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# Prediagnostic consumption of vitamin D, calcium and dairy products and colorectal cancer survival: results from the Newfoundland Colorectal Cancer Registry Cohort Study

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## Abstract

Vitamin D, Ca and dairy products are negatively associated with colorectal cancer (CRC) incidence, but little is known of their influence on CRC survival. To investigate prediagnostic intakes of vitamin D, Ca and dairy products for their relevance to CRC prognosis, we analysed 504 CRC patients enrolled in the Newfoundland Colorectal Cancer Registry Cohort Study who were diagnosed for the first time with CRC between 1999 and 2003. Follow-up for mortality and cancer recurrence was through April 2010. Data on diet and lifestyle factors were gathered via a validated, semi-quantitative FFQ and a Personal History Questionnaire. Multivariate Cox models estimated hazard ratios (HR) and 95 % CI for the relationship of prediagnostic intakes of vitamin D, Ca and dairy products with all-cause mortality (overall survival, OS) and disease-free survival (DFS) among CRC patients. We found that prediagnostic Ca intake from foods, but not total Ca intake, was negatively associated with all-cause mortality (HR for Q2 *v.* Q1, 0·44; 95 % CI, 0·26, 0·75). An inverse relationship was also seen in a dose–response fashion for prediagnostic cheese intake (HR for Q4 *v.* Q1, 0·57, 95 % CI, 0·34, 0·95, $P_{trend} = 0·029$). No evidence for modification by sex, physical activity, alcohol drinking and cigarette smoking was observed. In summary, high prediagnostic intakes of cheese and Ca from foods may be associated with increased survival among CRC patients. By manipulating diet, this study may contribute to the development of novel therapies that add to the armamentarium against CRC. Replication studies are required before any nutritional interventions are made available.

**Key words:** **Colorectal cancer: Cancer survival: Vitamin D: Calcium: Dairy products: Interaction**

Colorectal cancer (CRC), one of the most common cancer types in Western countries, accounts for an estimated total death of 9300 per year in Canada (12 % of all cancer deaths)[1,2]. The aetiology of CRC involves various modifiable lifestyle factors, especially diet, but to date, only intakes of alcoholic drinks and red and processed meat are regarded as convincing dietary risk factors for CRC[3].

Although dairy products have not appeared to have a significant influence on cancer risk until the late 1990s, evidence for an inverse association between dairy consumption and CRC has accumulated in recent years[4–7]. The main hypothesis underlying this inverse association with dairy products relates to their high Ca content, which may induce apoptosis[8], reduce cell proliferation[9] and bind proinflammatory secondary bile acids

**Abbreviation:** CRC, Colorectal cancer.

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and fatty acids to render them inert[10,11]. As an adequate level of vitamin D is essential for proper Ca absorption, the anticancer effects of dairy products and Ca are strongly dependent on vitamin D status. A published meta-analysis of data from nineteen prospective cohort studies on CRC (the WCRF/AICR Continuous Update Project (CUP))[6] reported a 17 % decreased risk per 400 g/d of total dairy products and a 9 % decreased risk per 200 g/d of milk intake. The CUP meta-analyses for dietary vitamin D and Ca also showed inverse associations with CRC risk, but indicated that evidence for vitamin D and Ca was limited[3].

Although the inverse associations between intakes of vitamin D, Ca and dairy products have been consistently seen, their impact on survival after a CRC diagnosis is largely unknown. The only four available studies on prediagnostic consumption of dairy products in relation to CRC survival have yielded inconclusive results. In the Japan Collaborative Cohort Study[12], high yogurt intake was associated with reduced risk of rectal cancer mortality in male, whereas others[11,13,14] yield null associations. The Cancer Prevention Study-II Nutrition Cohort Study[13] reported that only postdiagnostic intake of dairy products was relevant to survival in patients with CRC; yet a more recent research demonstrated no association for postdiagnostic total dairy intake[15]. Findings for dietary vitamin D (or 25-hydroxyvitamin D), Ca and CRC survival are similarly mixed[13,16,17]. In addition, these published reports were mainly conducted in the USA, Japan and Western Europe, but none of these were from the Canadian population. We, therefore, investigated whether prediagnostic consumption of vitamin D, Ca and dairy products (total, milk, yogurt, cheese and cream) is associated with CRC overall (all-cause death) and disease-free survival in a population-based cohort of CRC patients enrolled in the Newfoundland Colorectal Cancer Registry Cohort Study.

## Materials and methods

### Study population

The Newfoundland Colorectal Cancer Registry Cohort Study has been previously described[18–20]. Briefly, patients aged 20–75 years with a first-time diagnosis of pathologically confirmed CRC between 1999 and 2003 were enrolled through the Newfoundland Colorectal Cancer Registry ($n$ 737). Consenting patients received mail-in epidemiological questionnaires that assessed their diet and lifestyle habits from one year prior to diagnosis and were asked for access to their archived tumour tissue and medical records. The current analysis excluded patients with unknown vital status at the end of follow-up ($n$ 1), those who provided insufficient information on diet and other crucial covariates ($n$ 206) and those who reported total energetic intakes in the upper or lower 2·5 % ($n$ 26; 870 and 4330 kcal/d for men, 1010 and 5050 kcal/d for women, respectively). After exclusion, 504 eligible CRC patients remained in the final analytical cohort. A flow chart for the subject selection process is shown in Fig. 1. This study was carried out with the approval by the Human Investigation Committee of Memorial University of Newfoundland in accordance with the tenets of the Declaration of Helsinki. All participants provided informed consent.

### Diet assessment and baseline information collection

Information on demographics, socio-economic status, individual behaviours, medical history cancer and family history was gathered from detailed Family History Questionnaires and Personal History Questionnaires. Participants in the current study also completed a self-administered FFQ that included 169 food items, beverages and vitamin and mineral supplements at the time of recruitment. The semi-quantitative FFQ applied in this study was a modified version of the well-known Hawaii FFQ that had been adapted to include regional foods in Newfoundland[21,22]. The survey had been previously validated within the Newfoundland and Labrador population[23]. Total dairy foods consumed were calculated in grams per day by summing the daily consumption of milk, yogurt, cheese and cream. Milk included whole milk, 2 % milk, 2 % evaporated milk, 1 % or skim milk and milk shake. Yogurt included yogurt with <2·4 % fat and yogurt with 2·4 % fat or more. Cheese consisted of cream cheese, cheese, cheese light (6–15 % fat) and cheese ultralight (5 % or less), and cream included half and half, light sour cream, coffee cream, whipping cream, as well as sour or regular cream.

The dietary nutrient intakes for individuals were calculated by multiplying the frequency of consumption of each food item from the FFQ by the nutrient content of a typical portion size using the 2005 Canadian Nutrient file[24]. Nutrient values were adjusted for total energy using the residuals method[25]. The microsatellite instability status of the tumour DNA has been determined in our previous studies[18].

### Study outcomes

Study participants were followed for deaths, recurrence and metastasis from the date of cancer diagnosis until April 2010. Data on vital status were collected through a combination of active follow-up (follow-up Family History Questionnaires) and record linkage to death certificates, pathology reports, autopsy records, surgical reports, physicians' notes and the records from the Dr. H. Bliss Murphy Cancer Care Foundation. The main outcomes were overall survival (OS) and disease-free survival. The end point for the OS analysis was death from all-causes and for the disease-free survival analysis was all-cause death, CRC recurrence or metastasis, whichever occurred first. Participants who did not suffer an event of interest within the study duration were censored on the date of the last follow-up.

### Statistical analysis

Survival distributions across groups of baseline characteristics were compared with a log-rank test. Hazard ratios (HR) and 95 % CI representing the associations between a defined end point event and quartiles of prediagnostic intakes of vitamin D, Ca and dairy products were calculated with multivariable Cox regression models using the first quartile as the reference. Potential confounders were identified as variables known to be associated with CRC survival and altered the effect estimates by ≥ 10 % or a $P < 0{\cdot}1$ from the univariable analysis; those included sex, age at diagnosis, stage at diagnosis, marital status, total energy intake, reported chemoradiotherapy and microsatellite instability status. The assumption of proportional hazard

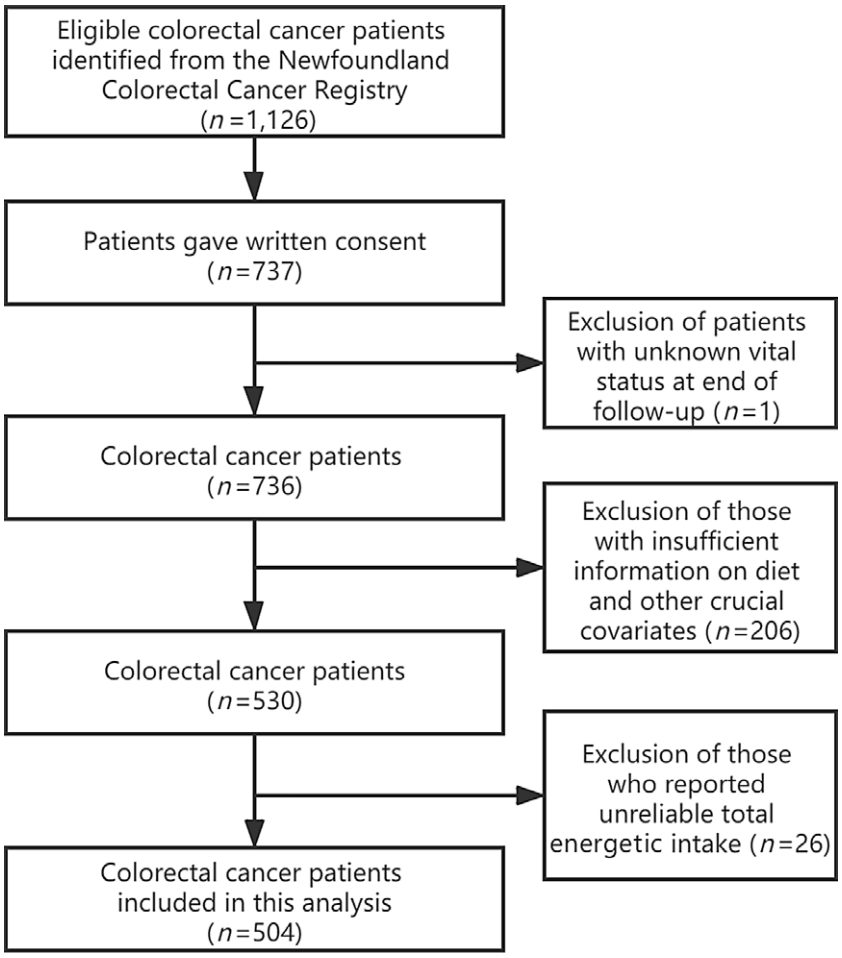


**Fig. 1.** Flow chart of the subject selection process.

rates over time was verified for each covariate by checking the parallelism of the Kaplan–Meier curves and testing the significance of an interaction term between the explanatory variable and the natural logarithm of follow-up time. The statistical linear trend was examined based on category median values. Potential interactions were assessed by testing the significance of multiplicative interaction terms using a Wald test for interaction as well as stratified analyses. Bonferroni correction for multiple comparisons was performed for nine nutrients/foods yielding an adjusted *P* value of 0·0056. *P* values were two-sided. All data analyses and management were performed in SAS software version 9.4 (SAS Institute Inc).

## Results

### *Patient characteristics*

Of the 504 CRC patients who were included in this study, a total of 159 (31·5 %) subjects died during follow-up (median follow-up time, 6·4 years, Table 1). The mean age of the study population was 60·9 ± 9·0 years, with 65·1 % having tumours at the colon subsite. In univariate analyses, old age at diagnosis, male gender, advanced stage at diagnosis (III/IV) and microsatellite stable/microsatellite instability-low tumours were significantly associated with worse all-cause mortality in this cohort. Except for total energy intake, salient characteristics were largely comparable between patients included and those excluded from the analysis due to lack of diet/disease-outcome data or unreliable total energetic intake (Supplementary Table 1).

### *Calcium, vitamin D and colorectal cancer survival*

We found longer OS time with higher dietary vitamin D intake; compared with the lowest quartile, the HR (95 % CI) were 0·52 (0·31, 0·87) for the second quartile and 0·57 (0·34, 0·95) for the third quartile (Table 2). This inverse association was limited to patients diagnosed with rectal cancer only. Likewise, for dietary Ca intake, the risk of all-cause death among CRC patients decreased by 56 % for subjects in the second quartile compared with those in the lowest quartile of consumption. No associations were observed among total vitamin D, total Ca intake and OS in CRC patients. Results were similar but less significant for disease-free survival.

### *Dairy products and colorectal cancer survival*

Compared with the lowest quartile, the third quartile of total dairy product intake was associated with a decreased risk of

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**Table 1.** Demographical and clinicopathological characteristics of study population
(Hazard ratios and 95 % confidence intervals; numbers and percentages; mean values and standard deviations, *n* 504)

| Characteristics | No. of patients | No. of deaths (%) | | Univariate | |
|---|---|---|---|---|---|
| | | *n* | % | HR | 95 % CI* |
| Age at diagnosis (years)† | | | | | |
| Mean | 60·9 | 62·0 | | 1·02 | 1·00, 1·03 |
| SD | 9·0 | 8·9 | | | |
| Sex | | | | | |
| Male | 306 | 106 | 34·6 | 1·00 | |
| Female | 198 | 53 | 26·8 | 0·70 | 0·50, 0·98 |
| BMI (kg/m$^2$) | | | | | |
| < 25·0 | 140 | 43 | 30·7 | 1·00 | |
| 25·0–29·9 | 203 | 70 | 34·5 | 1·06 | 0·72, 1·55 |
| ≥ 30 | 146 | 41 | 28·1 | 0·91 | 0·60, 1·40 |
| Marital status | | | | | |
| Single | 109 | 40 | 36·7 | 1·00 | |
| Married or living as married | 395 | 119 | 30·1 | 0·85 | 0·60, 1·22 |
| Tumour location | | | | | |
| Colon | 328 | 97 | 29·6 | 1·00 | |
| Rectum | 176 | 62 | 35·2 | 1·19 | 0·86, 1·63 |
| Stage at diagnosis | | | | | |
| I/II | 293 | 66 | 22·5 | 1·00 | |
| III/IV | 211 | 93 | 44·1 | 2·36 | 1·72, 3·24 |
| T stage | | | | | |
| T1 | 25 | 5 | 20·0 | 1·00 | |
| T2 | 100 | 23 | 23·0 | 1·11 | 0·42, 2·93 |
| T3 | 308 | 107 | 34·9 | 1·74 | 0·71, 4·26 |
| T4 | 19 | 8 | 42·1 | 1·98 | 0·64, 6·07 |
| N stage | | | | | |
| NX | 9 | 2 | 22·2 | 1·00 | |
| N0 | 264 | 66 | 25·1 | 1·29 | 0·32, 5·28 |
| N1 | 121 | 43 | 35·5 | 2·02 | 0·49, 8·35 |
| N2 | 55 | 30 | 54·6 | 3·74 | 0·89, 15·78 |
| M stage | | | | | |
| MX | 221 | 56 | 25·5 | 1·00 | |
| M0 | 154 | 43 | 27·9 | 1·15 | 0·77, 1·71 |
| M1 | 39 | 31 | 79·5 | 6·84 | 4·37, 10·71 |
| Chemoradiotherapy | | | | | |
| No | 100 | 38 | 38·0 | 1·00 | |
| Yes | 404 | 121 | 30·0 | 1·36 | 0·94, 1·95 |
| MSI status | | | | | |
| MSS/MSI-L | 423 | 146 | 34·5 | 1·00 | |
| MSI-H | 55 | 4 | 7·3 | 0·17 | 0·06, 0·46 |
| Smoking status | | | | | |
| Never smokers | | | | | |
| *n* | 138 | 36 | | 1·00 | |
| % | 27·4 | 26·1 | | | |
| Ever smokers | | | | | |
| *n* | 366 | 123 | | 1·27 | 0·87, 1·84 |
| % | 72·6 | 33·6 | | | |
| Total energy intake (kcal/d)† | | | | | |
| Mean | 2455·3 | 2491·5 | | 1·11 | 0·96, 1·27 |
| SD | 849·4 | 796·7 | | | |

MSI, microsatellite instability; MSI-H, microsatellite instability-high; MSS/MSI-L, microsatellite stable/microsatellite instability-low; HR, hazard ratio.
For some variables, totals may not add up due to missing values.
* Cox proportional hazard regression.
† Continuous variables presented as mean ± SD (standard deviation).

all-cause mortality in rectal cancer patients (Table 3). We also saw better survival in CRC patients with pre-diagnostic milk in the third quartile compared with those in the lowest quartile of consumption. A significant dose-survival advantage for high *v.* low cheese intake was observed (HR for Q4 *v.* Q1, 0·57; 95 % CI, 0·34, 0·95; $P_{trend} = 0·029$). However, no association was detected among yogurt, cream and CRC survival. Of note, we analysed nine diet–CRC survival relationships; Bonferroni adjustment for multiple testing yielded only one significant association between higher Ca intake and longer OS time for this agnostic analysis ($P < 0·0056$).

### *Interaction*

Many food habits are sex-specific and, in many instances, unhealthy diet is closely related to other poor lifestyle choices such as smoking, overuse of alcohol, and physical inactivity; we therefore investigated if the diet–CRC survival association

**Table 2.** Association of prediagnostic vitamin D and calcium intakes with colorectal cancer overall and disease-free survival (Hazard ratios and 95 % confidence intervals, *n* 478)

| | | Overall survival | | | | | | | Disease-free survival | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | Overall CRC | | Colon cancer | | Rectal cancer | | | Overall CRC | | Colon cancer | | Rectal cancer | |
| | Median intake | No. of events*/No. at risk | HR | 95 % CI† | HR | 95 % CI† | HR | 95 % CI† | No. of Events*/No. at Risk | HR | 95 % CI† | HR | 95 % CI† | HR | 95 % CI† |
| Dietary vitamin D (μg/d) | | | | | | | | | | | | | | | |
| Q1 | 3·4 | 37/119 | 1·00 | | 1·00 | | 1·00 | | 42/119 | 1·00 | | 1·00 | | 1·00 | |
| Q2 | 5·1 | 30/120 | 0·52 | 0·31, 0·87 | 0·68 | 0·36, 1·30 | 0·36 | 0·14, 0·89 | 37/120 | 0·62 | 0·39, 0·99 | 0·65 | 0·36, 1·17 | 0·68 | 0·31, 1·47 |
| Q3 | 6·6 | 32/119 | 0·57 | 0·34, 0·95 | 0·73 | 0·37, 1·44 | 0·44 | 0·19, 0·99 | 41/119 | 0·77 | 0·49, 1·20 | 0·80 | 0·44, 1·46 | 0·70 | 0·35, 1·40 |
| Q4 | 9·4 | 52/120 | 0·93 | 0·59, 1·45 | 1·35 | 0·74, 2·46 | 0·56 | 0·27, 1·18 | 58/120 | 1·09 | 0·72, 1·64 | 1·36 | 0·79, 2·32 | 0·80 | 0·41, 1·57 |
| $P_{\text{for trend}}$‡ | | | 0·709 | | 0·142 | | 0·290 | | | 0·273 | | 0·083 | | 0·634 | |
| Total vitamin D (diet + supplements; μg/d) | | | | | | | | | | | | | | | |
| Q1 | 3·7 | 35/119 | 1·00 | | 1·00 | | 1·00 | | 40/119 | 1·00 | | 1·00 | | 1·00 | |
| Q2 | 5·6 | 30/119 | 0·55 | 0·33, 0·94 | 0·73 | 0·37, 1·44 | 0·47 | 0·19, 1·14 | 39/119 | 0·76 | 0·48, 1·21 | 0·91 | 0·50, 1·68 | 0·64 | 0·30, 1·36 |
| Q3 | 7·6 | 42/120 | 0·90 | 0·56, 1·45 | 1·08 | 0·56, 2·08 | 0·83 | 0·39, 1·74 | 46·120 | 0·95 | 0·61, 1·48 | 1·14 | 0·63, 2·09 | 0·80 | 0·40, 1·57 |
| Q4 | 16·5 | 44/120 | 1·00 | 0·62, 1·60 | 1·47 | 0·79, 2·71 | 0·63 | 0·27, 1·44 | 53/120 | 1·25 | 0·81, 1·91 | 1·43 | 0·81, 2·52 | 1·03 | 0·52, 2·08 |
| $P_{\text{for trend}}$‡ | | | 0·334 | | 0·045 | | 0·463 | | | 0·072 | | 0·098 | | 0·514 | |
| Dietary Ca (mg/d) | | | | | | | | | | | | | | | |
| Q1 | 630·3 | 43/119 | 1·00 | | 1·00 | | 1·00 | | | 1·00 | | 1·00 | | 1·00 | |
| Q2 | 826·6 | 27/120 | 0·44 | 0·26, 0·75 | 0·55 | 0·28, 1·07 | 0·29 | 0·10, 0·82 | 48/119 | 0·59 | 0·37, 0·95 | 0·67 | 0·36, 1·24 | 0·51 | 0·22, 1·16 |
| Q3 | 1002·0 | 34/119 | 0·72 | 0·45, 1·15 | 0·87 | 0·46, 1·65 | 0·55 | 0·24, 1·23 | 32/120 | 0·85 | 0·55, 1·31 | 1·00 | 0·56, 1·80 | 0·66 | 0·33, 1·32 |
| Q4 | 1330·8 | 47/120 | 0·82 | 0·53, 1·26 | 1·05 | 0·58, 1·92 | 0·58 | 0·29, 1·18 | 42/119 | 1·10 | 0·74, 1·63 | 1·40 | 0·81, 2·42 | 0·82 | 0·45, 1·49 |
| $P_{\text{for trend}}$‡ | | | 0·980 | | 0·307 | | 0·199 | | 56/120 | 0·237 | | 0·051 | | 0·660 | |
| Total Ca (diet + supplements; mg/d) | | | | | | | | | | | | | | | |
| Q1 | 639·6 | 40/119 | 1·00 | | 1·00 | | 1·00 | | 46/119 | 1·00 | | 1·00 | | 1·00 | |
| Q2 | 853·7 | 33/119 | 0·64 | 0·38, 1·07 | 0·90 | 0·45, 1·80 | 0·42 | 0·16, 1·13 | 37/119 | 0·79 | 0·50, 1·26 | 1·04 | 0·55, 1·95 | 0·57 | 0·25, 1·30 |
| Q3 | 1056·7 | 31/120 | 0·70 | 0·43, 1·15 | 0·95 | 0·48, 1·91 | 0·49 | 0·22, 1·09 | 40/120 | 0·84 | 0·54, 1·31 | 1·02 | 0·55, 1·91 | 0·67 | 0·34, 1·32 |
| Q4 | 1462·8 | 47/120 | 1·03 | 0·66, 1·60 | 1·49 | 0·79, 2·83 | 0·66 | 0·32, 1·37 | 55/120 | 1·20 | 0·79, 1·80 | 1·58 | 0·88, 2·84 | 0·91 | 0·49, 1·69 |
| $P_{\text{for trend}}$‡ | | | 0·056 | | 0·076 | | 0·500 | | | 0·048 | | 0·061 | | 0·367 | |

CRC, colorectal cancer; HR, hazard ratio.

* Events are defined as all-cause deaths for overall survival and death/recurrence/metastasis (which occurred earliest) for disease-free survival; subjects with missing information on prediagnostic vitamin D or Ca intakes (*n* 26) were excluded from the analysis.

† Cox proportional hazard model adjusted for age at diagnosis, sex, stage at diagnosis, marital status, MSI status, chemoradiotherapy, and total energy intake where applicable.

‡ Test for linear trend was based on the median values for each quartile of intake.

**Table 3.** Association of prediagnostic dairy intakes with colorectal cancer overall and disease-free survival (Hazard ratios and 95 % confidence intervals, *n* 504)

| | | Overall survival | | | | | | | Disease-free survival | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | Overall CRC | | Colon cancer | | Rectal cancer | | | Overall CRC | | Colon cancer | | Rectal cancer | |
| | Median intake | No. of events*/No. at risk | HR | 95 % CI† | HR | 95 % CI† | HR | 95 % CI† | No. of events*/No. at risk | HR | 95 % CI† | HR | 95 % CI† | HR | 95 % CI† |
| Total dairy products (g/d) | | | | | | | | | | | | | | | |
| Q1 | 55·1 | 35/126 | 1·00 | | 1·00 | | 1·00 | | 40/126 | 1·00 | | 1·00 | | 1·00 | |
| Q2 | 220·2 | 46/125 | 1·03 | 0·64, 1·67 | 1·58 | 0·83, 3·02 | 0·50 | 0·22, 1·14 | 55/125 | 1·41 | 0·91, 2·19 | 2·02 | 1·12, 3·65 | 0·70 | 0·34, 1·42 |
| Q3 | 369·1 | 30/127 | 0·69 | 0·40, 1·18 | 0·99 | 0·48, 2·04 | 0·40 | 0·16, 0·97 | 37/127 | 0·85 | 0·52, 1·38 | 1·13 | 0·59, 2·14 | 0·51 | 0·24, 1·11 |
| Q4 | 697·5 | 48/126 | 1·10 | 0·67, 1·81 | 1·57 | 0·80, 3·10 | 0·68 | 0·29, 1·55 | 56/126 | 1·45 | 0·92, 2·29 | 1·88 | 1·02, 3·48 | 1·01 | 0·50, 2·06 |
| *P* for trend‡ | | | 0·712 | | 0·293 | | 0·582 | | | 0·207 | | 0·136 | | 0·722 | |
| Milk (g/d) | | | | | | | | | | | | | | | |
| Q1 | 2·6 | 39/123 | 1·00 | | 1·00 | | 1·00 | | 47/123 | 1·00 | | 1·00 | | 1·00 | |
| Q2 | 164·8 | 41/121 | 0·84 | 0·51, 1·36 | 0·73 | 0·38, 1·39 | 1·04 | 0·46, 2·34 | 45/121 | 0·97 | 0·62, 1·52 | 0·90 | 0·50, 1·62 | 1·02 | 0·49, 2·12 |
| Q3 | 257·0 | 30/131 | 0·59 | 0·35, 0·99 | 0·67 | 0·36, 1·25 | 0·57 | 0·21, 1·48 | 38/131 | 0·68 | 0·43, 1·07 | 0·66 | 0·37, 1·17 | 0·75 | 0·34, 1·65 |
| Q4 | 578·3 | 49/129 | 1·03 | 0·64, 1·65 | 1·09 | 0·61, 1·96 | 1·13 | 0·49, 2·64 | 58/129 | 1·22 | 0·80, 1·87 | 1·19 | 0·70, 2·03 | 1·34 | 0·64, 2·80 |
| *P* for trend‡ | | | 0·629 | | 0·471 | | 0·731 | | | 0·232 | | 0·353 | | 0·357 | |
| Yogurt (g/d) | | | | | | | | | | | | | | | |
| Q1 | 0 | 69/217 | 1·00 | | 1·00 | | 1·00 | | 83/217 | 1·00 | | 1·00 | | 1·00 | |
| Q2 | 8·6 | 9/33 | 1·21 | 0·57, 2·56 | 1·04 | 0·40, 2·69 | 2·24 | 0·57, 8·77 | 10/33 | 1·07 | 0·53, 2·15 | 0·89 | 0·35, 2·26 | 2·59 | 0·86, 7·86 |
| Q3 | 46·0 | 39/136 | 1·04 | 0·68, 1·60 | 1·12 | 0·63, 2·00 | 0·92 | 0·45, 1·88 | 47/136 | 1·01 | 0·69, 1·47 | 1·41 | 0·86, 2·32 | 0·58 | 0·32, 1·06 |
| Q4 | 175·0 | 42/118 | 1·08 | 0·67, 1·73 | 1·20 | 0·65, 2·18 | 0·99 | 0·44, 2·23 | 48/118 | 1·12 | 0·75, 1·67 | 1·57 | 0·94, 2·62 | 0·64 | 0·32, 1·27 |
| *P* for trend‡ | | | 0·826 | | 0·582 | | 0·815 | | | 0·544 | | 0·096 | | 0·299 | |
| Cheese (g/d) | | | | | | | | | | | | | | | |
| Q1 | 0 | 46/128 | 1·00 | | 1·00 | | 1·00 | | 54/128 | 1·00 | | 1·00 | | 1·00 | |
| Q2 | 5·3 | 35/135 | 0·88 | 0·54, 1·41 | 0·77 | 0·42, 1·42 | 1·14 | 0·50, 2·58 | 42/135 | 0·77 | 0·50, 1·18 | 0·69 | 0·40, 1·20 | 1·09 | 0·54, 2·17 |
| Q3 | 12·8 | 40/115 | 0·89 | 0·56, 1·43 | 0·78 | 0·43, 1·41 | 1·12 | 0·48, 2·57 | 45/115 | 0·81 | 0·53, 1·24 | 0·71 | 0·41, 1·23 | 1·10 | 0·55, 2·22 |
| Q4 | 30·0 | 38/126 | 0·57 | 0·34, 0·95 | 0·61 | 0·33, 1·15 | 0·43 | 0·17, 1·11 | 47/126 | 0·65 | 0·41, 1·02 | 0·77 | 0·44, 1·35 | 0·43 | 0·19, 0·94 |
| *P* for trend‡ | | | 0·029 | | 0·167 | | 0·048 | | | 0·098 | | 0·592 | | 0·019 | |
| Cream (g/d) | | | | | | | | | | | | | | | |
| Q1 | 0 | 109/359 | 1·00 | | 1·00 | | 1·00 | | 131/359 | 1·00 | | 1·00 | | 1·00 | |
| Q2 | 1·0 | 17/49 | 1·24 | 0·73, 2·12 | 1·09 | 0·54, 2·20 | 1·73 | 0·70, 4·29 | 17/49 | 0·97 | 0·57, 1·63 | 1·06 | 0·53, 2·12 | 1·01 | 0·43, 2·37 |
| Q3 | 3·9 | 13/49 | 0·55 | 0·29, 1·02 | 0·49 | 0·23, 1·04 | 0·65 | 0·19, 2·21 | 16/49 | 0·57 | 0·33, 1·00 | 0·51 | 0·25, 1·03 | 0·71 | 0·27, 1·90 |
| Q4 | 45·0 | 20/47 | 1·07 | 0·64, 1·77 | 0·93 | 0·48, 1·82 | 1·48 | 0·65, 3·37 | 24/47 | 1·22 | 0·76, 1·95 | 1·16 | 0·63, 2·13 | 1·51 | 0·70, 3·25 |
| *P* for trend‡ | | | 0·552 | | 0·970 | | 0·381 | | | 0·420 | | 0·727 | | 0·223 | |

CRC, colorectal cancer; HR, hazard ratio.

* Events are defined as all-cause deaths for overall survival and death/recurrence/metastasis (which occurred earliest) for disease-free survival.

† Cox proportional hazard model adjusted for age at diagnosis, sex, stage at diagnosis, marital status, MSI status, chemoradiotherapy, and total energy intake where applicable.

‡ Test for linear trend was based on the median values for each quartile of intake.

**Table 4.** Overall colorectal cancer survival in relation to quartiles of milk, cheese and calcium intakes by selected demographic and lifestyle characteristics of participants
(Hazard ratios and 95 % confidence intervals)

| | | Quartiles HR (95 % CI)† | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | | | Q2 | | Q3 | | Q4 | | | |
| | No. of events*/No. at risk | Q1 | HR | 95 % CI† | HR | 95 % CI† | HR | 95 % CI† | $P_{trend}$‡ | $P_{interaction}$§ |
| Milk | | | | | | | | | | |
| Sex | | | | | | | | | | |
| Male | 106/306 | 1·00 | 0·69 | 0·37, 1·28 | 0·53 | 0·28, 1·01 | 1·28 | 0·73, 2·25 | 0·131 | |
| Female | 53/198 | 1·00 | 1·07 | 0·47, 2·43 | 0·67 | 0·26, 1·71 | 0·77 | 0·32, 1·83 | 0·469 | 0·225 |
| Physical activity | | | | | | | | | | |
| ≤ 22·4 MET h/week | 67/235 | 1·00 | 0·79 | 0·39, 1·59 | 0·61 | 0·28, 1·33 | 0·64 | 0·29, 1·40 | 0·268 | |
| > 22·4 MET h/week | 92/268 | 1·00 | 0·88 | 0·43, 1·77 | 0·61 | 0·30, 1·22 | 1·13 | 0·60, 2·13 | 0·478 | 0·313 |
| Alcohol drinking | | | | | | | | | | |
| ≤ 7 drinks/week | 99/338 | 1·00 | 0·76 | 0·41, 1·40 | 0·51 | 0·26, 0·99 | 0·92 | 0·52, 1·63 | 0·809 | |
| > 7 drinks/week | 51/138 | 1·00 | 0·90 | 0·37, 2·18 | 0·69 | 0·28, 1·67 | 1·61 | 0·65, 3·97 | 0·286 | 0·550 |
| Cigarette smoking | | | | | | | | | | |
| Ever smokers | 123/366 | 1·00 | 0·95 | 0·52, 1·76 | 0·72 | 0·39, 1·30 | 1·24 | 0·71, 2·17 | 0·279 | |
| Never smokers | 36/138 | 1·00 | 0·73 | 0·31, 1·75 | 0·30 | 0·08, 1·12 | 0·66 | 0·21, 2·13 | 0·244 | 0·508 |
| Cheese | | | | | | | | | | |
| Sex | | | | | | | | | | |
| Male | 106/306 | 1·00 | 0·88 | 0·49, 1·59 | 1·19 | 0·67, 2·11 | 0·63 | 0·33, 1·20 | 0·165 | |
| Female | 53/198 | 1·00 | 0·97 | 0·41, 2·30 | 0·53 | 0·22, 1·29 | 0·59 | 0·25, 1·39 | 0·184 | 0·418 |
| Physical activity | | | | | | | | | | |
| ≤ 22·4 MET h/week | 67/235 | 1·00 | 0·89 | 0·43, 1·85 | 1·29 | 0·62, 2·66 | 0·68 | 0·31, 1·51 | 0·385 | |
| > 22·4 MET h/week | 92/268 | 1·00 | 0·88 | 0·46, 1·69 | 0·68 | 0·36, 1·32 | 0·42 | 0·20, 0·86 | 0·012 | 0·748 |
| Alcohol drinking | | | | | | | | | | |
| ≤ 7 drinks/week | 99/338 | 1·00 | 0·84 | 0·47, 1·52 | 1·00 | 0·57, 1·74 | 0·62 | 0·33, 1·17 | 0·164 | |
| > 7 drinks/week | 51/138 | 1·00 | 0·87 | 0·36, 2·14 | 0·72 | 0·29, 1·82 | 0·43 | 0·15, 1·21 | 0·093 | 0·519 |
| Cigarette smoking | | | | | | | | | | |
| Ever smokers | 123/366 | 1·00 | 1·03 | 0·35, 3·03 | 0·87 | 0·24, 3·12 | 1·00 | 0·28, 3·59 | 0·995 | |
| Never smokers | 36/138 | 1·00 | 0·81 | 0·46, 1·42 | 0·86 | 0·51, 1·45 | 0·47 | 0·26, 0·87 | 0·016 | 0·129 |
| Ca | | | | | | | | | | |
| Sex | | | | | | | | | | |
| Male | 106/306 | 1·00 | 0·54 | 0·29, 1·00 | 0·90 | 0·50, 1·61 | 1·06 | 0·62, 1·79 | 0·342 | |
| Female | 53/198 | 1·00 | 0·30 | 0·11, 0·82 | 0·48 | 0·21, 1·09 | 0·52 | 0·23, 1·16 | 0·344 | 0·199 |
| Physical activity | | | | | | | | | | |
| ≤ 22·4 MET h/week | 67/235 | 1·00 | 0·40 | 0·19, 0·88 | 0·60 | 0·27, 1·32 | 0·49 | 0·23, 1·05 | 0·187 | |
| > 22·4 MET h/week | 92/268 | 1·00 | 0·40 | 0·19, 0·87 | 0·67 | 0·34, 1·30 | 0·82 | 0·94, 1·67 | 0·529 | 0·221 |
| Alcohol drinking | | | | | | | | | | |
| ≤ 7 drinks/week | 99/338 | 1·00 | 0·38 | 0·20, 0·75 | 0·71 | 0·39, 1·30 | 0·73 | 0·43, 1·26 | 0·952 | |
| > 7 drinks/week | 51/138 | 1·00 | 0·90 | 0·37, 2·19 | 0·65 | 0·28, 1·50 | 1·24 | 0·55, 2·78 | 0·769 | 0·593 |
| Cigarette smoking | | | | | | | | | | |
| Ever smokers | 123/366 | 1·00 | 0·56 | 0·18, 1·72 | 0·53 | 0·19, 1·51 | 0·77 | 0·24, 2·49 | 0·395 | |
| Never smokers | 36/138 | 1·00 | 0·42 | 0·23, 0·81 | 0·77 | 0·43, 1·36 | 0·89 | 0·53, 1·50 | 0·497 | 0·733 |

HR, hazard ratio.
* Events are defined as all-cause deaths for overall survival and death/recurrence/metastasis (which occurred earliest) for disease-free survival.
† Cox proportional hazard model adjusted for age at diagnosis, sex, stage at diagnosis, marital status, MSI status, chemoradiotherapy and total energy intake where applicable.
‡ Test for linear trend was based on the median values for each quartile of intake.
§ $P_{for\ interaction}$ is computed with Wald method testing significance of multiplicative interaction term between dietary Ca/dairy intakes and respective stratified variable.

varied between strata defined by sex and selected lifestyle characteristics. Although the protective effect of cheese intake was only evident in patients with physical activity level > 22·4 MET h/week (HR for Q4 *v.* Q1, 0·42; 95 % CI, 0·20, 0·86; $P_{trend} = 0·012$) (Table 4), none of these examined factors showed statistically significant interaction with the intake of Ca and dairy products (milk and cheese) in relation to CRC overall survival.

## Discussion

Results of the present study demonstrate a nonlinear association between higher pre-diagnostic consumption of Ca from foods and lower risk of all-cause mortality in patients with CRC. Stratified analysis by selected demographic and lifestyle characteristics of patients found no statistically significant effect modification with Ca, milk or cheese in relation to CRC survival.

Increasing consumption of Ca and dairy products is associated with a reduced CRC risk on the basis of several meta-analyses[6,26]. However, only minimal studies have reported results on the prediagnostic intake of Ca and dairy products in relation to survival after CRC diagnosis. In a large Japanese cohort study of 45 181 men and 62 643 women[12], yogurt intake was inversely associated with rectal cancer mortality in men. The results of other three studies[11,13,14] showed, however, no association between prediagnostic intake of dairy and Ca and CRC survival. Nevertheless, a significant inverse association was observed for postdiagnostic consumption of Ca and milk in relation to all-cause death amongst CRC patients in the Cancer Prevention Study-II Nutrition Cohort Study[13].

Dairy products are the main foods rich in Ca, which is thought to lower CRC risk through its anti-proliferative effects in the colorectal epithelium by binding toxic bile and fatty acids, thereby neutralising mucosal toxicity[10]. In addition, Ca has been shown to prevent K-ras mutations[27] and to influence multiple intracellular signalling pathways, thus inducing differentiation in normal cells and apoptosis in malignant cells[8]. A number of clinical trials have reported a reduction in epithelial cell proliferation of the colorectum with high dietary intake of Ca and dairy products[28,29]. These mechanisms are consistent with our observations of an inverse association between intake of Ca pre-diagnosis and the risk of all-cause death amongst CRC patients in the current study. Notably, however, only dietary Ca rather than total Ca intake was associated with better survival. This might be attributed to differences between the bioavailability of Ca from foods as compared with that from supplements, or it may be because Ca supplementation did not reduce colorectal epithelial cell proliferation rates as suggested by human trial data[30].

Vitamin D increases the absorption of Ca from the intestine. Cell proliferation[31], invasion, metastasis[8] and angiogenesis[32] are broadly enhanced in a state of vitamin D deficiency. A growing body of literature has implicated the role of vitamin D in reducing CRC risk[33]. More recent data provide compelling evidence for a positive association between vitamin D deficiency and CRC-specific mortality[33–37]. Our findings are in line with previous reports showing beneficial influence of vitamin D on CRC survival, although our data illustrated a J-shaped relationship, with the strongest association observed among participants in the second quartile of total/dietary vitamin D intake. In contrast, many studies suggest that the anti-tumour effects of vitamin D are the strongest at the higher range of intake. This discrepancy might be attributed to the followings. First, high intake of vitamin D may be correlated with other risk factors, neutralising the putative protective effect of vitamin D[38]. For instance, some foods rich in lipid-soluble vitamin D are also rich sources of vitamin A, a mineral whose acute and chronic toxicity is well documented. Second, high concentration of vitamin D might influence *its* metabolism, resulting in increased 24-hydroxylation and thus decreased level of the biologically active $1\alpha,25(OH)_2$-vitamin $D_3$ within the target tissue[38]. Moreover, our ability to measure vitamin D level and accurately classify exposure was necessarily limited due to the lack of direct measure of sunlight exposure, a primary source of serum vitamin D[39]. Further research is clearly required before it will be possible to make more confident conclusions about the possible dose–response effect of vitamin D.

Our results indicate a stronger association in rectal cancer survival with vitamin D and total dairy intake as compared with colon cancer. This result may be contributed to the fundamental differences between these two anatomical sites. The colon and rectum differ in several ways relating to embryological origin, morphologic characteristics and physiologic and biochemical properties[40]. These distinctions are not limited to normal colon and rectum. It is well established that the oncogenesis of colon and rectal cancers differs in genetic features and tumour biology[41]. Logically, tumours of the rectum may therefore respond differently to dietary exposures than the colon. It has been previously shown that dietary Ca and vitamin D intakes have stronger inverse correlation with rectal cancer risk as opposed to cancers originating from the proximal colon[42,43]. Reasoning behind this association is still under investigation. There have been some data[43,44], including from our own research group[45], suggesting this relationship may be modulated by variations in the vitamin D receptor which correlates with improved rectal cancer survival. However, the exact mechanism remains undetermined and should be considered as a focus in future studies.

Intriguingly, we observed a dose–response survival advantage of high pre-diagnostic cheese intake. Findings of previous research on cheese consumption and CRC mortality have mostly been null[12,40]. A possible explanation for the null associations in prior research may be that the cheese intake in the populations studied was too low a dose for a reduction in the risk of death[41]. Our results suggest that >20 g/d of cheese consumption is required for a protective effect and yet the cut-off value for the highest group of cheese intake was much lower than this in previous studies[12,40]. As other dairy foods, cheese offers many of the same health benefits that are attributed to a high concentration of Ca, vitamin A, $B_{12}$, Zn and P. However, cheese is additionally rich in fatty acids and whey protein. Some common fatty acids in cheese, such as conjugated linoleic acid and phytanic acid, have been shown to inhibit the growth of colon cancer cells[42,43]. As well, several bioactive peptides produced in the hydrolysis of proteins in cheese manufacture have demonstrated potentially beneficial, biological activities including antioxidant, antitumour, immunomodulatory and anti-inflammatory effects[43]. Therefore, the unique nutritional composition of cheese may explain the beneficial influence on survival that is only observed for cheese rather than other dairy products among CRC patients.

A novel feature of our study is the inclusion of effect modification by known prognostic factors in the Ca/dairy products and CRC survival relationship. None of these factors examined showed significant interaction with dietary Ca or dairy product intakes, which is in line with the only available previous study that reported no interactions of dairy products with patients' baseline characteristics in relation to CRC mortality[11].

The strengths of our study include its relatively large sample size, a long-time follow-up from 1997 to 2010 and detailed questionnaire information. Limitations include a lack of information on postdiagnostic diet, which impeded us to evaluate the effect of diet and dietary modifications postdiagnosis on survival outcome. In addition, information on causes of death (ICD codes) was not available for the entire deceased patients; however, of those with such data (ninety one out of 159 patients), the majority (91·2 %) was due to CRC. Similarly, information on chemoradiation therapy was patient reported and thus the details including neoadjuvant *v.* adjuvant therapy or long-course *v.* short-course radiation were not available. Although our data were adjusted for the treatment with chemoradiotherapy, we acknowledge specific treatment regimens significantly contribute to survival and may skew the data. Further, the results may be skewed by recall bias as the participants recalled their dietary intakes from one year prior to diagnosis; however, this non-differential misclassification will usually produce bias towards the null.

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### Conclusions

Our results suggest that high prediagnostic intake of cheese and dietary Ca may be associated with improved survival after a diagnosis of CRC. These findings improve our understanding of dietary factors in CRC survival and suggest potential novel targets to improve therapeutic strategies for CRC patients (e.g. dietary manipulation of cheese and Ca intakes). More well-powered studies are needed to replicate these findings and provide insights into the dietary modulation of CRC.

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P. W. and Y. Z. conceived and designed the study. Y. Z. analysed the data and wrote the initial draft. Y. Z., J. Z., J. V., P. W., F. Y. S., J. R. W. and Y. J. K. revised the subsequent drafts. P. W., G. J. Z., P. S. P. and J. R. M. contributed to data collection.

The authors declare no conflict of interest.

## Supplementary material

For supplementary material/s referred to in this article, please visit https://doi.org/10.1017/S0007114521003299

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