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Original article

Dietary vitamin D intake and the bladder cancer risk: A pooled analysis of prospective cohort studies

Iris W.A. Boot [a], Anke Wesselius [a, *], Evan Y.W. Yu [a], Emily White [b], Margritt Brustad [c, d], Chloé Marques [e], Borje Ljungberg [f], Maurice P. Zeegers [a, g]

[a] Department Epidemiology, Maastricht University, Maastricht, the Netherlands
[b] Fred Hutchinson Cancer Research Center, Seattle, WA, USA
[c] Department of Community Medicine, The Arctic University of Norway, Hansines Veg 18, 9019 Tromsø, Norway
[d] The Public Dental Health Service Competence Center of Northern Norway, Tromso, Norway
[e] Université Paris-Saclay, UVSQ, Inserm "Exposome and Heredity" Team, CESP U1018, Gustave Roussy, Villejuif, France
[f] Department of Surgical and Perioperative Sciences, Urology and Andrology, Umeå University, Umeå, Sweden
[g] MBP Holding, Heerlen, the Netherlands

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SUMMARY

Background & aims: Diet may play an essential role in the aetiology of bladder cancer (BC). Vitamin D is involved in various biological functions which have the potential to prevent BC development. Besides, vitamin D also influences the uptake of calcium and phosphorus, thereby possibly indirectly influencing the risk of BC. The aim of the present study was to investigate the relation between vitamin D intake and BC risk.

Methods: Individual dietary data were pooled from ten cohort studies. Food item intake was converted to daily intakes of vitamin D, calcium and phosphorus. Pooled multivariate hazard ratios (HRs), with corresponding 95% confidence intervals (CIs) were obtained using Cox-regression models. Analyses were adjusted for gender, age and smoking status (Model 1), and additionally for the food groups fruit, vegetables and meat (Model 2). Dose–response relationships (Model 1) were examined using a nonparametric test for trend.

Results: In total, 1994 cases and 518,002 non-cases were included in the analyses. The present study showed no significant associations between individual nutrient intake and BC risk. A significant decreased BC risk was observed for high vitamin D intake with moderate calcium and low phosphorus intake (Model 2: $HR_{high\ vitD,\ mod\ Ca,\ low\ P}$: 0.77, 95% CI: 0.59–1.00). No significant dose–response analyses were observed.

Conclusion: The present study showed a decreased BC risk for high dietary vitamin D intake in combination with low calcium intake and moderate phosphorus intake. The study highlights the importance of examining the effect of a nutrient in combination with complementary nutrients for risk assessment. Future research should focus on nutrients in a wider context and in nutritional patterns.

1. Introduction

Bladder cancer (BC) represents the twelfth most common cancer worldwide with an estimated 573,278 new cases and 212,536 deaths in 2020 [1]. More than half of all BC cases occur in higher-income countries, with the highest incidence rates in North America and Europe and the lowest in Africa [1]. Due to high recurrence rates (i.e. 5-year recurrence rates of approximately 65% in patients with non-invasive or in situ tumors and 73% in patients with slightly more advanced disease at first diagnosis [2]) BC is the most expensive malignancy to treat of all cancers, with estimated costs ranging from USD89,287 to USD202,203 per patient [3,4]. Therefore, BC is an important public health problem.

BC is a complex disease not only influenced by genetic predisposition, but also lifestyle, environmental, and occupational exposures potentially play an important role in the development of BC [5]. The more established risk factors associated with BC risk include smoking, deleterious occupational exposure [6,7] and male sex [6,8]. Since the bladder is an important excretion organ, diet may also play an essential role in BC development. According to the

* Corresponding author.
E-mail address: anke.wesselius@maastrichtuniversity.nl (A. Wesselius).

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United States National Cancer institute, one third of all BC cases could have been prevented by adherence to dietary recommendations, hence the salient need to investigate potential associations between foods, nutrients and BC [9].

Previous epidemiological research on diet and BC reported that high amount of fluid, fruit, vegetable, yogurt, whole grain and dietary fibre intake were associated with a reduced BC risk [10–12], while higher intake of red meat, processed meat, barbecued meat, organ meat, pork, and total fat may increase BC risk [9,13,14]. Although these findings for individual food items lead to useful dietary recommendations, it remains unclear what nutrients or bioactive compounds are responsible for the observed effects on BC risk [15].

Vitamin D is mainly found in food items like fortified milk and fatty fish. Studies report that vitamin D promotes an overall increase in the strength of the immune system [16]. In addition, it has been shown that vitamin D exhibits canonically anticarcinogenic actions, including the modulation of the antiangiogenesis (i.e. the prevention of growth of new blood vessels that tumors need to grow) [17], and proapoptosis (i.e. a genetically determined process of cell self-destruction of DNA-damaged, superfluous or unwanted cells) [16,18,19]. With regard to BC, in vitro studies show that vitamin D intake is involved in the epithelial integrity, suggesting an essential role in BC development [20]. Furthermore, the active form of vitamin D (i.e. 1,25(OH)2D3) showed to be found to suppress the migration and invasion in human BC cell lines [21]. However, evidence from observational studies on the effect of vitamin D on BC risk is scarce and inconclusive. While most studies failed to identify an association between vitamin D and BC risk, meta-analyses showed an inverse association between vitamin D intake and BC risk in a dose–response manner [22,23]. Therefore, the present study aims to provide a more precise and quantitative estimate of the relation between vitamin D intake and BC risk, by pooling individual data from ten large cohort studies.

Besides its direct role on BC cancer, vitamin D might also have an indirect role on BC development via its crucial role in the absorption of both calcium and phosphorus [24]. Vitamin D deficiency results in a decline in intestinal calcium and phosphorus absorption leading to hypocalcemia. Since it has been shown that calcium might protect against cancer development [25], hypocalcemia may contribute to BC development.

It has been speculated that exposure of cells to a high serum inorganic phosphate concentration may signal alterations in cell functions that lead to delirious effects such as cancer and hypertension [26].

As a second aim, the present study will, therefore, assess the effect of calcium and phosphorus intake on BC risk and their combined effect with vitamin D intake.

2. Materials and methods

2.1. Study population

Data were derived from the *BL*adder cancer *E*pidemiology and *N*utritional *D*eterminants study (BLEND): a large international consortium on dietary factors and BC risk, compromising a total of 11,000 cases and over 680,000 non-cases aged between 18 and 100 years from different countries in Europe, America, Asia and Australia [27]. Currently, BLEND consists of 19 case–control and seventeen cohort studies.

The present study pooled data from the BLEND cohort studies only. Ten cohort studies, including a total of 1994 cases and 518,002 non-cases, were included in our analyses. Included studies were the VITamins And Lifestyle study (VITAL) [28] and the European Prospective Investigation into Cancer and nutrition (EPIC) [29,30] (Table 1).

2.2. Data collection and coding

Details on the methodology of the BLEND consortium have been described elsewhere [27]. All included studies used a self-administered or trained interviewer administered food frequency questionnaire (FFQ) that was validated on either food groups [31–36], and/or energy intake [32,33,37]. The period of recalling the dietary intake and the method used to validate the intake differed per study. In brief, the Vital study used a time reference for all dietary questions of “in the last 3 months” and used 24-h dietary recalls and a 4-day food record to validate the dietary intake of the participants [38], while studies included in the EPIC study used either a 7-day food consumption diary or 24-h dietary recalls to validate the reported dietary intake of the participants during the preceding year [39]. The collected dietary data was harmonized and categorized by using the hierarchical Eurocode 2 food coding system developed by the European Union [40], besides, weekly, monthly or yearly intake were converted to weekly food intake.

As a second step, all recoded food items were converted into nutrients by using the United States Department of Agriculture (USDA) food composition database [41]. This database has been validated for nutrients and food components [42]. For this, we chose the nutrient content per 100 g of generic food items where possible. Raw products were preferred over cooked/boiled for fruits, whereas for meat, fish, vegetables (except for salad vegetables) and pulses roasted/cooked/boiled/grilled was preferred over raw. More details have been described elsewhere [43].

The final nutrient intake was converted from weekly intake to daily intake (i.e. for each nutrient a nutrient in grams/day was created) and expressed as percentage of total daily calorie intake. If possible, portion sizes were adapted from individual studies, and otherwise based on USDA database information.

Person-years of follow-up for each participant was calculated from date of study enrolment until date of BC diagnosis, or date of ending follow up (e.g. date of death, loss to follow-up, or study exit), whichever came first.

Each study ascertained incident BC with International Classification of Diseases for Oncology (ICD-O-3 code C67) using population-based cancer registries, health insurance records, or medical records. The term BC is used for all urinary bladder neoplasms. BCs were classified into non-muscle invasive bladder cancer (NMIBC) and muscle invasive bladder cancer (MIBC). NMIBC included non-invasive papillary carcinomas confined to the urothelium (stage Ta), and carcinomas that invaded the lamina propria of the bladder wall (stage T1). High grade flat non-invasive carcinomas confined to the urothelium (carcinoma in situ; CIS) without other concomitant tumour stages [i.e. T1/Ta (classified to non-muscle invasive prior) or MIBC] were also classified as NMIBC. MIBC included carcinomas that invaded into the detrusor muscle (stage T2), carcinomas that invaded into the peri-vesical tissue (stage T3), and carcinomas that invaded adjacent tissues and organs (most often the prostate or uterus, stage T4).

In addition to information on dietary intake, the BLEND data also included study characteristics (design, method of dietary assessment, recall time of dietary intake and geographical region), participant demographics (age, sex and ethnicity), BC pathology (MNIBC and MIBC), and smoking status (current/former/never and pack years), which were all measured at baseline [27].

2.3. Statistical analysis

Baseline differences between cases and non-cases were examined by t-test for continuous variables and Chi-square test

Table 1
Baseline characteristics of the included cohort studies.

	VITAL		EPIC		EPIC		EPIC		EPIC		EPIC	
Country	USA		Denmark		France		Germany		Italy		Spain	
Mean follow-up, years (±SD)	6.74 (±1.50)		10.93 (±2.50)		10.39 (±2.56)		9.88 (±2.80)		11.23 (±2.39)		12.07 (±2.22)	
	No.	**%**	**No.**	**%**	**No.**	**%**	**No.**	**%**	**No.**	**%**	**No.**	**%**
Subject status												
Total	**69,182**	**100**	**56,005**	**100**	**64,484**	**100**	**49,453**	**100**	**45,188**	**100**	**40,439**	**100**
Cases	345	0.50	391	0.70	31	0.05	207	0.42	187	0.41	151	0.37
Men	*268*	*77.68*	*303*	*77.49*	*0*	*0*	*147*	*71.01*	*129*	*68.98*	*125*	*82.78*
Women	*77*	*22.32*	*88*	*22.51*	*31*	*100*	*60*	*28.99*	*58*	*31.02*	*26*	*17.22*
Non-cases	68,837	99.50	55,614	99.30	64,453	99.95	49,246	99.58	45,001	99.59	40,288	99.63
Men	*33,325*	*48.41*	*26,461*	*47.58*	*0*	*0*	*21,402*	*43.46*	*13,954*	*31.01*	*15,247*	*37.85*
Women	*35,512*	*51.59*	*29,153*	*52.42*	*64,453*	*100*	*27,844*	*56.54*	*31,047*	*68.99*	*25,041*	*62.15*
Sex												
Men	33,593	48.56	26,764	47.79	0	0	21,549	43.57	14,083	31.17	15,372	38.01
Women	35,589	51.44	29,241	52.21	64,484	100	27,904	56.43	31,105	68.83	25,067	61.99
Age (years)												
<50												
Cases	2	0.11	0	0	5	0.02	39	0.16	39	0.18	41	0.18
Non-cases	1804	99.89	0	0	27,045	99.98	23,621	99.84	21,524	99.82	22,610	99.82
50–59												
Cases	71	0.23	203	0.54	10	0.04	77	0.50	91	0.55	61	0.52
Non-cases	30,697	99.77	37,613	99.46	24,406	99.96	15,348	99.50	16,327	99.45	11,603	99.48
60–69												
Cases	132	0.55	188	1.03	16	0.12	91	0.88	56	0.81	49	0.80
Non-cases	23,765	99.45	18,001	98.97	12,866	99.88	10,272	99.12	6897	99.19	6073	99.20
≥70												
Cases	140	1.10	0	0	0	0	0	0	1	0.39	0	0
Non-cases	12,571	98.90	0	0	136	100	5	100	253	99.61	2	100
X^2 (p)	144.44 (<0.001)		43.72 (<0.001)		20.79 (<0.001)		91.48 (<0.001)		62.13 (<0.001)		59.56 (<0.001)	
TNM stage												
MIBC	110	32.84	39	24.07	5	18.52	36	25.17	19	15.97	7	12.73
Male	*91*	*82.73*	*29*	*74.36*	*0*	*0*	*30*	*83.33*	*17*	*89.47*	*7*	*100*
Female	*19*	*17.27*	*10*	*25.64*	*5*	*100*	*6*	*16.67*	*2*	*10.53*	*0*	*0*
NMIBC	225	67.16	123	75.93	22	81.48	107	74.83	100	84.03	48	87.27
Male	*168*	*74.67*	*91*	*73.98*	*0*	*0*	*80*	*74.77*	*66*	*66.00*	*38*	*79.17*
Female	*57*	*25.33*	*32*	*26.02*	*22*	*100*	*27*	*25.23*	*34*	*34.00*	*10*	*20.83*
Smoking status												
Cases												
Never	85	24.64	50	12.79	16	51.61	50	24.15	37	19.79	28	18.54
Current light			37	9.46	1	3.23	16	7.73	30	16.04	21	13.91
Current heavy			144	36.83	5	16.13	55	26.57	54	28.88	49	32.45
Current unknown	53	15.36	30	7.67	1	3.23	3	1.45	5	2.67	12	7.95
Former light												
Former heavy												
Former unknown	207	60.00	130	33.25	8	25.81	83	40.10	61	32.2	41	27.15
Non-cases												
Never	32,819	47.68	19,574	32.20	45,526	70.63	22,605	45.90	20,493	45.54	22,363	55.51
Current light			5493	9.88	3082	4.78	4993	10.14	6734	14.96	5304	13.17
Current heavy			11,349	20.41	2009	3.12	4794	9.73	5341	11.87	3991	9.91
Current unknown	5609	8.15	2258	4.06	815	1.26	551	1.12	400	0.89	1528	3.79
Former light												
Former heavy												
Former unknown	30,409	44.18	16,940	30.46	13,021	20.20	16,303	33.11	12,033	26.74	7102	17.63
X^2 (p)	79.56 (<0.001)		120.13 (<0.001)		19.97 (0.001)		85.29 (<0.001)		81.48 (<0.001)		128.26 (<0.001)	
Vitamin D[a]												
Mean (±SD)												
Cases	2.36 (±3.06)		0.11 (±0.10)		0.11 (±0.07)		0.23 (±0.15)		0.15 (±0.07)		0.17 (±0.13)	
Non-cases	2.13 (±3.00)		0.11 (±0.10)		0.09 (±0.06)		0.21 (±0.12)		0.15 (±0.08)		0.16 (±0.11)	
t (p)	−1.39 (0.16)		0.04 (0.97)		−1.39 (0.17)		−3.32 (0.0009)		−0.13 (0.90)		−1.45 (0.15)	
Calcium[b]												
Mean (±SD)												
Cases	0.62 (±0.36)		0.22 (±0.12)		0.66 (±0.40)		0.48 (±0.12)		0.54 (±0.09)		0.44 (±0.12)	
Non-cases	0.61 (±0.34)		0.23 (±0.13)		0.55 (±0.21)		0.49 (±012)		0.53 (±0.12)		0.46 (±0.12)	
t (p)	−0.77 (0.44)		2.29 (0.02)		−2.88 (0.004)		1.28 (0.20)		−1.31 (0.19)		1.59 (0.11)	
Phosphorus[b]												
Mean (±SD)												
Cases	0.58 (±0.23)		0.38 (±0.32)		0.95 (±0.43)		0.84 (±0.34)		1.02 (±0.29)		0.76 (±0.28)	
Non-cases	0.56 (±0.23)		0.41 (±0.33)		0.79 (±0.37)		0.88 (±0.37)		1.05 (±0.43)		0.78 (±0.38)	
t (p)	−1.32 (0.19)		2.17 (0.03)		−2.32 (0.02)		1.49 (0.14)		1.02 (0.31)		0.56 (0.57)	

Country	EPIC		EPIC		EPIC		EPIC		Overall	
	Sweden		The Netherlands		UK		Norway			
Mean follow-up, years (±SD)	13.12 (±3.51)		11.81 (±2.53)		11.14 (±2.51)		9.73 (±1.44)		10.54 (±3.02)	
	No.	**%**	**No.**	**%**	**No.**	**%**	**No.**	**%**	**No.**	**%**

Table 1 (*continued*)

Country	EPIC		EPIC		EPIC		EPIC		Overall	
	Sweden		The Netherlands		UK		Norway			
Subject status										
Total	**49,309**	**100**	**37,094**	**100**	**75,017**	**100**	**33,825**	**100**	**519,996**	**100**
Cases	303	0.61	107	0.29	248	0.33	24	0.07	1994	0.38
Men	*227*	*74.92*	*50*	*46.73*	*172*	*69.35*	*0*	*0*	*1421*	*71.26*
Women	*76*	*25.08*	*57*	*53.27*	*76*	*30.65*	*24*	*100*	*573*	*28.74*
Non-cases	49,006	99.39	36,987	99.71	74,769	99.67	33,801	99.93	518,002	99.62
Men	*22,311*	*45.53*	*9747*	*26.35*	*22,297*	*29.82*	*0*	*0*	*164,744*	*31.80*
Women	*26,695*	*54.47*	*27.240*	*73.65*	*52,472*	*70.18*	*33,801*	*100*	*353,258*	*68.20*
Sex										
Men	22,538	45.71	9797	26.41	22,469	29.95	0	0	166,165	31.96
Women	26,771	54.29	27,297	73.59	52,548	70.05	33,825	100	353,831	68.04
Age (years)										
<50										
Cases	29	0.15	12	0.07	22	0.06	13	0.06	202	10.13
Non-cases	19,102	99.85	16,147	99.93	39,437	99.94	21,270	99.94	192,560	37.17
50–59										
Cases	57	0.43	59	0.43	48	0.31	11	0.09	688	34.50
Non-cases	13,336	99.57	13,685	99.57	15,540	99.69	12,531	99.91	191,086	36.89
60–69										
Cases	192	1.34	35	0.52	97	0.75	0	0	856	42.93
Non-cases	14,166	98.66	6761	99.48	12,799	99.25	0	0	111,600	21.54
≥70										
Cases	25	1.03	1	0.25	81	1.15	0	0	248	12.44
Non-cases	2402	98.97	394	99.75	6993	98.85	0	0	22,756	4.39
X^2 (p)	204.62 (<0.001)		47.40 (<0.001)		302.67 (<0.001)		0.79 (0.37)		1100.00 (<0.001)	
TNM stage										
MIBC	n.a.	n.a.	22	21.15	5	100	n.a.	n.a.	243	25.58
Male			*11*	*50.00*	*4*	*80.00*			*189*	*77.78*
Female			*11*	*50.00*	*1*	*20.00*			*54*	*22.22*
NMIBC	n.a.	n.a.	82	78.85			n.a.	n.a.	707	74.42
Male			*38*	*46.34*					*481*	*68.03*
Female			*44*	*53.66*					*226*	*31.97*
Smoking status										
Cases										
Never	69	22.77	21	19.63	75	30.24	3	12.50	434	21.77
Current light	31	10.23	14	13.08	5	2.02	9	37.50	164	8.22
Current heavy	59	19.47	37	34.58	25	10.08	4	16.67	432	21.66
Current unknown	19	6.27	4	3.74	18	7.26			145	7.27
Former light										
Former heavy										
Former unknown	125	41.25	31	28.97	125	50.40	8	33.33	819	41.07
Non-cases										
Never	24,128	49.23	14,148	38.25	41,863	55.99	12,043	35.63	255,562	49.34
Current light	5410	11.04	5443	14.72	4232	5.66	7387	21.85	48,078	9.28
Current heavy	4903	10.00	4790	12.95	2685	3.59	3524	10.43	43,386	8.38
Current unknown	1288	2.63	1068	2.89	2194	2.93	426	1.26	16,137	3.12
Former light										
Former heavy										
Former unknown	13,277	27.09	11,538	31.19	23,795	31.82	10,421	30.83	154,839	29.89
X^2 (p)	107.26 (<0.001)		48.67 (<0.001)		106.37 (<0.001)		7.53 (0.11)		917.97 (<0.001)	
Vitamin D[a]										
Mean (±SD)										
Cases	0.24 (±0.23)		0.27 (±0.22)		0.23 (±0.15)		0.17 (±0.04)		0.56 (±1.52)	
Non-cases	0.18 (±0.19)		0.23 (±0.14)		0.16 (±0.13)		0.16 (±0.07)		0.42 (±1.29)	
t (p)	−4.86 (<0.001)		−3.13 (0.0017)		−8.23 (<0.001)		−0.92 (0.36)		−5.00 (<0.001)	
Calcium[b]										
Mean (±SD)										
Cases	0.37 (±0.15)		0.40 (±0.07)		0.47 (±0.13)		0.46 (±0.09)		0.44 (±0.24)	
Non-cases	0.37 (±0.13)		0.41 (±0.07)		0.53 (±0.19)		0.46 (0.09)		0.47 (±0.21)	
t (p)	0.11 (0.91)		1.78 (0.08)		4.90 (<0.001)		0.31 (0.76)		7.82 (<0.001)	
Phosphorus[b]										
Mean (±SD)										
Cases	1.06 (±0.77)		0.90 (±0.25)		0.78 (±0.21)		0.78 (±0.14)		0.75 (±0.46)	
Non-cases	1.11 (±0.64)		0.92 (±0.34)		0.72 (±0.26)		0.81 (±0.42)		0.78 (±0.43)	
t (p)	1.33 (0.18)		0.67 (0.50)		−3.52 (0.0004)		0.35 (0.73)		3.69 (0.0002)	

Abbreviations: VITAL, the VITamins And Lifestyle study; EPIC, European Prospective Investigation into Cancer and nutrition; SD, standard deviation; n.a.: not available; MIBC: muscle invasive bladder cancer; NMIBC: non muscle invasive bladder cancer.

[a] Nutrient values measured per day in micrograms per calorie, *1000.

[b] Nutrient values measured per day in milligrams per calorie.

for categorical variables. To assess the association between dietary vitamin D intake and BC risk, cox proportional hazard regression analysis was used to obtain hazard ratios (HRs) and corresponding 95% confidence intervals, stratified by study centre. Scaled Schoenfeld residuals were estimated for each covariate to test the proportional hazards assumption. In addition, the appropriateness of the use of the log-normal distribution was tested using a Wald test, and no evidence of violation was found [44].

Nutrient intake was classified in tertiles (low/moderate/high intake), based on the distribution of nutrient intake per calorie of the entire population. The Cox-regression model used low consumers as the reference group and associations were computed adjusted for the predefined confounders age, sex (male/female), smoking status (was defined as a dummy variable: 0 [never smokers]; 1 [current light smokers (*i.e.* smoking less than 20 pack-years)]; 2 [current heavy smokers (*i.e.* smoking more than 20 pack-years)]; 3 [current smokers (no information on pack-years)]; 4 [former light smokers (*i.e.* smokers who ceased smoking over 1 year prior and smoked less than 20 pack-years)]; 5 [former heavy smokers (*i.e.* smokers who ceased smoking over 1 year prior and smoked more than 20 pack-years)]; 6 [former smokers (smokers who ceased smoking over 1 year prior and no information on pack-years)])) (model 1) [6,7], and in addition for the predefined food groups associated with BC risk vegetable, fruit and meat intake, and the associated nutrients calcium and phosphorus, all classified in tertiles based on the distribution of nutrient intake per calorie of the entire population (low/moderate/high intake) (model 2).

To understand the relevance of the effect modification, the main interaction terms between vitamin D consumption (low/moderate/high) and sex, BC subtype (MIBC/NMIBC), calcium intake (low/moderate/high) and phosphorus intake (low/moderate/high) were added to the model. P-interaction <0.05 was considered statistically significant where upon all analyses were stratified for the covariate of interest.

In addition to the vitamin D analysis, separate analyses were performed for the individual effect of calcium, and phosphorus intake on BC risk and their combined effect with vitamin D intake. Sensitivity analyses were performed in which BC cases diagnosed within the first 2 years after recruitment were excluded.

Based on a priori hypothesis, subgroup analyses were performed by sex and BC subtype (i.e. NMIBC and MIBC). In addition, dose–response analyses of vitamin D intake (plotted on the x-axis, defined as vitamin D intake per calorie) and HR (adjusted for age, sex and smoking status, plotted on the y-axis) were performed by using a nonparametric test for trend.

All statistical analyses were performed using Stata14 (StataCorp LLC, College Station, TX).

3. Results

3.1. Baseline characteristics

Baseline characteristics of the study population are described in Table 1. In total, 1994 cases and 518,002 non-cases were included in our analyses. Cases were older than non-cases (59.66 vs 52.42 years, $p < 0.001$), more likely to be current or former smokers (37.15% and 41.07% versus 20.78% and 29.89% respectively, $p < 0.001$) and approximately three times more male than female cases (1421 versus 573). Compared to non-cases, cases consumed more vitamin D (0.0.00056 μg per calorie versus 0.00042 μg per clorie, $p < 0.001$) and less calcium (0.44 mg per calorie versus 0.47 mg per calorie, $p < 0.001$) and phosphorus (0.75 mg per calorie versus 0.78 mg per calorie, $p = 0.0002$).

3.2. Nutrients and BC risk

Overall results No significant associations were observed between moderate or high dietary vitamin D intake compared to low dietary vitamin D intake and BC risk in the overall analysis, nor in the stratified analyses by sex (men/women) or BC type (MIBC/NMIBC) (Table 2).

3.3. Test for interaction

No significant interactions were observed between dietary vitamin D intake with sex (men/women), BC subtype (MIBC/NMIBC), dietary calcium intake or dietary phosphorus intake (Table 3).

3.4. Calcium

No significant associations were observed between dietary calcium intake and BC risk in the overall analysis or in the analyses stratified by gender (men/women) (Table 4). When combining vitamin D and calcium intake, no significant associations with BC

Table 2
Hazard ratios and 95% confidence intervals for BC according to dietary vitamin D intake per calorie in the BLEND study.

	Vitamin D				
	Low	Moderate	High	P	n
Overall					
Model 1	1	1.14 (1.01–1.29)	1.12 (0.99–1.26)	<0.001	519,996
Model 2	1	1.12 (0.99–1.27)	1.06 (0.93–1.21)	<0.001	519,996
- Sex					
Men					
Model 1	1	1.11 (0.96–1.29)	1.09 (0.94–1.26)	<0.001	166,165
Model 2	1	1.10 (0.95–1.27)	1.03 (0.89–1.20)	<0.001	166,165
Women					
Model 1	1	1.20 (0.96–1.50)	1.21 (0.97–1.52)	<0.001	353,831
Model 2	1	1.18 (0.94–1.47)	1.14 (0.89–1.47)	<0.001	353,831
- BC subtype					
MIBC					
Model 1	1	1.17 (1.01–1.35)	1.07 (0.93–1.24)	<0.001	519,289
Model 2	1	1.16 (1.00–1.34)	1.03 (0.88–1.21)	<0.001	519,289
NMIBC					
Model 1	1	1.13 (1.00–1.29)	1.13 (1.00–1.28)	<0.001	519,753
Model 2	1	1.11 (0.98–1.26)	1.06 (0.92–1.22)	<0.001	519,753

Model 1: adjusted for sex, age, and smoking status Model 2: adjusted for sex, age, smoking status, vegetable intake, fruit intake and meat intake.

Table 3
Test for interaction between dietary vitamin D per calorie intake and sex, BC subtype, dietary calcium per calorie intake and dietary phosphorus per calorie intake on BC risk.

Interaction	p-value
Vitamin D * gender	
- Moderate * female	0.55
- High * female	0.29
Vitamin D * BC subtype	
- Moderate * MIBC	0.86
- High * MIBC	0.71
Vitamin D * Calcium	
- Moderate * moderate	0.06
- Moderate * high	0.58
- High * moderate	0.07
- High * high	0.33
Vitamin D * Phosphorus	
- Moderate * moderate	0.89
- Moderate * high	0.69
- High * moderate	0.64
- High * high	0.92

[1]: adjusted for sex, age, and smoking status.

Table 4
Hazard ratios and 95% confidence intervals for BC according to dietary calcium intake per calorie in the BLEND study.

	Calcium				
	Low	Moderate	High	P	n
Overall					
Model 1	1	1.02 (0.90–1.14)	0.99 (0.87–1.13)	<0.001	519,996
Model 2	1	1.02 (0.91–1.15)	1.02 (0.89–1.17)	<0.001	519,996
- Sex					
Men					
Model 1	1	1.06 (0.92–1.22)	0.99 (0.85–1.15)	<0.001	166,165
Model 2	1	1.06 (0.93–1.23)	1.03 (0.88–1.20)	<0.001	166,165
Women					
Model 1	1	0.91 (0.74–1.14)	0.99 (0.78–1.26)	<0.001	353,831
Model 2	1	0.92 (0.74–1.14)	1.00 (0.78–1.28)	<0.001	353,831

Model 1: adjusted for sex, age, and smoking statusModel 2: adjusted for sex, age, smoking status, vegetable intake, fruit intake, meat intake, vitamin D intake and phosphorus intake.

Table 6
Hazard ratios and 95% confidence intervals for BC according to dietary phosphorus intake per calorie in the BLEND study.

	Phosphorus				
	Low	Moderate	High	P	n
Overall					
Model 1	1	1.01 (0.89–1.13)	1.07 (0.94–1.21)	<0.001	519,996
Model 2	1	0.99 (0.88–1.12)	1.05 (0.92–1.20)	<0.001	519,996
- Sex					
Men					
Model 1	1	0.99 (0.85–1.14)	1.06 (0.91–1.24)	<0.001	166,165
Model 2	1	0.97 (0.84–1.13)	1.06 (0.91–1.23)	<0.001	166,165
Women					
Model 1	1	1.06 (0.84–1.34)	1.08 (0.85–1.37)	<0.001	353,831
Model 2	1	1.04 (0.82–1.31)	1.04 (0.81–1.32)	<0.001	353,831

Model 1: adjusted for sex, age, and smoking statusModel 2: adjusted for sex, age, smoking status, vegetable intake, fruit intake, meat intake, vitamin D intake and calcium intake.

risk were observed compared to low intakes of both nutrients (Table 5).

3.5. Phosphorus

No significant associations were observed between moderate or high dietary phosphorus intake compared to low intake and BC risk in the overall and stratified analyses (Table 6).

When combining vitamin D and phosphorus intake, no significant associations with BC risk were observed for any of the intake levels (Table 7).

3.6. Vitamin D, calcium and phosphorus

When combining dietary vitamin D intake with both dietary calcium and phosphorus intake, a significant decreased BC risk was observed for high vitamin D intake with moderate calcium intake and low phosphorus intake (Model 2: $HR_{high\ vitD,\ mod\ Ca,\ low\ P}$: 0.77, 95% CI: 0.59–1.00). No other significant associations were observed (Table 8).

3.7. Removal of early BC cases

After removing BC cases diagnosed within the first 2 years after study enrollment, a similar significant decreased BC risk was observed for high vitamin D intake with moderate calcium intake and low phosphorus intake. No other significant results were observed (Supplementary Table 1-6).

3.8. Dose response analyses

None of the assessed nutrients showed an overall significant dose–response relation with BC risk (p = 0.31, 0.09 and 0.10 for vitamin D, calcium and phosphorus, respectively). Neither did the dose–response analysis among women and men reach significance (Figs. 1–9).

Table 5
Hazard ratios and 95% confidence intervals for BC according to dietary vitamin D intake per calorie, stratified for calcium intake per calorie in the BLEND study (n = 525,235).

		HR (95% CI)	N (case/control)	P
Low Vitamin D	Low Calcium			
	Model 1	1	76,922 (363/76,559	<0.001
	Model 2	1	76,922 (363/76,559	<0.001
	Moderate Calcium			
	Model 1	0.79 (0.61–1.02)	42,514 (79/42,435)	
	Model 2	0.81 (0.63–1.05)	42,514 (79/42,435)	
	High Calcium			
	Model 1	0.89 (0.69–1.15)	53,896 (86/53,810)	
	Model 2	0.94 (0.72–1.22)	53,896 (86/53,810)	
Moderate Vitamin D	**Low Calcium**			
	Model 1	1.06 (0.88–1.26)	40,318 (185/40,133)	
	Model 2	1.04 (0.87–1.24)	40,318 (185/40,133)	
	Moderate Calcium			
	Model 1	1.13 (0.93–1.36)	67,025 (210/66,815)	
	Model 2	1.13 (0.93–1.36)	67,025 (210/66,815)	
	High Calcium			
	Model 1	1.02 (0.94–1.25)	65,989 (203/65,786)	
	Model 2	1.05 (0.86–1.28)	65,989 (203/65,786)	
High Vitamin D	**Low Calcium**			
	Model 1	1.03 (0.87–1.21)	56,092 (301/55,791)	
	Model 2	0.99 (0.83–1.17)	56,092 (301/55,791)	
	Moderate Calcium			
	Model 1	1.06 (0.90–1.26)	63,793 (308/63,485)	
	Model 2	1.03 (0.86–1.22)	63,793 (308/63,485)	
	High Calcium			
	Model 1	1.06 (0.88–1.28)	53,447 (259/53,188)	
	Model 2	1.03 (0.85–1.25)	53,447 (259/53,188)	

Model 1: adjusted for sex, age, and smoking statusModel 2: adjusted for sex, age, smoking status, vegetable intake, fruit intake and meat intake.

Table 7
Hazard ratios and 95% confidence intervals for BC according to dietary vitamin D intake per calorie stratified for phosphorus intake per calorie in the BLEND study (n = 525,235).

		HR (95% CI)	N (case/control)	P
Low Vitamin D	Low Phosphorus			
	Model 1	1	85,165 (334/84,831)	<0.001
	Model 2	1	85,165 (334/84,831)	<0.001
	Moderate Phosphorus			
	Model 1	1.00 (0.78–1.28)	43,478 (86/43,392)	
	Model 2	1.01 (0.79–1.30)	43,478 (86/43,392)	
	High Phosphorus			
	Model 1	1.00 (0.79–1.26)	44,689 (108/44,581)	
	Model 2	1.01 (0.80–1.28)	44,689 (108/44,581)	
Moderate Vitamin D	**Low Phosphorus**			
	Model 1	1.11 (0.92–1.34)	37,869 (165/37,704)	
	Model 2	1.08 (0.90–1.31)	37,869 (165/37,704)	
	Moderate Phosphorus			
	Model 1	1.13 (0.94–1.36)	69,209 (209/69,000)	
	Model 2	1.11 (0.93–1.35)	69,209 (209/69,000)	
	High Phosphorus			
	Model 1	1.18 (0.97–1.43)	66,254 (224/66,030)	
	Model 2	1.18 (0.97–1.43)	66,254 (224/66,030)	
High Vitamin D	**Low Phosphorus**			
	Model 1	1.15 (0.94–1.41)	50,298 (254/50,044)	
	Model 2	1.10 (0.90–1.35)	50,298 (254/50,044)	
	Moderate Phosphorus			
	Model 1	1.06 (0.89–1.26)	60,645 (294/60,351)	
	Model 2	1.01 (0.84–1.20)	60,645 (294/60,351)	
	High Phosphorus			
	Model 1	1.16 (0.98–1.37)	62,389 (320/62,069)	
	Model 2	1.10 (0.92–1.31)	62,389 (320/62,069)	

Model 1: adjusted for sex, age, and smoking statusModel 2: adjusted for sex, age, smoking status, vegetable intake, fruit intake, meat intake and calcium intake.

Table 8
Hazard ratios and 95% confidence intervals for BC according to dietary vitamin D intake per calorie, stratified for phosphorus and calcium intake per calorie in the BLEND study (n = 525,235).

			HR (95% CI)	N (case/control)	P
Low Vitamin D	**Low Calcium**	**Low Phosphorus**			
		Model 1	1	553,852 (295/53,557)	<0.001
		Model 2	1	553,852 (295/53,557)	<0.001
		Moderate Phosphorus			
		Model 1	0.96 (0.64–1.44)	9447 (27/9420)	
		Model 2	0.96 (0.64–1.45)	9447 (27/9420)	
		High Phosphorus			
		Model 1	1.01 (0.71–1.43)	13,623 (41/13,582)	
		Model 2	1.01 (0.71–1.43)	13,623 (41/13,582)	
	Moderate Calcium	**Low Phosphorus**			
		Model 1	0.62 (0.37–1.06)	10,598 (15/10,583)	
		Model 2	0.65 (0.38–1.11)	10,598 (15/10,583)	
		Moderate Phosphorus			
		Model 1	0.84 (0.57–1.25)	14,832 (29/14,803)	
		Model 2	0.86 (0.58–1.28)	14,832 (29/14,803)	
		High Phosphorus			
		Model 1	0.84 (0.58–1.21)	17,084 (35/17,049)	
		Model 2	0.86 (0.59–1.24)	17,084 (35/17,049)	
	High Calcium	**Low Phosphorus**			
		Model 1	0.73 (0.47–1.13)	20,715 (24/20,691)	
		Model 2	0.80 (0.50–1.21)	20,715 (24/20,691)	
		Moderate Phosphorus			
		Model 1	0.98 (0.66–1.46)	19,199 (30/19,169)	
		Model 2	1.04 (0.69–1.55)	19,199 (30/19,169)	
		High Phosphorus			
		Model 1	0.95 (0.65–1.40)	13,982 (32/13,950)	
		Model 2	0.99 (0.67–1.47)	13,982 (32/13,950)	
Moderate Vitamin D	**Low Calcium**	**Low Phosphorus**			
		Model 1	1.06 (0.85–1.32)	18,404 (110/18,294)	
		Model 2	1.04 (0.83–1.30)	18,404 (110/18,294)	
		Moderate Phosphorus			
		Model 1	1.05 (0.77–1.43)	13,705 (48/13,657)	
		Model 2	1.04 (0.76–1.42)	13,705 (48/13,657)	
		High Phosphorus			
		Model 1	1.01 (0.67–1.51)	8209 (27/8182)	
		Model 2	1.00 (0.67–1.50)	8209 (27/8182)	

Table 8 (*continued*)

			HR (95% CI)	N (case/control)	P
	Moderate Calcium	**Low Phosphorus**			
		Model 1	1.20 (0.84–1.70)	10,695 (39/10,656)	
		Model 2	1.20 (0.84–1.71)	10,695 (39/10,656)	
		Moderate Phosphorus			
		Model 1	1.06 (0.82–1.37)	31,222 (86/31,136)	
		Model 2	1.06 (0.81–1.37)	31,222 (86/31,136)	
		High Phosphorus			
		Model 1	1.16 (0.90–1.51)	25,108 (85/25,023)	
		Model 2	1.17 (0.90–1.52)	25,108 (85/25,023)	
	High Calcium	**Low Phosphorus**			
		Model 1	0.73 (0.44–1.23)	8770 (16/8754)	
		Model 2	0.75 (0.44–1.25)	8770 (16/8754)	
		Moderate Phosphorus			
		Model 1	1.06 (0.80–1.40)	24,282 (75/24,207)	
		Model 2	1.08 (0.82–1.43)	24,282 (75/24,207)	
		High Phosphorus			
		Model 1	1.08 (0.84–1.39)	32,937 (112/32,825)	
		Model 2	1.11 (0.86–1.44)	32,937 (112/32,825)	
High Vitamin D	**Low Calcium**	**Low Phosphorus**			
		Model 1	1.12 (0.88–1.43)	19,990 (124/19,866)	
		Model 2	1.09 (0.86–1.39)	19,990 (124/19,866)	
		Moderate Phosphorus			
		Model 1	0.80 (0.62–1.03)	20,271 (82/20,189)	
		Model 2	0.77 (0.59–1.00)	20,271 (82/20,189)	
		High Phosphorus			
		Model 1	1.16 (0.90–1.48)	15,831 (95/15,736)	
		Model 2	1.12 (0.87–1.44)	15,831 (95/15,736)	
	Moderate Calcium	**Low Phosphorus**			
		Model 1	0.95 (0.69–1.31)	14,493 (57/14,436)	
		Model 2	0.93 (0.67–1.28)	14,493 (57/14,436)	
		Moderate Phosphorus			
		Model 1	1.13 (0.98–1.43)	23,414 (126/23,288)	
		Model 2	1.10 (0.87–1.38)	23,414 (126/23,288)	
		High Phosphorus			
		Model 1	1.05 (0.84–1.32)	25,886 (125/25,761)	
		Model 2	1.02 (0.81–1.29)	25,886 (125/25,761)	
	High Calcium	**Low Phosphorus**			
		Model 1	1.08 (0.79–1.46)	15,815 (73/15,742)	
		Model 2	1.06 (0.78–1.44)	15,815 (73/15,742)	
		Moderate Phosphorus			
		Model 1	1.04 (0.79–1.36)	16,960 (86/16,874)	
		Model 2	1.01 (0.77–1.32)	16,960 (86/16,874)	
		High Phosphorus			
		Model 1	1.06 (0.82–1.36)	20,672 (100/20,572)	
		Model 2	1.03 (0.80–1.33)	20,672 (100/20,572)	

Model 1: adjusted for sex, age, and smoking status
Model 2: adjusted for sex, age, smoking status, vegetable intake, fruit intake and meat intake.

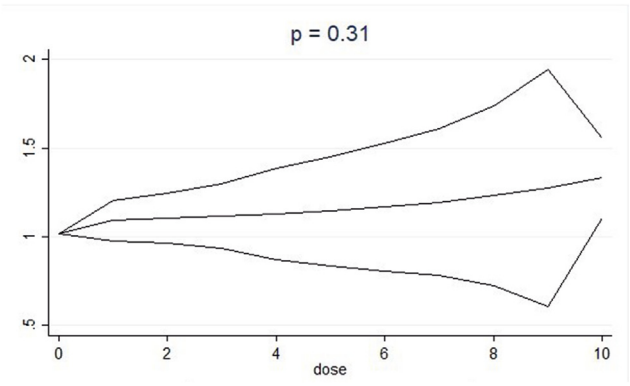

Fig. 1. Dose response analysis (x-axis: vitamin D intake per calorie dose; y-axis: HR for BC, with 95% CI) (n = 525,243). Vitamin D dose = 0.0001 μg per calorie per day. Abbreviations: HR: hazard ratio; BC: bladder cancer; CI: confidence interval; μg: microgram.

4. Discussion

The present study showed a decreased BC risk for high dietary vitamin D intake in combination with low calcium intake and moderate phosphorus intake. No significant associations were observed when analysing the nutrients separately. In addition, no significant dose–response association was observed.

Despite the hypothesized protective effect of vitamin D the present study did not find a reversed association between dietary vitamin D intake and BC risk. A meta-analysis by Chen et al. [22], focusing on the role of vitamin D intake from diet and supplements, could also not confirm the hypothesized protective effect of vitamin D. Here a null association was observed. Since a meta-analysis focussing on serum vitamin D levels showed that serum vitamin D decreased BC risk [23], a possible explanation for our null findings might be that the current study does not adequately reflect the bioavailability of this vitamin, which is also highly affected by UV light exposure [6] and supplement intake. In addition, the uptake

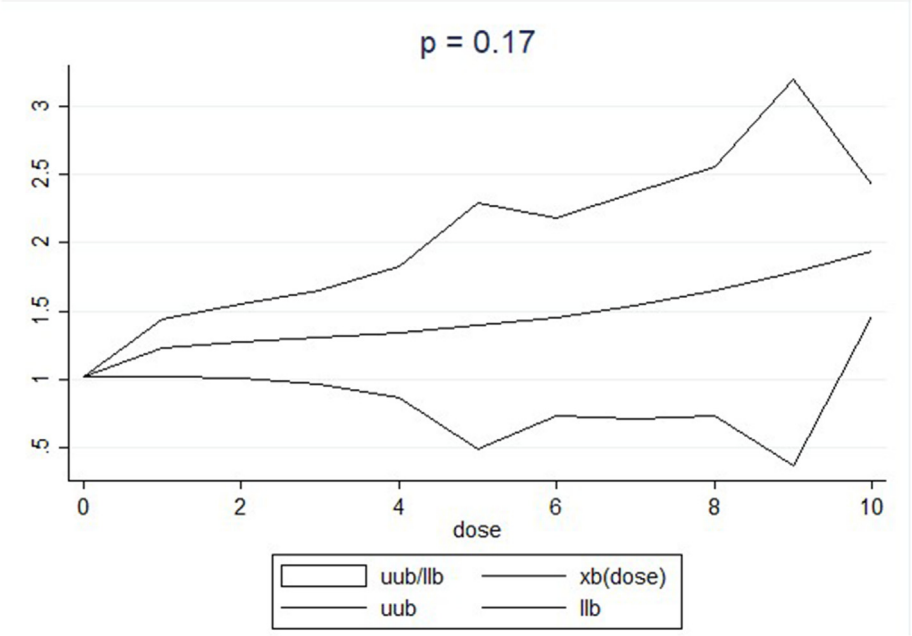

Fig. 2. Dose response analysis among women (x-axis: vitamin D intake per calorie dose; y-axis: HR for BC, with 95% CI) (n = 356,204). Vitamin D dose = 0.0001 μg per calorie per day. Abbreviations: HR: hazard ratio; BC: bladder cancer; CI: confidence interval; μg: microgram.

can depend on digestive enzymes in the gut, such as acidic pH of gastric juice [45], and the active form of vitamin D can be down regulated due to high intakes of calcium and phosphorus [46]. However, vitamin D intake with low levels of both calcium and phosphorus did not confirm this hypothesis. Previously conducted observational studies on the effect of vitamin D intake on cancer types other than BC often also lack to confirm the potential cancer protective effect of this vitamin. For example, a cross-sectional study showed that the dietary vitamin D intake was not associated with cervical- ovarian- and endometrial cancer [47]. A Spanish cohort study analyzing obesity-related cancers also failed to show an association between vitamin D intake and these obesity-related cancer types [48]. In addition, a non-association was found for non-melanoma skin cancer [49]. These might strengthen our suggestion that observational studies lack the ability to adequately reflect the vitamin D bioavailability. Another possible explanation for our null-findings might be that most individuals included in the present study consumed less vitamin D than recommended by the National Institutes of Health; 15–20 μg per day (i.e. 0.006–0.01 μg per calorie) [50] (low consumption group: average vitamin D intake = 0.000062 μg per calorie; moderate consumption group: average vitamin D intake = 0.00014 μg per calorie; high consumption group: average vitamin D intake = 0.0011 μg per calorie). This could have abolished the potentially positive effect of vitamin D on BC risk.

Previous experimental studies showed that calcium has the ability to stimulate cell proliferation to repair damaged cells, thereby potentially playing a role in cancer prevention [25]. In the present study this hypothesis could not be confirmed. The principal function of vitamin D in calcium homeostasis is to increase calcium absorption from the intestine, thereby encouraging the cancer protective property of calcium [25]. Vitamin D, however, is just one of the many mechanisms involved in the intestinal absorption of calcium [51]. The review of Kadio et al. (2016) suggested a general molecular mechanism whereby calcium might trigger carcinogenesis [52]. As higher vitamin D intake is shown to increase calcium

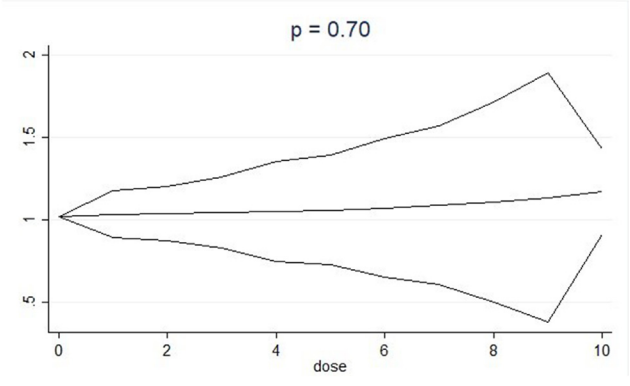

Fig. 3. Dose response analysis among men (x-axis: vitamin D intake per calorie dose; y-axis: HR for BC, with 95% CI) (n = 169,035). Vitamin D dose = 0.0001 μg per calorie per day. Abbreviations: HR: hazard ratio; BC: bladder cancer; CI: confidence interval; μg: microgram.

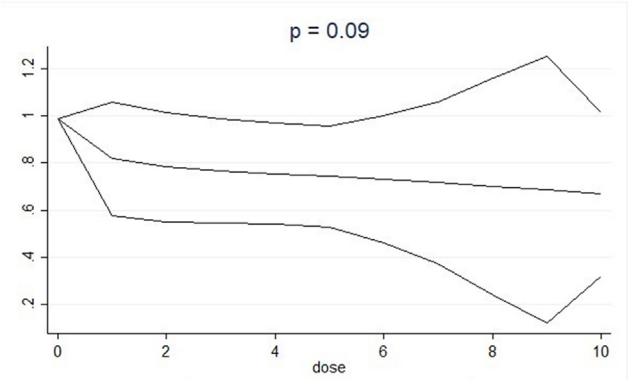

Fig. 4. Dose response analysis (x-axis: calcium intake per calorie dose; y-axis: HR for BC, with 95% CI) (n = 525,243). Calcium dose = 0.1 mg per calorie per day. Abbreviations: HR: hazard ratio; BC: bladder cancer; CI: confidence interval.

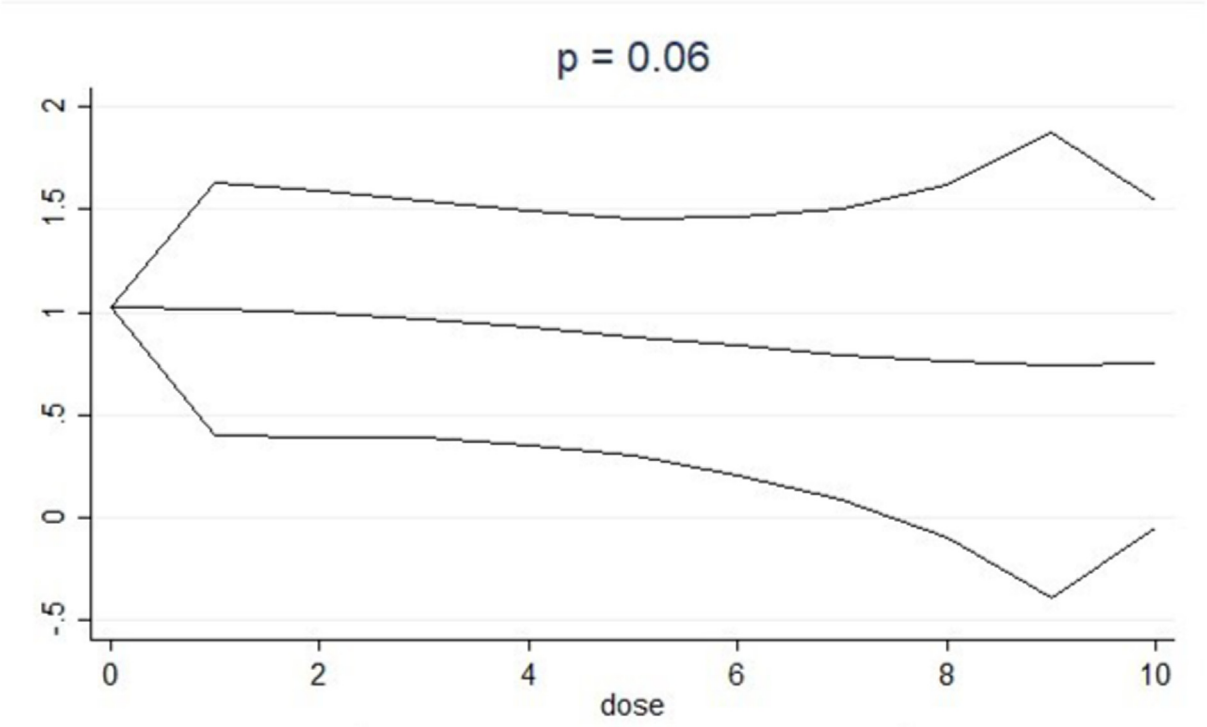

Fig. 5. Dose response analysis among women (x-axis: calcium intake per calorie dose; y-axis: HR for BC, with 95% CI) (n = 356,208). Calcium dose = 0.1 mg per calorie per day. Abbreviations: HR: hazard ratio; BC: bladder cancer; CI: confidence interval.

uptake from the intestine [24], this calcium influx-dependent pathway might explain the non-significant findings of this study. It has been hypothesized that this pathway mediates the connection between the external/environmental factors and their subsequently induced nuclear interactions and changes, leading to the cancer cascade [52]. As calcium's molecular action in cancer varies greatly, depending on criteria such as local tissular uptake, tissue type, and the nature and the chronicity of the stimulus [52], future research should focus on whether high calcium concentrations are likely to initiate BC development.

Contrary to previous experimental studies that showed that high serum inorganic phosphate levels may play a role in cancer development [26], the current study did not observe a significant association between phosphorus intake and BC risk. It is hypothesized that vitamin D intake stimulates intestinal phosphorus absorption [24]. Again this could not be confirmed in the present study when analysing phosphorus intake and vitmain D intake together.

When analysing the intake of vitamin D, phosphorus and calcium together it is suggested that intake of phosphorus pose cancerous effects. Being the only significant result in this study, this study empasizes the importance of taking into account the influence of complementary or opposing nutrients for risk assessment of an individual nutrient [46].

After exclusion of cases diagnosed within the first 2 years of study enrolment, results did not change, thereby suggesting that the link between vitamin D and cancer might not be a two-way causal relationship. Although previous studies linked vitamin D serum levels to advanced cancers [53], studies establishing cause and effect of this association are lacking. Therefore, future research

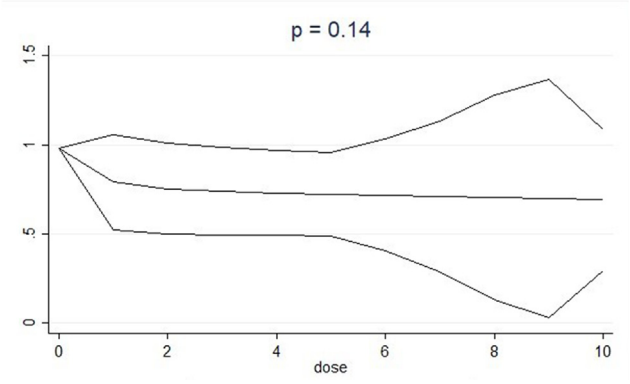

Fig. 6. Dose response analysis among men (x-axis: calcium intake per calorie dose; y-axis: HR for BC, with 95% CI) (n = 169,035). Calcium dose = 0.1 mg per calorie per day. Abbreviations: HR: hazard ratio; BC: bladder cancer; CI: confidence interval.

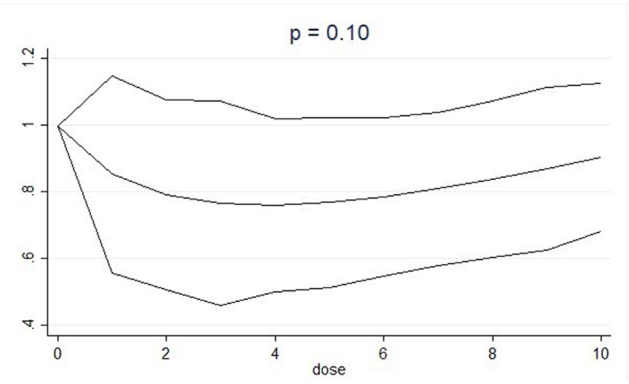

Fig. 7. Dose response analysis (x-axis: phosphorus intake per calorie dose; y-axis: HR for BC, with 95% CI) (n = 525,243). Phosphorus dose = 0.1 mg per calorie per day. Abbreviations: HR: hazard ratio; BC: bladder cancer; CI: confidence interva.

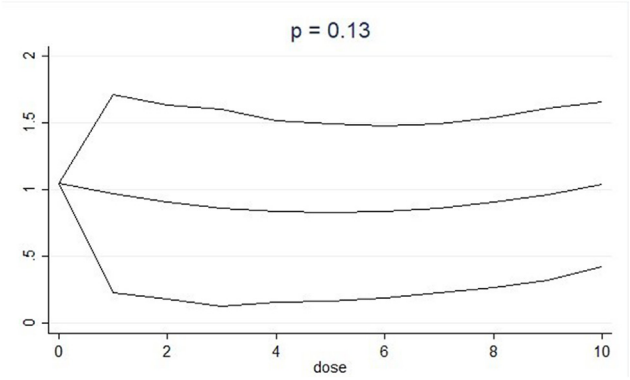

Fig. 8. Dose response analysis among women (x-axis: phosphorus intake per calorie dose; y-axis: HR for BC, with 95% CI) (n = 356,208). Phosphorus dose = 0.1 mg per calorie per day. Abbreviations: HR: hazard ratio; BC: bladder cancer; CI: confidence interval.

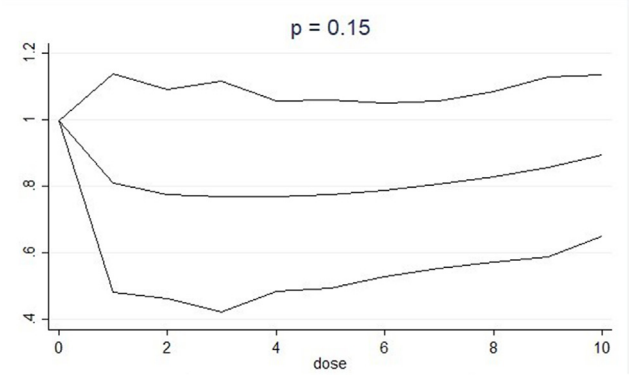

Fig. 9. Dose response analysis among men (x-axis: phosphorus intake per calorie dose; y-axis: HR for BC, with 95% CI) (n = 169,035). Phosphorus dose = 0.1 mg per calorie per day. Abbreviations: HR: hazard ratio; BC: bladder cancer; CI: confidence interval.

should not only focus on the causal effect of vitamin D on BC risk, but additionally investigate the influence of cancer on vitamin D levels.

4.1. Limitations

Although BLEND is one of the largest known pooled cohort studies investigating the association between dietary vitamin D intake and the risk of developing BC, allowing for detailed analyses with enough statistical power, it has several limitations. First, limited information was available for possible BC risk factors, such as body mass index, physical activity, socioeconomic status, and occupational exposures. Nevertheless, current literature shows only a small proportion of BC cases can be attributed to these factors [54–57]. In addition, no information was available on comorbidities that may make people alter their diet [58] or the bioavailability of vitamin D [45,59,60], or of which the drugs may disrupt vitamin D metabolism and vitamin D function [61].

Secondly, most of the included studies did not provide information on supplement use. Therefore, we were unable to take supplemental vitamin intake into account, which may have led to an underestimation of the true effect of vitamin D.

Besides, vitamin D can be retrieved via both food and sun exposure [6]. However, since all analyses were stratified by study centre, thereby taking sun hours of different regions into account, the lack of data on sun exposure is expected to be minor.

A third limitation arises from the use of FFQs, which could lead to recall bias, systematic and random error when estimating nutrient intake. Future research with more homogeneous data collection could therefore provide a more definite answer. However, since the dietary intake of all included studies was validated, recall bias has likely only played a minor role in our study. In addition, measurement error could be negligible, considering the large sample size.

Fourthly, although people are less likely to change their dietary habits at an older age, they were only measured at baseline and we were, therefore, unable to take possible changes of dietary habits over time into account. This could have led to misclassification of long-term exposure [62]. However, the Netherlands Cohort Study, a cohort study that also assessed dietary intakes using an FFQ, repeated the questionnaire 5 years after baseline, and showed only a minor decline in average intake for all food items [63].

Fifthly, a single database was used for the conversion of food into nutrient intake. Since the food composition of similar food items may differ between different countries, the use of country specific food composition tables might be more accurate. Previous studies, however, showed that the use of a common food composition database advantages over the use of country specific food composition databases in that errors are consistent between the countries [64].

At last, results obtained from cohort studies on diet and cancer risk cannot always rule out the possibility of reversed causality. Since there is no evidence that people are likely to alter their diet in the period before BC diagnosis, we decided not to exclude study participants who received a BC diagnosis within a short period of follow-up from our main analyses.

5. Conclusion

Although the present study suggests a decreased BC risk for high dietary vitamin D intake in combination with low calcium intake and moderate phosphorus intake, future large prospective research and lab studies are needed to confirm these findings. In addition, future research should focus on nutrients in a wider context and in nutritional patterns.

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Author contribution

Study conception and design: IB and AW; Analyses and interpretation of data: IB and AW; Drafting of the manuscript: IB and AW; Revised the manuscript: AW, MPZ; Provided the data: EW, MB, CM, BL; Approved the manuscript: all authors.

Conflicts of interest

All the authors declare no conflict of interest.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.clnu.2023.05.010.

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