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Relationships between adherence to the WCRF/AICR cancer prevention recommendations and WNT pathway-related markers of colorectal cancer risk

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Abnormal WNT signalling is implicated in the aetiology of both sporadic and inherited forms of colorectal cancer (CRC)⁽¹⁾, including abnormal expression and methylation of members of the WNT pathway, and can lead to dysregulated crypt cell proliferation. The majority of CRCs are sporadic and risk is strongly influenced by lifestyle factors, including diet and physical activity. The WCRF/AICR cancer prevention recommendations⁽²⁾ include maintaining a healthy body weight, limiting intakes of red meat and processed foods, a low alcohol intake and a diet rich in plant-based foods such as grains and vegetables. Within the EPIC Study, participants with higher adherence to the WCRF/AICR guidelines had a 27 % reduced CRC risk than those with the lowest scores⁽³⁾. However, in the UK Women's Cohort Study, there were no significant associations between adherence score and cancers of the proximal colon, distal colon or rectum⁽⁴⁾. This study aimed to investigate the relationships between adherence to the WCRF/AICR cancer prevention recommendations and WNT pathway-related markers of CRC risk. This is the first study to investigate relationships between adherence to these cancer prevention recommendations and molecular mechanisms underlying the effects of lifestyle on CRC risk.

This study used dietary and lifestyle data from 75 healthy participants recruited as part of the DISC Study. A total adherence score was derived from scores for seven of the recommendations plus smoking status. Expression of WNT pathway genes and regulatory microRNAs by qPCR, *SFRP1* methylation by pyrosequencing, and colonic crypt proliferative state were assessed in colorectal mucosal biopsies. Relationships between total adherence score and the measured outcomes were analysed using Spearman's rank correlation analysis. Unpaired t-tests were used to examine the effects of scores for individual recommendations.

With a maximum total adherence score of 8, mean total adherence score was 3.2 (range 1–6). Adherence to the recommendations on alcoholic drinks, dietary fibre, physical activity and animal foods appeared to cluster. Total adherence score was inversely correlated with expression of *c-MYC* ($p = 0.039$) and *WNT11* ($p = 0.025$) and with colonic crypt width ($p = 0.026$) and volume ($p = 0.036$). Adherence to the recommendation on body fatness was associated with reduced expression of *AXIN2* ($p = 0.025$) and *GSK3 β* ($p = 0.027$). Decreased expression of *CTNNT1* ($p = 0.046$) and *WNT11* ($p = 0.034$) was observed in participants who met the recommendation for dietary fibre intake. Expression of the oncogenic *miR-17* was 20 % lower in these participants ($p = 0.030$) and also reduced in those adhering to the recommendation for fruit and vegetable intake ($p = 0.035$). *WNT11* expression was reduced in participants performing at least 30 minutes of moderate physical activity per day ($p = 0.033$).

The findings from this study provide evidence for positive effects of adherence to the WCRF/AICR cancer prevention recommendations on WNT pathway-related markers of CRC risk and suggest that these dietary factors act early in the tumorigenesis pathway.

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