"Double-dose vitamin D lowers cancer risk in women over 55" *J Fam Pract* 2007; 56:907–910.	
PURLs review form	
Randomized Controlled Trials	
SECTION 1: IDENTIFYING INFORMATION	
1.1 Citation	Lappe JM, Travers-Gustafson D, Davies KM et al. Vitamin D supplementation reduces cancer risk: results of a randomized trial. *Am J Clin Nutr* 2007; 85:1586–1591
1.2 PubMed ID	17556697
1.3 Reviewer name	Sarah-Anne Schumann MD
1.4 Reviewer affiliation	Department of Family Medicine, University of Chicago
1.5 Date review assigned	n/a
SECTION 2: DETAILED STUDY DESCRIPTION	
2.1 Number of patients starting each arm of the study?	Participants were randomly assigned to 3 groups: placebo (calcium placebo plus vitamin D placebo, n=266), calcium only (calcium [1400 mg calcium citrate or 1500 mg calcium carbonate] plus vitamin D placebo, n=416) and calcium + D (1000 IU [25 mcg] vitamin D plus calcium [as above], n=403)
2.2 Main characteristics of study patients? (Inclusions, exclusions, demographics, settings, etc.)	Rural Nebraska. 1180 women were enrolled. All were older than age 55, with no known cancer, and adequate mental and physical health to allow an expected 4 years of participation in the trial
2.3 Intervention(s) (treatment, procedure, drug, other therapy, policy, etc.) being investigated?	See 2.1
2.4 Comparisons of treatment(s), placebo, usual care and/or no treatment?	Placebo, calcium, calcium/vitamin D
2.5 Length of follow-up? (Note specified endpoints, eg, death, cure, pain relief, etc.)	4 years
2.6 What outcome measures are used? List all measures used to assess effectiveness	The study's primary outcomes were related to skeletal status and calcium economy. Cancer incidence was one of the secondary outcomes
2.7 What is the effect of the intervention(s)? (Include absolute risk, relative risk, NNT, CI, *P*-values, etc.)	Fifty women developed non-skin cancer during the study; 13 in the first year, and 37 during the second to fourth years. Excluding cancer diagnosed in the first year (based on the assumption that these cancers were already present, though undiagnosed at entry into the study), the relative risk

	reduction (RRR) for the Ca+D group was 0.232 (confidence interval [CI], 0.09–0.60; *P*<.005), and the RRR for the Ca-only group was 0.587 (CI, 0.29–1.21; *P*=0.147) compared with the placebo group. Number needed to treat (NNT) to prevent 1 case of cancer for the Ca+D group is 21, with an absolute risk reduction of 0.048, or approximately 5%. Using baseline 25(OH)D concentration as the predictor variable and cancer as the outcome variable in logistic regression, the researchers predicted a 35% reduced risk of cancer for every 25 nmol/L (10 ng/mL) increase in serum 25(OH)D
SECTION 3: INTERNAL VALIDITY	
3.1 Study addresses an appropriate and clearly focused question	Well addressed
3.2 Random allocation to comparison groups	Well addressed
3.3 Concealed allocation to comparison groups	Well addressed
3.4 Subjects and investigators kept "blind" to comparison group allocation status?	Well addressed
3.5 Comparison groups are similar at the start of the trial	Well addressed
3.6 Were there any differences between the groups/arms of the study besides the intervention(s) under investigation? If yes, please indicate whether the differences are a potential source of bias	Well addressed
3.7 Were all relevant outcomes measured in a standardized, valid, and reliable way?	Well addressed
3.8 Are patient oriented outcomes included? If yes, what are they?	Yes, cancer incidence
3.9 What percent dropped out and were lost to follow-up? Could this percentage bias the results? How?	86% of the participants completed the 4-year study. Every 6 months, the compliance was assessed by bottle weight. Mean adherence (taking ≥80% of assigned doses) was 85.7% for vitamin D and 74.4% for calcium. Serum samples were analyzed for 25(OH)D at baseline and then on a yearly basis
3.10 Was there intention-to-treat analysis? If not, could this bias the results? How?	Yes
3.11 If a multi-site study, are results	n/a

comparable for all sites?	
3.12 Is the funding for the trial a potential source of bias? If yes, what measures, if any, were taken to insure scientific integrity?	No
SECTION 4: EXTERNAL VALIDITY	
4.1 To which patients might the findings apply? Include patients in the study and other patients to whom the findings may be generalized	This study was for postmenopausal women, but given the other evidence from numerous other studies, can apply to all adults
4.2 In what care settings might the findings apply, or not apply?	Primary care and specialty care
4.3 To which clinicians or policy makers might the findings be relevant?	All clinicians, also policy-makers who recommend RDA of vitamins, as this dose is higher than current recommendations
SECTION 5: REVIEW OF SECONDARY LITERATURE	
5.1 DynaMed excerpts	There is limited evidence that vitamin D supplementation decreases the risk of some types of cancer and may decrease all-cause mortality
5.2 DynaMed citation/access date	Becker KL. Vitamin D intake and supplementation. Dynamed [database online]. Updated June 28, 2007. Available at: www.dynamicmedical.com. Accessed on 7/5/07
5.3 UpToDate excerpts	Recommends that patients with osteoporosis take 700-800 IU vitamin D daily; no mention of decreased cancer risk
5.4 UpToDate citation/access date	Rosen, HN. Vitamin D therapy in osteoporosis. UpToDate [database online]. Updated February 21, 2007. Available at www.uptodate.com. Accessed on 7/11/07
5.5 PEPID PCP excerpts	Vitamin D indications: hypocalcemia, hypoparathyroidism, rickets, osteomalacia
5.6 PEPID citation/access data	Vitamin D. PepidPCP [database online]. Available at www.pepidonline.com. Accessed August 6, 2007
5.7 Recommendations for PEPID PCP	**Possible relevant topics:** Postmenopausal women Well woman care Health maintenance Cancer prevention Indications for vitamins Vitamin D **Recommended addition:** "Vitamin D supplementation of 1000 IU daily prevents all-cause cancer in post-menopausal women."

5.8 Other excerpts (USPSTF recommendations; other guidelines; etc.)	The US Preventive Services Task Force (USPSTF) concludes that the evidence is insufficient to recommend for or against the use of supplements of vitamins A, C, or E; multivitamins with folic acid; or antioxidant combinations for the prevention of cancer or cardiovascular disease
5.9 Citations for other excerpts	US Preventive Services Task Force. *Routine Vitamin Supplementation to Prevent Cancer and Cardiovascular Disease: Recommendations and Rationale*. June 2003. Agency for Healthcare Research and Quality, Rockville, MD. Available at: www.ahrq.gov/clinic/3rduspstf/vitamins/vitaminsrr.htm. Accessed October 23, 2007
SECTION 6: CONCLUSIONS	
6.1 How well does the study minimize sources of internal bias and maximize internal validity? (Give one number on a scale of 1 to 7; 1=extremely well, 4 = neutral, 7 = extremely poorly)	**2**
6.2 If 6.1 was coded as 4 or below, please describe the potential bias and how it could affect the study results. Specifically, what is the likely direction in which potential sources of internal bias might affect the study results?	
6.3 Are the results of this study relevant to the health care needs of patients cared for by "full scope" family physicians, general internists, general pediatricians, and/or general obstetricians/gynecologists without significant changes in programs or policies such as the organization or financing of practice? (Give one number on a scale of 1 to 7; 1 = absolutely relevant, 4 = neutral, 7 = not at all relevant)	**2** The primary challenge is likely to be that posed by the competing demands and limited resources inherent in delivering all preventive health services in the primary care setting
6.4 Please explain your reasoning for your response to item 6.3 regarding the relevance to the health care of patients cared for by generalist physicians?	Easy to recommend a vitamin supplement (time constraint is main issue) and relevant to postmenopausal women and perhaps to all adults
6.5 What is the main recommendation for change in practice (if any)? Include a description of the change in practice,	This randomized trial provides strong evidence that we should recommend doubling the currently recommended daily amount (increase from 400–600 IU up to 1000 IU) of vitamin D_3 daily to lower future risk of cancer in women older than age 55 who do not get adequate vitamin D from sun

the indications, and the target population	exposure or diet
SECTION 7: EDITORIAL DECISION	
7.1 FPIN PURLs editorial decision	PURL
7.2 Editor	Bernard Ewigman, MD, MSPH, Department of Family Medicine, The University of Chicago
7.3 Date of decision	
7.4 Brief summary of decision	Although this was a secondary outcome, relative risk reduction (RRR) for the Ca+D group was 0.232 (CI, 0.09–0.60, *P*<.005), and therefore highly unlikely to be a chance finding. 1000 IU is twice the usual dose of Vitamin D and twice the dose used in the prior RCT that showed no decrease in cancer. The findings are consistent with prior epidemiological studies and make sense pathophysiologically. Finally, the risk of any adverse effects from this dose of Vitamin D is very low. Of course, in climates where there is adequate sun exposure, this is not an issue. But in climates in which sun exposure is limited, this is a practice changer