



Original Research

Vitamin D status after colorectal cancer diagnosis and patient survival according to immune response to tumour



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Abbreviations: 25(OH)D, 25-hydroxyvitamin D; BMI, body mass index; CI, confidence interval; CIMP, CpG island methylator phenotype; FFPE, formalin-fixed paraffin-embedded; HPFS, Health Professionals Follow-up Study; IPW, inverse probability weighting; LINE-1, long interspersed nucleotide element-1; MSI, microsatellite instability; NHS, Nurses' Health Study; SD, standard deviation; USA, United States of America.

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Abstract Background: High-level plasma 25-hydroxyvitamin D [25(OH)D] has been associated with lower colorectal cancer incidence and mortality. Considering evidence indicating immunomodulatory effects of vitamin D, we hypothesised that survival benefits from high systemic vitamin D level might be stronger for colorectal carcinoma with lower immune response to tumour.

Methods: Using 869 colon and rectal cancer cases within the Nurses' Health Study and Health Professionals Follow-up Study, we assessed the prognostic association of postdiagnosis 25(OH)D score [derived from diet and lifestyle variables to predict plasma 25(OH)D level] in strata of levels of histopathologic lymphocytic reaction. The Cox proportional hazards regression model was adjusted for potential confounders, including microsatellite instability, CpG island methylator phenotype, LINE-1 methylation, *PTGS2* (cyclooxygenase-2) expression and *KRAS*, *BRAF* and *PIK3CA* mutations.

Results: The association of postdiagnosis 25(OH)D score with colorectal cancer-specific mortality differed by levels of peritumoural lymphocytic reaction ($p_{\text{interaction}} = 0.001$). Multivariable-adjusted mortality hazard ratios for a quintile-unit increase of 25(OH)D score were 0.69 [95% confidence interval (CI), 0.54–0.89] in cases with negative/low peritumoural lymphocytic reaction, 1.08 (95% CI, 0.93–1.26) in cases with intermediate peritumoural reaction and 1.25 (95% CI, 0.75–2.09) in cases with high peritumoural reaction. The survival association of the 25(OH)D score did not significantly differ by Crohn's-like lymphoid reaction, intratumoural periglandular reaction or tumour-infiltrating lymphocytes.

Conclusions: The association between the 25(OH)D score and colorectal cancer survival is stronger for carcinomas with lower peritumoural lymphocytic reaction. Our results suggesting interactive effects of vitamin D and immune response may contribute to personalised dietary and lifestyle intervention strategies.

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1. Introduction

In colorectal cancer, high levels of lymphocytic reaction to tumour have been associated with prolonged patient survival [1–5]. Evidence supports the effectiveness of therapeutic antibodies that target immune checkpoint proteins such as *PDCD1* (programmed cell death 1, PD-1) and *CD274* (*PDCD1* ligand 1, PD-L1) in various cancers, including microsatellite instability (MSI)-high colorectal carcinoma [6–8]. Colorectal cancer consists of heterogeneous groups of neoplasms with varying sets of genetic and epigenetic alterations that are influenced by exogenous and endogenous factors [9–12]. A better

understanding of inter-individual differences in anti-tumour effects of immunomodulatory factors would help develop personalised immunotherapeutic strategies [13].

High levels of plasma 25-hydroxyvitamin D [25(OH)D] are associated with lower incidence and mortality of colorectal cancer [14–19]. Vitamin D is hydroxylated in the liver to produce 25(OH)D, and plasma 25(OH)D level serves as a standard indicator of vitamin D activity. It is then hydroxylated further in the kidneys to produce a hormonally active metabolite, 1,25-dihydroxyvitamin D (also known as calcitriol) [20]. Some immune cells can also enzymatically convert 25(OH)D to calcitriol

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