Relationships between vitamin D and *WIF-1* methylation as a marker of colorectal cancer risk

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Colorectal Cancer

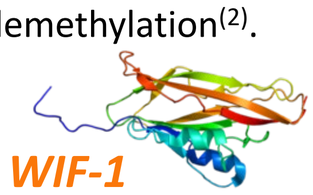
- Colorectal Cancer (CRC) is the 2nd largest cancer killer in the UK, causing 16,000 deaths per year[1].
- CRC risk is strongly modulated by lifestyle and dietary factors such as:

Obesity | Dietary fibre | Red meat

- Evidence suggests that vitamin D reduces CRC risk.

How does vitamin D reduce colorectal cancer risk?

- The WNT signalling pathway regulates processes in the large bowel, such as cell proliferation, and is hyperactive in CRC.
- WNT inhibitors, such as *Wnt Inhibitory Factor-1 (WIF-1),* suppress WNT pathway activity and are downregulated in CRC.
- Vitamin D may increase expression of WNT inhibitors through a process called demethylation[2].
- Demethylation removes obstacles from specific regions of DNA called CpG sites, allowing the cell to activate the gene.



Aim:

To investigate relationships between vitamin D status and methylation of the WNT inhibitor *WIF-1* in colorectal biopsies as a marker of CRC risk.

Methods

- Colorectal biopsies were collected from 40 healthy volunteers recruited to the Biomarkers of RIsk of Colorectal Cancer Follow Up (BFU) study.
- Vitamin D levels were measured in blood and participants were divided into higher or lower vitamin D status groups by dichotomising at the median (66.5 nmol/L).
- Colorectal *WIF-1* methylation levels were quantified as shown in *Figure 1*.

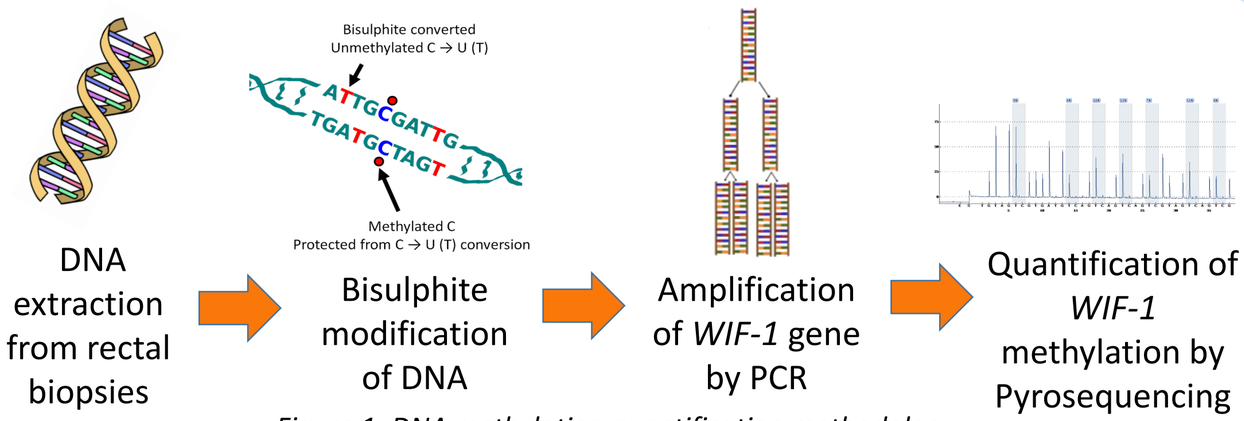


Figure 1: DNA methylation quantification methodology.

Results

Colorectal *WIF-1* methylation in BFU participants

Mean colorectal *WIF-1* methylation was 59% and ranged from 47% to 71% across the 4 CpG sites analysed *(Figure 2*).

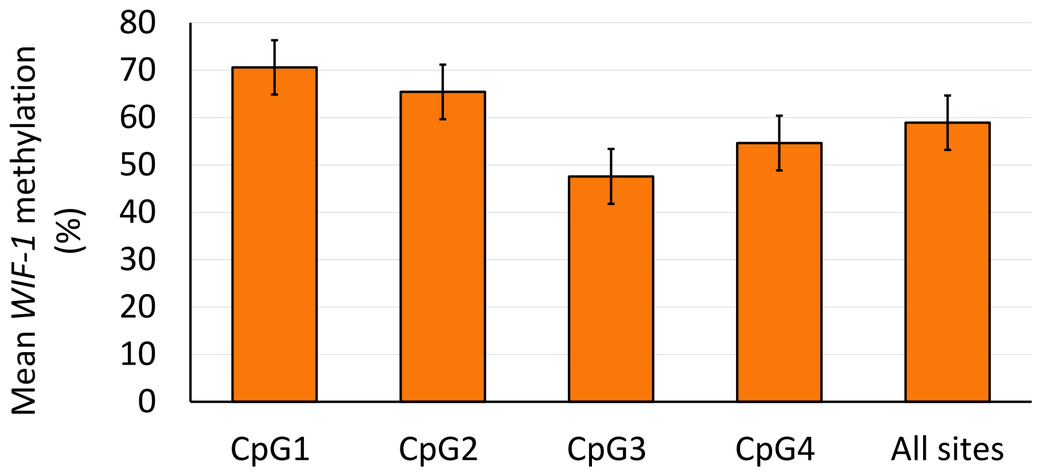


Figure 2: Colorectal WIF-1 methylation levels at the analysed CpG sites. Data are presented as means and error bars represent SEM.

Differences in *WIF-1* methylation according to vitamin D status

There were no significant differences in mean colorectal *WIF-1* methylation between higher and lower vitamin D status groups (*Figure 4*).

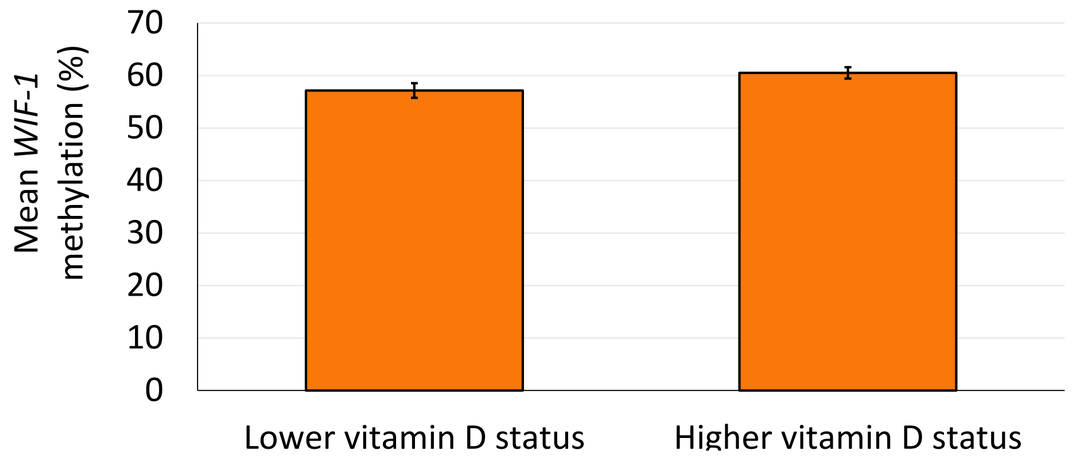


Figure 4: Mean colorectal WIF-1 methylation across all CpG sites in BFU participants with lower and higher vitamin D status. Data are presented as means and error bars represent SEM.

Relationships between vitamin D concentrations and colorectal *WIF-1* methylation

No significant relationships between plasma vitamin D concentrations and colorectal *WIF-1* methylation levels were observed (*Figure 3*).

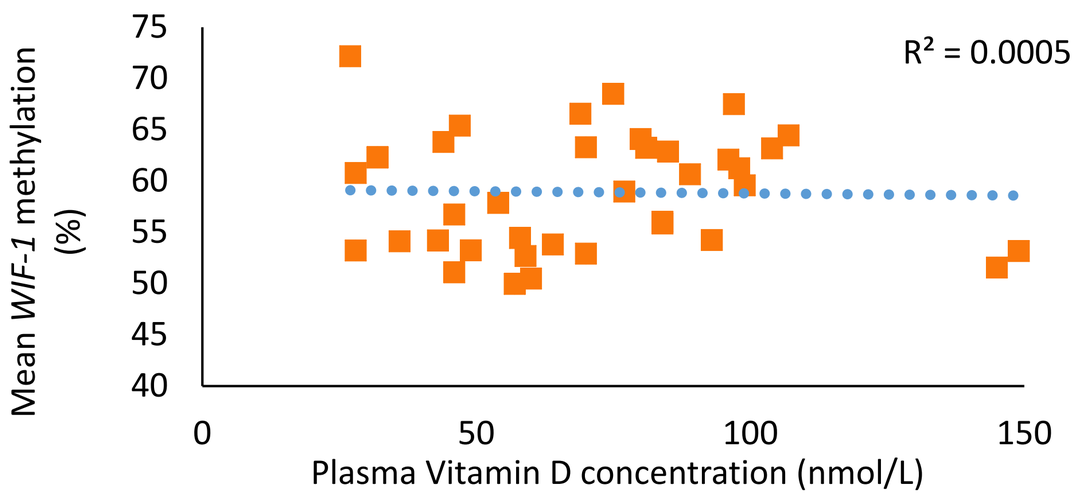


Figure 3: Relationships between plasma vitamin D concentrations and colorectal WIF-1 methylation in BFU participants.

Discussion & Conclusions

- In the BFU Study, there were no relationships between vitamin D and colorectal *WIF-1* methylation as a marker of CRC risk.
- These findings suggest that vitamin D does not modulate *WIF-1* methylation in the healthy colorectal mucosa. However, other WNT inhibitors, such as *DKK1* and *SFRP*s, should be investigated.
- In the future, a larger sample size and a randomised-controlled trial study design would be the gold standard to investigate the effects of vitamin D on markers of CRC risk.

REFERENCES

1. McCullough et al. (2019) *Journal of the National Cancer Institute* 111(2):158-169
2. O'Brien et al. (2018) *Breast Cancer Research* 20(1):70