Prenatal Vitamin D: a risk factor for chronic disease?

Robyn M Lucas MBChB PhD FAFPHM
National Centre for Epidemiology and Population Health, The Australian National University, Canberra, Australia

Background: Vitamin D status is implicated in a variety of chronic diseases – multiple sclerosis, type 1 and 2 diabetes, various cancers, osteoporosis, psychiatric illness and cardiovascular diseases. Most work has focused on current or immediately antecedent vitamin D status or latitude of residence (thought to be a proxy for vitamin D levels). Here we review evidence of the importance of prenatal vitamin D to chronic disease susceptibility.

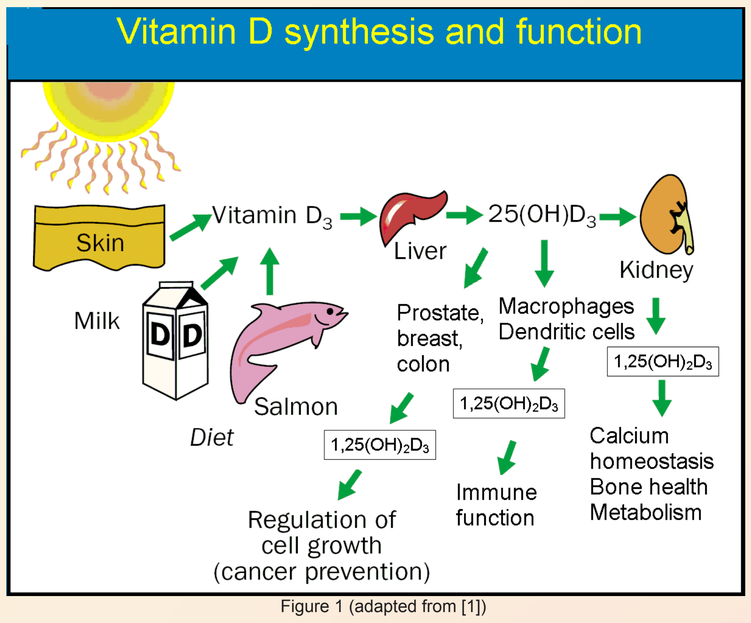

Figure 1 (adapted from [1])

Vitamin D [1]

Synthesis:
- >90% derives from UVB (290-315nm) irradiation of skin
- Only a small contribution from diet (variable by geographic location)
- Precursor metabolized in the liver to 25(OH)D
- Metabolized in kidney and other target tissues, to the active 1,25(OH)2D3.

Control:
Continued sunlight exposure converts pre-vitamin D and vitamin D3 into biologically inert photoproducts; 1,25(OH)2D3 induces its own destruction by enhancing the expression of hydroxylases.

Factors altering cutaneous production of vitamin D3:
- Age: decreased efficiency in old age
- Darker skin pigmentation requires longer exposure to make equivalent amount of vitamin D3
- UVB-absorbing sunscreens decrease vitamin D production
- Obesity decreases efficiency of vitamin D production
- Time of day, season and latitude alter the number of ambient UVB photons and therefore vitamin D production in the skin.

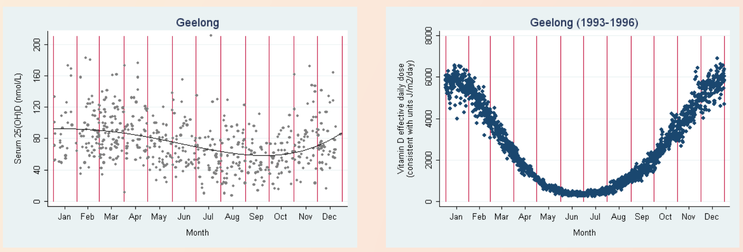

Figure 2 [2]. Seasonal variation in actual serum 25(OH)D (dots) and predicted serum 25(OH)D (solid line) (left), and simulated vitamin D effective daily dose (right) in the Geelong region, Victoria, Australia

Physiologic effects of vitamin D:
- Acts via a nuclear vitamin D receptor (VDR)
- Maintain serum calcium concentration by increasing intestinal calcium absorption. When there is insufficient calcium intake, vitamin D bone effects enhance mobilization of calcium from the skeleton to maintain calcium levels (severe deficiency results in rickets in children, and osteomalacia in adults and contributes to the development of osteoporosis).
- Induces cell cycle arrest, promotes differentiation, induces apoptosis; inhibits tumor invasion and angiogenesis
- VDR present in small intestine, colon, osteoblasts, activated T and B lymphocytes, beta-islet cells, most organs (brain, heart, skin, gonads, prostate, breast) and mononuclear cells.
- Stimulates insulin production, promotes TSH secretion and has effects on myocardial contractility
- Inhibits Th-1 type immune function in adult (memory) cells; induces a Th-1 to Th-2 shift
- In cord blood (naïve) T cells, inhibits both Th-1 and Th-2 differentiation
- Induces T regulatory cells
- Enhances phagocytosis by white blood cells

Genetics:

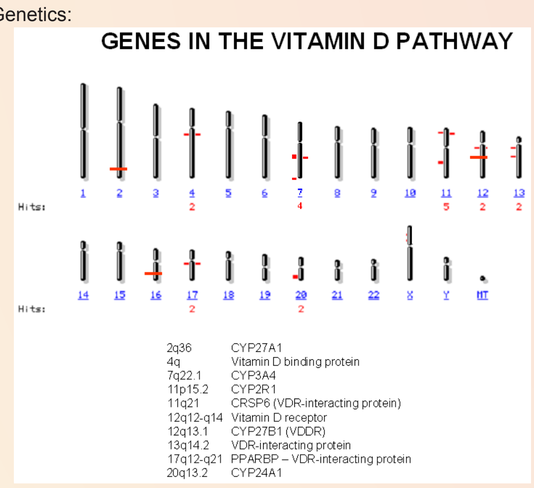

Figure 3. Genes in the vitamin D pathway

Vitamin D status (measured as serum levels of 25(OH)D, nmol/L):

	Current (variable)	Proposed
Vitamin D sufficiency:	>50	>80
Vitamin D insufficiency:	25-50	50-80
Vitamin D deficiency:	<25	<50

Recommended daily intake (1ug=40IU):

Table 1: Adequate Intake for vitamin D for infants, children, and adults[5]

Age	Current	Tolerable upper intake
0-12 months	200 IU	1,000 IU
1 to 13 years	200 IU	2,000 IU
14 to 18 years	200 IU	2,000 IU
19 to 50 years	200 IU	2,000 IU
51 to 70 years	400 IU	2,000 IU
71+ years	600 IU	2,000 IU

Proposed: 400IU/day in infants; possibly >2000IU/day in adults

Pregnancy:
- Significant changes occur in maternal calcium metabolism during pregnancy to ensure the availability of extra calcium required for fetal skeletal growth.
- Vitamin D requirements are increased 4-5 fold. Serum 25(OH)D concentrations may decrease during pregnancy, with the greatest decline in the third trimester; but serum 1,25(OH)2D3 concentrations increase 50-100% over the non-pregnant state during the second trimester and by 100% during the third trimester[6]. Placenta contains 1-alpha hydroxylase to convert 25(OH)D to 1,25(OH)2D3.

General effects of prenatal vitamin D on health

Experimental studies:
- In rats, maternal dietary vitamin D depletion results in reduced fetal growth.[7]
- Perinatal administration may permanently decrease receptor density of other steroid hormones, resulting in changes in sexual behaviour in male rats. [8]

Observational studies:
- Vitamin D deficiency common during pregnancy, particularly in dark-skinned and/or veiled women.[9]
- Significant direct correlation between maternal vitamin D intake and maternal weight gain during pregnancy [10]
- Low maternal vitamin D status or intake may be associated with:
  - Lower birthweight: each additional microgram (40IU) of vitamin D intake (diet + supplements) was associated with an 11g (95%CI 1.2-20.7) increase in birth weight.[11]
  - Shorter gestation (by 0.7 week; 95% CI -1.3, -0.1) [12]
  - Shorter knee-heel length (4.3mm smaller; 95% CI -7.3, -1.3) [12]
  - Reduced mineral accretion
  - Neonatal hypocalcemia
  - Decreased postnatal linear growth and weight gain

Conclusion: Vitamin D deficiency could be an additional factor in the etiology of the small baby syndrome, defining the "Thrifty phenotype" hypothesis.

Effects on later bone health

Patterns of occurrence:
- Winter season of birth associated with lower bone mineral content (BMC) in newborns cf summer birth.[14]

Observational studies:
- Children born to mothers with low vitamin D levels or low UVB exposure in late pregnancy had significantly lower whole body BMC at age 9 years.[14] [16]
- Indian mothers with suboptimal vitamin D status have offspring with reduced intrauterine and postnatal skeletal development; supplementation of pregnant mothers with vitamin D is associated with increased skeletal growth and/or bone mass/density in the offspring.[15]

Genetic studies:

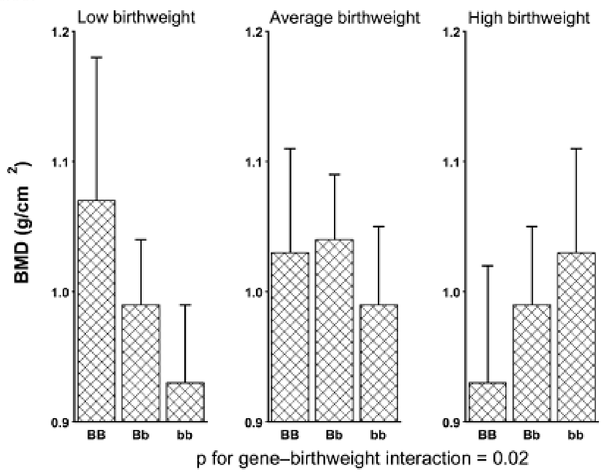

Figure 4. Relation between vitamin D receptor genotype (BB, Bb, bb). Birthweight and lumbar spine BMD [14]

- Individuals with the VDR BB genotype had lower bone density than those with the bb genotype (meta-analysis).
- Statistically significant interaction between VDR genotype and birthweight as determinants of bone mineral density (BMD) in 165 men and 126 women aged 61-73 years [17]:
  - bb genotype and low birthweight – tend to have low bone density; bb and higher birthweight - tend to have high bone density (see Figure 4)
  - These trends were little affected by adjustment for adult weight, ie the environmental effect modification occurs during intrauterine rather than postnatal, life.

Biological mechanisms:
- Fetal bone growth is mainly during the last trimester relies on increased placental calcium transport capacity which is partly controlled by vitamin D levels.[14]

Conclusion: There is potential for low vitamin D levels in late pregnancy to have long-lasting effects on bone architecture.

Asthma: vitamin D as protective

Observational studies:
- Two studies show that low maternal vitamin D intake during pregnancy (32 weeks) is associated with increased wheezing symptoms in children at age 5y: Ever wheeze (highest vs lowest quintiles of median energy-adjusted vitamin D intake IU/day): adjOR = 0.48 (95% CI 0.25, 0.91), p for trend = 0.01. Lower maternal vitamin D intake during pregnancy associated with decreased bronchodilator responsiveness (p = 0.04).[41]
- 100IU increase in intake associated with lower risk of wheeze of OR+0.81 (0.74, 0.89) regardless of whether the intake was from diet or supplements. Strongest protective effect was seen when the LMP was in winter – multivariate OR per 100IU/day increase was 0.62 (0.47, 0.83) for LMP in winter compared with 0.85(0.75,0.97) in other seasons [41]

Genetic studies:
- Inconsistent findings of associations between polymorphisms in the VDR gene and asthma and allergy[42].
- VDR maps to chromosome 12q near a region commonly linked to asthma, but VDR probably influences asthma and allergy in a complex manner[43]

Asthma: Vitamin D as a risk factor

Patterns of occurrence:
- Rise in allergic diseases over time is paralleled by use of vitamin D supplementation[44], ie vitamin D in early life may increase risk of allergic diseases.
- Increasing asthma prevalence with decreasing latitude[45-47]

Observational studies:
- In a birth cohort, vitamin D supplementation in the first year of life (>2000IU/day) **increased** the risk of asthma and atopy (at least one positive skin prick test) at age 31 y.[48] Regular supplementation during the first year vs other: adjOR = 1.33, (95%CI 1.07-1.64), p = 0.01 for atopy; adjOR=1.33, (1.12-1.58), p=0.001 for allergic rhinitis; OR 1.33, (0.97-1.82), p=0.08 for asthma.

Biological mechanisms:
- 1,25(OH)2D3 may induce a Th-1 to Th2 (allergic) phenotype shift.

Conclusion: Vitamin D late in gestation increases surfactant synthesis and assists in lung maturation [40]. While low maternal vitamin D levels may increase the risk of allergy and asthma in offspring, vitamin D supplementation in infancy may be associated with increased risk. Timing of exposure may be of critical importance.

Type 1 diabetes

Patterns of occurrence:
- Some conflicting results, but generally increased risk with winter-spring season of birth; decreased risk with summer-fall season of birth
- Negative latitudinal gradient in incidence which correlates most strongly with winter ambient UVR and in the youngest age group (Lucas, unpublished)

Experimental studies:
- No protective effect of vitamin D intake prenatally or in infancy in the NOD mouse.[33]

Observational studies:
- 63% decreased risk of islet cell antibodies in offspring with a SD increase in recalled maternal dietary vitamin D intake during pregnancy (vitamin D SD = 155.6IU).[34]
- Recalled maternal use of cod liver oil (a potent source of vitamin D) during pregnancy associated with decreased risk of type 1 diabetes in offspring (adjOR = 0.36, 95% CI 0.14-0.90).[35]
- Vitamin D supplementation in the first year of life associated with decreased frequency of type 1 diabetes (adjRR for regular vs no supplementation 0.12, 95% CI 0.03-0.51) [36]
- In a multi-centre case-control study vitamin D supplementation in early life was associated with a decreased risk of type I diabetes (adjOR=0.67 (95% CI 0.53-0.86)[37]

A risk factor for MS, schizophrenia, brain tumours or epilepsy?

Vitamin D is involved in normal brain development: [18]
- Genes encoding enzymes involved in vitamin D metabolism are expressed in brain cells, eg 25 hydroxylase, 1,25 hydroxylase and 24 hydroxylase [19]
- Vitamin D3 involved in the biosynthesis of neurotrophic factors and neurotransmitters
- VDR present in the neuroepithelium during early neurogenesis and, at later stages, in the subventricular zone (one of the major CNS areas able to maintain neural stem cell generation throughout life)
- The VDR gene is specifically expressed within developing neurons of rodent dorsal root ganglia, suggesting a role for vitamin D in peripheral nervous system development.

Vitamin D deficiency prenatally (in rats) is associated with: [20-22]
- Heavier and longer brain at birth which normalises by adulthood, if vitamin D levels are restored
- Enlarged lateral ventricles at birth; persistent in adulthood
- Decreased cortical thickness at birth
- Increased cell proliferation, increased mitosis and impaired apoptosis. [23]
- Decreased expression of NGF, GDNF and low affinity neurotrophin receptor ($p75^{NTR}$) (persists in adulthood)
- Dysregulation of a number of brain proteins involved in oxidative phosphorylation, redox balance, cytoskeleton maintenance, calcium homeostasis, chaperoning, post-translational modifications, synaptic plasticity and neurotransmission (persistent in adulthood).
- May be a critical window during late gestation where hypovitaminosis D is sufficient to precipitate an altered adult behavioural phenotype.[24]

Schizophrenia

Patterns of occurrence:
- 5-8% winter-spring excess of births [25]
- Increased incidence of schizophrenia in dark-skinned migrants to NW Europe
- Higher incidence of schizophrenia in urban than in rural births
- Significant association between schizophrenia incidence in males and a low duration of sunshine in the months immediately before and after birth as a result of the El Nino.

Experimental studies:
- In rats, offspring of vitamin D deficient mothers had significant impairment of latent inhibition (ability to ignore irrelevant stimuli), a feature often associated with schizophrenia. Offspring of mothers transiently depleted showed subtle and discrete alterations in learning and memory.[26]

Observational studies:
- Regular or irregular vitamin D supplementation during the first year of life is associated with reduced risk of schizophrenia in males RR=0.08, 95% CI 0.01, 0.95; RR=0.12, 0.02-0.90 respectively but not females.

Brain tumours and epilepsy

Patterns of occurrence:
- Excess winter births in children with astrocytomas and ependymomas.[27] (may reflect increased cellular proliferation found in the developing brains of embryos exposed to low prenatal vitamin D or by alteration of epigenetic programs established during early brain development).
- Excess winter births (Jan-Feb) in adult glioma patients; trough in Jul-Aug. Consistent with importance of a seasonally varying exposure during the pre- or postnatal period.[28]
- Excess of winter births (Dec-Mar) in adults with epilepsy; trough in Sept.

Multiple Sclerosis (MS)

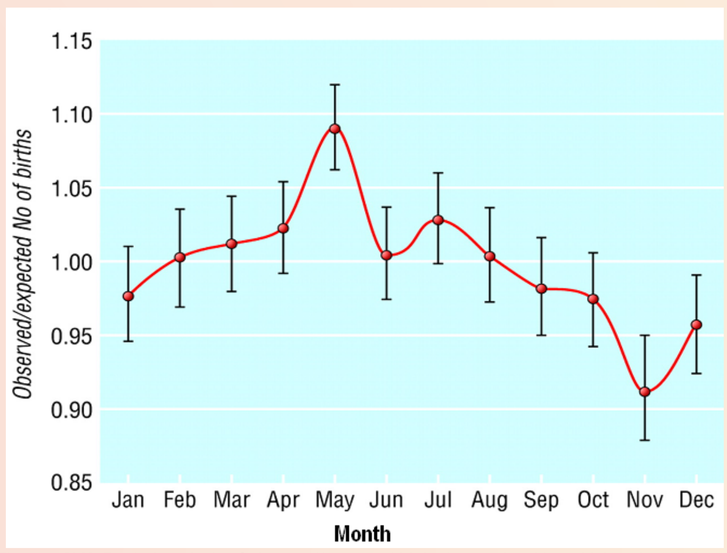

Figure 5 [29]. Pooled analysis of observed/expected births in people with multiple sclerosis in Canadian, British, Danish, and Swedish studies (n = 42045 with 95% confidence intervals).

Patterns of occurrence:
- Excess May births (9.1%) in northern hemispheres MS patients; trough in Nov (8.5%) compared to population controls (see Figure 5). Implicates factors operating during gestation or shortly after birth in later onset of MS.[29]
- Maternal parent-of-origin effect in multiple sclerosis susceptibility implicates factors acting prenatally: age-adjusted full-sibling risk for MS = 3.11%. Risk for half-siblings =1.89% (significantly lower, p=0.006); risk for maternal half-siblings = 2.35%; paternal half-siblings= 1.31% for paternal half-siblings (p=0.048).[30]
- Also latitudinal gradients in MS prevalence and incidence and observational evidence that vitamin D[31] or early life UVR exposure[32] are protective for the development of MS.

Conclusion: Normal brain development requires precise spatial and temporal regulation of both cellular proliferation and elimination.[23]. There is mounting evidence that vitamin D deficiency prenatally could lay the foundation for a range of adult nervous system disorders – in conjunction with genetic susceptibility and additional specific postnatal exposures, eg infection, substance abuse, stress.

A risk factor for later cardiovascular disease?

Low prenatal vitamin D:
- Considerable evidence linking low levels of vitamin D during adulthood with hypertension, the metabolic syndrome, obesity and heart disease
- Neonatal rats whose mothers had low 25(OH)D levels during pregnancy had significantly lower heart weights (143 v174g), decreased citrate synthase and 3-hydroxyacyl CoA dehydrogenase activity and 15% lower myofibrillar protein content, ie there was a general slowing of neonatal cardiac development.[49]

Excessive prenatal vitamin D:
- Abnormal large vessel calcification and supravalvular aortic stenosis reported with infantile hypercalcemia in UK in 1960s due to the concurrent use of multiple foodstuffs containing vitamin D, eg cod-liver oil and supplemented milk powders.[50]
- In rats, high dose vitamin D during gestation and early development resulted in adverse changes in elastin content and organisation in the aorta consistent with increased later risk of hypertension or aneurysm.[51]
- Piglets of sows fed vitamin D (mean blood level=75nmol/L) developed coronary lesions 6 weeks after birth

Conclusion: low prenatal vitamin D may have significant adverse effects on cardiac development; high prenatal vitamin D levels may have adverse effects on the vascular system.

Effects on prostate gland development

- In rats, higher levels of prenatal dietary vitamin D3 associated with increased prostatic weight in prepubertal (35% (p<0.007)) and adult (68%(p<0.005)) rats, and histologically more differentiated and mature prostatic architecture.[52]
- Mounting evidence that higher vitamin D levels in adult life may be protective for the development of prostate cancer, ie there may be both prenatal and ongoing effects on prostate gland differentiation related to vitamin D levels.

Risk of Crohn's disease

- Possibly lower risk if born in summer (OR=0.64, 95%CI 0.44-0.91)[38]
- Linkage between VDR polymorphism and risk of developing Crohn's disease [39](significantly more homozygotes for the *TaqI* polymorphism (genotype "*tt*") among patients with Crohn's disease than patients with ulcerative colitis or controls (OR=1.99, 95% CI 1.14-3.47)
- Biologically plausible through effects on immune regulation and self-tolerance

Implications: Maternal vitamin D supplementation could be an important public health measure to decrease risk for a range of chronic diseases. However, there is sufficient evidence that high vitamin D levels may also increase disease risk that further research is required, using innovative study methods to limit recall error of an exposure that has occurred many years before disease onset.

References

1. Am J Clin Nutr, 2004. **80**(6 Suppl):1678S-88S.
2. Environmental Health Perspectives, 2007. epub ahead of print.
3. Pediatr Res, 2002. **52**(1):12-8.
4. Trends Biochem Sci, 2004. **29**(12):664-73.
5. Institute of Medicine, *Dietary Reference Intakes*. 1999
6. Am J Clin Nutr, 1998. **67**(4):693-701.
7. Br J Nutr, 1998. **79**(4):315-27.
8. Horm Res, 1999. **51**(6):280-3.
9. Am J Clin Nutr, 2006. **84**(2):350-3.
10. BMC Pregnancy Childbirth, 2007. **7**:1.
11. Cmaj, 2006. **174**(9):1273-7.
12. J Clin Endocrinol Metab, 2006. **91**(3):906-12.
13. Am J Clin Nutr, 2004. **80**(6 Suppl):1748S-51S.
14. J Nutr, 2005. **135**(11):2728S-34S.
15. J Clin Endocrinol Metab, 2006. **91**(8):2994-3001.
16. Lancet, 2006. **367**(9504):36-43.
17. Paediatr Perinat Epidemiol, 2001. **15**(3):211-9.
18. Trends Endocrinol Metab, 2002. **13**(3):100-5.
19. Proteomics, 2007. **7**(5):769-80.
20. Neuroscience 2003. **118**:641-653.
21. Int Rev Neurobiol, 2004. **59**:351-80.
22. J Steroid Biochem Mol Biol, 2004. **89-90**(1-5):557-60.
23. Brain Res Dev Brain Res, 2004. **153**(1):61-8.
24. Psychoneuroendocrinology, 2007. **32**(3):227-34.
25. Schizophr Res, 1997. **28**(1):1-38.
26. Behav Brain Res, 2005. **161**(2):306-12.
27. Neurology, 2005. **64**(7):1317.
28. Neurology, 2004. **63**(2):276-81.
29. Bmj, 2005. **330**(7483):120.
30. Lancet, 2004. **363**(9423):1773-4.
31. Neurology, 2004. **62**(1):60-5.
32. Bmj, 2003. **327**(7410):316.
33. Horm Metab Res, 2004. **36**(9):620-4.
34. Diabetes Care, 2003. **26**(12):3237-42.
35. Diabetologia, 2000. **43**(9):1093-8.
36. Lancet, 2001. **358**(9292):1500-3.
37. Diabetologia, 1999. **42**(1):51-4.
38. Inflamm Bowel Dis, 2005. **11**(6):597-9.
39. Gut, 2000. **47**(2): p. 211-4.
40. J Steroid Biochem Mol Biol, 2004. **89-90**(1-5):93-7.
41. Am J Clin Nutr, 2007. **85**(3): p. 788-95; 853-9.
42. Am J Respir Crit Care Med, 2004. **170**(9):967-73.
43. Am J Respir Crit Care Med, 2004. **170**(10):1057-65.
44. Allergy, 1999. **54**(7):757-9.
45. Environ Health Perspect, 2003. **111**(4):518-23.
46. Allergy, 2004. **59**(3):306-14.
47. J Pediatr (Rio J), 2006. **82**(5):341-6.
48. Ann N Y Acad Sci, 2004. **1037**:84-95.
49. J Mol Cell Cardiol, 1995. **27**(6):1245-50.
50. Cardiovasc Res, 2003. **57**(1):284.
51. Cardiovasc Res, 2002. **55**(2):369-74.
52. Prostate, 1999. **41**(3):181-9.