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Higher intakes of dietary vitamin D, calcium and dairy products are inversely associated with the risk of colorectal cancer: a case–control study in China

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Abstract

The effects of dietary vitamin D, Ca and dairy products intakes on colorectal cancer risk remain controversial. The present study investigated the association between these dietary intakes and the risk of colorectal cancer in Guangdong, China. From July 2010 to December 2018, 2380 patients with colorectal cancer and 2389 sex- and age-matched controls were recruited. Dietary intake data were collected through face-to-face interviews using a validated FFQ. Unconditional multivariable logistic regression models were used to calculate the OR and 95 % CI after adjusting for various confounders. Higher dietary vitamin D and Ca intakes were associated with 43 and 52 % reductions in colorectal cancer risk, with OR of 0·57 (95 % CI 0·46, 0·70) and 0·48 (95 % CI 0·39, 0·61), respectively, for the highest quartile (*v.* the lowest quartile) intakes. A statistically significant inverse association was observed between total dairy product intake and colorectal cancer risk, with an adjusted OR of 0·32 (95 % CI 0·27, 0·39) for the highest *v.* the lowest tertile. Subjects who drank milk had a 48 % lower risk of colorectal cancer than those who did not (OR 0·52, 95 % CI 0·45, 0·59). The inverse associations of dietary vitamin D, Ca, total dairy products and milk intakes with the risk of colorectal cancer were independent of sex and cancer site. Our study supports the protective effects of high dietary vitamin D, Ca and dairy products intakes against colorectal cancer in a Chinese population.

Key words: **Vitamin D: Calcium: Dairy products: Milk: Colorectal cancer**

Globally, colorectal cancer is the fourth most commonly diagnosed cancer and the third leading cause of cancer death[1]. In 2018, 1·85 million colorectal cancer cases and 880 792 related deaths were reported worldwide[1]. Epidemiological evidence indicates the importance of dietary factors, such as vitamin D, Ca and dairy products, with regard to the risk of colorectal cancer[2–4]. Garland and Garland first suggested a possible protective effect of vitamin D against colorectal carcinogenesis in 1980[5]. Since then, several mechanisms have been proposed to explain the role of vitamin D in colorectal cancer risk reduction, including the inhibition of epithelial cell proliferation[6,7], induction of target tissue differentiation[8], modulation of cellular immune functions[9], induction of carcinoma cell apoptosis[10,11], regulation of antioxidant genes[12] and gut microbiota[13]. Ca was reported to protect against colorectal cancer by binding secondary bile acids and ionised fatty acids in the colon and thus reducing the toxic effects of these factors on epithelial cells[14]. Although dairy products contain nutrients such as vitamin D and Ca that have been postulated to reduce the risk of colorectal cancer[15], they also have high-fat contents that can increase colonic bile acid levels and, consequently, the risk of colorectal cancer[16].

Abbreviations: MET, metabolic equivalent task; RR, risk ratio.

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Some epidemiological studies have examined the associations between dietary vitamin D, Ca and dairy products and the risk of colorectal cancer. However, these studies yielded mixed results. A meta-analysis published in 2011[17] and a 2008 case–control study in Scotland with 2070 cases and 2793 controls[18] observed a decrease in the risk of colorectal cancer with increased dietary vitamin D consumption. The European Prospective Investigation into Cancer and Nutrition reported statistically significant inverse associations between dietary Ca, total dairy products as well as milk intakes and the risk of colorectal cancer[19]. However, other studies including a 2009 meta-analysis[20], five cohort studies[3,21–24], five case–control studies[25–29] and one nested case–control study[30] concluded that no strong association existed between dietary vitamin D[3,20,21,24–26,29,30], dietary Ca[3,21–24,26], total dairy products[3,21,22,24–26] and milk[3,23,24,26–28] intakes and colorectal cancer risk.

To date, most relevant epidemiological studies have been conducted in Western countries, where dietary habits differ from those in China[31,32]. For example, the consumption of dairy products, especially milk, is lower in China than in Western countries[32]. No previous study has focused on the association between the dietary intakes of vitamin D, Ca and dairy products and the risk of colorectal cancer in Chinese population. Only one relevant study of the Singapore Chinese population failed to identify any relationships of dietary vitamin D, Ca and total dairy products intakes with the risk of colorectal cancer[33]. Therefore, we performed this case–control study to assess the associations of dietary vitamin D, Ca and dairy products intakes with the risk of colorectal cancer among residents of Guangdong province, China. We hypothesised that the intakes of these dietary components would be inversely associated with the risk of colorectal cancer.

Methods

Study subjects

The details of this ongoing case–control study of the association between lifestyle factors and colorectal cancer risk in Guangdong, China, which began in July 2010, have been reported previously[34,35]. Briefly, potential case subjects aged 30–75 years were recruited consecutively from the surgical units of the Sun Yat-sen University Cancer Centre in Guangzhou, China. Cases selected for study inclusion involved patients with histologically confirmed, incident, primary colorectal cancer diagnosed no more than 3 months before the recruitment interview, who were natives of Guangdong province or had lived in Guangdong for at least 5 years. Potential participants were excluded if they had a history of cancer or could not understand or speak Mandarin/Cantonese. From July 2010 to December 2018, 2669 eligible cases were identified and 2403 were successfully interviewed, yielding a response rate of 90·03 %. Of these, 266 patients did not complete the interview because of communication barriers, fatigue and/or refusal. Among the cases who completed the FFQ, 23 who had an energy intake that was too low or too high (<3347 or >17 573 kJ/d (<800 or >4200 kcal/d) for men, <2510 or >14 644 kJ/d (<600 or >3500 kcal/d) for women)[36] were excluded from the analysis. Finally, 2380 cases were included in the analysis.

The present study used two control groups that were frequency-matched to cases by 5-year age group and sex. The controls had no history of any cancer and were subject to all other above-described eligibility criteria. The first control group was selected from the Department of Otorhinolaryngology, Vascular Surgery and Plastic and Reconstructive Surgery in the First-affiliated Hospital of Sun Yat-sen University. These patients presented with chronic otitis media, sudden deafness, chronic sinusitis, vocal cord polyp, varicose veins, trigeminal neuralgia, facial paralysis and orthopaedics during the same time period. A total of 1413 (89·77 %) of 1574 eligible hospital-derived controls were successfully interviewed. The second control group was recruited from among residents in the same community as the cases via advertisements, written invitations or referrals. A total of 976 community-derived controls were interviewed successfully.

We assumed that there were 25 % of people with higher dietary vitamin D, Ca and total dairy products intakes among the general population, and the estimated OR between the consumption of these dietary components and colorectal cancer risk was 0·77[18–20], the type I error rate was <0·05 ($\alpha = 0{\cdot}05$), the power of test was 90 % ($\beta = 0{\cdot}10$) and the response rate was 90 %. On the basis of these assumptions, we required a sample size of 1936 cases.

The study has been performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki and its later amendments. The protocols and procedures of the present study were approved by the Ethical Committee of School of Public Health, Sun Yat-sen University. All participants in the present study signed informed consent form before the interview.

Data collection

Trained interviewers conducted face-to-face interviews using a structured questionnaire. Information was collected on subjects' socio-demographic characteristics, body measurements (weight and height) and lifestyle factors (e.g. active and passive smoking, alcohol consumption and physical activity) and family history of cancer among first-degree relatives and previous disease history. Data on menstrual and reproductive factors were also obtained from female subjects. Relevant medical information (e.g. diagnoses and pathological findings) were abstracted from medical records. The BMI was calculated as the ratio of the body weight (kg) to the squared height (m^2). In the present study, regular smokers were defined as those who had smoked ≥1 cigarette/d for >6 consecutive months. Passive smokers were defined as non-smokers who were exposed to the exhalations of smokers for >15 min/d on ≥1 d/week. Regular alcohol consumption was defined as consumption ≥1 time/week for ≥6 consecutive months during the past year. The physical activity level was evaluated based on self-reported occupational, household and recreational physical activities during the previous year. Information was also collected about the frequency (d/week) and duration (h/d) of household and recreational physical activities. Occupational activity was classified according to the working intensity as follows (examples were provided): (a) not working; (b) long-time sitting; (c) low intensity; (d) moderate

intensity or (e) vigorous intensity. Household and recreational physical activities were categorised as light (e.g. walking), moderate (e.g. jogging, mountaineering, playing table tennis) and vigorous physical activity (e.g. running, playing football/basketball). The mean metabolic equivalent task (MET)-h value of each physical activity was determined by estimating the average of all comparable activities in the Compendium of Physical Activities[37,38]. The MET-h/week during the past 1 year was computed using the following equation: number of d/week × number of h/d × MET of a specific type of activity = MET-h/week.

Dietary intake information was collected from the study subjects using a validated eighty-one-item FFQ[39]. The main food groups included in the FFQ were cereals, legumes, vegetables, fruits, red and processed meats, poultry, fish and other seafoods, eggs, dairy products and nuts. Subjects were asked to report the frequency of intake and portion size of each type of food during the year preceding diagnosis for cases or interview for controls.

The average daily intakes of dietary vitamin D, dietary Ca and dairy products were measured by summing the portion of products consumed each time, frequency of consumption and nutritional content of each food item. The US Department of Agriculture Food Composition Database[40] was used to calculate the dietary vitamin D intake. The intakes of energy and other nutrients (e.g. dietary Ca and dairy products) were calculated based on the 2002 Chinese Food Composition Table[41]. Dairy products intake was assessed by dry weight to account for the considerable difference in the nutrient contents of 100 g portions of solid and liquid foods. The FFQ included eight dairy food products: whole milk, skimmed/low-fat milk, whole milk powder, skimmed/low-fat milk powder, yogurt, milk tea, cheese and ice cream. One hundred grams of whole milk, skimmed/low-fat milk, whole milk powder, skimmed/low-fat milk powder, yogurt, milk tea, cheese and ice cream contain 89·8, 89·8, 2·3, 2·3, 84·7, 86·7, 43·5 and 78·3 g of water, respectively[41]. The total dairy food intake was calculated by summing the daily consumptions of all eight dairy foods by dry weight. Food photographs were provided to assist the participants with estimations of the consumed amounts of food.

The validity and reproducibility of the FFQ were evaluated in a sample of women who lived in the same region. The energy-adjusted Pearson's correlation coefficients between the FFQ and six 3-d dietary records were 0·25–0·65 for nutrients, 0·30–0·68 for food groups and 0·48 for Ca and dairy products[39].

Statistical analysis

All data analyses were performed using SPSS 21.0 (SPSS Inc.). To analyse the differences between cases and controls, continuous variables were evaluated using *t* tests or Wilcoxon signed-sum tests and categorical variables were evaluated using χ^2 tests. Dietary nutrient intakes were adjusted for the total energy intake using the regression residual method[42]. Dietary vitamin D and Ca intakes were categorised into quartiles (Q1–Q4), and total dairy products intakes were categorised into tertiles (T1–T3) based on the distributions among the controls. As milk was the main dairy product, we divided the subjects into two groups depending on their milk consumption status to examine the association between milk intake and the risk of colorectal cancer. Unconditional multivariable logistic regression models were used to estimate the OR and 95 % CI for the associations of dietary vitamin D, Ca, total dairy products and milk intakes with the risk of colorectal cancer, using the lowest quartile (tertile) group or the non-milk-drinking group as the reference.

Tests for trend were performed by entering categorical variables as continuous variables in the multiple regression models to determine whether there were dose–response relationships between these nutrients and food intakes and risk of colorectal cancer. Several potential confounders were included in multivariable-adjusted models according to comparisons of the baseline characteristics of cases and controls or previous reported confounders. The confounding variables included age, sex (male/female), residence (urban/rural), marital status (married/others), educational level (primary school or below/junior high school/senior high school or secondary technical school/college or above), occupation (administrator or other white-collar worker/blue-collar worker/farmer or others), income (<2000/2001–5000/5001–8000/>8001 yuan/month), occupational activity (not working/sedentary/light occupation/moderate occupation/heavy activity occupation), household and recreational physical activities, smoking status (current/never or past), alcohol consumption (yes/no), first-degree relative with cancer (yes/no) and BMI. The intakes of vegetables, fruit, red meat and dietary fibre, as well as age at menarche (women only), were also adjusted in the final model.

An analysis stratified by dietary vitamin D intake values below and above the median intake of 6·14 μg/d was conducted to evaluate the potential modifying effect on dietary Ca intake and colorectal cancer risk. Stratified analysis by sex was also conducted. The interactions were evaluated using multiplicative models that included the product term in a multivariable logistic regression. Subgroup analyses by cancer site (i.e. colon or rectal) and sources of controls (hospital-derived controls and community-derived controls) were also conducted. In addition, we conducted sensitivity analysis by using only community-derived controls or hospital-derived controls. Inverse probability of treatment weighting approach was used to reduce the impact of the potential confounding factors in our study. In order to compare the results of the unconditional logistic regression model mentioned above, potential confounders which were included in the previous multivariable-adjusted model were added to the model as confounders when calculating the propensity score. Hosmer–Lemeshow test was used to evaluate the goodness-of-fit of the model. In the present study, all *P* values were two-sided and a *P* value < 0·05 was considered to denote statistical significance.

Results

The total 2380 cases included 1356 men and 1024 women. Moreover, the study included 1476, 828 and seventy-six cases of tumours in the colon, rectum and the junction of the sigmoid colon and rectum, respectively. The socio-demographic and selected characteristics of the study participants are shown in Table 1. Compared with the controls, more cases lived in rural areas and had a lower level of education. The cases also included higher proportions of married participants and farmers, with

Table 1. Socio-demographic characteristics and selected risk factors of colorectal cancer in the study population*
(Numbers and percentages; mean values and standard deviations; medians and 25th, 75th percentiles)

	Cases (*n* 2380)		Controls (*n* 2389)		
Variables	*n*	%	*n*	%	*P*
Age (years)					
Mean	56·98		56·70		0·335
SD	10·23		9·99		
Sex					
Men	1356	57·0	1361	57·0	0·997
Women	1024	43·0	1028	43·0	
Residence					
Urban	1540	64·7	1881	78·7	<0·001
Rural	840	35·3	508	21·3	
Marital status					
Married	2263	95·1	2215	92·7	0·001
Unmarried/divorced/widowed	117	4·9	174	7·3	
Educational level					
Primary school or below	749	31·5	496	20·8	<0·001
Junior high school	668	28·1	601	25·2	
Senior high school/secondary technical school	578	24·3	645	27·0	
College or above	385	16·2	647	27·1	
Occupation					
Administrator/other white-collar worker	329	13·8	453	19·0	<0·001
Blue-collar worker	522	21·9	485	20·3	
Farmer/others	1529	64·2	1451	60·7	
Income (yuan/month)					
<2000	338	14·2	272	11·4	<0·001
2001–5000	773	32·5	879	36·8	
5001–8000	706	29·7	754	31·6	
>8001	563	23·7	484	20·3	
Occupational activity					
Not working	945	39·7	1197	50·1	<0·001
Sedentary	432	18·2	393	16·5	
Light occupation	398	16·7	435	18·2	
Moderate occupation	281	11·8	218	9·1	
Heavy activity occupation	324	13·6	146	6·1	
Household and recreational physical activities (MET-h/week)					
Median	28·88		35·00		<0·001
25th, 75th percentiles	9·00, 52·50		16·69, 56·00		
Regular smoker	930	39·1	731	30·6	<0·001
Passive smoker	666	28·0	678	28·4	0·761
Regular drinker	424	17·8	339	14·2	0·001
First degree relative with cancer	335	14·1	200	8·4	<0·001
BMI (kg/m^2)					
Mean	23·24		23·46		0·014
SD	3·19		3·11		
Age at menarche (years)†					
Mean	14·84		14·35		<0·001
SD	2·71		3·26		
Menopausal status†					
Premenopausal	290	28·3	323	31·4	0·125
Postmenopausal	734	71·7	705	68·6	

MET, metabolic equivalent task.
* Continuous variables were evaluated using *t* tests or Wilcoxon rank-sum tests. Categorical variables were evaluated using χ^2 tests.
† Among female subgroup.

higher incomes, heavier occupational activities, fewer household and recreational physical activities and lower BMI. Cases had a higher frequency of smoking and alcohol drinking and were more likely to report a first-degree relative to cancer. Among female individuals, cases had a later age at menarche than controls. No significant differences in age, sex, passive smoking and menopausal status were identified between cases and control subjects.

The mean dietary vitamin D intakes were 5·69 and 6·81 μg/d for cases and controls, respectively. The corresponding mean dietary Ca intakes were 406·94 and 468·21 mg/d, respectively, while the mean total dairy product intakes by dry weight were 4·02 and 9·50 g/d, respectively. Compared with controls, cases had lower dietary intakes of total energy, vegetables, fruit, fish, eggs, fibre, vitamin D, Ca, total dairy products and milk and a higher intake of red meat. No significant difference in total fat intake was observed between cases and controls (Table 2).

Table 3 presents the OR and 95 % CI of colorectal cancer according to dietary vitamin D intake quartile for all subjects

Table 2. Consumption of selected dietary variables among colorectal cancer cases and controls (Mean values; medians and 25th, 75th percentiles)

	Cases (*n* 2380)			Controls (*n* 2389)			
	Mean	Median	25th, 75th percentiles	Mean	Median	25th, 75th percentiles	*P**
Energy (kcal†/d)	1566·33	1499·93	1216·33, 1840·69	1635·32	1541·21	1263·19, 1906·00	<0·001
Total fat (g/d)‡	34·07	32·25	24·27, 41·91	33·83	32·52	25·90, 40·23	0·520
Vegetables (g/d)‡	417·04	390·64	285·64, 515·49	443·83	419·72	314·53, 537·28	<0·001
Fruit (g/d)‡	109·78	88·36	43·92, 151·70	151·59	127·86	70·75, 200·34	<0·001
Red meat (g/d)‡	117·63	109·80	76·07, 149·60	97·53	89·58	57·74, 128·42	<0·001
Fish (g/d)‡	59·06	39·71	18·47, 75·94	65·36	46·84	23·51, 87·20	<0·001
Eggs (g/d)‡	21·10	17·21	7·70, 27·86	25·21	21·19	11·82, 35·75	<0·001
Dietary fibre (g/d)‡	8·95	8·61	7·04, 10·46	9·93	9·57	8·00, 11·57	<0·001
Dietary vitamin D (μg/d)‡	5·69	4·87	3·17, 7·24	6·81	6·14	4·17, 8·69	<0·001
Dietary Ca (mg/d)‡	406·94	379·62	294·84, 485·86	468·21	444·28	344·37, 565·34	<0·001
Total dairy products (g/d)‡	4·02	0·00	0·00, 3·80	9·50	4·04	0·00, 15·89	<0·001
Milk (g/d)‡	21·38	0·00	0·00, 8·24	49·49	0·00	0·00, 73·27	<0·001

* Wilcoxon rank-sum test comparing the median consumption levels between cases and controls.
† To convert kcal to kJ, multiply by 4·184.
‡ Consumption was adjusted for total energy intake by the regression residual method.

and separately for men and women and for colon and rectal cancer. The dietary vitamin D intake was significantly inversely associated with the colorectal cancer risk. After adjusting for potential confounders, the multivariable OR was 0·57 (95 % CI 0·46, 0·70, $P_{trend} < 0·001$) for the highest quartile *v.* the lowest quartile. Stratified analysis by sex and subgroup analysis by cancer site revealed that the significant inverse association between dietary vitamin D intake and colorectal cancer risk was found in both sexes and in both colon and rectal cancers. Moreover, there was no significant interaction of sex with the association between dietary vitamin D intake and the risk of colorectal cancer ($P_{interaction} = 0·578$).

Table 4 presents the associations of dietary Ca intake with the risk of colorectal cancer for all subjects and separately for men and women and for colon and rectal cancer. A significant inverse association was observed between the dietary Ca intake and colorectal cancer risk. The highest quartile intake was associated with a 52 % reduction in risk relative to the lowest quartile (OR 0·48, 95 % CI 0·39, 0·61, $P_{trend} < 0·001$). The results of analyses stratified by sex and cancer site yielded similar patterns, indicating that the significant inverse associations were found between dietary Ca intake and colorectal cancer in both sexes and at both cancer sites. Moreover, no interaction of colorectal cancer risk was observed on the relationship between sex and dietary Ca intake ($P_{interaction} = 0·105$).

The intakes of total dairy products and of milk were associated with decreased risks of colorectal cancer. For total dairy products, the adjusted OR for the highest tertile *v.* the lowest tertile was 0·32 (95 % CI 0·27, 0·39, $P_{trend} < 0·001$). Subjects who drank milk exhibited a 48 % reduction in the risk of colorectal cancer *v.* those who did not (OR 0·52, 95 % CI 0·45, 0·59). Significant inverse associations were observed between the intakes of total dairy products and milk and the risk of colorectal cancer in both sexes and at both cancer sites. However, a sex-modified interaction was only observed in the association of the risk of colorectal cancer with the intake of milk, but not of total dairy products (Tables 5 and 6).

An interaction effect between dietary Ca and vitamin D intakes was observed on the risk of colorectal cancer ($P_{interaction} = 0·040$). Compared with the lowest category, the highest category of both dietary vitamin D and Ca intake was associated with a 57 % lower risk of colorectal cancer (OR of Q2–Q4: 0·59, 95 % CI 0·47, 0·75; 0·45, 95 % CI 0·36, 0·57; 0·43, 95 % CI 0·34, 0·55, respectively) (data not shown).

Subgroup analysis by hospital-derived controls and community-derived controls showed that no significant difference was found between the intakes of dietary vitamin D, Ca, total dairy products and milk and colorectal cancer risk when using either groups (data not shown). Sensitivity analysis by using only community-derived controls or hospital-derived controls also showed that the results were relatively stable (data not shown). After using inverse probability of treatment weighting approach, similar results were obtained (highest intake level *v.* lowest intake level, OR 0·57, 95 % CI 0·47, 0·69 for dietary vitamin D; OR 0·46, 95 % CI 0·37, 0·57 for dietary Ca; OR 0·32, 95 % CI 0·27, 0·37 for total dairy products; OR 0·50, 95 % CI 0·45, 0·57 for milk). The *P* value was 0·807 in the Hosmer–Lemeshow goodness-of-fit of test (data not shown in table).

Discussion

The findings of this case–control study suggest that the intakes of dietary vitamin D, Ca, total dairy products and milk were inversely associated with the risk of colorectal cancer. Moreover, these inverse associations were observed in both sexes and in both colon and rectal cancers.

In 2011, a meta-analysis of six cohort studies, one nested case–control study and two case–control studies found a negative association between the dietary vitamin D intake and risk of colorectal cancer (summary risk ratio (RR) = 0·88, 95 % CI 0·80, 0·96)[17]. Similarly, a case–control study of 2070 cases and 2793 controls from the Study of Colorectal Cancer in Scotland found an inverse relationship between dietary vitamin D consumption and the risk of colon cancer (OR 0·77, 95 % CI 0·63, 0·94)[18]. Our findings were consistent with those of earlier studies. In addition, one meta-analysis[20], two cohort studies[3,21], one nested case–control study[30] and one

Table 3. Colorectal cancer in relation to the consumption of dietary vitamin D
(Numbers; odds ratios and 95 % confidence intervals; medians and 25th, 75th percentiles)

	Q1*	Q2*		Q3*		Q4*		
Dietary vitamin D	OR	OR	95 % CI	OR	95 % CI	OR	95 % CI	P_{trend}
All subjects (*n* 2380/2389)								
No. of cases/controls	933/597	637/597		460/598		350/597		
Intake (μg/d)								
Median	2·90	5·12		7·27		10·92		
25th, 75th percentiles	2·17, 3·59	4·65, 5·63		6·64, 7·83		9·61, 13·44		
Crude OR	1	0·68	0·59, 0·80	0·49	0·42, 0·58	0·38	0·32, 0·44	<0·001
Adjusted OR1†	1	0·71	0·60, 0·83	0·56	0·47, 0·67	0·42	0·35, 0·50	<0·001
Adjusted OR2‡	1	0·78	0·66, 0·92	0·67	0·56, 0·81	0·57	0·46, 0·70	<0·001
Men (*n* 1356/1361)								
No. of cases/controls	511/340	355/340		276/341		214/340		
Intake (μg/d)								
Median	2·89	4·95		7·09		10·62		
25th, 75th percentiles	2·14, 3·49	4·51, 5·46		6·52, 7·74		9·44, 13·03		
Crude OR	1	0·70	0·57, 0·85	0·54	0·44, 0·66	0·42	0·34, 0·52	<0·001
Adjusted OR1†	1	0·64	0·51, 0·80	0·56	0·45, 0·71	0·41	0·32, 0·52	<0·001
Adjusted OR2‡	1	0·74	0·59, 0·94	0·73	0·56, 0·94	0·61	0·46, 0·80	<0·001
Women (*n* 1024/1028)								
No. of cases/controls	422/257	282/257		184/257		136/257		
Intake (μg/d)								
Median	2·90	5·36		7·47		11·42		
25th, 75th percentiles	2·20, 3·70	4·85, 5·87		6·84, 8·01		9·84, 13·65		
Crude OR	1	0·67	0·53, 0·84	0·44	0·34, 0·56	0·32	0·25, 0·42	<0·001
Adjusted OR1†	1	0·76	0·60, 0·97	0·55	0·42, 0·71	0·44	0·33, 0·58	<0·001
Adjusted OR2‡	1	0·82	0·63, 1·05	0·61	0·46, 0·81	0·53	0·38, 0·73	<0·001
$P_{interaction}$§								0·578
Colon cancer (*n* 1476/2389)								
No. of cases/controls	528/597	409/597		306/598		233/597		
Intake (μg/d)								
Median	2·97	5·16		7·25		10·96		
25th, 75th percentiles	2·24, 3·61	4·67, 5·65		6·63, 7·80		9·64, 13·47		
Crude OR	1	0·78	0·65, 0·92	0·58	0·48, 0·69	0·44	0·36, 0·53	<0·001
Adjusted OR1†	1	0·78	0·65, 0·93	0·64	0·52, 0·77	0·48	0·39, 0·59	<0·001
Adjusted OR2‡	1	0·88	0·73, 1·07	0·78	0·63, 0·96	0·68	0·54, 0·86	0·001
Rectal cancer (*n* 828/2389)								
No. of cases/controls	371/597	207/597		142/598		108/597		
Intake (μg/d)								
Median	2·91	5·13		7·27		10·80		
25th, 75th percentiles	2·17, 3·59	4·67, 5·64		6·62, 7·85		9·59, 13·39		
Crude OR	1	0·56	0·46, 0·68	0·38	0·31, 0·48	0·29	0·23, 0·37	<0·001
Adjusted OR1†	1	0·62	0·50, 0·77	0·48	0·38, 0·61	0·35	0·27, 0·45	<0·001
Adjusted OR2‡	1	0·66	0·53, 0·83	0·60	0·44, 0·74	0·46	0·34, 0·62	<0·001

* Cut-off values for quartiles of dietary vitamin D intake were 4·05, 6·00 and 8·47 μg/d for men and 4·36, 6·34 and 8·87 μg/d for women.
† Adjusted for age, sex, marital status, residence, educational level, occupation, income level, occupational activity, household and recreational physical activities, smoking status, alcohol drinking, family history of cancer, BMI, age at menarche and total energy intake. Exception: men not adjusted for age at menarche.
‡ Adjusted for age, sex, marital status, residence, educational level, occupation, income level, occupational activity, household and recreational physical activities, smoking status, alcohol drinking, family history of cancer, BMI, age at menarche, total energy intake, vegetable, fruit, red meat, dietary fibre and dietary Ca intake. Exception: men not adjusted for age at menarche.
§ Interaction effect between sex and dietary vitamin D intake.

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Table 4. Colorectal cancer in relation to the consumption of dietary calcium
(Numbers; odds ratios and 95 % confidence intervals; medians and 25th, 75th percentiles)

	Q1*	Q2*		Q3*		Q4*		
Dietary Ca	OR	OR	95 % CI	OR	95 % CI	OR	95 % CI	P_{trend}
All subjects (*n* 2380/2389)								
No. of cases/controls	953/597	636/597		445/598		346/597		
Intake (mg/d)								
Median	280·55	392·80		496·31		667·34		
25th, 75th percentiles	235·61, 314·35	368·47, 417·46		467·63, 529·63		610·82, 751·72		
Crude OR	1	0·67	0·57, 0·78	0·47	0·40, 0·55	0·36	0·31, 0·43	<0·001
Adjusted OR1†	1	0·67	0·57, 0·79	0·51	0·43, 0·60	0·43	0·36, 0·51	<0·001
Adjusted OR2‡	1	0·69	0·58, 0·81	0·54	0·45, 0·66	0·48	0·39, 0·61	<0·001
Men (*n* 1356/1361)								
No. of cases/controls	569/340	352/340		260/341		175/340		
Intake (mg/d)								
Median	275·32	379·68		478·46		639·53		
25th, 75th percentiles	231·31, 307·61	356·33, 403·99		454·37, 510·47		588·23, 715·35		
Crude OR	1	0·62	0·51, 0·76	0·46	0·37, 0·56	0·31	0·25, 0·39	<0·001
Adjusted OR1†	1	0·63	0·50, 0·78	0·45	0·36, 0·56	0·32	0·24, 0·41	<0·001
Adjusted OR2‡	1	0·67	0·53, 0·84	0·51	0·39, 0·67	0·40	0·29, 0·55	<0·001
Women (*n* 1024/1028)								
No. of cases/controls	384/257	284/257		185/257		171/257		
Intake (mg/d)								
Median	289·25	410·18		517·76		702·25		
25th, 75th percentiles	245·26, 326·06	383·87, 435·84		490·36, 551·08		638·45, 788·28		
Crude OR	1	0·74	0·59, 0·93	0·48	0·38, 0·62	0·45	0·35, 0·57	<0·001
Adjusted OR1†	1	0·77	0·60, 1·00	0·60	0·46, 0·77	0·60	0·46, 0·79	<0·001
Adjusted OR2‡	1	0·78	0·60, 1·01	0·61	0·45, 0·82	0·63	0·45, 0·87	0·002
$P_{interaction}$§								0·105
Colon cancer (*n* 1476/2389)								
No. of cases/controls	565/597	411/597		282/598		218/597		
Intake (mg/d)								
Median	283·31	391·76		497·06		665·14		
25th, 75th percentiles	236·44, 316·02	368·27, 417·30		468·29, 530·19		607·91, 753·62		
Crude OR	1	0·73	0·61, 0·86	0·50	0·42, 0·60	0·39	0·32, 0·47	<0·001
Adjusted OR1†	1	0·73	0·61, 0·87	0·54	0·44, 0·65	0·44	0·36, 0·54	<0·001
Adjusted OR2‡	1	0·78	0·64, 0·94	0·61	0·49, 0·76	0·55	0·43, 0·71	<0·001
Rectal cancer (*n* 828/2389)								
No. of cases/controls	358/597	206/597		152/598		112/597		
Intake (mg/d)								
Median	280·66	393·57		498·90		667·34		
25th, 75th percentiles	238·50, 316·68	368·81, 417·73		469·17, 530·63		610·93, 753·24		
Crude OR	1	0·58	0·47, 0·71	0·42	0·34, 0·53	0·31	0·25, 0·40	<0·001
Adjusted OR1†	1	0·59	0·48, 0·74	0·50	0·39, 0·63	0·39	0·30, 0·51	<0·001
Adjusted OR2‡	1	0·59	0·47, 0·74	0·50	0·38, 0·66	0·41	0·29, 0·56	<0·001

* Cut-off values for quartiles of dietary Ca intake were 336·46, 429·55 and 547·22 mg/d for men and 360·12, 462·53 and 589·92 mg/d for women.
† Adjusted for age, sex, marital status, residence, educational level, occupation, income level, occupational activity, household and recreational physical activities, smoking status, alcohol drinking, family history of cancer, BMI, age at menarche and total energy intake. Exception: men not adjusted for age at menarche.
‡ Adjusted for age, sex, marital status, residence, educational level, occupation, income level, occupational activity, household and recreational physical activities, smoking status, alcohol drinking, family history of cancer, BMI, age at menarche, total energy intake, fruit, red meat and dietary fibre intake. Exception: men not adjusted for age at menarche.
§ Interaction effect between sex and dietary Ca intake.

Table 5. Colorectal cancer according to tertiles of total dairy products intake
(Numbers; odds ratios and 95 % confidence intervals; medians and 25th, 75th percentiles)

	T1*	T2*		T3*		
Total dairy products	OR	OR	95 % CI	OR	95 % CI	P_{trend}
All subjects (*n* 2380/2389)						
No. of cases/controls	1374/795	713/798		293/796		
Intake (g/d)						
Median	0·00	3·49		22·02		
25th, 75th percentiles	0·00, 0·00	1·77, 6·83		15·75, 27·54		
Crude OR	1	0·52	0·45, 0·59	0·21	0·18, 0·25	<0·001
Adjusted OR1†	1	0·57	0·50, 0·66	0·27	0·23, 0·32	<0·001
Adjusted OR2‡	1	0·63	0·54, 0·72	0·32	0·27, 0·39	<0·001
Men (*n* 1356/1361)						
No. of cases/controls	783/453	420/455		153/453		
Intake (g/d)						
Median	0·00	2·72		19·81		
25th, 75th percentiles	0·00, 0·00	1·23, 5·57		14·18, 25·64		
Crude OR	1	0·53	0·45, 0·64	0·20	0·16, 0·24	<0·001
Adjusted OR1†	1	0·57	0·47, 0·69	0·24	0·19, 0·30	<0·001
Adjusted OR2‡	1	0·64	0·52, 0·78	0·30	0·23, 0·38	<0·001
Women (*n* 1024/1028)						
No. of cases/controls	591/342	293/343		140/343		
Intake (g/d)						
Median	0·00	5·15		24·43		
25th, 75th percentiles	0·00, 0·00	2·60, 8·34		18·11, 29·40		
Crude OR	1	0·49	0·40, 0·60	0·24	0·19, 0·30	<0·001
Adjusted OR1†	1	0·58	0·47, 0·73	0·32	0·24, 0·41	<0·001
Adjusted OR2‡	1	0·62	0·50, 0·78	0·36	0·27, 0·47	<0·001
$P_{interaction}$§						0·066
Colon cancer (*n* 1476/2389)						
No. of cases/controls	846/795	448/798		182/796		
Intake (g/d)						
Median	0·00	3·64		22·15		
25th, 75th percentiles	0·00, 0·00	1·83, 6·90		15·76, 27·76		
Crude OR	1	0·53	0·45, 0·61	0·22	0·18, 0·26	<0·001
Adjusted OR1†	1	0·57	0·49, 0·67	0·26	0·21, 0·32	<0·001
Adjusted OR2‡	1	0·64	0·54, 0·75	0·31	0·25, 0·38	<0·001
Rectal cancer (*n* 828/2389)						
No. of cases/controls	480/795	244/798		104/796		
Intake (g/d)						
Median	0·00	3·77		22·24		
25th, 75th percentiles	0·00, 0·00	1·91, 7·20		15·89, 27·45		
Crude OR	1	0·50	0·42, 0·61	0·22	0·17, 0·27	<0·001
Adjusted OR1†	1	0·60	0·49, 0·73	0·30	0·23, 0·39	<0·001
Adjusted OR2‡	1	0·65	0·53, 0·80	0·35	0·27, 0·45	<0·001

* Cut-off values for tertiles of total dairy products intake were 0·32 and 9·89 g/d for men and 1·41 and 13·41 g/d for women.
† Adjusted for age, sex, marital status, residence, educational level, occupation, income level, occupational activity, household and recreational physical activities, smoking status, alcohol drinking, family history of cancer, BMI, age at menarche and total energy intake. Exception: men not adjusted for age at menarche.
‡ Adjusted for age, sex, marital status, residence, educational level, occupation, income level, occupational activity, household and recreational physical activities, smoking status, alcohol drinking, family history of cancer, BMI, age at menarche, total energy intake, vegetable, fruit, red meat and dietary fibre intake. Exception: men not adjusted for age at menarche.
§ Interaction effect between sex and total dairy products intake.

case–control study[25] did not support a statistically significant inverse association between dietary vitamin D intake and the colorectal cancer risk.

There are some possible explanations that might help to account for these inconsistent results. First, in the present study, the mean dietary vitamin D intakes were 5·69 and 6·81 μg/d for cases and controls, respectively, which were relatively higher than the intakes reported in Europe (4·0–4·3 μg/d)[30], Finland (3·5–3·8 μg/d)[24] or France (2·61 μg/d)[21]. The dietary vitamin D intakes in other populations may be too low to reveal a protective role against colorectal cancer. Furthermore, vitamin D produced in the skin through UV irradiation accounts for 80–90 % of vitamin D in the blood[43]. Therefore, the association between dietary vitamin D intake and the risk of colorectal cancer may be confounded by endogenous vitamin D production in the skin in response to sunlight exposure. However, our model adjusted occupational activity as well as household and recreational physical activities (MET-h/week), which correlate strongly with sunlight exposure. The serum 25-hydroxyvitamin D level, which reflects both dietary and skin-produced vitamin D[44], was shown to be negatively associated with the risk of colorectal cancer[45,46]. Our study findings reveal a potential benefit of even low amounts of dietary vitamin D in terms of reducing the colorectal cancer risk.

Table 6. Colorectal cancer according to milk intake
(Numbers; odds ratios and 95 % confidence intervals; medians and 25th, 75th percentiles)

	Not drink	Drink		
Milk	OR	OR	95 % CI	P_{trend}
All subjects (*n* 2380/2389)				
No. of cases/controls	1681/1208	699/1181		
Intake (g/d)				
Median	0·00	58·10		
25th, 75th percentiles	0·00, 0·00	15·56, 134·60		
Crude OR	1	0·43	0·38, 0·48	<0·001
Adjusted OR1*	1	0·48	0·43, 0·55	<0·001
Adjusted OR2†	1	0·52	0·45, 0·59	<0·001
Men (*n* 1356/1361)				
No. of cases/controls	970/683	386/678		
Intake (g/d)				
Median	0·00	52·82		
25th, 75th percentiles	0·00, 0·00	14·43, 128·07		
Crude OR	1	0·40	0·34, 0·47	<0·001
Adjusted OR1*	1	0·44	0·37, 0·52	<0·001
Adjusted OR2†	1	0·49	0·41, 0·59	<0·001
Women (*n* 1024/1028)				
No. of cases/controls	711/525	313/503		
Intake (g/d)				
Median	0·00	62·27		
25th, 75th percentiles	0·00, 0·00	17·04, 150·40		
Crude OR	1	0·46	0·38, 0·55	<0·001
Adjusted OR1*	1	0·54	0·44, 0·65	<0·001
Adjusted OR2†	1	0·56	0·46, 0·68	<0·001
$P_{interaction}$‡				0·032
Colon cancer (*n* 1476/2389)				
No. of cases/controls	1037/1208	439/1181		
Intake (g/d)				
Median	0·00	60·62		
25th, 75th percentiles	0·00, 0·00	16·43, 142·37		
Crude OR	1	0·43	0·38, 0·50	<0·001
Adjusted OR1*	1	0·49	0·42, 0·57	<0·001
Adjusted OR2†	1	0·53	0·46, 0·62	<0·001
Rectal cancer (*n* 828/2389)				
No. of cases/controls	584/1208	244/1181		
Intake (g/d)				
Median	0·00	65·23		
25th, 75th percentiles	0·00, 0·00	18·12, 149·34		
Crude OR	1	0·43	0·36, 0·51	<0·001
Adjusted OR1*	1	0·51	0·42, 0·61	<0·001
Adjusted OR2†	1	0·53	0·44, 0·64	<0·001

* Adjusted for age, sex, marital status, residence, educational level, occupation, income level, occupational activity, household and recreational physical activities, passive smoking, alcohol drinking, family history of cancer, BMI, age at menarche and total energy intake. Exception: men not adjusted for age at menarche.
† Adjusted for age, sex, marital status, residence, educational level, occupation, income level, occupational activity, household and recreational physical activities, smoking status, alcohol drinking, family history of cancer, BMI, age at menarche, total energy intake, vegetable, fruit, red meat and dietary fibre intake. Exception: men not adjusted for age at menarche.
‡ Interaction effect between sex and milk intake.

Some previous studies examined the association between dietary Ca intake and colorectal cancer risk and reported results consistent with our findings. A 2009 meta-analysis of seventeen cohort studies and seventeen case–control studies observed a reduced risk of colorectal cancer with increasing dietary Ca intake (summary RR 0·77, 95 % CI 0·71, 0·81)[20]. A 2004 pooled analysis of eight cohort studies reached the same conclusion (summary RR 0·86, 95 % CI 0·78, 0·95)[47]. A prospective study[19] and a nested case–control study[30] from the European Prospective Investigation into Cancer and Nutrition cohort and a case–control study from the Fukuoka Colorectal Cancer Study[25] also observed a negative relationship between the dietary Ca intake and risk of colorectal cancer (RR 0·78, 95 % CI 0·69, 0·88; OR 0·69, 95 % CI 0·50, 0·96 and OR 0·64, 95 % CI 0·45, 0·93, respectively). However, five prospective studies[3,21–23,33] and two case–control studies[18,26] reported non-significant inverse associations of dietary Ca intake with colorectal cancer risk.

In our study, cases and controls reported mean dietary Ca consumption levels of 406·94 and 468·21 mg/d, respectively, which were lower than the intake levels reported in Western populations[21,22,24,26]. However, a pooled analysis[47] and two cohort studies[3,48] reported that relatively moderate doses of Ca may reduce the risk of colorectal cancer, whereas higher doses (>1000 mg/d) would yield little additional benefit. Furthermore, the dietary sources of Ca differ between Chinese and Western populations. In our study, vegetables were the primary dietary source of Ca (45 %), whereas dairy products were the main source of dietary Ca in Western populations[49].

The protective effect of vegetable-derived Ca on colorectal cancer may be partially attributable to other beneficial dietary components in vegetables. Furthermore, in this dataset, increased vegetable consumption was associated with a decreased risk of colorectal cancer[50]. This may explain the inconsistencies between our results and those of other studies. Therefore, our promising result supports a protective role for dietary Ca consumption against colorectal cancer.

The present study also provides evidence regarding the association of a high intake of total dairy products and milk with a decreased risk of colorectal cancer. Consistent with this result, a meta-analysis of twelve cohort studies suggested that the intakes of total dairy products and milk were inversely associated with the risk of colorectal cancer (RR 0·81, 95 % CI 0·74, 0·90 for total dairy products; RR 0·83, 95 % CI 0·74, 0·93 for milk)[4]. A prospective European Prospective Investigation into Cancer and Nutrition study of 477 122 subjects, including 4513 colorectal cancer cases, drew the same conclusion (RR 0·77, 95 % CI 0·70, 0·86 for total dairy products; RR 0·81, 95 % CI 0·73, 0·90 for milk)[19]. Another meta-analysis of fifteen cohort studies[51] and a pooled analysis of eight cohort studies[47] suggested a negative relationship between milk consumption and the risk of colorectal cancer. However, three cohort studies from America[22], Japan[25] and France[21] reported that the decreased risk of colorectal cancer was only associated with the intake of milk, but not of total dairy products.

Differences in dietary habits and the relative proportions of foods within the total dairy products category across different populations contributed to the variability among reports. This category includes yogurt, cheese, ice cream and milk tea, in addition to milk. Notably, the protective effect of milk may be attributed to its relatively high contents of vitamin D and Ca, for which the anti-cancer mechanisms have been explained above. However, other constituents of milk, such as lactoferrin, lactose, casein, conjugated linoleic acid and butyric acid, may also play protective roles against colorectal cancer[52,53]. Other dairy products, such as cheese, ice cream and milk tea, have relatively high-fat contents, particularly saturated fat, which can increase colonic bile acid levels and thus increase the risk of colorectal cancer[16,52]. A case–control study from Japan found that a higher intake of dairy products other than milk was associated with an increased risk of colorectal cancer[25]. Other studies have also observed a positive relationship between cheese intake and colorectal cancer risk, although these findings were not statistically significant[27,51,54]. The hypothesised protective effects of dairy products against colorectal cancer are attributed to milk, which accounts for most of the consumption of total dairy products. However, this dietary category also includes some products such as cheese which may increase the colorectal cancer risk. In our population, milk accounted for 72 % of the total dairy products intake, a relatively higher rate than those reported in Western or Japanese populations[21,25,55]. The beneficial effects of milk may be masked by the harmful effects of other dairy products such as cheese. This may explain why we observed inverse associations of colorectal cancer with both the consumption of total dairy products and of milk, whereas other studies only observed the association with milk consumption.

Vitamin D can affect Ca absorption in the gut[56] and thus affects the mechanism by which Ca exerts its anticarcinogenic effects[15,57]. Consistent with previous experimental results, our study observed a synergistic effect of Ca and vitamin D on the reduction of colorectal cancer risk. In Japan, a cohort study[58] and a case–control study[25] reported a stronger inverse association between the dietary intake of Ca and colorectal cancer risk among participants with a higher intake of dietary vitamin D. Similarly, a case–control study from Italy found a lower risk of colorectal cancer among participants with higher intakes of both dietary vitamin D and Ca [59]. Therefore, the existing epidemiological evidence supports a synergistic preventive effect of vitamin D and Ca against colorectal cancer.

In the present study, we observed inverse associations of the intakes of dietary vitamin D, Ca, total dairy products and milk with the risk of colorectal cancer in both sexes. Similarly, a cohort study from the National Institutes of Health-American Association of Retired Persons Diet and Health Study in the USA found that high dietary intakes of Ca and total dairy products were associated with decreased risks of colorectal cancer in both sexes[60]. However, other studies observed inverse associations of these nutrients and foods intake with the risk of colorectal cancer only in women[49,61] or in men[62]. Further studies are needed to clarify this issue.

A subgroup analysis by cancer site revealed that the inverse associations of colorectal cancer risk with the dietary intakes of vitamin D, Ca, total dairy products and milk were observed for both colon and rectal cancers. Consistent with our results, two above-mentioned meta-analysis[17,20] and a prospective study conducted by European Prospective Investigation into Cancer and Nutrition[19] revealed significant inverse associations of dietary vitamin D[17], dietary Ca [20], total dairy products and milk intakes[19] with both colon and rectal cancers. However, other studies reported inconsistent results[25,59,63].

Our study had the following strengths. First, it was the first study to examine the associations of the intakes of dietary vitamin D, Ca and dairy products with the risk of colorectal cancer in a native Chinese population. Second, a validated FFQ was used to assess the frequency and quantity of dietary vitamin D, Ca and dairy products intakes. Third, a wide range of potential confounders, including non-dietary and dietary factors, were adjusted in the analysis. Fourth, our study included a relatively large sample, compared with previous case–control studies. This provided adequate power to explore small associations with colorectal cancer risk.

However, the present study also had some limitations. First, it is difficult to rule out selection bias in hospital-based case–control studies. In our study, colorectal cancer patients were recruited consecutively from only one hospital, Sun Yat-sen University Cancer Centre, the largest cancer centre in Southern China. Still, the colorectal cancer patients at this hospital and at other large hospitals in Guangdong or elsewhere in mainland China shared similar clinical characteristics[64,65]. Moreover, the high participation rate (90·03 % for cases and 89·77 % for hospital-derived controls) in our study also helped to reduce selection bias. Second, recall bias is another common concern associated with retrospective studies. To reduce this bias, we included only newly diagnosed cases and attempted to interview the patients

very shortly after diagnosis (average time interval of 10·1 d). Furthermore, we provided photographs of usual food portion sizes to assist participants with the quantification of their food intakes. Third, measurement errors were unavoidable when assessing nutrient intakes, which resulted in the misclassification of individual intakes. However, such random measurement errors tend to result in null rather than spurious associations. Fourth, the calculated exposure to vitamin D and Ca did not include the intake of supplements, which might limit our evaluation of the associations of total vitamin D and Ca intakes with the colorectal cancer risk. However, other studies reported only minor differences between the total vitamin D and Ca intakes (including dietary and supplemental sources) and the intakes attributable solely to dietary sources[26,47]. Moreover, it was reported that in China, only 0·19–1·01 % and 0·24–1·19 % of adults took vitamin D and Ca supplements, respectively[66]. Fifth, the present study did not measure serum 25-hydroxyvitamin D level which is a marker of systemic vitamin D exposure. However, two confounding factors, occupational activity as well as household and recreational physical activities (MET-h/week) which were highly correlated with sun exposure, were included in the multivariable-adjusted models. Sixth, even though there were significant differences between the cases and controls in socio-demographic characteristics, these different variables were added into the multivariable-adjusted models as potential confounders. Furthermore, inverse probability of treatment weighting analysis was used to reduce the potential confounding effect, and significant differences in characteristics of case and control subjects were rigorously adjusted by using this approach. Similar results obtained after using the inverse probability of treatment weighting demonstrated the robustness of our model. Finally, although we adjusted a wide range of potential confounders, residual confounding factors may have remained. We could not exclude that control subjects who ate less meat and more plant-based foods had a healthier dietary pattern than the cases.

In conclusion, our study showed that the intakes of dietary vitamin D, Ca, total dairy products and milk were inversely associated with the risk of colorectal cancer in a Chinese population.

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The authors declare that there are no conflicts of interest.

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