

Supplementary Online Content

Urashima M, Ohdaira H, Akutsu T, et al. Effect of vitamin D supplementation on relapse-free survival among patients with digestive tract cancers: the AMATERASU randomized clinical trial [published April 9, 2019]. *JAMA*. doi:10.1001/jama.2019.2210

eFigure 1. Risk of Relapse or Death and All-Cause Death by Patient's Average 25(OH)D Level Over the Course of the Trial

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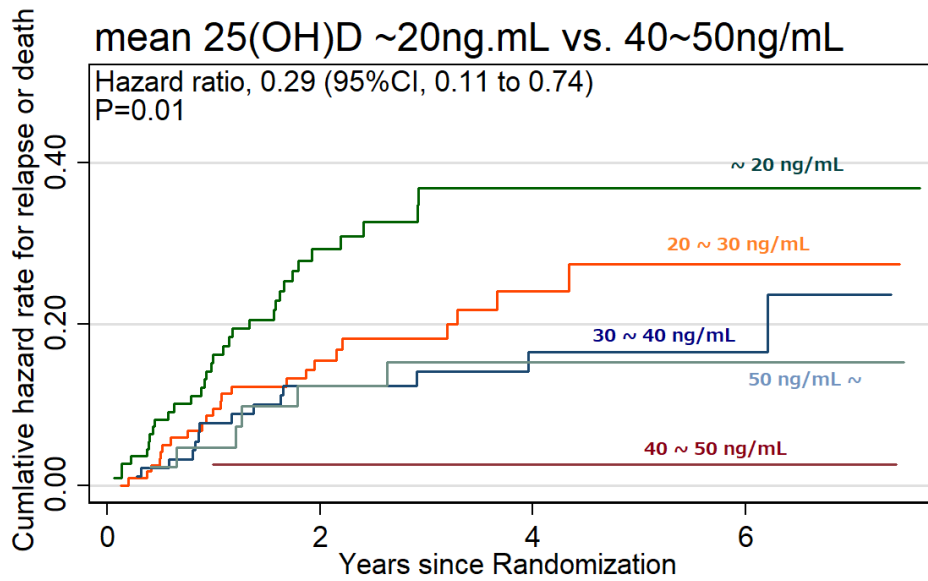
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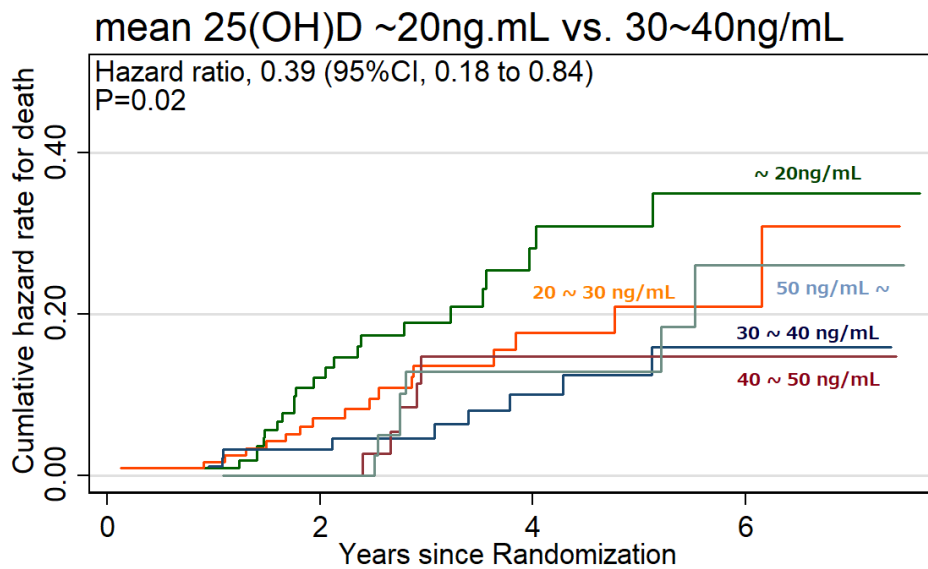
This supplementary material has been provided by the authors to give readers additional information about their work.



Number at risk				
~20ng/mL	114	64	29	10
20ng/mL~	123	78	32	9
30ng/mL~	94	70	39	17
40ng/mL~	39	38	21	8
50ng/mL~	43	37	25	7

eFigure 1A. Post hoc analysis of mean 25(OH)D grouping: Risk of relapse or death

Cumulative hazard curves of relapse or death were drawn stratified by the patient's average 25(OH)D level over the course of the trial: 25(OH)D low, <20 ng/mL (green); intermediate, 20 to < 30 ng/mL (orange); high, 30 to < 40 ng/mL (blue); very high, 40 to < 50 ng/mL (brown); extremely high, ≥ 50 ng/mL (light blue).



Number at risk				
~20ng/mL	114	78	36	13
20ng/mL~	123	87	37	12
30ng/mL~	94	76	43	17
40ng/mL~	39	39	21	8
50ng/mL~	43	42	28	7

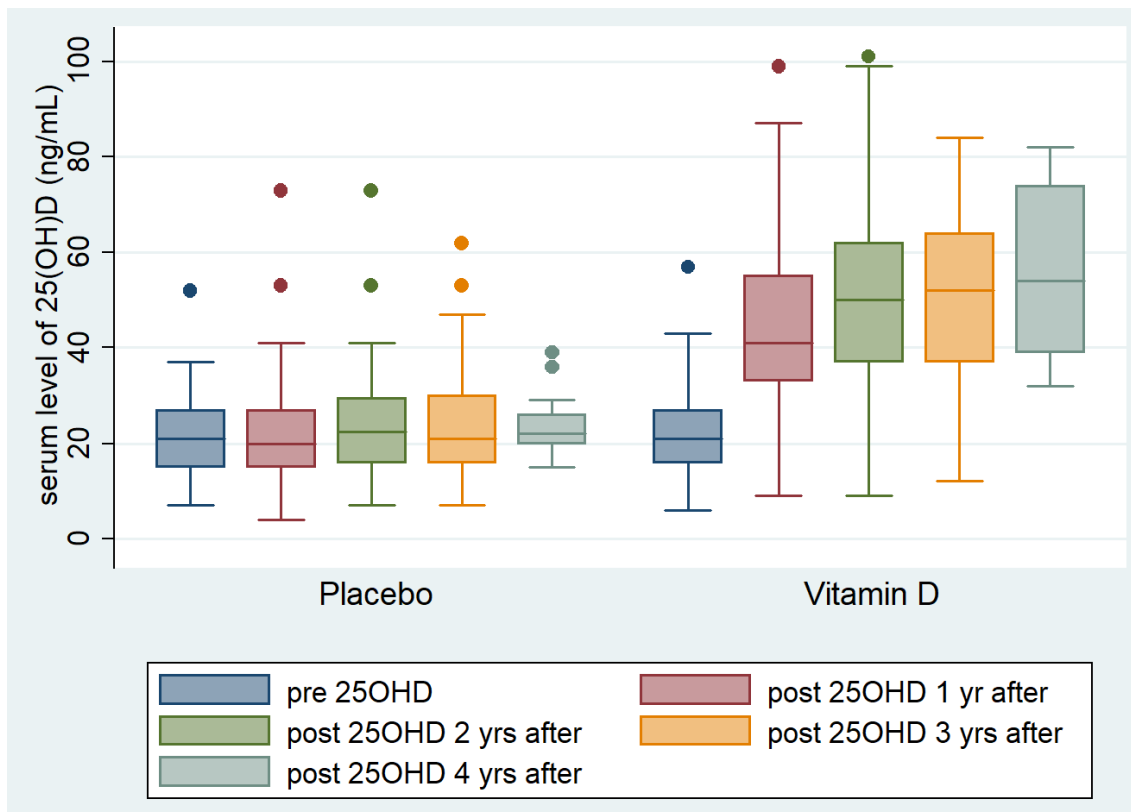
eFigure 1B. Post hoc analysis of mean 25(OH)D grouping: All-cause death

Cumulative hazard curves of all-cause death were drawn stratified by the patient's average 25(OH)D level over the course of the trial: 25(OH)D low, <20 ng/mL (green); intermediate, 20 to < 30 ng/mL (orange); high, 30 to < 40 ng/mL (blue); very high, 40 to < 50 ng/mL (brown); extremely high, ≥ 50 ng/mL (light blue).

eTable 1. Cox proportional hazard model by patient's mean 25(OH)D level over the course of the trial

			Relapse or death	All-cause death
	Active	Placebo	HR (95%CI) P	HR (95%CI) P
	n (%)	n (%)	AHR*, 95%CI, P	AHR*, 95%CI, P
< 20 ng/mL	40 (16)	74 (45)	reference	reference
20 to < 30 ng/mL	56 (23)	67 (41)	0.62 (0.37 to 1.02) 0.06 0.61 (0.37 to 1.01) 0.05	0.66 (0.35 to 1.24) 0.20 0.64 (0.34 to 1.20) 0.16
30 to < 40 ng/mL	71 (29)	23 (14)	0.47 (0.27 to 0.84) 0.01 0.44 (0.24 to 0.82) 0.009	0.39 (0.18 to 0.84) 0.02 0.33 (0.15 to 0.74) 0.007
40 to < 50 ng/mL	39 (16)	0 (0)	0.29 (0.11 to 0.74) 0.01 0.26 (0.10 to 0.71) 0.008	0.44 (0.17 to 1.16) 0.10 0.34 (0.12 to 0.96) 0.04
≥ 50 ng/mL	42 (17)	1 (0.6)	0.44 (0.21 to 0.96) 0.04 0.40 (0.18 to 0.92) 0.03	0.55 (0.24 to 1.29) 0.17 0.43 (0.17 to 1.08) 0.07
Total	248 (60)	165 (40)		

*AHR: Hazard ratio adjusted with vitamin D supplementation.



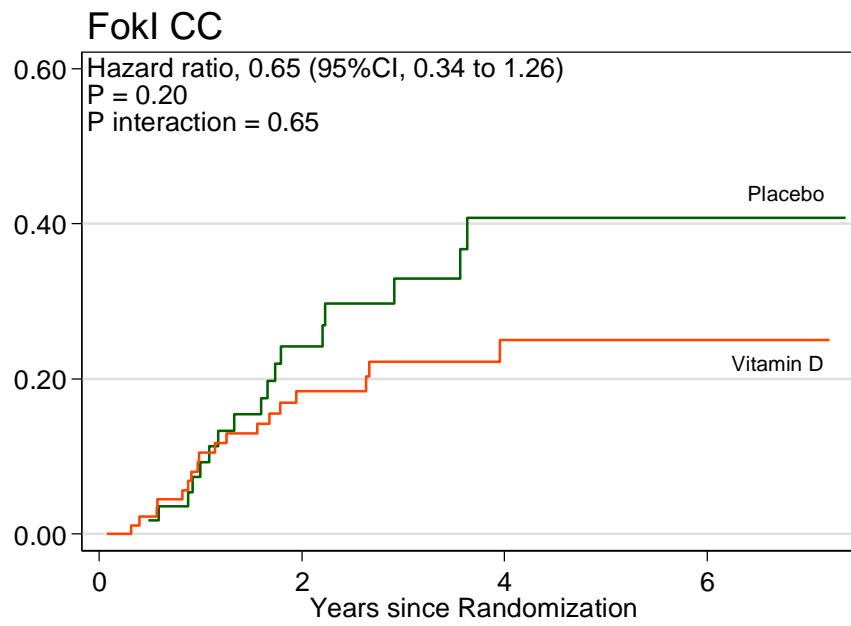
eFigure 2. Changes of 25(OH)D levels over study period.

Serum levels of 25(OH)D were shown by box plot, measured before (pre), and every year within the same calendar month 1, 2, 3, and 4 years after starting supplements. Left is showing placebo group and right is vitamin D group.

eTable 2. Cox proportional hazard model by subgroup of 25(OH)D level with multiple imputation

	baseline serum 25(OH)D level	
	0 to <20 ng/mL HR (95%CI) P	20 to 40 ng/mL HR (95%CI) P
Relapse or death	1.15 (95%CI, 0.65 to 2.05) P=0.63	0.46 (95%CI, 0.24 to 0.86) P=0.02
All-cause death	1.36 (95%CI, 0.66 to 2.81) P=0.41	0.60 (95%CI, 0.28 to 1.30) P=0.20

Because data for serum 25(OH)D at baseline were missing in 3 (1%) vitamin D group and 4 (2%) placebo group patients, multiple imputation was used for these missing data.

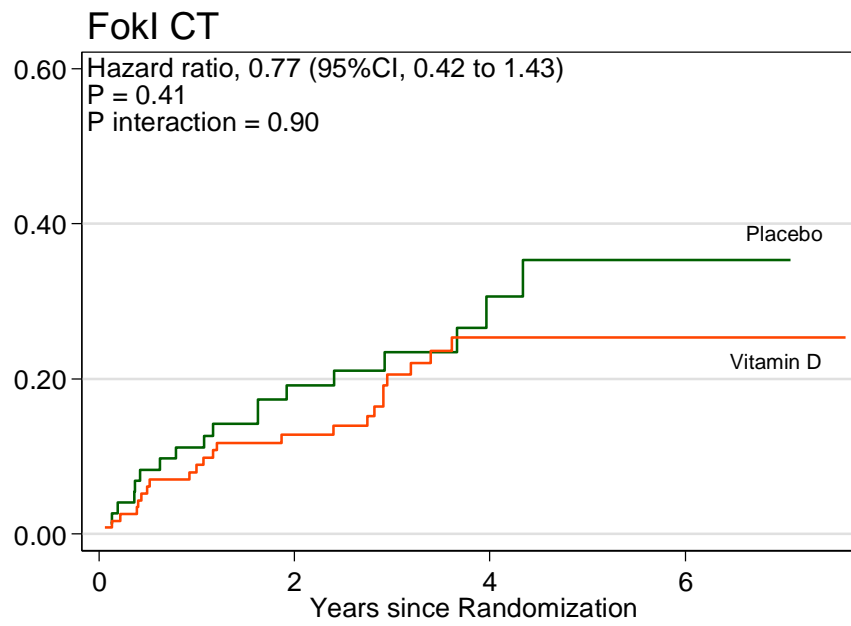


No. at risk table

Placebo	57	37	19	8
Vitamin D	92	64	35	9

eFigure 3A. Prespecified subgroup analysis of FokI/CC.

Cumulative hazard curves of relapse or death were drawn in subgroup of patients with polymorphism of FokI/CC.

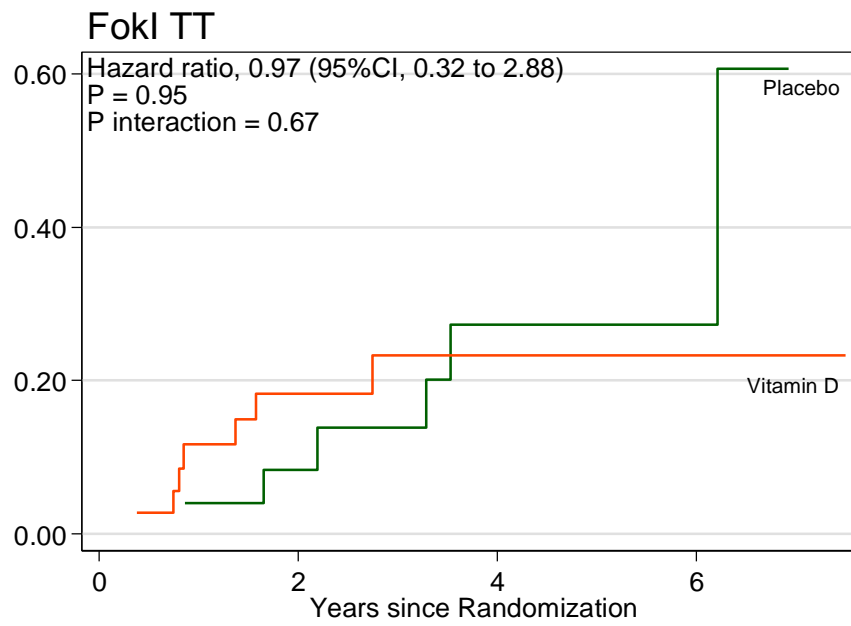


No. at risk table

Placebo	75	53	24	5
Vitamin D	117	89	48	23

eFigure 3B. Prespecified subgroup analysis of FokI/CT.

Cumulative hazard curves of relapse or death were drawn in subgroup of patients with polymorphism of FokI/CT.

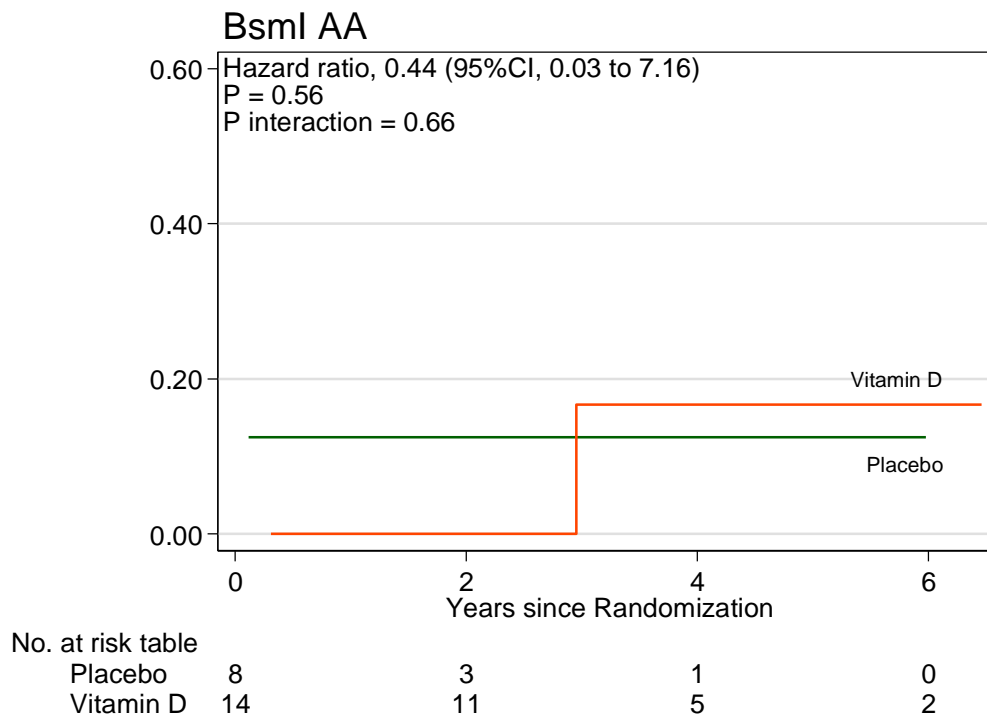


No. at risk table

Placebo	25	18	10	3
Vitamin D	36	21	10	3

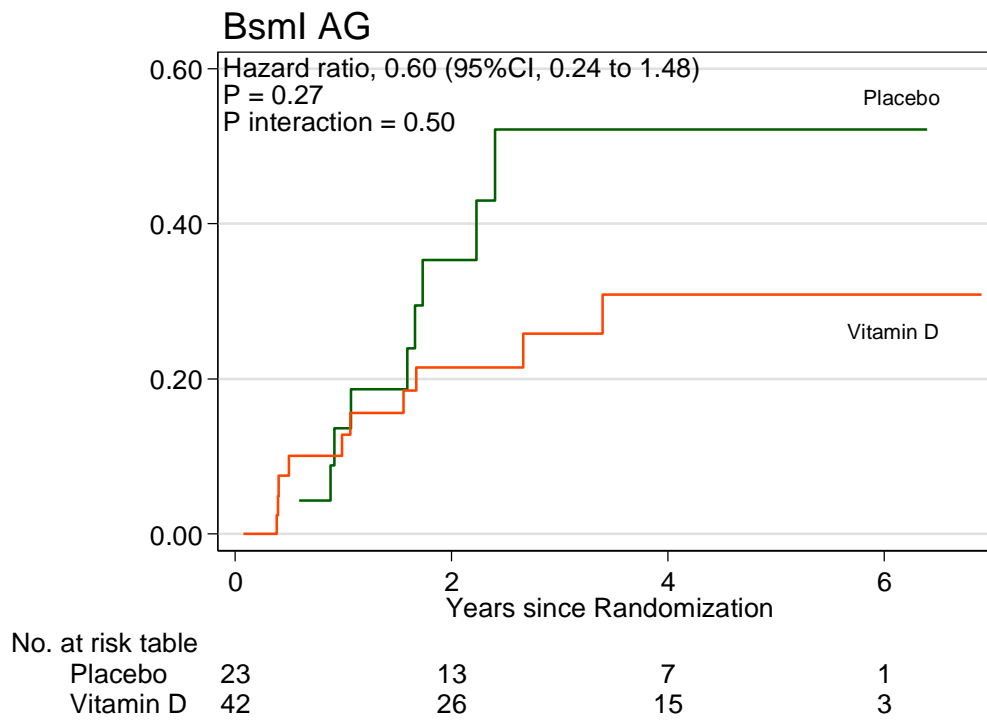
eFigure 3C. Prespecified subgroup analysis of FokI TT.

Cumulative hazard curves of relapse or death were drawn in subgroup of patients with polymorphism of FokI TT.



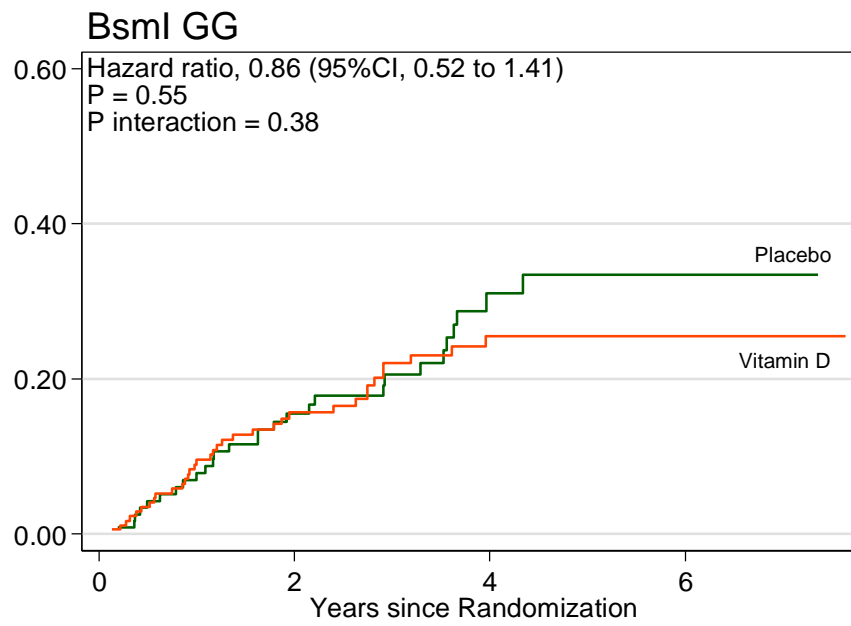
eFigure 3D. Prespecified subgroup analysis of Bsm/AA.

Cumulative hazard curves of relapse or death were drawn in subgroup of patients with polymorphism of Bsm/AA.



eFigure 3E. Prespecified subgroup analysis of Bsm/AG.

Cumulative hazard curves of relapse or death were drawn in subgroup of patients with polymorphism of Bsm/AG.

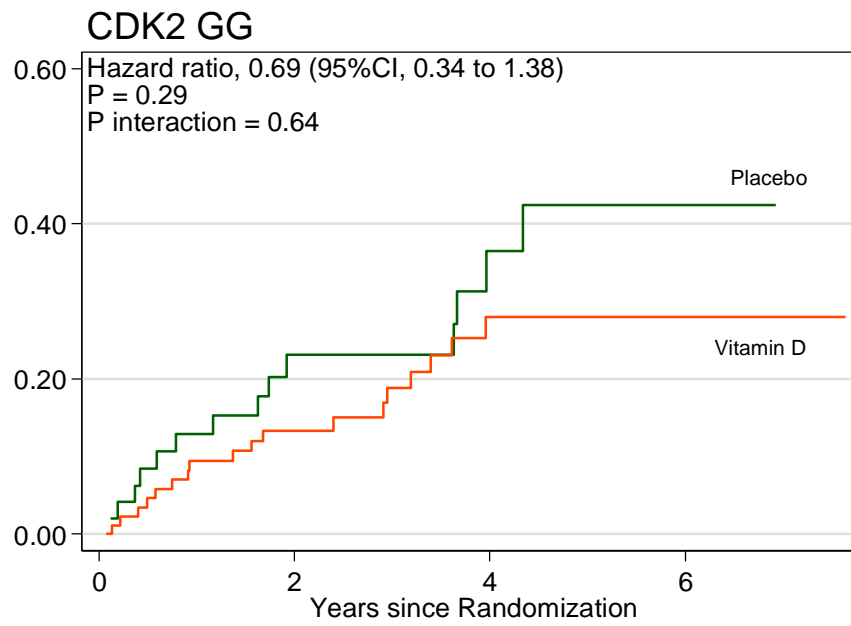


No. at risk table

Placebo	119	88	43	13
Vitamin D	175	125	72	29

eFigure 3F. Prespecified subgroup analysis of Bsm/ GG.

Cumulative hazard curves of relapse or death were drawn in subgroup of patients with polymorphism of Bsm/ GG.

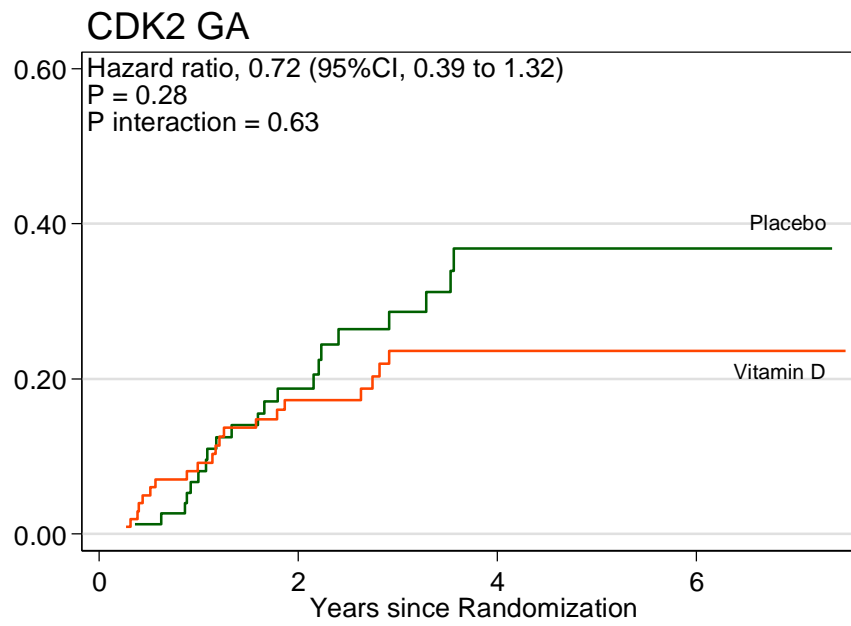


No. at risk table

Placebo	49	32	18	5
Vitamin D	89	62	34	7

eFigure 3G. Prespecified subgroup analysis of CDK2 GG.

Cumulative hazard curves of relapse or death were drawn in subgroup of patients with polymorphism of CDK2 GG.

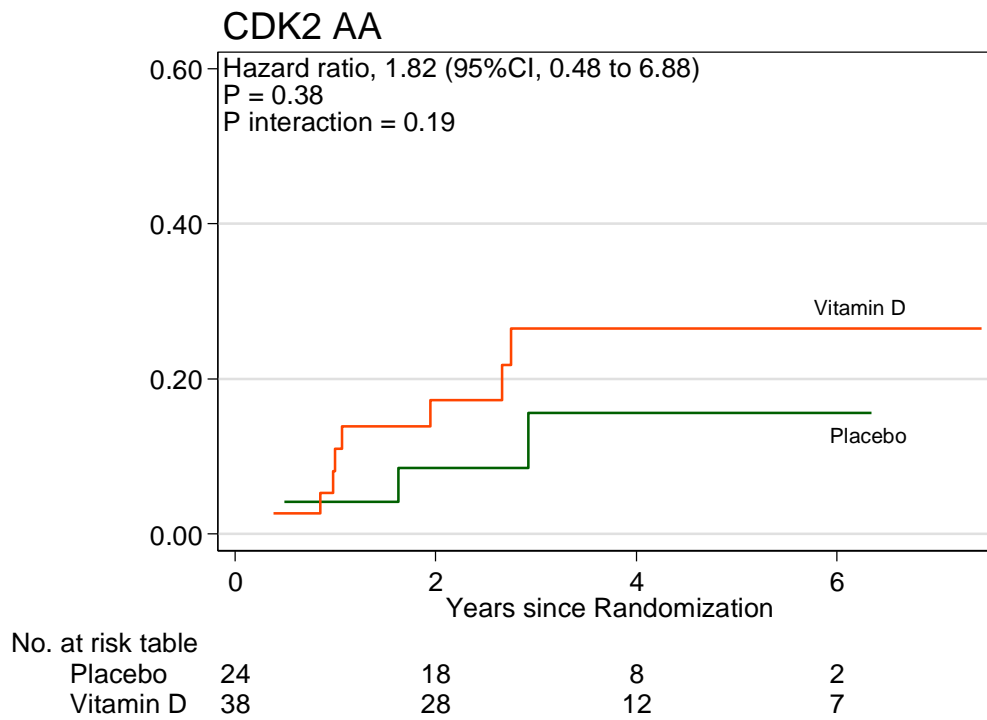


No. at risk table

Placebo	77	54	25	7
Vitamin D	103	72	46	20

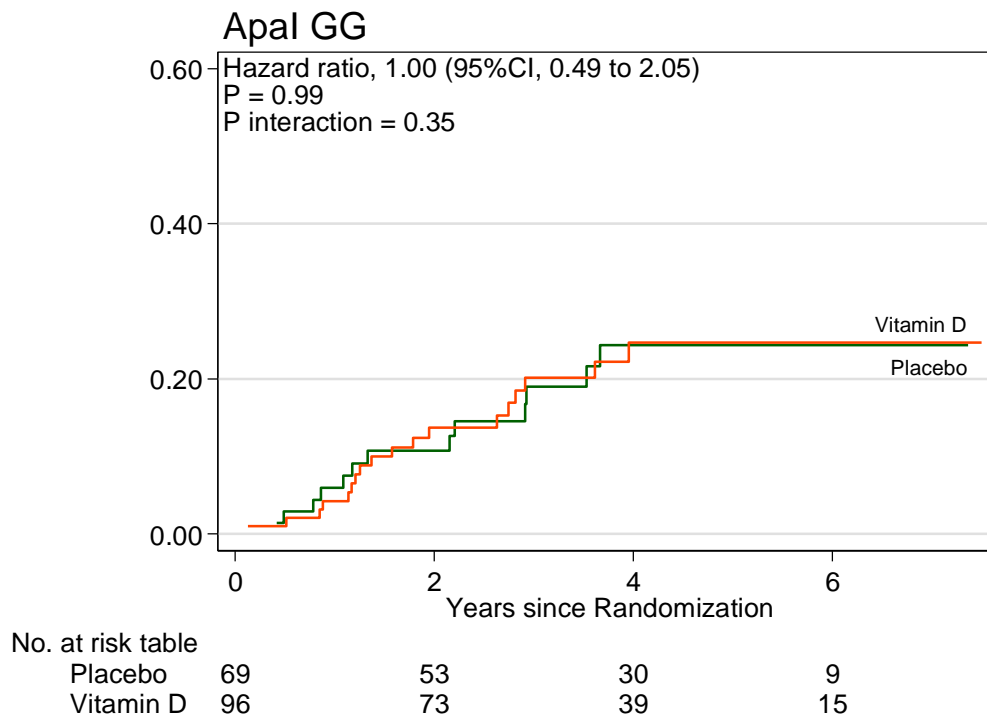
eFigure 3H. Prespecified subgroup analysis of CDK2 GA.

Cumulative hazard curves of relapse or death were drawn in subgroup of patients with polymorphism of CDK2 GA.



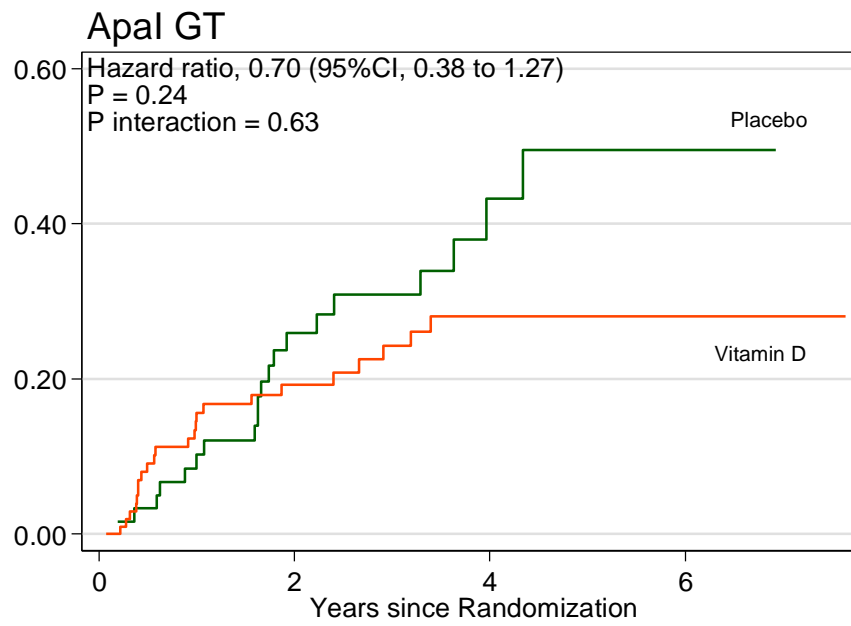
eFigure 3I. Prespecified subgroup analysis of CDK2 AA.

Cumulative hazard curves of relapse or death were drawn in subgroup of patients with polymorphism of CDK2 AA.



eFigure 3J. Prespecified subgroup analysis of Apa1 GG.

Cumulative hazard curves of relapse or death were drawn in subgroup of patients with polymorphism of Apa1 GG.

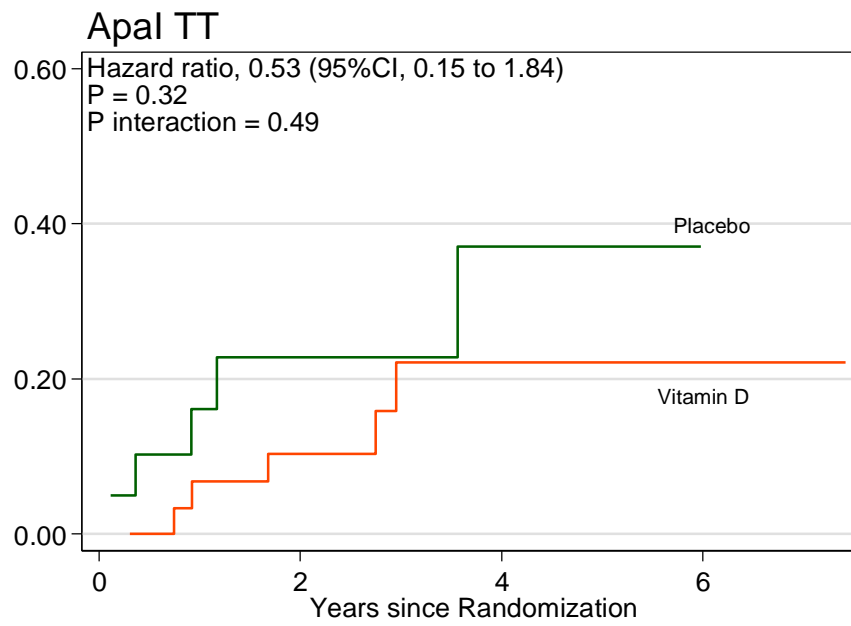


No. at risk table

Placebo	61	42	18	5
Vitamin D	104	65	40	14

eFigure 3K. Prespecified subgroup analysis of Apa1 GT.

Cumulative hazard curves of relapse or death were drawn in subgroup of patients with polymorphism of Apa1 GT.

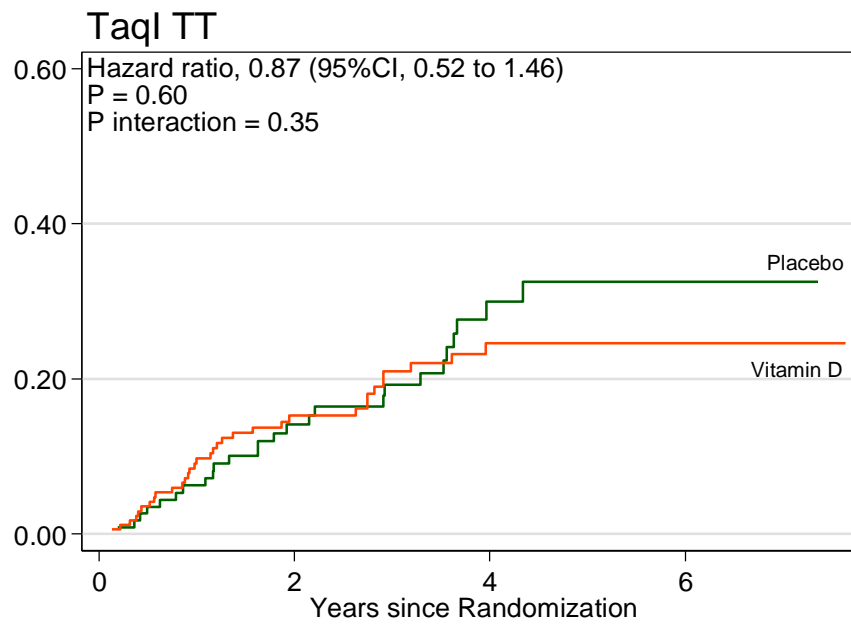


No. at risk table

Placebo	20	9	3	0
Vitamin D	31	24	13	5

eFigure 3L. Prespecified subgroup analysis of Apa/ TT.

Cumulative hazard curves of relapse or death were drawn in subgroup of patients with polymorphism of Apa/ TT.

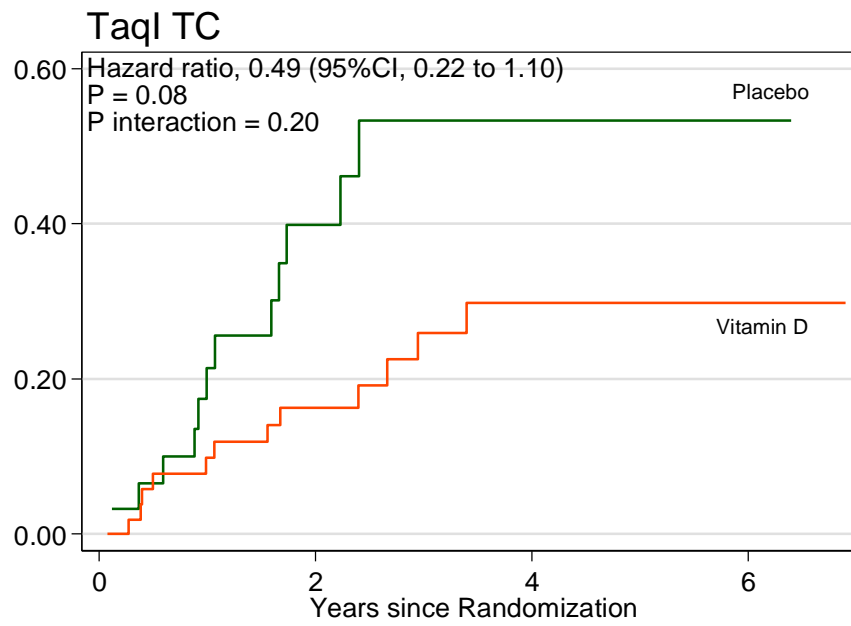


No. at risk table

Placebo	115	86	42	13
Vitamin D	172	122	70	29

eFigure 3M. Prespecified subgroup analysis of TaqI TT.

Cumulative hazard curves of relapse or death were drawn in subgroup of patients with polymorphism of TaqI TT.

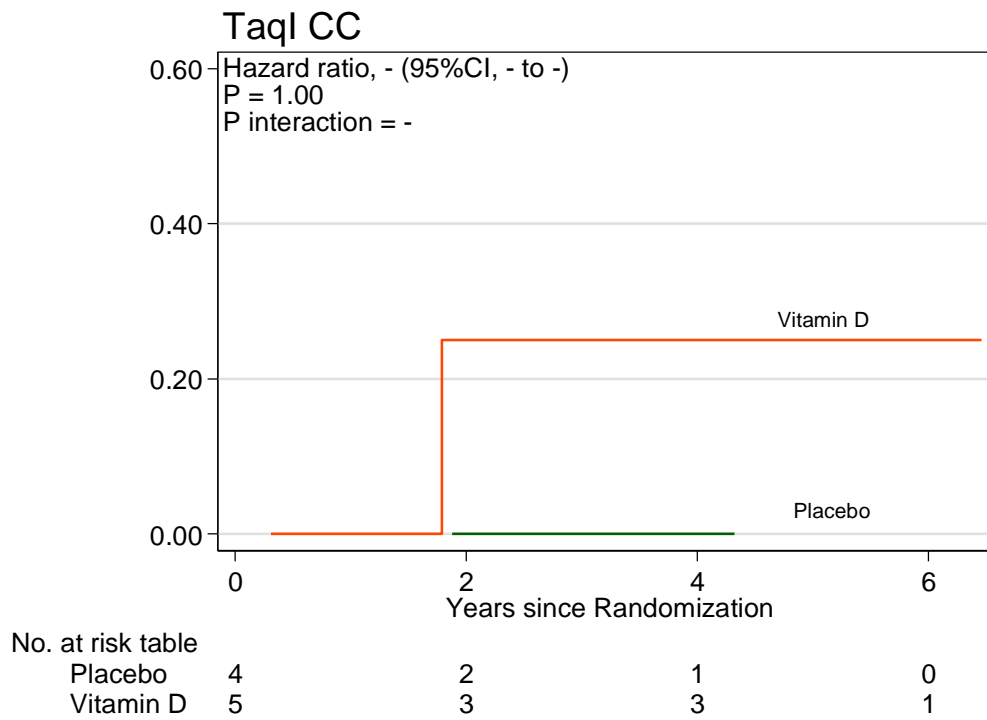


No. at risk table

Placebo	31	16	8	1
Vitamin D	54	37	19	4

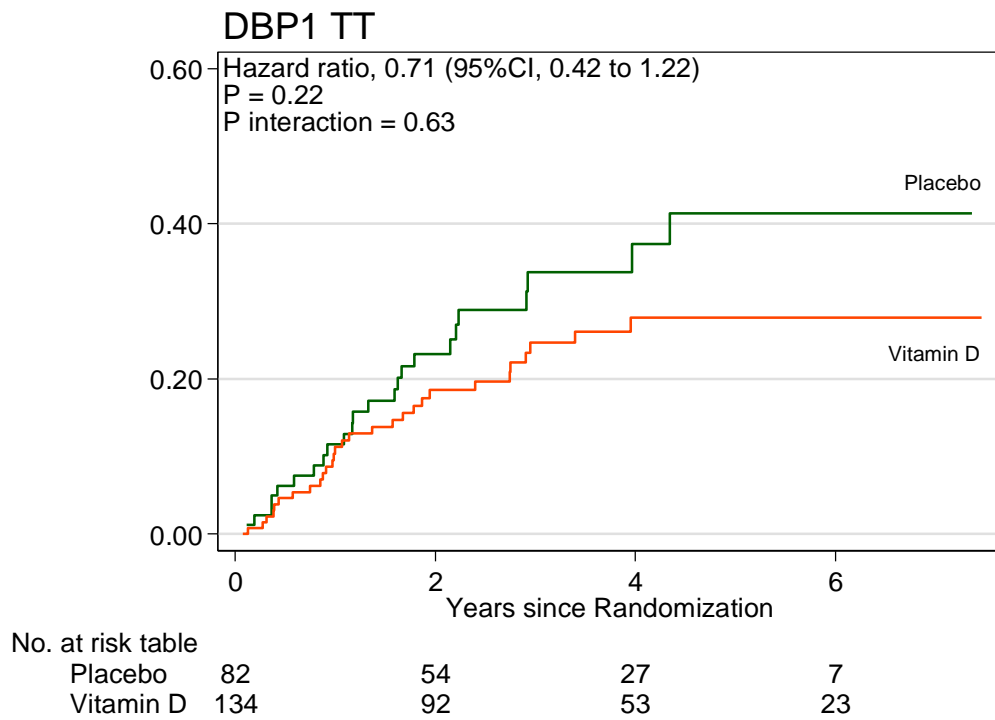
eFigure 3N. Prespecified subgroup analysis of TaqI/TC.

Cumulative hazard curves of relapse or death were drawn in subgroup of patients with polymorphism of TaqI/TC.



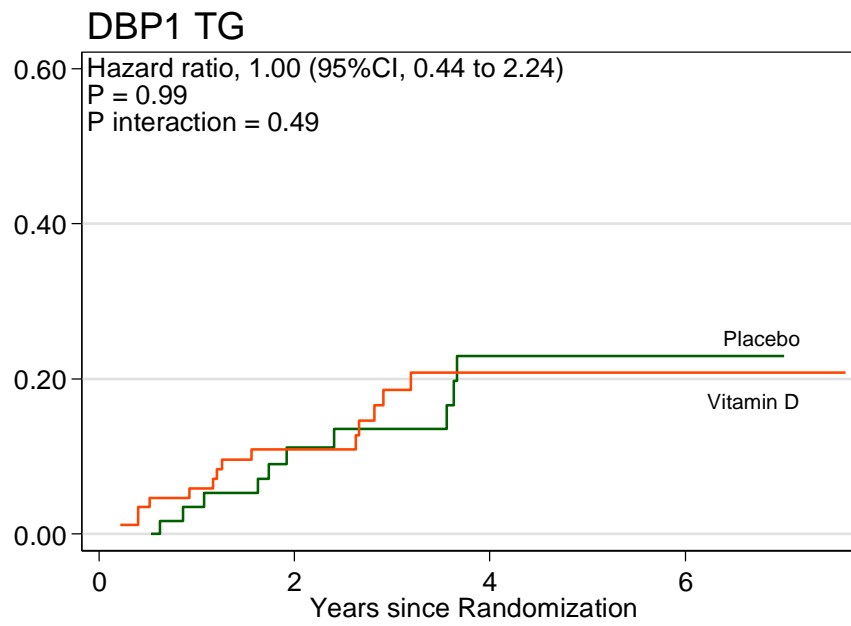
eFigure 30. Prespecified subgroup analysis of TaqI CC.

Cumulative hazard curves of relapse or death were drawn in subgroup of patients with polymorphism of TaqI CC.



eFigure 3P. Prespecified subgroup analysis of DBP1 TT.

Cumulative hazard curves of relapse or death were drawn in subgroup of patients with polymorphism of DBP1 TT.

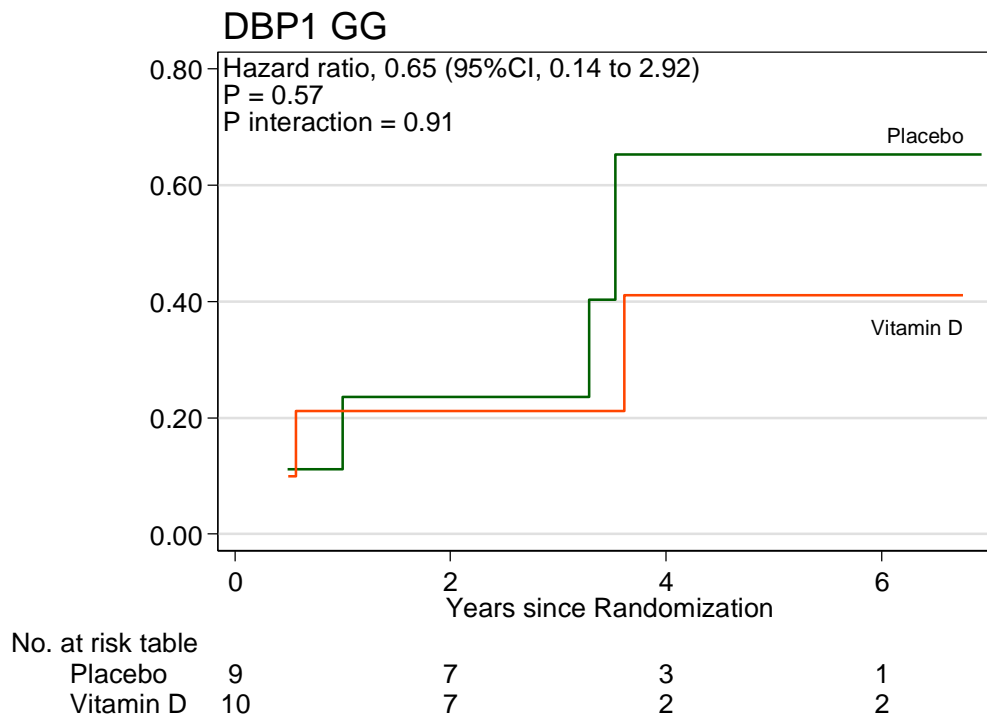


No. at risk table

Placebo	59	43	21	6
Vitamin D	87	63	37	9

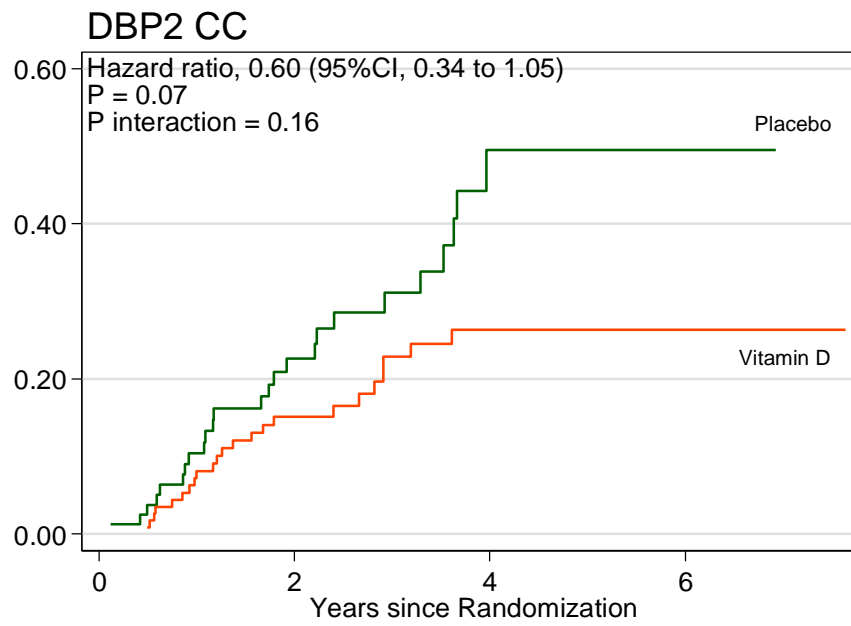
eFigure 3Q. Prespecified subgroup analysis of DBP1 TG.

Cumulative hazard curves of relapse or death were drawn in subgroup of patients with polymorphism of DBP1 TG.



eFigure 3R. Prespecified subgroup analysis of DBP1 GG.

Cumulative hazard curves of relapse or death were drawn in subgroup of patients with polymorphism of DBP1 GG.

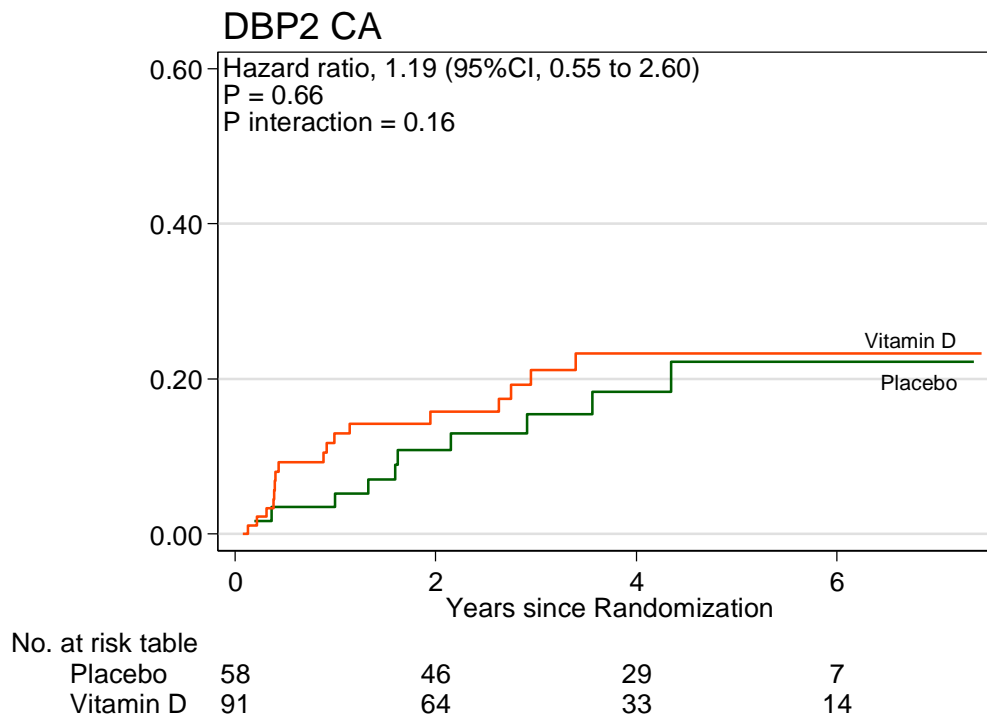


No. at risk table

Placebo	81	52	18	6
Vitamin D	115	78	49	15

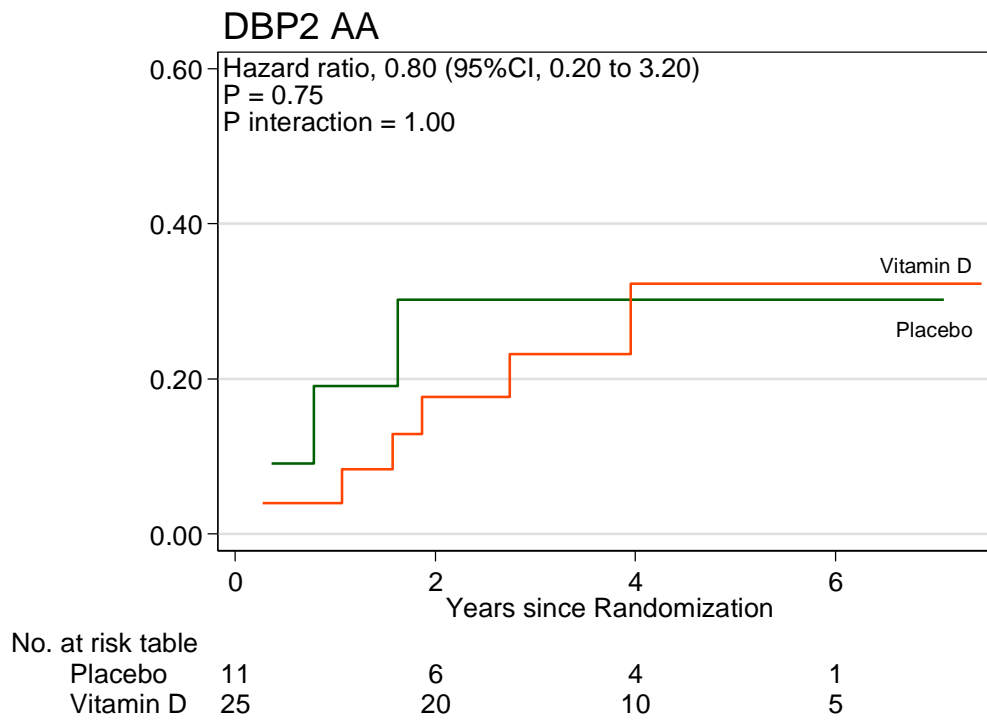
eFigure 3S. Prespecified subgroup analysis of DBP2 CC.

Cumulative hazard curves of relapse or death were drawn in subgroup of patients with polymorphism of DBP2 CC.



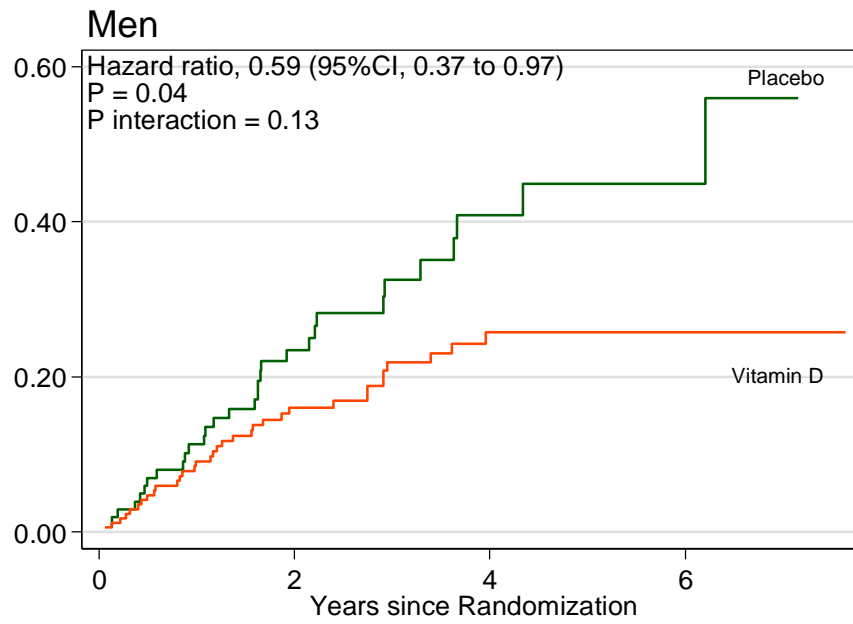
eFigure 3T. Prespecified subgroup analysis of DBP2 CA.

Cumulative hazard curves of relapse or death were drawn in subgroup of patients with polymorphism of DBP2 CA.



eFigure 3U. Prespecified subgroup analysis of DBP2 AA.

Cumulative hazard curves of relapse or death were drawn in subgroup of patients with polymorphism of DBP2 AA.

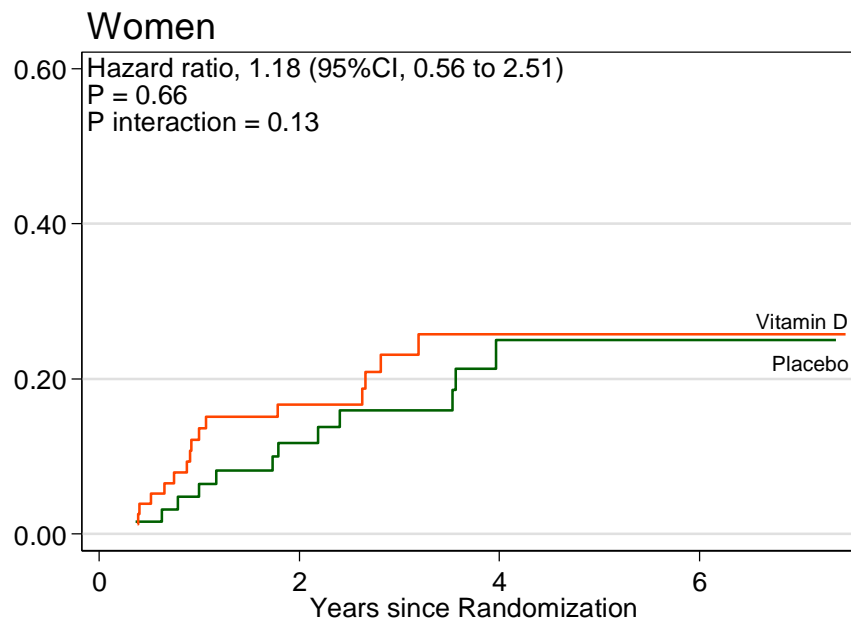


No. at risk table

Placebo	103	64	28	9
Vitamin D	173	120	65	30

eFigure 4A. Post hoc subgroup analysis of men.

Cumulative hazard curves of relapse or death were drawn in subgroup of men.



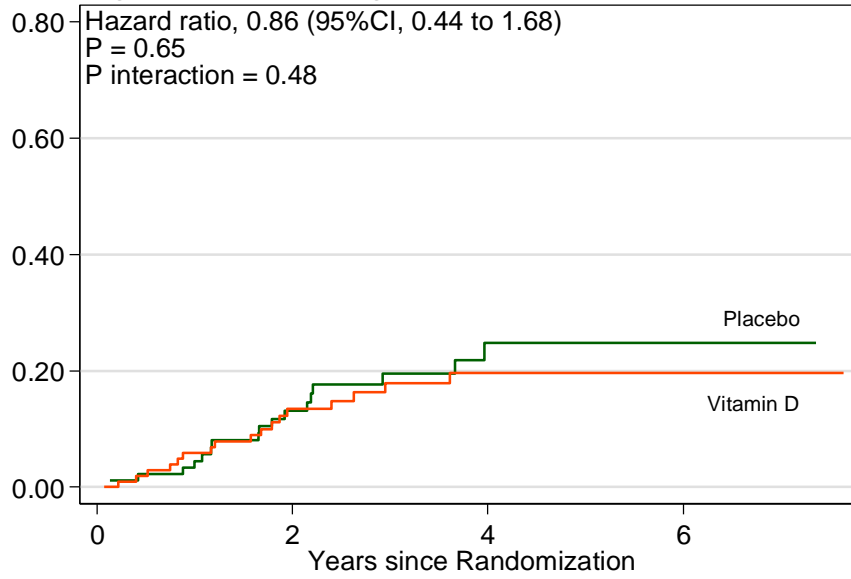
No. at risk table

Placebo	63	49	26	7
Vitamin D	78	56	28	5

eFigure 4B. Post hoc subgroup analysis of women.

Cumulative hazard curves of relapse or death were drawn in subgroup of women.

Age 65 and younger



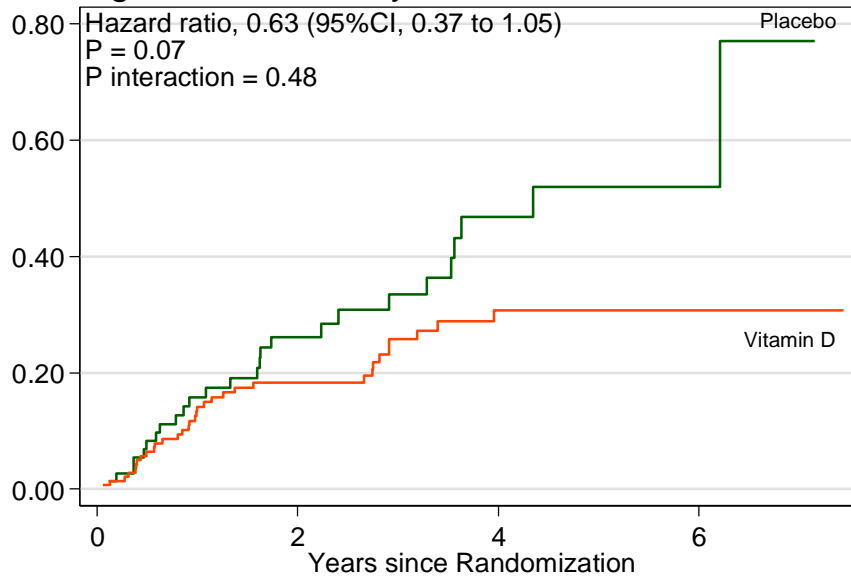
No. at risk table

Placebo	91	68	33	11
Vitamin D	106	76	45	18

eFigure 5A. Post hoc subgroup analysis of younger than median (≤ 65 years of age).

Cumulative hazard curves of relapse or death were drawn in subgroup of participants with age of 65 and younger.

Age older than 65 years

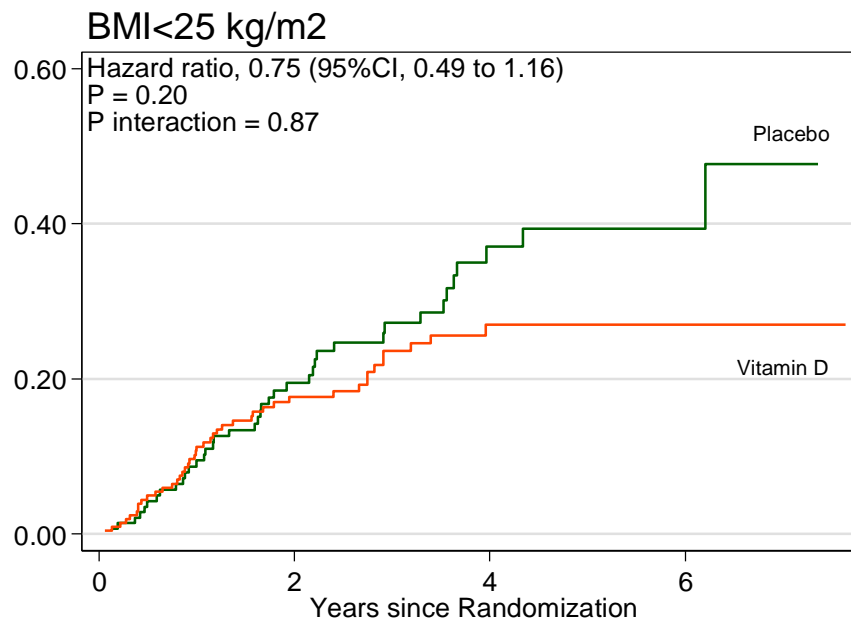


No. at risk table

Placebo	75	45	21	5
Vitamin D	145	100	48	17

eFigure 5B. Post hoc subgroup analysis of older than median (> 65 years of age).

Cumulative hazard curves of relapse or death were drawn in subgroup of participants older than 65 years of age.

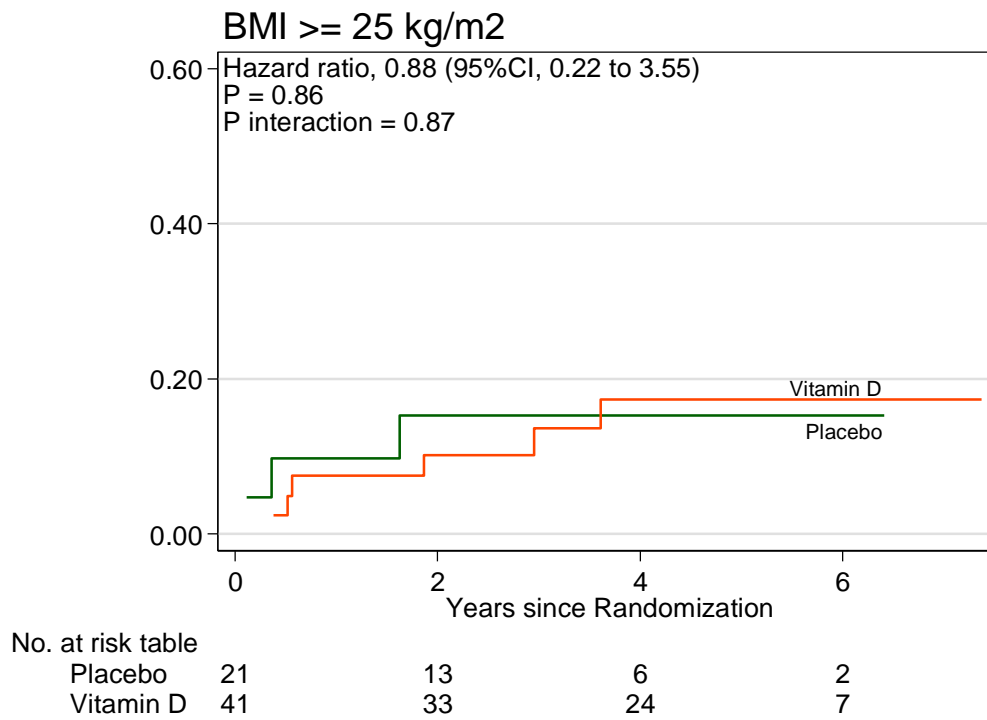


No. at risk table

Placebo	144	99	47	14
Vitamin D	208	141	68	28

eFigure 6A. Post hoc subgroup analysis of BMI <25 kg/m².

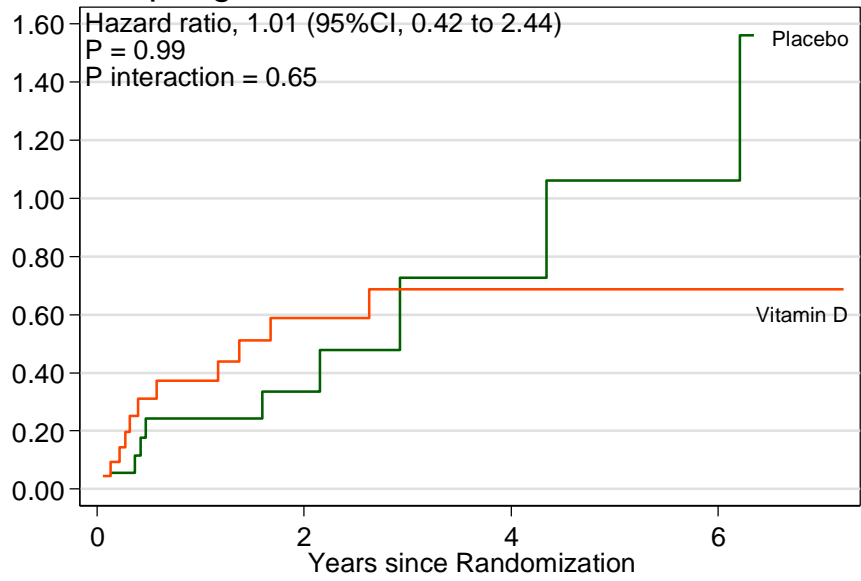
Cumulative hazard curves of relapse or death were drawn in subgroup of participants with BMI <25 kg/m².



eFigure 6B. Post hoc subgroup analysis of BMI ≥ 25 kg/m².

Cumulative hazard curves of relapse or death were drawn in subgroup of participants with BMI ≥ 25 kg/m².

Esophageal cancer



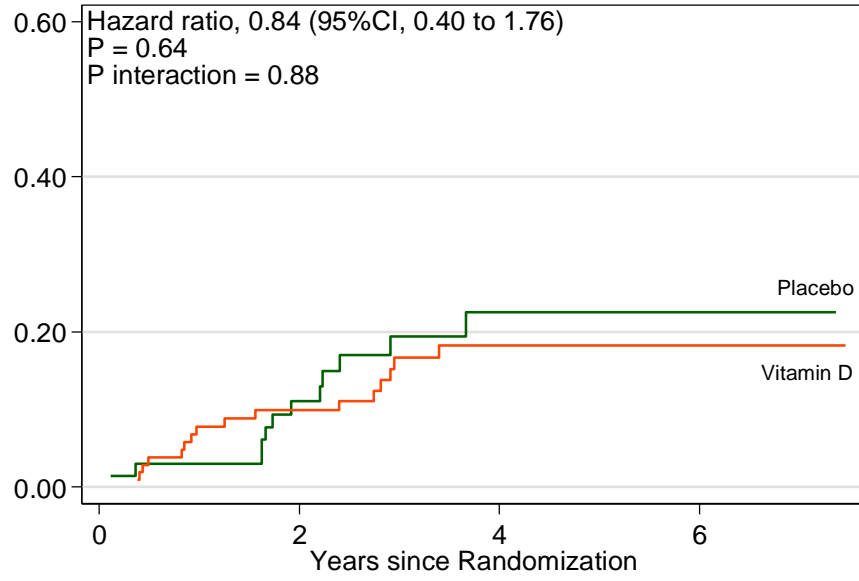
No. at risk table

Placebo	18	7	3	2
Vitamin D	22	11	4	2

eFigure 7A. Subgroup analysis of esophageal cancer.

Cumulative hazard curves of relapse or death were drawn in subgroup of patients with esophageal cancer.

Gastric cancer



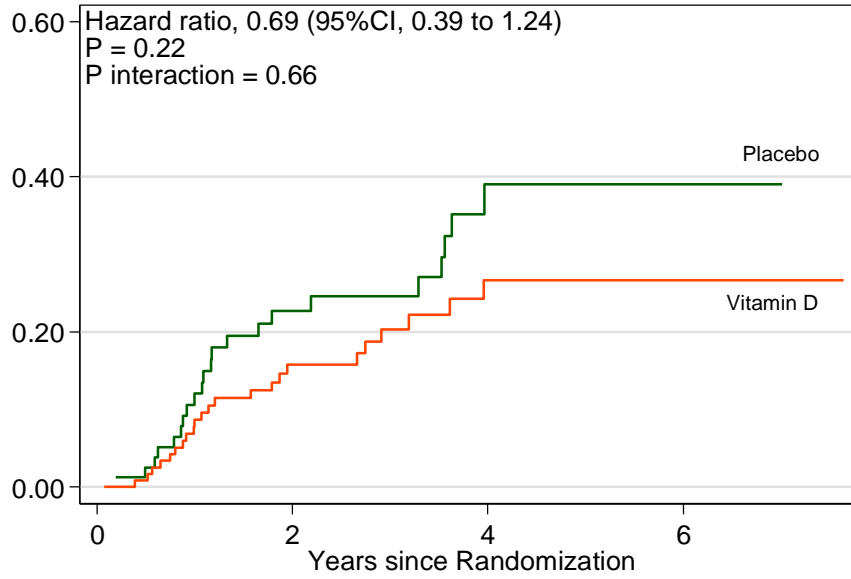
No. at risk table

Placebo	68	53	26	8
Vitamin D	106	84	50	17

eFigure 7B. Subgroup analysis of gastric cancer.

Cumulative hazard curves of relapse or death were drawn in subgroup of patients with gastric cancer.

Colorectal cancer

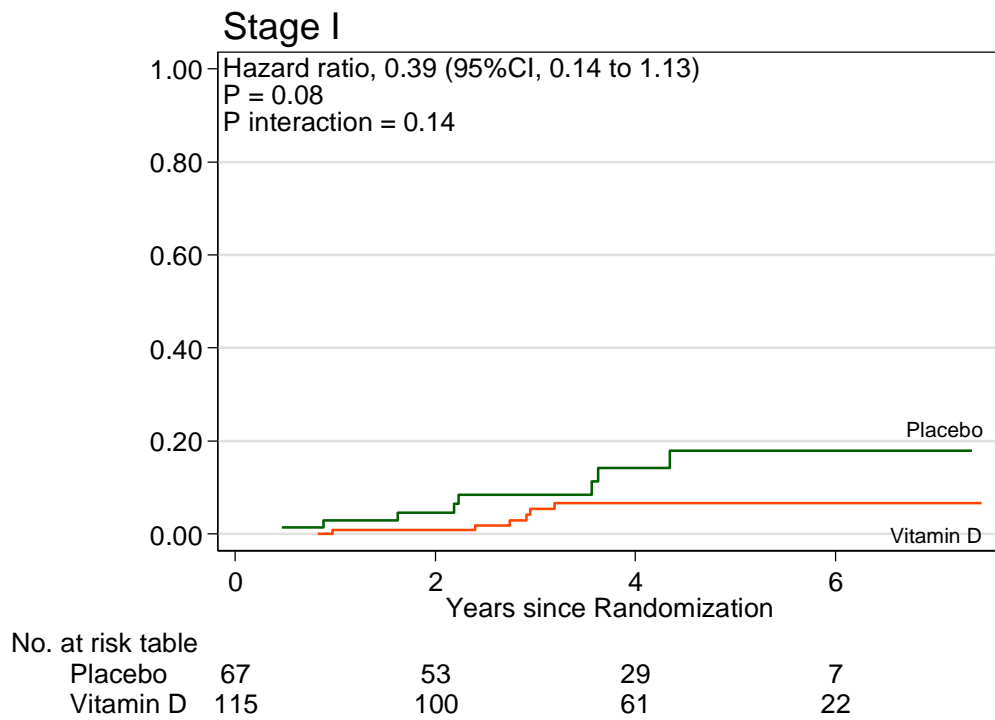


No. at risk table

Placebo	79	52	25	6
Vitamin D	122	80	38	15

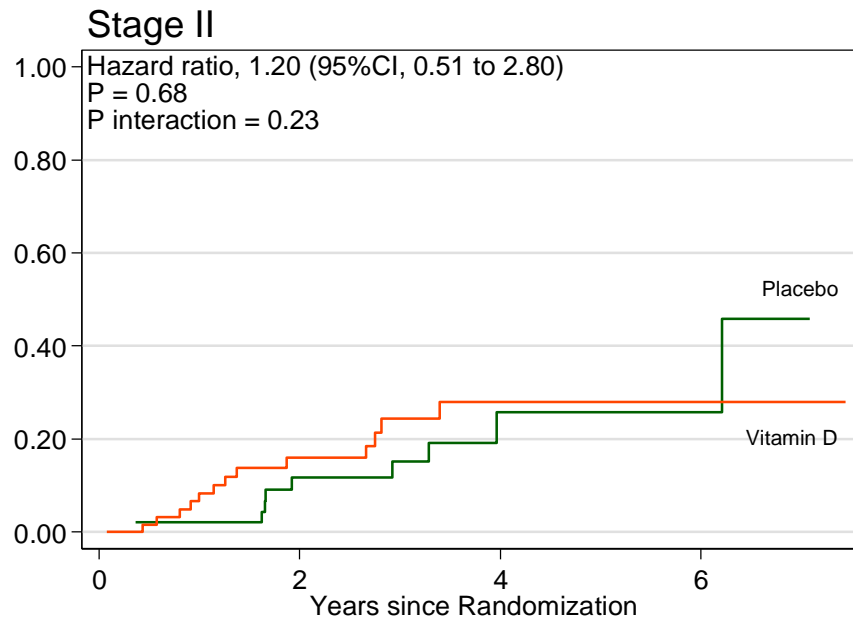
eFigure 7C. Subgroup analysis of colorectal cancer.

Cumulative hazard curves of relapse or death were drawn in subgroup of patients with colorectal cancer.



eFigure 8A. Post hoc subgroup analysis of stage I.

Cumulative hazard curves of relapse or death were drawn in subgroup of patients with stage I.

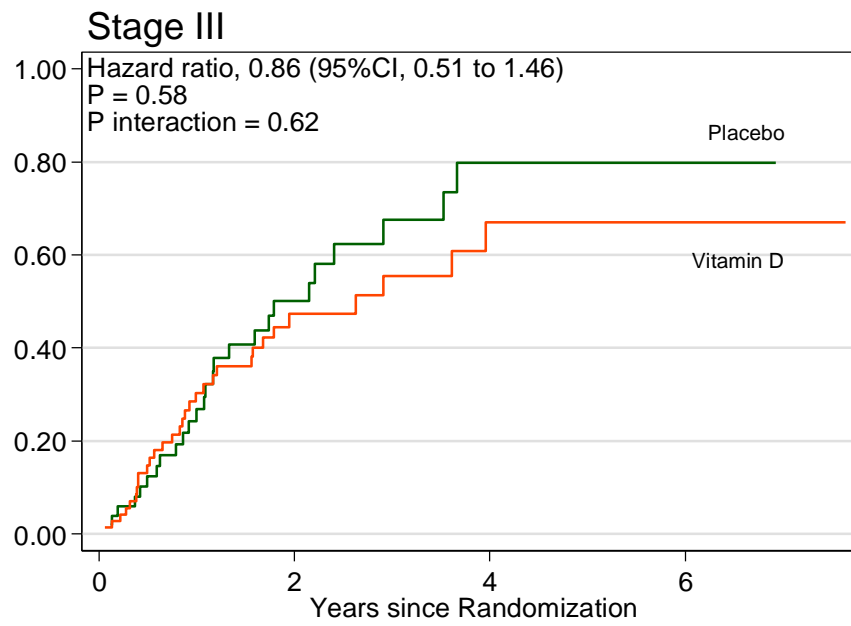


No. at risk table

Placebo	48	34	14	6
Vitamin D	63	42	18	7

eFigure 8B. Post hoc subgroup analysis of stage II.

Cumulative hazard curves of relapse or death were drawn in subgroup of patients with stage II.



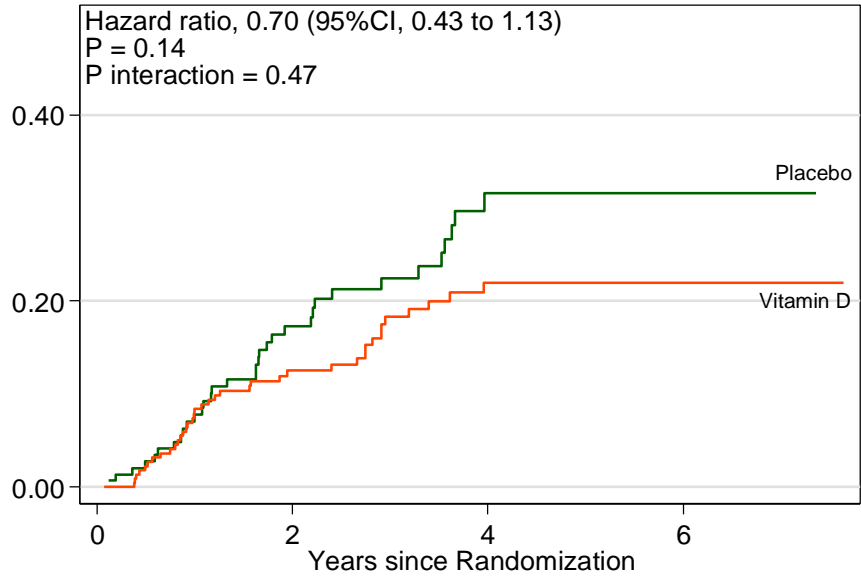
No. at risk table

Placebo	51	26	11	3
Vitamin D	73	34	14	6

eFigure 8C. Post hoc subgroup analysis of stage III.

Cumulative hazard curves of relapse or death were drawn in subgroup of patients with stage III.

Adenocarcinoma



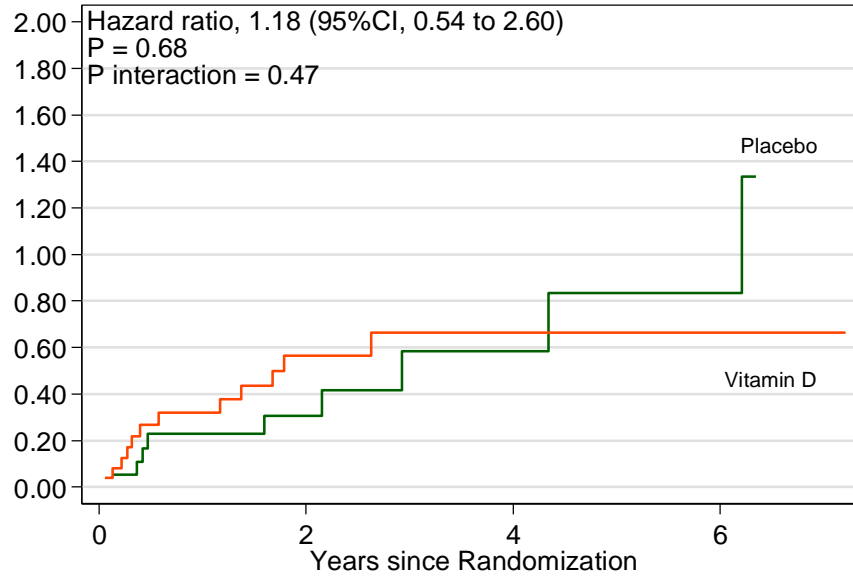
No. at risk table

Placebo	147	104	50	14
Vitamin D	226	164	89	33

eFigure 9A. Post hoc subgroup analysis of adenocarcinoma.

Cumulative hazard curves of relapse or death were drawn in subgroup of patients with adenocarcinoma.

Non-adenocarcinoma



No. at risk table

Placebo	19	9	4	2
Vitamin D	25	12	4	2

eFigure 9B. Post hoc subgroup analysis of non-adenocarcinoma.

Cumulative hazard curves of relapse or death were drawn in subgroup of patients with non-adenocarcinoma.