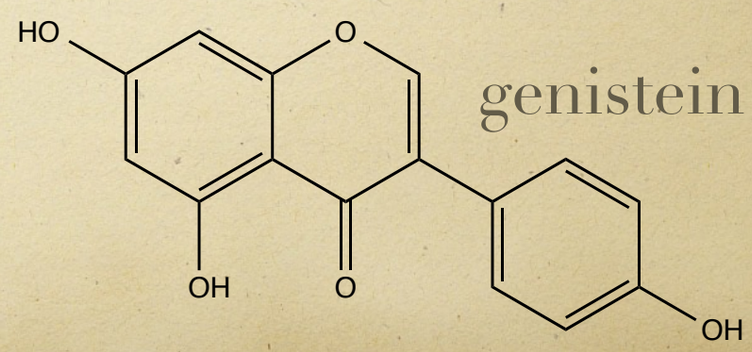
- Higher intake of legumes and higher serum genistein protective (Travis 2009)
- Soy protein intake (w/ or w/o isoflavones) reduces HGPIN compared to milk protein 40 g qd after 6 mon (Hamilton-Reeves 2008)
- Soy isoflavones 60 mg qd reduces tPSA in early prostate cancer (Kumar 2004)

Isoflavones Trial

- n=52, full range of past tx (WW, RP, RT, ADT), full range of Gleason scores, 6 months (deVere White 2004)

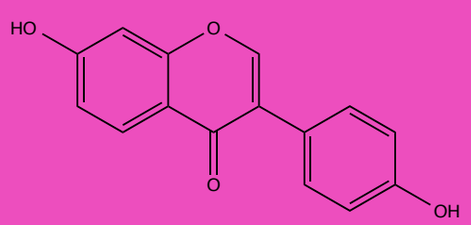
- 450 mg genistein w/ 450 mg other isoflavones w/ Ganoderma mushroom polysaccharides qd

- 8 of 13 with WW had no rise or >50% decline in tPSA

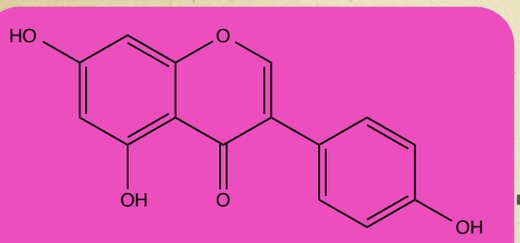


genistein

Importance of Equol Conversion



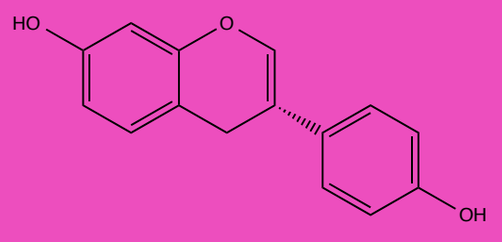
daidzein



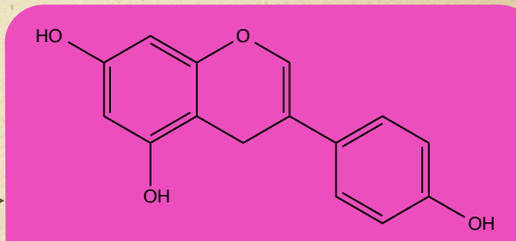
genistein

Slackia isoflavoniconvertens

Ref: Matthies 2012



S-equol



5-hydroxyequol

30-50% of adult population can form equol (Matthies 2008)

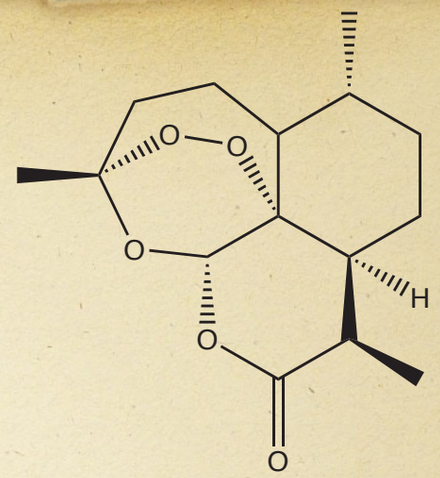
Isoflavones

- Review of existing 11 clinical trials (Messina 2006)
- Dose range: 60–900 mg isoflavones/d from soy
- Sample sizes: 8–62
- Duration: 20–360 d
- 4 of 8 studies in prostate cancer patients showed PSAV slowing

Isoflavones in kudzu

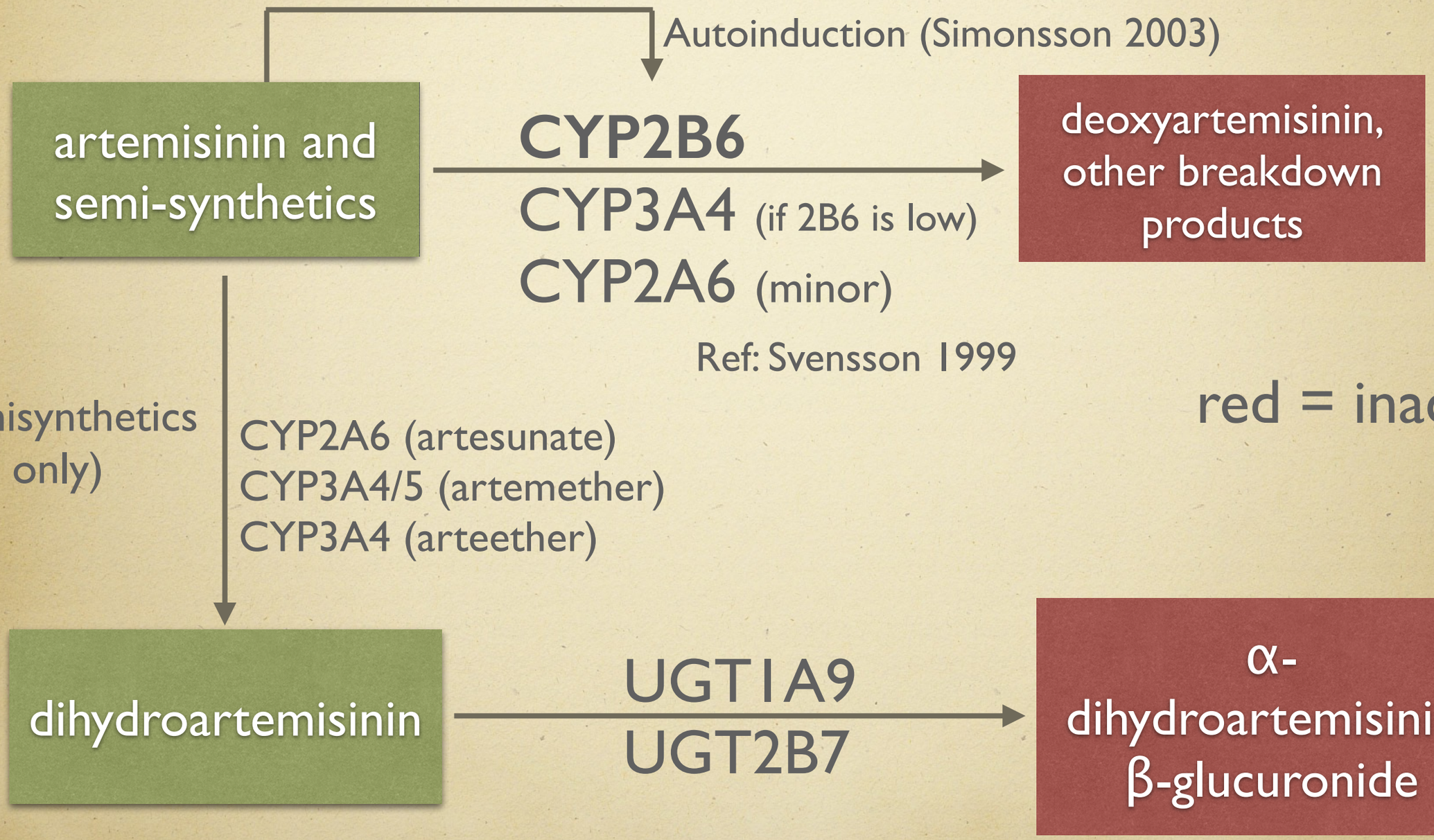
- *Pueraria montana* (kudzu)--10x higher levels than soy (Kaufman 1997)
- Not present in pure white commercial starch (look for brown)
- Completely safe, widely used as food in Asia
- All legumes have isoflavones (black beans, navy beans good sources)--not all have huge PR firms

Artemisia annua



- Case studies with various human neoplasms (Singh 2006; Berger 2005).
- Iron not necessary for antineoplastic activity.
- Autoinduces intestinal CYP2D6; requires pulsed dosing (see next slide)
- Also metabolized by intestinal CYP3A4 (non-inducible).
- Other compounds synergistic (pump inhibitors, absorption enhancers)

Pharmacokinetics



Artemisinin dosing

- Initial: 300-400 mg tid x 7 d
- Grapefruit juice first 3-4 days
- Monitor for neuropathies (rare at 300 mg tid)
- Take with 3-5 ml tincture or 2-3 g capsules tid
- Enhanced by combination with butyric acid, 10+ g qd po (Anticancer Res 2005;25:4325-31)

Results with Artemisinin in non-RP Patients

- 6/10 (60%) overall met criteria for efficacy (PSA kinetics improvement or stabilization)
- 3/10 (30%) had *negative* PSADT and PSAV
- 1/10 (10%) had biopsy-proven elimination of HGPIN
- 2/10 (20%) lost to follow-up
- 1/10 (10%) chose RP, no sign of spread at surgery
- 1/10 (10%) provided no follow-up data

Age, Race	Stage, Gleason	Cores Positive	tPSA post-RP
61, W	T2a, 4+3, 4+4	5/12	0.03
54, W	T1c, 3+3	1/6	0.03
68, AA	T1c, ?	6/6	0.06
63, W	T1c, 3+3	?	0.2
51, W	T2b, 5+4	?	0.47

Patient	Tx Duration	PSADT (yr)	PSAV (ng/ml/yr)
61, W	10 mon	negative	negative
54, W	4 mon	1.07	0.12
68, AA	3 mon	unknown	unknown
63, W	22 mon	0.75	3.17
51, W	10 mon	0.38	1.77

Immune Support

- Surprisingly little research (compared to other cancers) esp. w/ *Trametes versicolor* (clinical trials ongoing at Bastyr University right now)
- Lentinan (from *Lentinula edodes*) 2 mg IV q wk very helpful in advanced disease (Tari 1994)
- Mushrooms by themselves are clearly not sufficient (deVere White 2002; Sumiyoshi 2010), must be combined with other tx

Modified Citrus Pectin

- Anti-metastatic by blocking galectin receptors
- A reminder that metastasis is not random
- The only clinical study of this was a small one for prostate cancer
- Many preclinical studies
- Dose: 5 g qd-tid

Punica granatum Clinical Trials

- Initial trial: All patients post-RP or radiation therapy, tPSA<5, 8 oz Pom Wonderful per day, PSADT increased from 15 to 54 mo. No significant adverse effects (Pantuck 2006)

- Small randomized trial confirmed these results in men with low-grade cancer using 1 and 3 g extracts (Paller 2013)

Pomegranate Synergy?

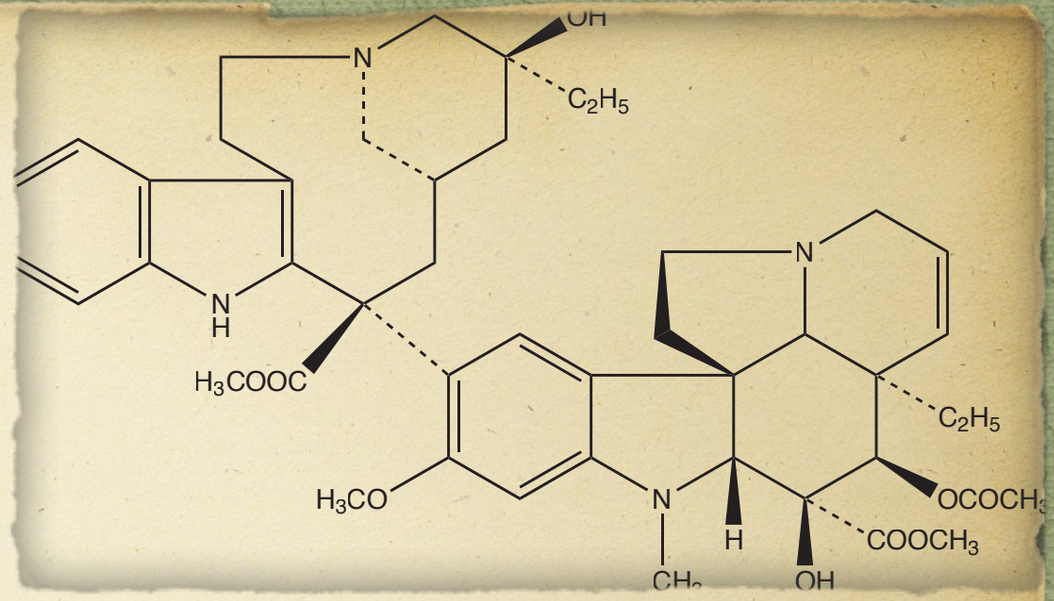
- Seed oil, pericarp, and fermented juice
- DU145 human pr ca cells tested in vitro
- All fractions synergistic
- Food/herbs are not reducible without losing something.
- Ref: Lansky 2005

Anticancer Herbs of Interest

Annona muricata	*Zizyphus spinosa*
Catharanthus roseus	*Cephalotaxus fortunei*
Mahonia aquifolium	*Dicentra formosa*
Phytolacca americana	*Trichosanthes kirilowii*
Rheum palmatum	

Annona muricata

Catharanthus roseus



vinblastine

Mahonia aquifolium

Phytolacca americana

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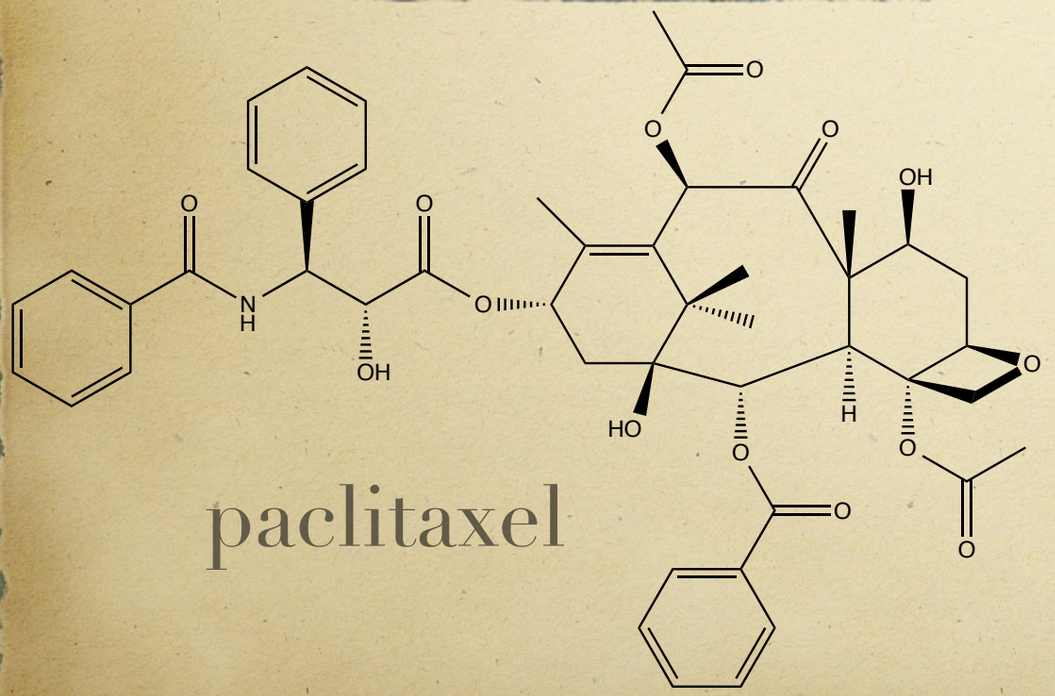
Rheum palmatum

Zizyphus jujube



paclitaxel

Taxus brevifolia

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Cephalotaxus harringtonii

Dicentra formosa

Trichosanthes kirilowii

References

Albertsen PC, Hanley JA, Fine J (2005) "20-year outcomes following conservative management of clinically localized prostate cancer" *JAMA* 293(17):2095-101.

Alibhai SM, Klotz LH (2004) "A systematic review of randomized trials in localized prostate cancer" Can J Urol 11(1):2110-7.

Andriole GL, Grubb RL III, Buys SS, et al. PLCO Project Team (2009) “Mortality results from a randomized prostate-cancer screening trial” *N Engl J Med* 360(13):1310-19.

Barba M, Yang L, Schünemann HJ, et al. (2009) “Urinary estrogen metabolites and prostate cancer: a case-control study and meta-analysis” *J Exp Clin Cancer Res* 28:135.

Berger TG, Dieckmann D, Efferth T, et al. (2005) "Artesunate in the treatment of metastatic uveal melanoma--first experiences" *Oncol Rep* 14(6):1599-603.

Bettuzzi S, Brausi M, Rizzi F, Castagnetti G, et al. (2006) "Chemoprevention of human prostate cancer by oral administration of green tea catechins in volunteers with high-grade prostate intraepithelial neoplassia: A preliminary report from a one-year proof-of-principle study" *Cancer Res* 66:1234-40.

Bill-Axelson A, Holmberg L, Ruutu M, et al. (2005) "Scandinavian Prostate Cancer Group Study No. 4. Radical prostatectomy versus watchful waiting in early prostate cancer" *N Engl J Med* 352:1977-84.

Boyd LK, Mao XY, Xue LY, et al. (2012) “High-resolution genome-wide copy-number analysis suggest a monoclonal origin of multifocal prostate cancer” *Genes Chromosomes Cancer* 51:579-89.

Brawer MK (1999) “Prostate-specific antigen: current status” *CA Cancer J Clin* 49:264–81.

Cuzick J, Fisher G, Kattan MW, et al. (2006) "Long-term outcome among men with conservatively treated localised prostate cancer" *Br J Cancer* 95(9):1186-94.
deVere White RW, Hackman RM, Soares SE, et al. (2002) "Effects of a mushroom mycelium extract on the treatment of prostate cancer" *Urology* 60(4):640-4.
deVere White RW, Hackman RM, Soares SE, et al. (2004) "Effects of a genistein-rich extract on PSA levels in men with a history of prostate cancer" *Urology* 63(2):259-63.
Dewell A, Weidner G, Sumner MD, et al. (2008) "A very-low-fat vegan diet increases intake of protective dietary factors and decreases intake of pathogenic dietary factors" *J Am Diet Assoc* 108:347-56.
Eggener SE, Scardino PT, Walsh PC, et al. (2011) "Predicting 15-year prostate cancer specific mortality after radical prostatectomy" *J Urol* 185:869–75.
Etminan M, Takkouche B, Caamaño-Isorna F (2004) "The role of tomato products and lycopene in the prevention of prostate cancer: a meta-analysis of observational studies" *Cancer Epidemiol Biomarkers Prev* 13(3):340-5.
Fleming C, Wasson JH, Albertsen PC, et al. (1993) "A decision analysis of alternative treatment strategies for clinically localized prostate cancer. Prostate Patient Outcomes Research Team" *JAMA* 269(20):2650-8.
Frattaroli J, Weidner G, Dnistrian AM, et al. (2008) "Clinical events in Prostate Cancer Lifestyle Trial: Results from two years of follow-up" *Urology* 72:1319-23.

Hamilton-Reeves JM, Rebello SA, Thomas W, et al. (2007) “Soy protein isolate increases urinary estrogens and the ratio of 2:16alpha-hydroxyestrone in men at high risk of prostate cancer” *J Nutr* 137(10):2258-63.
Hamilton-Reeves JM, Rebello SA, Thomas W, et al. (2008) "Effects of soy protein isolate consumption on prostate cancer biomarkers in men with HGPIN, ASAP, and low-grade prostate cancer" *Nutr Cancer* 60(1): 7-13.
Heath EI, Heilbrun LK, Li J, et al. (2010) “A phase I dose-escalation study of oral BR-DIM (BioResponse 3,3'- Diindolylmethane) in castrate-resistant, non-metastatic prostate cancer” *Am J Transl Res* 2(4):402-11.
Iversen P, Madsen PO, Corle DK (1995) "Radical prostatectomy versus expectant treatment for early carcinoma of the prostate. Twenty-three year follow-up of a prospective randomized study" *Scand J Urol Nephrol Suppl* 172:65-72.
Kaufman PB, Duke JA, Brielmann H, et al. (1997) "A comparative survey of leguminous plants as sources of the isoflavones, genistein and daidzein: Implications for human nutrition and health" *J Altern Complement Med* 3(1):7-12.
Kjellman A, Akre O, Norming U, et al. (2009) “15-Year follow up of a population based prostate cancer screening study” *J Urol* 181:1615 21.
Kong D, Heath E, Chen W, et al. (2012) "Loss of let-7 up-regulates EZH2 in prostate cancer consistent with the acquisition of cancer stem cell signatures that are attenuated by BR-DIM" *PLoS One* 7(3):e33729.
Kumar NB, Cantor A, Allen K, et al. (2009) "The specific role of isoflavones in reducing prostate cancer risk" *Prostate* 59:141-7.
Kurahashi N, Sasazuki S, Iwasaki M, et al. (2007) “Green tea consumption and prostate cancer risk in Japanese men: A prospective study” *Am J Epidemiol* 167(1):71-77.

Labrie F, Candas B, Cusan L, et al. (2004) “Screening decreases prostate cancer mortality: 11-year follow-up of the 1988 Quebec prospective randomized controlled trial” *Prostate* 59(3):311–18.
Lansky EP, Jiang W, Mo H, et al. (2005) "Possible synergistic prostate cancer suppression by anatomically discrete pomegranate fractions" *Invest New Drugs* 23(1):11-20.
Liu B, Mao Q, Cao M, Xie L (2012) “Cruciferous vegetables intake and risk of prostate cancer: A meta-analysis” *Int J Urol* 19(2):134-41.
Lu-Yao GL, Albertsen PC, Moore DF, et al. (2009) "Outcomes of localized prostate cancer following conservative management" *JAMA* 302(11):1202-9.
Markushin Y, Gaikwad N, Zhang H, et al. (2006) “Potential biomarker for early risk assessment of prostate cancer” *Prostate* 66(14):1565-71.
Matthies A, Clavel T, Gütschow M, et al. (2008) "Conversion of daidzein and genistein by an anaerobic bacterium newly isolated from the mouse intestine" *Appl Environ Microbiol* 74(15):4847-52.
Matthies A, Loh G, Blaut M, Braune A (2012) "Daidzein and genistein are converted to equol and 5-hydroxy-equol by human intestinal *Slackia isoflavoniconvertens* in gnotobiotic rats" *J Nutr* 142(1):40-6.
Messina M, Kucuk O, Lampe JW (2006) “An overview of the health effects of isoflavones with an emphasis on prostate cancer risk and prostate-specific antigen levels” *J AOAC Int* 89(4):1121-34.
Muti P, Westerlind K, Wu T, et al. (2002) “Urinary estrogen metabolites and prostate cancer: A case-control study in the United States” *Cancer Causes Control* 13(10):947-55.

Nguyen JY, Major JM, Knott CJ, et al. (2006) "Adoption of a plant-based diet by patients with recurrent prostate cancer" *Integr Cancer Ther* 5(3):214-23.
Ornish D, Weidner G, Fair WR, et al. (2005) "Intensive lifestyle changes may affect the progression of prostate cancer" *J Urol* 174:1065-70.
Ornish D, Magbanua MJM, Weidner G, et al. (2008) "Changes in prostate gene expression in men undergoing an intensive nutrition and lifestyle intervention" *Proc Natl Acad Sci USA* 105(24):8369-74.
Paller CJ, Ye X, Wozniak PJ, et al. (2013) "A randomized phase II study of pomegranate extract for men with rising PSA following initial therapy for localized prostate cancer" *Prostate Cancer Prostatic Dis* 16(1): 50-5.
Pantuck AJ, Leppert JT, Zomorodian N, et al. (2006) "Phase II study of pomegranate juice for men with rising prostate-specific antigen following surgery or radiation for prostate cancer" *Clin Cancer Res*12(13): 4018-26.

Sandblom G, Varenhorst E, Lofman O, et al. (2004) “Clinical consequences of screening for prostate cancer: 15 years follow-up of a randomised controlled trial in Sweden” *Eur Urol* 46:717–24.
Schröder FH, Hugosson J, Roobol MJ, et al. (2009) “Screening and prostate-cancer mortality in a randomized European study” *N Engl J Med* 360:1320-8.
Simonsson USH, Jansson B, Hai TN, et al. (2003) “Artemisinin autoinduction is caused by involvement of cytochrome P450 2B6 but not 2C9” *Clin Pharmacol Ther* 74(1):32-43.
Singh NP, Panwar VK (2006) "Case report of a pituitary macroadenoma treated with artemether" *Integr Cancer Ther* 5(4):391-4.
Sumiyoshi Y, Hashine K, Kakehi Y, et al. (2010) "Dietary administration of mushroom mycelium extracts in patients with early stage prostate cancers managed expectantly: A phase II study" *Jpn J Clin Oncol* 40(10): 967-72.
Svensson US, Ashton M (1999) "Identification of the human cytochrome P450 enzymes involved in the in vitro metabolism of artemisinin" *Br J Clin Pharmacol* 48(4):528-35.
Tari K, Satake I, Nakagomi K, et al. (1994) "Effect of lentinan for advanced prostate carcinoma" *Acta Urol Japon* 40:119-23 [in Japanese].
Teas J, Cunningham JE, Fowke JH, et al. (2005) “Urinary estrogen metabolites, prostate specific antigen, and body mass index among African-American men in South Carolina” *Cancer Detect Prev* 29(6):494-500.
Travis RC, Spencer EA, Allen NE, et al. (2009) "Plasma phyto-oestrogens and prostate cancer in the European Prospective Investigation into Cancer and Nutrition" *Br J Cancer* 100(11):1817-23.
Zheng J, Yang B, Huang T, et al. (2011) “Green tea and black tea consumption and prostate cancer risk: An exploratory meta-analysis of observational studies” *Nutr Cancer* 63(5):663-72.

Glossary

ADT = androgen deprivation therapy
cdTRUSP = color Doppler transrectal ultrasound of the prostate
CRP = C-reactive protein
CTC = circulating tumor cells
DRE = digital rectal exam
E1 = estrone; E2 = estradiol
eMRS = endorectal magnetic resonance spectroscopy
fPSA = free PSA
GnRH = gonadotropin-releasing hormone
HGPIN = high-grade prostatic intraepithelial neoplasia
HIFU = high-intensity focused ultrasound
IGF-1 = insulin-like growth factor-1
NNS = number needed to screen
NNT = number needed to treat
NPV = negative predictive value
PAP = prostatic acid phosphatase
PPV = positive predictive value
PSA = prostate-specific antigen
PSADT = PSA doubling time
PSAV = PSA velocity
RP = radical prostatectomy
T1C = stage T1C of prostate cancer (PSA detected only cancer)
tPSA = total PSA
TRUSP = transrectal ultrasound of the prostate
UTI = urinary tract infection
WW = watchful waiting