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Vitamin D and calcium intake in relation to risk of endometrial cancer: a systematic review of the literature

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Abstract

Objective—In response to a recent ecologic study of UV exposure and endometrial cancer incidence, we present the epidemiologic evidence on the relation between intake of vitamin D and its metabolically related nutrient, calcium, and the occurrence of endometrial cancer.

Methods—We conducted a systematic literature review and meta-analysis of vitamin D and calcium in relation to endometrial cancer, including peer-reviewed manuscripts published up to May 2007. Random and fixed effects summary estimates were computed.

Results—Pooled analyses of the three case-control studies of dietary vitamin D and endometrial cancer uncovered heterogeneous results that were not significant in random or fixed effects analyses. Cut-points for the highest vitamin D intakes ranged from >244 to >476 IU/day. Qualitatively similar findings were observed for dietary calcium. Only two studies provided estimates for calcium supplements (random effects OR=0.62, 95% CI 0.39–0.99; fixed effects OR=0.62, 95% CI 0.42–0.93, for top vs bottom category, *p* for heterogeneity=0.25).

Conclusions—The limited epidemiological evidence suggests no relation between endometrial cancer in the ranges of dietary vitamin D examined, and suggests a possible inverse association for calcium from supplements. Prospective studies, ideally including plasma 25(OH) D to estimate vitamin D input from diet and sun exposure, are needed to further explore these hypotheses.

Keywords

endometrial neoplasms; calcium; dietary; vitamin D; diet; dietary supplements

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Precís (25 words) In this systematic review and meta-analysis of published epidemiologic data, calcium, but not dietary vitamin D, was modestly inversely associated with risk of endometrial cancer.

INTRODUCTION

Few dietary factors besides obesity have been consistently convincingly related to endometrial cancer risk in systematic literature review (World Cancer Research Fund & American Institute for Cancer Research, 1997) (Bandera et al., 2007c).

A recently published ecological study of UV irradiation (Mohr et al., 2007) and endometrial cancer incidence supported a role for vitamin D in the etiology of this cancer (Grant 2002; Grant and Garland, 2006). Although the vitamin D hypothesis is intriguing, ecological studies are subject to important shortcomings limiting causal inference (Mohr et al., 2007;Schwartz & Porta, 2007). For example, UV exposure may be a proxy for physical activity, which is inversely related to endometrial cancer risk (Bandera et al., 2007c).

Vitamin D and calcium are highly correlated in the diet and are metabolically interrelated (Heaney et al., 1997). Both have anti-proliferative and pro-differentiation effects in vitro (Lipkin & Newmark, 1999), and may work synergistically to reduce cancer risk (Grau et al., 2003;Lappe et al., 2007). We therefore provide the results of a systematic literature review and meta-analysis of vitamin D, calcium, and endometrial cancer risk conducted to support the 2007 WCRF/AICR Report on Food, Nutrition, Physical Activity and the Prevention of Cancer (Bandera et al., 2007c) to encourage more research in this area.

METHODS

Our general methods followed the WCRF Specification Manual for systematic literature reviews, available online at www.wcrf.org. Further details are provided elsewhere (Bandera et al., 2007c). Interpretation of the evidence may not represent the views of WCRF and may differ from those in the upcoming 2007 WCRF/AICR report summarizing evidence related to food, nutrition, physical activity, and cancer risk.

Search strategy

Searches were conducted in July 2003, October 2004, and December 2005. Databases included Medline, ISI Web, Embase, Biosis, Ingenta, CINAHL, Science Direct, LILACS, Pascal, ExtraMed, and Allied CompMEd. For this manuscript we also monitored the literature using *PubMed Alerts* for all new papers on endometrial cancer through May 2007.

Exposure terms and methods can be found in the appendix of another manuscript (Bandera et al., 2007a). PubMed terms used specifically for vitamin D and calcium included vitamin D [tiab] OR vitamin [tiab] AND D[tiab] OR calcium [tiab] OR supplements [tiab]. We additionally added the following MeSH terms to supplement this subject: ultraviolet rays OR cholecalciferol OR ergocalciferol OR sunburn.

Manuscript selection and data extraction

Of the 285 papers identified evaluating some aspect of nutrition, diet, physical activity and endometrial cancer, 3 mentioned vitamin D (Barbone et al., 1993;Negri et al., 1996;Salazar-Martinez et al., 2005) and 5 (Barbone et al., 1993;Negri et al., 1996;Salazar-Martinez et al., 2005;Tzonou et al., 1996;Terry et al., 2002) mentioned calcium.

Data were extracted by trained research personnel on study characteristics and results using an Access® program developed by Leeds University under WCRF sponsorship. Each entry was reviewed by at least one of us. We abstracted study-specific risk estimates from the model that adjusted most completely for known risk factors for endometrial cancer.

Statistical analysis

We estimated random and fixed effects pooled risk estimates across studies using the "metan" package (version 1.86) for STATA. Heterogeneity was assessed by conducting Q tests and quantifying the degree of heterogeneity by estimating the I^2 index (Huedo-Medina et al., 2006).

For studies not reporting confidence intervals, these were estimated based on the number of cases and controls in each category of exposure (Jewell, 2003). One paper (Tzonou et al., 1996) included estimates for calcium only for 250 mg increments (linear model); we therefore estimated OR (95% confidence interval (CI)) quartile comparisons using the cut points provided.

RESULTS

We found no intervention or cohort studies on vitamin D or calcium and endometrial cancer. As shown in Table 1, only three hospital-based case control studies (Barbone et al., 1993;Negri et al., 1996;Salazar-Martinez et al., 2005) reported on the association of dietary vitamin D and endometrial cancer risk and offered conflicting results. Meta-analyses of vitamin D and endometrial cancer were null (random-effects pooled OR=0.85, 95% CI 0.34–2.13; fixed-effects pooled OR=1.14 (95% CI 0.83–1.56) with high heterogeneity among studies (I^2: 85.7%; p value for heterogeneity: 0.001).

These same case-control studies (Barbone et al., 1993;Negri et al., 1996;Salazar-Martinez et al., 2005) and a fourth (Tzonou et al., 1996) examined the association between calcium intake and risk of endometrial cancer (Table 2). Our meta-analysis suggested a non-significant inverse association but heterogeneity was high (random effects OR=0.60, 95% CI 0.26–1.36; fixed effects OR=0.92, 95% CI 0.68–1.25; I^2: 81.6%, p value for heterogeneity: 0.001). Both case-control studies that examined the role of calcium supplement use (Barbone et al., 1993;Terry et al., 2002) reported ORs below one. The random and fixed-effects pooled estimates from these two studies were OR=0.63, 95% CI 0.39–0.99 and OR=0.62, 95% CI 0.42–0.93, respectively (I^2: 23.5%, p for heterogeneity: 0.25).

DISCUSSION

Our systematic literature review of vitamin D, calcium and endometrial cancer indicates that the evidence is sparse and inconclusive. The three published case-control studies of vitamin D, which evaluated only dietary intake, found inconsistent associations with endometrial cancer. Five case-control studies evaluated the relationship between dietary and supplemental calcium and were generally inconsistent but offered some support for an inverse association with supplemental calcium. There were no prospective studies on this topic.

Although these findings offer little support for the vitamin D and endometrial cancer hypothesis (Mohr et al., 2007), several methodological limitations may have hampered the ability of these studies to observe an association. All analyses examining vitamin D were hospital-based case-control studies (Barbone et al., 1993;Negri et al., 1996;Salazar-Martinez et al., 2005), which are subject to recall and selection biases. Two of the studies had a limited number of cases ($\leq$ 103) (Barbone et al., 1993;Salazar-Martinez et al., 2005). Vitamin D intakes in these studies were considerably lower than amounts thought to raise blood 25(OH)D to levels associated with lower cancer risk (Bertone-Johnson et al., 2005;Giovannucci et al., 2006;Bischoff-Ferrari et al., 2006). None of these studies assessed individual vitamin D supplements or endogenous vitamin D synthesis from sun exposure, which can be considerable, especially in Caucasians (Hollis, 2005).

The question of whether vitamin D influences endometrial carcinogenesis is worthy of further exploration in studies with better vitamin D exposure information as such a role is biologically plausible. Endometrial tissue contains the vitamin D receptor (Vienonen et al., 2004), a ligand-activated, nuclear transcription regulating factor that regulates production of proteins involved in cell proliferation and differentiation (Uitterlinden et al., 2005). The ligand for the VDR, 1,25 $(OH)_2D$, can be synthesized in endometrial tissue (Becker et al., 2007). Provision of vitamin D substrate (25(OH)D, storage form of the vitamin), for local vitamin D activation would be expected to be beneficial.

Supplemental calcium was associated with a lower risk of endometrial cancer, but because only two case-control studies provided data on supplemental calcium, these findings are preliminary. The literature with respect to calcium and endometrial carcinogenesis is limited. In a rodent model, calcium reduces fat-induced cell proliferation by maintaining intracellular calcium concentrations (Jacobson et al., 1989) and greater fat intakes has been related to endometrial cancer risk (Bandera et al., 2007b). Calcium has been inversely associated with risk of breast cancer, another hormone-dependent cancer (Mccullough et al., 2005;Shin et al., 2002). Calcium may also influence risk through its metabolic relationship with vitamin D: calcium supplementation lowers $1,25(OH)_2D$ levels (Sanchez et al., 1997), theoretically sparing 25(OH)D from conversion to $1,25(OH)_2D$. Substrate preservation may render 25(OH)D more available for endometrial tissue-specific synthesis of $1,25(OH)_2D$.

CONCLUSIONS

The current evidence for a role of dietary vitamin D or calcium in endometrial carcinogenesis is too limited to draw any conclusions. The available epidemiological studies may have missed a true association due to misclassification of vitamin D status when only considering the low range from dietary sources, and potentially missing the relevant time frame of exposure. The modest inverse relationship observed between calcium supplementation and endometrial cancer may be explained by bias, confounding, or chance, and needs replication. Additional large, prospective studies of calcium and vitamin D -- including measures of sun exposure, and preferably, 25(OH)D levels, are warranted.

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Table 1

Associations (OR, 95% CI) between vitamin D intake and endometrial cancer risk, case-control studies.

	Country	Age	n Cases	n Controls	Study Type	Exposure	Contrast	OR (95% CI)	P trend	Covariate adjustment*					
										A	B	C	D	E	F
3	United States	cases mean age: 64 years controls mean age: 63 years	103	236	Hospital-based case-control	Vitamin D, IU	244.3+ vs. < 164.1	0.8 (0.4–1.5)	0.81	1	1	1	1	1	3
	Italy and Switzerland	31–75	368	713	Hospital-based case-control	Vitamin D, mg/day	1.19+ vs. < 0.39	1.8	<0.01	1	1	1			
nez, 2005	Mexico	18–81	85	629	Hospital-based case-control	Vitamin D, mg/day	360+ vs. <214	0.38 (0.18–0.82)	0.003	1	1	1			1
3	United States	cases mean age: 64 years controls mean age: 63 years	103	236	Hospital-based case-control	Vitamin D from supplements	Ever vs. never use	1.7 (1.0–3.0)		1	1	1	1	1	3

columns: A = Age; B = BMI/weight; C = Total Energy; D = Smoking; E = HRT/ERT use; F = Reproductive factors

Table 2

Associations (OR, 95% CI) between dietary and supplemental calcium and endometrial cancer risk, case-control studies.

Author, Year	Country	Age	n Cases	n Controls	Study Type	Exposure	Contrast	OR (95% CI)	P trend	Covariate adjustment*					
										A	B	C	D	E	F
Barbone, 1993	United States	cases mean age: 64 years, controls mean age: 63 years	103	236	Hospital-based case-control	Calcium, mg/day	752.5+ vs. < 568.7	0.7 (0.4–1.3)	0.12	1	1	1	1	1	3
Negri, 1996	Italy and Switzerland	31–75	368	713	Hospital-based case-control	Calcium, mg/day	1147+ vs. < 492	1.5	NS	1	1	1			
Tzonou, 1996	Greece	Unknown	145	298	Hospital-based case-control	Calcium, mg/day	250 mg increments	0.48 (0.27–0.84)		1	1	1	1	1	5
Salazar-Martinez, 2005	Mexico	18–81	85	629	Hospital-based case-control	Calcium, mg/day	1205+ vs. <800	0.39 (0.17–0.89)	0.002	1	1	1			1
CALCIUM SUPPLEMENTS															
Barbone, 1993	United States	cases mean age: 64 years, controls mean age: 63 years	103	236	Hospital-based case-control	Calcium supplement use	Ever vs. never use	0.8 (0.4–1.3)		1	1	1	1	1	3
Terry, 2002	Sweden	50–74	709	2877	Population-based case-control	Calcium supplement use	Daily vs. Never	0.5 (0.3–0.9)	0.04	1	1		1		
Terry, 2002	Sweden	50–74	709	2877	Population-based case-control	Calcium supplement use (dairy intake below median)	Daily vs. Never	0.3 (0.1–0.7)	0.01	1	1		1		
Terry, 2002	Sweden	50–74	709	2877	Population-based case-control	Calcium supplement use (dairy intake above median)	Daily vs. Never	0.8 (0.4–1.5)	0.39	1	1		1		

*Adjustment columns: A = Age; B = BMI/weight; C = Total Energy; D = Smoking; E = HRT/ERT use; F = Reproductive factors