

1 Genetic predictors of circulating 25-hydroxyvitamin D and prognosis after colorectal cancer

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36 **Abstract:**

37 **Background:**

38 Low serum 25-hydroxyvitamin D (25(OH)D) concentrations in colorectal cancer (CRC) patients have
39 been consistently associated with higher mortality in observational studies. It is unclear whether low
40 25(OH)D levels directly influence CRC mortality. To minimize bias, we use genetic variants
41 associated with vitamin D levels to evaluate the association with overall and CRC-specific survival.

42 **Methods:**

43 Six genetic variants have been robustly identified to be associated with 25(OH)D levels in genome-
44 wide association studies. Based on data from the International Survival Analysis in Colorectal Cancer
45 Consortium (ISACC) the individual genetic variants and a weighted genetic risk score were tested for
46 association with overall and CRC-specific survival using Cox proportional hazards models in 7 657
47 stage I-IV CRC patients of which 2 438 died from any cause and 1 648 died from CRC.

48 **Results:**

49 The 25(OH)D decreasing allele of single nucleotide polymorphism (SNP) rs2282679 (*GC*) was
50 associated with poorer CRC-specific survival, although not significant after multiple-testing
51 correction. None of the other five SNPs showed an association. The genetic risk score showed non-
52 significant associations with increased overall (HR=1.54, 95% CI:0.86-2.78) and CRC-specific
53 mortality (HR=1.76, 95% CI:0.86-3.58). A significant increased risk of overall mortality was observed
54 in women (HR=3.26, 95% CI:1.45-7.33, p-value for heterogeneity=0.01) and normal-weight individuals
55 (HR=4.14, 95% CI:1.50-11.43, p-value for heterogeneity=0.02).

56 **Conclusions:**

57 Our results provided little evidence for an association of genetic predisposition of lower vitamin D
58 levels with increased overall or CRC-specific survival, although power might have been an issue.

59 **Impact:**

60 Further studies are warranted to investigate the association in specific subgroups.

61

62 **Introduction:**

63 Colorectal cancer (CRC) belongs to the most common cancer types (third) and is the second leading
64 cause of cancer related death globally (1). Despite improved therapy regimens which have led to
65 increased survival after diagnosis, survival time is still limited for advanced stages (2).

66 One of the factors with potential prognostic relevance is 25(OH)D levels since the vitamin D receptor
67 is highly expressed in the colon (3,4). The most stable and therefore most reliable indicator of
68 circulating vitamin D is 25(OH)D; it is influenced by both dietary intake and skin synthesis by sun
69 exposure (5). Low levels of 25(OH)D have been consistently found associated with reduced overall
70 (hazard ratio (HR): 0.68, 95% confidence interval (CI): 0.55–0.85) and CRC-specific survival (HR:
71 0.67, 95% CI: 0.57–0.78), as evidenced in a recent meta-analysis (6). Therefore, vitamin D status
72 could be a potential modifiable factor for improving prognosis in CRC patients.

73 It is unclear whether a genetic predisposition of higher/lower vitamin D levels is involved in
74 mechanisms leading to better survival or whether low vitamin D levels are primarily an indicator for
75 poor health (7). Studies assessing post-diagnostic vitamin D concentrations need to be interpreted with
76 caution as lower vitamin D levels in patients with poorer health could also be due to behavior changes
77 after diagnosis and treatment e.g. less sun exposure. The association between postdiagnostic vitamin D
78 and survival after CRC in observational studies could thus reflect confounding or reverse causation.

79 Previous genome-wide association studies (GWAS) have identified six single nucleotide
80 polymorphisms (SNPs) associated with circulating 25(OH)D levels at genome-wide significance (p-
81 value 5×10^{-8}) (8,9). The four SNPs with the strongest influence on vitamin D levels have been
82 replicated by several studies (8,9,32). As genetic variants are randomly allocated during gamete
83 formation independent of environmental factors, confounding should not play a role. Therefore,
84 determining associations using vitamin D-related genetic variants could help minimize confounding
85 bias and reverse causation.

86 We aimed to estimate the relationship of these six vitamin D related genetic variants with overall and
87 CRC-specific survival in studies collaborating in the International Survival Analysis in Colorectal
88 Cancer Consortium (ISACC).

89

90 **Materials and Methods:**

91 **Study population and genotype data:**

92 This analysis is based on 7 657 CRC patients from 10 studies with available genotyping and follow-up
93 data participating in the ISACC Consortium. The studies are Darmkrebs: Chancen der Verhuetung
94 durch Screening (DACHS) (10,11), Diet, Activity and Lifestyle Study (DALIS) (12), Cancer
95 Prevention Study II Nutrition cohort (CPSII) (13), Health Professionals Follow-up Study (HPFS) (14),
96 Nurses' Health Study (NHS) (15-17), Physicians' Health Study (PHS) (18); Prostate, Lung, Colorectal
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98 Cancer Family Registry Study (PMH-CCFR), VITamins And Lifestyle Study (VITAL) (21) and
99 Woman's Health Initiative (WHI) (22) (Supplementary Table 1). Nine of the ten studies are also
100 included in the Genetics and Epidemiology of Colorectal Cancer Consortium (GECCO) (23) and one
101 study, CPS II, is part of the Colorectal Cancer Transdisciplinary consortium (CORECT) (24). Details
102 on the consortia and studies have been described previously (13,23,24) and study descriptions are
103 provided in the supplementary information (Supplementary Table 1). Participant overlap between the
104 studies has been excluded. All participants provided written, informed consent and studies were
105 approved by their respective institutional review boards. Demographic and lifestyle factors were
106 queried by in-person interviews or self-filled questionnaires. A multistep data harmonization
107 procedure was carried out centrally for pooled analyses (25). Details of assessment of survival in the
108 individual studies have been previously published (10,12-14,17,21,26-29). In short, vital status was
109 obtained either using active follow-up with confirmation of death by review of death certificates or
110 medical records or the studies used linkage to state death records or state cancer registries. Alive
111 patients were censored at the date of last follow-up or data linkage.

112 **Genotype data and imputation**

113 All included studies provided genotype information. See previously published reports for details on
114 genotyping, quality assurance and imputation (23,24,30). Imputation was conducted using the
115 imputation panel of the Haplotype Reference Consortium (31). Exclusion of SNPs was based on call
116 rate (<98% in GECCO; <95% in CORECT), Hardy-Weinberg equilibrium in controls (p -value< 1×10^{-6})

117 ⁴) or low minor allele frequency ($\leq 1\%$). Patients were assigned values of 0, 1, or 2 for having 0 (wild-
118 type homozygous), 1 (heterozygous) or 2 (homozygous for the risk allele) alleles associated with
119 lower vitamin D levels for each SNP. For imputed SNPs, patients received continuous values between
120 0 and 2.

121 **SNP selection and Genetic Risk Score**

122 Six SNPs, which were found associated with 25(OH)D levels at genome-wide significance (p-
123 value $< 5 \times 10^{-8}$) in a GWAS of European populations, were selected (8,9,32) (Table 1). Two of these
124 SNPs have been recently discovered by the SUNLIGHT Consortium (8), which also confirmed the
125 other four previously identified SNPs (9). The six SNPs explain around 2.8% of the variance in
126 circulating 25(OH)D levels (8).

127 Linkage disequilibrium between the individual SNPs was checked, and no strong correlation was
128 detected ($R^2 < 0.01$). A weighted genetic risk score (GRS) consisting of the six SNPs was calculated for
129 each person as the sum of the number of vitamin D decreasing alleles weighted by their effect on
130 vitamin D levels as reported in Jiang et al. (8). As Jiang et al. used natural log transformed vitamin D
131 levels as outcome in their GWAS, units of the GRS are not easily interpretable. The risk score ranges
132 between 0 and 0.432. Results are reported per one unit increase in risk score.

133 According to Milaneschi et al. (33) a one unit increase in this risk score is associated with a change of
134 5.29nmol/l (95% CI:4.18-6.39).

135 **Statistical analysis:**

136 The association of the individual SNPs with overall survival and CRC-specific survival was assessed
137 using cox proportional hazard models. Analyses were adjusted for age, sex and principal components
138 (PCs) of genetic ancestry to control for potential confounding due to population substructure (PCs
139 were calculated using the EIGENSTRAT method (<https://reich.hms.harvard.edu/software>)). Three PCs
140 were used for Analysis of GECCO studies used three PC and 10 PCs were used for CPSII from the
141 CORECT consortium. Analyses were conducted for GECCO and CORECT studies separately. Fixed-
142 effects meta-analysis was employed to get summary results for GECCO and CORECT. Bonferroni
143 correction was used to account for multiple testing of six single SNP tests ($p < 0.05/6 = 0.0083$).

144 Additional stratified analyses were carried out by sex, cancer site (colon/rectum), stage (stage 1-local,
145 stage 2,3-regional, stage 4-distant) and BMI categories (self-reported pre-diagnostic BMI) in kg/m²
146 (BMI 18.5–24.9 for normal weight, 25-30 for overweight, >30 for obese, excluding the 1% with
147 BMI<18.5). Heterogeneity was assessed using likelihood ratio tests which compare the models
148 including / excluding interaction term.

149 To calculate time-to-event, date of diagnosis was considered as the starting point and follow-up time
150 was censored at death or end of follow-up, whichever occurred first. For calculation of CRC-specific
151 survival, censoring was done at the time of death for all patients who died from other causes than CRC
152 The reverse Kaplan-Meier method was employed for calculation of median follow-up time (34).

153 **Results:**

154 Of 7 657 CRC patients included for this analysis, 2 438 died from any cause and 1 648 died from CRC
155 after a median follow-up time of 54.8 month (interquartile range: 27.7-73.6 months). Supplementary
156 Table 2 shows selected characteristics of the study population and numbers per GECCO/CPSII.
157 Among patients included, 54.6% were women and 45.4% were men.

158 The association of the vitamin D associated SNPs with overall and with CRC-specific survival were
159 similar, see Table 2. None of the six SNPs were statistically significantly associated with overall
160 survival. There was a significant association between SNP rs2282679 and CRC specific survival (HR:
161 1.08, 95% CI: 1.00-1.16) (Table 2), which did not remain significant when applying a Bonferroni
162 corrected p-value of <0.0083. None of the other five SNPs showed significant associations with CRC
163 specific survival. Results per GECCO/CPSII studies are shown in Supplementary Table 3 for overall
164 survival and CRC-specific survival.

165 The GRS representing genetically determined lower levels of vitamin D was not significantly
166 associated with risk of death after CRC diagnosis (HR per one unit of GRS: 1.54, 95% CI: 0.86-2.78)
167 (Table 3). For CRC-specific survival, a similar non-significant association was found for lower
168 genetically determined levels of vitamin D (HR per one unit of GRS: 1.76, 95% CI: 0.86-3.58).

169 Exploration of effect heterogeneity yielded differential associations for overall survival according to
170 sex and BMI (Table 3). A higher GRS was significantly associated with increased overall mortality
171 (HR: 3.26, 95% CI: 1.45-7.33) in women and not in men (HR: 0.68, 95% CI: 0.29-1.62). In addition,
172 the association of higher GRS with increased overall mortality was only significant in normal weight
173 patients (HR: 4.14, 95% CI: 1.50-11.43) but not obese patients (HR: 1.67, 95% CI: 0.53-5.26). In
174 overweight patients the SNP association was in the opposite direction (HR: 0.55, 95% CI: 0.21-1.45).
175 No significant differential associations were found for CRC-specific survival, but associations in the
176 subgroups were generally similar to that for overall survival in magnitude and direction (Table 3).

177 **Discussion**

178 In this large study, we investigated the association between six genetic variants and a GRS associated
179 with vitamin D levels and overall and CRC-specific survival. The single SNPs and GRS were not
180 significantly associated with overall/CRC-specific survival. We found significant effect heterogeneity
181 by sex and BMI in the association of GRS for vitamin D and overall survival.

182 Recent large observational studies reported inverse associations between serum 25(OH)D levels and
183 survival after CRC (4,35,36). Except for one study that used pre-diagnostic 25(OH)D levels (35) all
184 studies used post-diagnostic vitamin D levels which could already have been influenced by the disease
185 or a poor health status after treatment (4,36). We and others have thus employed vitamin D related
186 genetic variants as instrumental variables to evaluate the association with CRC mortality in order to
187 minimize bias due to reverse causation and confounding.

188 A recent study that investigated only rs2282679 (*GC* gene) found a non-significant association with
189 reduced overall survival in 489 CRC patients, corroborating our findings. Additionally, they reported a
190 significant association of the vitamin D lowering allele with poorer disease-free survival (37),
191 however, CRC-specific survival was not investigated. A further study that investigated three SNPs
192 rs2282679 (*GC*), rs10741657 (*CYP2R1*) and rs12785878 (*DHCR7*) in association with time to
193 recurrence in patients with stages II and III colon cancer found only rs2282679 to be significantly
194 associated with decreased time to recurrence in the subgroup of patients who underwent only surgery
195 (38).

196 Mendelian randomization (MR) studies on vitamin D levels have also been conducted. These MR
197 studies were not conducted specifically in CRC patients and CRC-specific death was not investigated
198 as outcome in any of these studies. A former large MR study of 95 766 participants investigated the
199 association of SNPs associated with lower vitamin D levels (using a GRS score of two SNPs in the
200 *DHCR7* gene and two SNPs in the *CYP2R1* gene explaining around 1% in variation in vitamin D
201 levels) with all-cause mortality and cancer-specific mortality and found that the genetic instrument
202 was associated with increased all cause and cancer-specific mortality (39). In contrast to that, a study
203 in women of 33 682 participants and 3 985 cancer cases found no significant association of a five SNP

204 instrument and overall or cancer mortality (40). A recent study using UK Biobank data (438 870
205 participants and 6 998 cancer-specific deaths) did not find evidence for genetically determined low
206 vitamin D levels (using five vitamin D related variants, four of them overlapping with the variants
207 used in our study) and increased cancer mortality (41). The variance in vitamin D levels explained by
208 a genetic instrument using the previously known four SNPs, which were confirmed by Jiang et al., was
209 estimated to be approximately 5% (42). Jiang et al. estimated that the six SNPs used in our study
210 explain around 2.8% of genetic variation; 7.5% of variation was explained by all common GWAS
211 variants (8).

212 We found sex-differences in the association of the GRS with overall survival. Some observational
213 studies have also observed differences by sex (43) or significant associations of vitamin D levels with
214 cancer incidence (44) or mortality only in women (45) but not in men. In the present study, the GRS
215 conferring lower vitamin D levels was found associated with worse prognosis only in women. One
216 reason for this could be stronger associations of vitamin D levels with diseases that are more common
217 in women than in men, like breast cancer (46) and osteoporosis (47). But whether the vitamin D
218 related SNPs are also associated with breast cancer mortality or mortality after osteoporosis (e.g. as
219 consequence of fractures) is unclear. A lookup in the BCAC consortium including 42 124 patients with
220 3 733 breast cancer-specific deaths showed that rs2282679 is not associated with breast cancer specific
221 mortality (<http://bcac.ccge.medschl.cam.ac.uk/>). A SNP in the vitamin D receptor gene, which was
222 previously reported to be significantly associated with higher breast cancer specific mortality in 498
223 breast cancer patients (48), has not been found associated with vitamin D levels in GWAS. In addition,
224 our finding of higher mortality with a GRS for lower 25(OH)D levels only in normal weight people is
225 interesting and it is consistent with results of a recent RCT in the VITAL study of vitamin D
226 supplementation and all cancer incidence (49) which found lower all-cancer incidence only in normal
227 weight participants receiving vitamin D compared to placebo and not in overweight or obese
228 participants. It is known that overweight and obese people have lower levels of vitamin D compared to
229 normal weight people (7) which could be due to sequestration of vitamin D in adipose tissues or
230 dilution of ingested vitamin D (7). In this case higher levels of 25(OH)D would be needed for
231 protection in overweight/obese individuals. Also there is a difference in direction of point estimates

232 when comparing the overweight and obese groups. Since the confidence intervals are large, these
233 differences could be due to chance because of power issues for the subgroup analyses and therefore
234 needs to be investigated in further larger studies.

235 Regarding mortality after CRC diagnosis, RCTs of vitamin D supplementation are also being
236 conducted. Two recent meta-analysis reported that vitamin D supplementation reduced all-cancer
237 death by 16% (50) and 13% (51), CRC death was not specifically investigated. One small RCT has
238 been published (52) on vitamin D supplementation in CRC patients which was conducted in Croatia
239 and randomized 71 metastatic CRC patients to either standard chemotherapy or standard
240 chemotherapy plus 2000IU vitamin D. No difference in overall or progression-free survival between
241 groups was observed (52). A further RCT of 139 metastatic CRC patients reported in a conference
242 abstract a longer progression-free survival in patients who received high vitamin D supplementation
243 compared to low vitamin D supplementation (53). A more recent RCT found suggestive evidence that
244 high dose compared to standard-dose vitamin D supplementation combined with chemotherapy could
245 improve survival for patients with advanced or metastatic CRC (54). Supplementation for CRC
246 patients might have a different effect on mortality after CRC compared to genetically determined
247 differences in vitamin D levels. And this RCT suggests that higher than physiologic levels may lead to
248 improvement in survival.

249 Strengths of our study include the large sample size, which is the largest published sample size among
250 CRC survivors to date for investigation of the association of vitamin D related genetic variants with
251 overall and CRC-specific survival. We used the latest published set of SNPs discovered in GWAS to
252 be associated with vitamin D levels. The association of vitamin D related SNPs with CRC-specific
253 survival has been investigated for the first time. Moreover, all included studies carried out a
254 comprehensive follow-up with long follow-up duration. Our study has also some limitations. As this
255 study is based on populations of European descent, the generalizability to other populations is limited.
256 The advantage is that we were able to minimize bias due to confounding by population stratification.
257 We did not have serum measurements of vitamin D levels available for all included studies; therefore
258 we were not able to analyze the strength of the association of the SNPs with vitamin D levels in our

259 study. Although our study has a large sample size, power to conduct a Mendelian randomization study
260 is still limited due to the moderate association of the SNPs with decreasing vitamin D levels.

261 In conclusion, this is the first study to examine the most recent set of vitamin D related SNPs
262 discovered in GWAS with respect to overall and also CRC-specific mortality among CRC patients. We
263 did not find evidence for an association of genetically determined lower vitamin D levels and higher
264 mortality. The potential effect heterogeneity by sex and BMI requires confirmation. Further larger
265 studies are warranted to investigate the association of vitamin D levels and survival after CRC also in
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512

Tables

Table 1: Single nucleotide polymorphisms identified in genome-wide association analyses for circulating 25-hydroxyvitamin D concentrations

SNP	Chr	Gene	Effect allele ^a	beta ^b	Standard error
rs2282679	4	GC	G	-0.089	0.0023
rs10741657	11	CYP2R1	G	-0.031	0.0022
rs12785878	11	DHCR7	G	-0.036	0.0022
rs6013897	20	CYP24A1	A	-0.026	0.0027
rs10745742	12	AMDHD1	C	-0.017	0.0022
rs8018720	14	SEC23A	C	-0.017	0.0029

Abbreviations: Chr, chromosome; SNP, single nucleotide polymorphism.

^aeffect allele of the vitamin D level decreasing allele.

^b beta value and standard error as reported in Jiang et al. (8) for the association of the genetic variants with natural log transformed vitamin D levels.

Table 2: Association between the vitamin D decreasing allele of vitamin D related genetic variants and overall and CRC-specific mortality after CRC diagnosis

SNP	No (total)	No (events ^a)	HR ^b	95% CI	p-value
Overall mortality					
rs2282679	7657	2438	1.06	1.00-1.13	0.07
rs10741657	7657	2438	0.99	0.93-1.05	0.75
rs12785878	7657	2438	1.05	0.98-1.11	0.17
rs6013897	7657	2438	0.95	0.89-1.02	0.19
rs10745742	7657	2438	1.00	0.95-1.06	0.94
rs8018720	7657	2438	0.98	0.91-1.05	0.57
CRC-specific mortality					
rs2282679	7657	1648	1.08	1.00-1.16	<0.05
rs10741657	7657	1648	0.99	0.92-1.06	0.73
rs12785878	7657	1648	1.04	0.96-1.13	0.31
rs6013897	7657	1648	0.97	0.88-1.05	0.44
rs10745742	7657	1648	1.00	0.93-1.07	0.97
rs8018720	7657	1648	0.97	0.89-1.07	0.57

Abbreviations: CI, confidence interval, GRS, genetic risk score; HR, hazard ratio; No, number; SNP, single nucleotide polymorphism.

^aMedian follow-up time: 54.8 months (interquartile range: 27.7-73.6)

^bAdjusted for age, sex, genotyping phase and 3 PC for GECCO, and 10 PC for CPSII, respectively.

Table 3: Association between GRS for vitamin D levels and mortality after CRC diagnosis stratified according subgroups

Group	Overall mortality ^b					CRC-specific mortality ^c				
	N (total)	N (events)	HR ^a	95% CI	p-het ^d	N (total)	N (events)	HR ^a	95% CI	p. het ^d
GRS	7657	2438	1.54	0.86-2.78		7657	1648	1.76	0.86-3.58	
Sex										
Female	4182	1278	3.26	1.45-7.33	0.01	4179	912	3.32	1.28-8.60	0.15
Male	3473	1160	0.68	0.29-1.62		3466	736	0.78	0.27-2.29	
Cancer site										
Colon	5824	1870	1.49	0.76-2.92	0.98	5816	1230	1.34	0.58-3.06	0.64
Rectum	1755	535	1.46	0.41-5.16		1753	395	3.16	0.74-13.20	
Stage										
Stage 1 / local	2325	356	3.88	0.79-19.00	0.39	2324	95	11.07	0.56-217.56	0.65
Stage 2,3 / regional	4010	1124	1.27	0.54-3.01		4004	710	1.52	0.52-4.48	
Stage 4 / distant	939	788	2.04	0.69-6.02		936	735	1.67	0.55-5.13	
BMI										
Normal	2549	824	4.14	1.50-11.43	0.02	2545	563	3.78	1.12-12.78	0.51
Overweight	3190	961	0.55	0.21-1.45		3185	645	0.93	0.28-3.01	
Obese	1771	594	1.67	0.53-5.26		1770	306	1.32	0.33-5.28	

Abbreviations: CI, confidence interval, GRS, genetic risk score; HR, hazard ratio; No, number; p.het, p-value for heterogeneity; SNP, single nucleotide polymorphism.

^aAdjusted for age, sex, genotyping phase and 3 PC for GECCO, and 10 PC for CPSII, respectively.

^b weighted genetic risk score for overall survival is computed out of the sum of vitamin D decreasing alleles of the six vitamin D associated SNPs multiplied by their effect on vitamin D levels (e.g. beta from Table 1). The HR indicates risk of death per 1 unit change in GRS. The risk score ranges between 0 and 0.432. One unit change in GRS is associated to a change in vitamin D levels of 5.29nmol/l according to Milaneschi et al (33).

^c weighted genetic risk score for CRC-specific survival is computed out of the sum of vitamin D decreasing alleles of the six vitamin D associated SNPs multiplied by their effect on vitamin D levels (e.g. beta from Table 1). The HR indicates risk of death per 1 unit decrease in GRS. The risk score ranges between 0 and 0.432. One unit change in GRS is associated to a change in vitamin D levels of 5.29nmol/l according to Milaneschi et al. (33).

^d p-value calculated using likelihood ratio tests comparing the model with and without interaction term.

Data and Materials Availability

Genotyping data of the GECCO studies are available at the database of Genotypes and Phenotypes (dbGaP) for download at the accession number: phs001078.v1.p1.

Genetic predictors of circulating 25-hydroxyvitamin D and prognosis after colorectal cancer

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