Milk and Egg Are Risk Factors for Adverse Effects of Capecitabine-Based Chemotherapy in Chinese Colorectal Cancer Patients

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Abstract

Background: Chemotherapy-induced adverse effects (CIAEs) remain a challenging problem due to their high incidences and negative impacts on treatment in Chinese colorectal cancer (CRC) patients. We aimed to identify risk factors and predictive markers for CIAEs using food/nutrition data in CRC patients receiving post-operative capecitabine-based chemotherapy.

Methods: Food/nutrition data from 130 Chinese CRC patients were analyzed. Univariate and multivariate analyses were used to identify CIAE-related food/nutrition factors. Prediction models were constructed based on the combination of these factors. The area under the receiver operating characteristic curve (AUROC) was used to evaluate the discrimination ability of models.

Results: A total of 20 food/nutrition factors associated with CIAEs were identified in the univariate analysis after adjustments for total energy and potential confounding factors. Based on multivariate analysis, we found that, among these factors, dessert, eggs, poultry, and milk were associated with several CIAEs. Most importantly, poultry was an overall protective factor; milk and egg were risk factors for hand-foot syndrome (HFS) and bone marrow suppression (BMS), respectively. Developed multivariate models in predicting grade 1 to 3 CIAEs and grade 2/3 CIAEs both had good discrimination (AUROC values from 0.671 to 0.778, 0.750 to 0.946 respectively), which had potential clinical application value in the early prediction of CIAEs, especially for more severe CIAEs.

Conclusions: Our findings suggest that patients with high milk and egg intakes should be clinically instructed to control their corresponding dietary intake to reduce the likelihood of developing HFS and BMS during capecitabine-based chemotherapy, respectively.

Trial registration: ClinicalTrials.gov Identifier: NCT03030508.

Keywords

anemia, bone marrow suppression, capecitabine, chemotherapy-induced adverse effects, chemotherapy-induced nausea and vomiting, colorectal cancer, food/nutrition factor, hand-foot syndrome

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**Introduction**

Capecitabine is a prodrug of 5-fluorouracil (5-FU). It has been widely used in the treatment of various solid tumors, such as colon, rectum, breast, and gastric cancers in both adjuvant and neoadjuvant settings. Capecitabine can be applied alone or combined with other cytotoxic agents, including oxaliplatin, irinotecan, or cisplatin. The National Comprehensive Cancer Network (NCCN) guidelines of the US recommend capecitabine-based chemotherapy as a first-line chemotherapy regimen for stage II, III, and IV colorectal cancer (CRC), which is one of the most common malignant tumors worldwide. CRC ranks third in incidence and second in mortality rate worldwide.

Despite its promising treatment outcomes, capecitabine-based chemotherapy can also induce many adverse effects (chemotherapy-induced adverse effects, CIAEs). Nausea and vomiting (NV), hand-foot syndrome (HFS), and bone marrow suppression (BMS) are the 3 common adverse effects caused by capecitabine according to literatures and our ongoing observational clinical trial. These CIAEs hamper the successful completion of anti-cancer treatment, bringing a highly burdensome condition for patients, and even threaten life if left untreated.

In order to facilitate clinicians to develop personalized treatment strategies through CIAE prediction, it is urgent to identify all the important risk factors for CIAEs. Increasing evidence points out that nutrition factors are related to the CIAE susceptibility. Our previous study confirmed the association between variations in endogenous metabolites and the CIAE susceptibility. For example, there was a positive relation between pre-operative urine 4-pyridoxic acid and HFS, which is an indicator of vitamin B6 catabolism during inflammation. The level of vitamin B6 is remarkably dependent on dietary intake. Our earlier studies have also found a series of potential valuable hematological/body parameters to predict CIAEs in CRC patients, some of which have been reported as predictors of CIAE risk in various cancer patients. These parameters are also under the influence of nutrition factors in both short and long terms. What’s more, Kim et al showed that nutritional supplements can elicit beneficial effects on pancreatic and bile duct cancer patients receiving chemotherapy. Therefore, we propose that food/nutrition factors are potential markers for CIAEs.

In this study, we performed a nutrition survey based on a modified and simple Food-Frequency Questionnaire 25 (FFQ25) for middle-aged and elderly residents in Shanghai, China. FFQ25 showed reasonable reproducibility and validity of the major dietary patterns, compared with the full-length Food-Frequency Questionnaire. And it is considered easier to use with convenience. The purpose of this study was to test the hypothesis that food/nutrition factors exert influence on the susceptibility to certain CIAEs and even can be used as predictive markers in CRC patients receiving post-operative capecitabine-based chemotherapy.

**Materials and Methods**

**Patient Enrollment**

Patients with recorded food/nutrition data and CIAE(s) per cycle who received capecitabine after radical surgery were enrolled in this study. They were selected from a registered ongoing clinical trial (registered at www.clinicaltrials.gov, NCT03030508) at Shanghai Changzheng Hospital from January 2018 to June 2019. Recruited subjects in CRC patients were (1) over 18 years old and (2) diagnosed with CRC by biopsy examination. The exclusion criteria were: (1) pregnant and lactating women, (2) patients with hypersensitivity to fluorouracil or severe metabolic failure, (3) patients with severe infection, (4) patients with cancers other than CRC within the first 5 years of CRC surgery, and (5) patients with any pre-operative anti-neoplastic medication. This study was approved by Biomedical Research Ethics Committee of Shanghai Changzheng Hospital (No. 2016SL007), and written informed consent was obtained from every patient.

CIAEs were assessed according to Common Terminology Criteria for Adverse Events (CTCAE v4.03), based on which the CIAEs were graded from grade 0 (no symptom of a certain CIAE) to grade 4 (the most severe symptom of a certain CIAE). The occurrence of all incidences (grade 1-3) and severe incidences (grade 2/3) of each CIAE were studied. The clinical characteristics (sex, age, height, weight, and body mass index [BMI]) for all the enrolled patients were also collected.

**Nutritional Status Assessment**

The 25 food-item FFQ25 questionnaire about diet in the past 1 year was issued to patients after their radical surgery and was completed before the start of adjuvant chemotherapy (See detailed explanation on FFQ25 in Supplemental Methods). Patient’s daily dietary intake amount of each food and total energy intake was calculated according to the collected data on the frequency and amount of food intake, referred to China Food Composition Tables 2002 and 2004. Combining these 2 elements and the nutrition content of each food, the daily amount of various nutrient intake (protein, fat, carbohydrate, dietary fiber, cholesterol, vitamin A [VA], vitamin B1 [VB1], vitamin B2 [VB2], vitamin C [VC], vitamin E [VE], calcium, iron, and zinc) was also calculated. The frequency of food intake was defined as follows: “never,” “less than once a month,” “1-3 times per month,” “1-2 times per week,” “3-4 times per week,” “5-6 times per week,” “once a day,” “2 times per day,” “≥3 times per day,” and their corresponding conversion factors are: 0.00, 0.03,
0.07, 0.21, 0.50, 0.79, 1.00, 2.00, 3.00. The weight of each food per serving is expressed in terms of “Liang” that is a traditional weight unit commonly used in Chinese, and 1 Liang equals to 50 g. The amount of daily food intake was calculated from the FFQ25 using the following formula:

\[
\text{Total energy intake} = \sum_{n=1}^{i} (f_1 \times f_2 \times E_i)
\]

\[
\text{nutrition content of food} = \sum_{n=1}^{i} (f_1 \times f_2 \times N_i)
\]

in which, \(f_1\) is the conversion factor for frequency, \(f_2\) is the conversion factor for intake, \(E\) is the energy from each food, \(N\) is the nutrition content from each food, and \(i\) equals to 1 to 25 food items (25 items in total).

**Plasma Metabolome Profile**

In order to further prove the existence of the changes in food/nutrition factors, the correlation between CIAE-related food/nutrition factors and CIAE-related plasma metabolome profile from 36 out of the 130 enrolled patients were analyzed. The plasma metabolome data of the 36 patients was acquired from published data. To put it briefly, an UHPLC system coupled to a quadruple time-of-flight mass spectrometer was utilized for the metabolome assays. All the samples were screened separately under both positive and negative ionization modes, and the detailed methods of data pre-processing about metabolome were described in our previous study.7

**Statistical Analysis**

Descriptive statistics were conducted to investigate the demographic characteristics of patients as well as the information of CIAEs. Principal variance component analysis (PVCA) was applied to study the influence of potential confounding factors of age, body weight, height, BMI on food/nutrition data, and those with continuous values were converted to discrete variables. Total energy intake has been proven to be related to intakes of food and nutrients. Subsequently, the residual method was used to adjust the impact of total energy intake on food/nutrition data. Further, in order to remove the effect of the identified potential confounding factors, our data were then adjusted through the removeBatchEffect method in the “limma” package.

The univariate logistic regression analysis was employed for 2 different conditions: grade 1 to 3 versus grade 0, and grade 2/3 versus grade 0 to identify potential factors associated with all CIAEs and severe CIAEs respectively. On the basis of these significant relative food/nutrition factors, multivariate logistic regression analysis was then performed to further identify independent factors and construct a prediction model for each CIAE. The discrimination ability of each model was determined by the area under the receiver operating characteristic curve (AUROC) using “pROC” package. The best cut-off values for their predictive probabilities were determined by the maximum value of the Youden index (in the range of 0.6 sensitivity and 0.6 specificity). The “limma” package was applied for differential metabolome analysis. Spearman correlation was utilized to assess associations between food/nutrient intake and differentially expressed metabolites in plasma samples using cor.test () function. All statistical analyses were performed using R software (version 4.0.4), and \(P < .05\) was considered to indicate statistical significance.

**Results**

**Patient and CIAE Characteristics**

Amongst 139 participants initially enrolled in this study, a total of 130 CRC patients from 31 to 88 years old, with the diagnosis of advanced CRC (stages II, III, and IV), were included in this study for final analysis; 83 (63.8%) patients were males, and 47 (36.2%) were females. They all received 3-week-cycle capecitabine-based adjuvant XELOX (capecitabine plus oxaliplatin) chemotherapy. During each cycle, patients received oxaliplatin (0.16-2 g/day) intravenously on day 1 and capecitabine (1.5 g/day) per oral for the first 2 weeks. The demographic characteristics and observed CIAEs during chemotherapy of these patients are described in Supplemental Table S1. The variations of these clinical covariates in our data are shown in Figure 1A.

Figure 1B displays the incidence of each CIAE. HFS had the highest incidence (64.6%), followed by CINV (54.6%), nausea (51.5%), BMS (43.8%), and vomiting (35.4%); and the incidences of the other CIAEs were all lower than 30%. In addition, the majority of patients suffered from CIAEs with grade 1 to 2. Higher incidences of grade 2/3 CIAEs were observed in CINV, nausea, HFS, and BMS, all of which were higher than 10% than the other CIAEs. It is noteworthy that the total incidences of CINV and nausea were approximately 50%, and grade 2/3 accounted for at least 20%. Thus, an understanding of these CIAEs and their related food/nutrition factors is crucial. The correlation clustering results of the CIAE grades showed the relationship among the CIAEs (Figure 1C).
Adjustment for Confounding Factors and Univariate Analysis

Traditionally, food and nutrition factors were adjusted for the total energy intake via the residual method alone. Therefore, we first applied this normalization method and then performed univariate analysis (Supplemental Table S3). We found that a total of 15 factors were associated with CIAEs. Association of HFS with dessert, milk, VB2, and calcium were observed; besides, BMS was influenced by eggs, VB2, and nuts. Milk, VB2, and calcium were risk factors for grade 1 to 3 HFS, and dessert was a protective factor for grade 1 to 3 HFS. For grade 1 to 3 BMS, eggs, VB2, and nuts were risk factors; for grade 2/3 BMS, nuts were a risk factor. In terms of food/nutrition factors, eggs were risk factors for BMS, leukopenia, TCP, and anemia. On the other hand, milk was a risk factor for HFS, diarrhea, and anemia.

The potential confounding factors exert influence on food consumption and nutrition factors (Figure 1A), the effects of which were further eliminated using the removeBatchEffect method after the residual method. Then we repeated the univariate analysis (Table 1). Among all the 20 factors in relation to CIAEs, HFS was influenced by dessert, milk, VB2, calcium, and poultry; CINV was influenced by dessert and poultry; the only influential factor for nausea was dessert; BMS was influenced by eggs, VB2, dessert, poultry, and nuts. Milk, VB2, and calcium were risk factors for HFS, and dessert and poultry were protective factors for HFS; for CINV, both dessert and poultry were protective factors; nausea negatively correlated with dessert; eggs, VB2, and nuts were risk factors for BMS, and dessert and poultry were protective factors. Overall, eggs were risk factors for BMS, leukopenia, TCP, and anemia. Poultry, on the other hand, was a protective factor for HFS, CINV, BMS, leukopenia, TCP, IALT, and IAST. Dessert was a protective factor for HFS, CINV, nausea, BMS, and diarrhea.

In general, the results of the 2 normalization methods were very similar to each other. Poultry was an overall protective factor; milk and eggs were risk factors for HFS and BMS, respectively. However, we found that the additional normalization for confounding factors gave more CIAE-related food/nutrition factors (20 relative factors) than normalization only for total energy intake (15 relative factors). On top of this, the number of statistically significant associations between food/nutrition factors and CIAEs based on confounding factor-normalized data (29 associations with grade1-3 CIAEs and 23 associations with grade 2/3 CIAEs) were also higher than
Table 1. Univariate Analysis of Factors Significantly Associated With CIAEs Using Data Normalized by the Combination of the Residual Method and Confounding Factors.

| CIAEs         | Food and nutrition factors | Grade 1-3 vs Grade 0 | Grade 2/3 vs Grade 0 |
|---------------|----------------------------|----------------------|---------------------|
|               | OR (95% CI)                | P                    | OR (95% CI)         | P            |
| HFS Calcium   | 1.004 (1.001-1.007)        | .0115                | —                   | —            |
| Dessert       | 0.113 (0.015-3.589)        | .0204                | —                   | —            |
| Milk          | 1.782 (1.099-3.029)        | .0246                | 2.707 (1.296-6.124) | .0107        |
| Poultry       | —                          | —                    | 0 (0-0.022)         | .0026        |
| VB2           | 8.899 (1.874-49.443)       | .0085                | —                   | —            |
| CINV Dessert  | 0.126 (0.016-0.671)        | .0297                | —                   | —            |
| Poultry       | —                          | —                    | 0.037 (0.001-0.75)  | .0446        |
| Nausea Dessert| 0.151 (0.02-0.782)         | .0430                | —                   | —            |
| BMS Eggs      | 2.901 (1.552-5.755)        | .0013                | 5.26 (1.518-23.795) | .0164        |
| Nuts          | —                          | —                    | 11.468 (3.85-114.434) | .0258       |
| Poultry       | —                          | —                    | 0.005 (0-0.325)     | .0254        |
| VB2           | 4.895 (1.182-23.078)       | .0348                | —                   | —            |
| Vomiting Beers| —                          | —                    | 0 (0-0)             | .0034        |
| Leukopenia Eggs| 2.668 (1.332-5.736)     | .0078                | —                   | —            |
| Poultry       | 0.05 (0.002-0.738)         | .0483                | —                   | —            |
| TCP Eggs      | 3.313 (1.611-7.433)        | .0019                | —                   | —            |
| Poultry       | —                          | —                    | 0.001 (0-0.226)     | .0240        |
| Tubers        | —                          | —                    | 13.582 (1.141-149.01) | .0300       |
| Diarrhea Calcium| 1.004 (1.001-1.007)   | .0131                | 1.006 (1.001-1.011) | .0238        |
| Dessert       | 0.041 (0.002-0.573)        | .0329                | —                   | —            |
| Manufactured meat| 0 (0-0)                  | .0210                | —                   | —            |
| Milk          | 1.753 (1.055-2.957)        | .0309                | 2.787 (1.277-6.662) | .0121        |
| VB2           | 5.521 (1.053-33.297)       | .0487                | —                   | —            |
| IALT Beers    | 0 (0-0.035)                | .0239                | 0 (0-0)             | .0033        |
| DGV           | 0.577 (0.325-0.948)        | .0432                | —                   | —            |
| FWS           | 0.056 (0.002-0.722)        | .0496                | 0 (0-0.052)         | .0139        |
| Iron          | 0.827 (0.683-0.981)        | .0393                | —                   | —            |
| Poultry       | 0.01 (0-0.252)             | .0090                | 0 (0-0.009)         | .0092        |
| Sweet drinks  | —                          | —                    | 0 (0-0)             | .0154        |
| Tubers        | —                          | —                    | 0 (0-0.0132)        | .0492        |
| VA            | 0.598 (0.996-1)            | .0138                | —                   | —            |
| IAST Beers    | 0 (0-0.132)                | .0346                | 0 (0-0.004)         | .0250        |
| Cholesterol   | —                          | —                    | 1.011 (1-1.023)     | .0433        |
| Poultry       | 0.005 (0-0.191)            | .0075                | —                   | —            |
| Red meat      | —                          | —                    | 9.188 (0.838-102.457) | .0489       |
| Zinc          | —                          | —                    | 1.844 (0.97-3.5)    | .0477        |
| Constipation Nuts| 8.048 (1.147-58.644)   | .0333                | —                   | —            |
| Anemia Eggs   | 2.399 (1.028-6.01)         | .0492                | —                   | —            |
| Neutropenia FWS| 0.005 (0-0.264)          | .0189                | 0 (0-0.195)         | .0275        |
| Rice          | 1.552 (0.996-2.426)        | .0496                | —                   | —            |
| Seafood       | —                          | —                    | 0 (0-0.578)         | .0476        |
| Sweet drinks  | —                          | —                    | 0 (0-0.194)         | .0415        |

Univariate logistic analysis was performed using data normalized by the combination of the residual method and confounding factors. The data were firstly normalized by the residual method, and then it was further normalized by the potential confounding factors (sex, age, height, weight, and body mass index [BMI]) by removeBatchEffect method in limma. In brief, after applying the residual method and removeBatchEffect method to the original data, we obtained a new expression matrix, with the same dimensions as our original dataset. This new expression matrix has been adjusted for both total energy intake and potential confounding factors of age, body weight, height, BMI. Further analyses were performed on the adjusted data. CIAEs are sorted in descending order based on their incidence rate. “—” values that are not statistically significant.

Abbreviations: BMS: bone marrow suppression; CI: confidence interval; CIAEs: chemotherapy-induced adverse effects; CINV: chemotherapy-induced nausea and vomiting; DGV: dark green vegetables; FWS: food with stuffing; HFS: hand-foot syndrome; IALT: alanine aminotransferase increased; IAST: aspartate aminotransferase increased; OR: odds ratio; TCP: thrombocytopenia; VA: vitamin A; VB2: vitamin B2.
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Table 2. Multivariate Analysis of Factors Associated With CIAEs Using Data Normalized by the Combination of the Residual Method and Confounding Factors.

| CIAEs       | Food and nutrition factors | Grade 1-3 vs Grade 0 | Grade 2/3 vs Grade 0 |
|-------------|----------------------------|----------------------|----------------------|
|             |                            | OR (95% CI)          | P                    |
| HFS         | Milk                       | 1.431 (0.727-2.916)  | —                    |
|             | Poultry                    | —                    | —                    |
| BMS         | Dessert                    | 0.113 (0.011-0.8)    | 0.0497               |
|             | Eggs                       | 3.346 (1.419-8.692)  | 0.0085               |
|             | Nuts                       | —                    | —                    |
|             | Poultry                    | —                    | —                    |
| Leukopenia  | Eggs                       | 2.65 (1.315-5.756)   | 0.0090               |
|             | Poultry                    | 0.048 (0.002-0.771)  | 0.0483               |
| TCP         | Poultry                    | —                    | —                    |
| Diarrhea    | Manufactured meat          | 0 (0-0.01)           | 0.0469               |
| IALT        | Beers                      | 0 (0-0.195)          | 0 (0-0.712.577)      |
| IAST        | Beers                      | 0 (0-0.744)          | 0 (0-0.065)          | 0.0385               |
|             | Poultry                    | 0.007 (0-0.261)      | 0.0129               |
| Neutropenia | FWS                        | 0.007 (0-0.459)      | 0.0349               |

Statistically significant factors in univariate logistic analysis using data normalized by the combination of the residual method and confounding factors were entered in the multivariate logistic analysis. In brief, after applying the residual method and removeBatchEffect method to the original data, we obtained a new expression matrix, with the same dimensions as our original dataset. This new expression matrix has been adjusted for both total energy intake and potential confounding factors of age, body weight, height, BMI. Further analyses were performed on the adjusted data.

Abbreviations: BMS: bone marrow suppression; CI: confidence interval; CIAEs: chemotherapy-induced adverse effects; FWS: food with stuffing; HFS: hand-foot syndrome; IALT: alanine aminotransferase increased; IAST: aspartate aminotransferase increased; OR: odds ratio; TCP: thrombocytopenia.

the residual-normalized data (15 associations with grade1-3 CIAEs and 12 associations with grade 2/3 CIAEs) as shown in Table 1 and Supplemental Table S3. Besides these, the results generated from confounding factor-normalized data were more consistent with the result of CIAE clustering analysis. For example, HFS, CINV, nausea, and vomiting were clustered into cluster I. On the basis of normalization for confounding factors, univariate factor analysis revealed that dessert was the common protective factor for HFS, CINV, and nausea, which was in line with the result of cluster analysis (Figure 1C; Table 1). On the other hand, this type of similarity was not observed based on the residual-normalized data. Taken together, we decided to use the confounding factor-normalized data for subsequent analysis.

Multivariate Analysis

Multivariate analysis further showed that dessert, milk, eggs, FWS, manufactured meat, poultry, nuts, and beers were independent factors for CIAEs (Table 2). Amongst them, poultry, and eggs were common factors for several CIAEs. Poultry was a general protective factor for HFS, BMS, leukopenia, TCP, and IAST; dessert was a protective factor for BMS. On the contrary, milk was a risk factor for HFS, and eggs were a risk factor for BMS and leukopenia.

Correlation Between CIAE-Related Food/Nutrition Factors and Plasma Metabolome

Correlation analysis demonstrated the remarkable association between the potential nutritional markers of CIAEs and multiple CIAE-related endogenous plasma metabolites (Figure 3), which further validated the effects of dietary intake. A single food factor, milk, retained in the multivariate analysis, was related to significantly altered 7 metabolites for HFS susceptibility, and all 4 food/nutrition factors (dessert, eggs, nuts, and poultry) showed significant association with 18 metabolites for BMS susceptibility.

Development of CIAE Prediction Models

We developed combined prediction models for CIAEs, which ultimately retained the significantly relevant nutrition predictors from the univariate analysis. Results showed that the AUROC of the developed models ranges from 0.574 to 0.946. Of these, the AUROC of 9 models were less than 0.7, 7 were between 0.7 and 0.8, 5 were greater than 0.8, and two were greater than 0.9. We identified that 12 of the grade 1 to 3 (leukopenia, diarrhea, IALT, IAST, and neutropenia) and grade 2/3 (HFS, BMS, TCP, diarrhea, IALT, IAST, and neutropenia) CIAEs in total had relatively modest predictive performances (AUROC higher than 0.7), which account for a third of the total prediction models.
(Supplemental Table S4 and Figure S2). More importantly, there were 5 models in predicting grade 2/3 (HFS, BMS, IALT, IAST, and neutropenia) demonstrating excellent performance with AUROC values higher than 0.8, implying better accuracy than models in predicting grade 1 to 3 CIAEs. On the other hand, CINV’s prediction model had a lower AUROC (0.671), which was also relatively acceptable. Similarly, the AUROC of the grade 1 to 3 models of HFS and BMS were 0.671 and 0.696, respectively. This indicated that the grade 1 to 3 model for HFS and BMS was not as accurate as the models for grade 2/3 ones (Figure 2 and Supplemental Table S4).

Utilizing the analysis of AUROC, we found that the best cut-off value for the food/nutrient factors to identify the grade 2/3 HFS risk of these patients was milk (100 ml/day) > 0.950, poultry (100 g/day) < 0.077; regarding identifying the grade 2/3 BMS risk of these patients was eggs (100 g/day) > 1.058, Nuts (100 g/day) > 0.108, and Poultry (100 g/day) < 0.018 (Table 3).

**Discussion**

In this study, we investigated the contribution of dietary intakes on CIAE susceptibility in Chinese CRC patients receiving capecitabine-based chemotherapy for the first time. Our findings support our hypothesis that food/nutrition factors affect the susceptibility to certain CIAEs and they can also be used as predictive markers in predicting CIAEs. Milk and eggs were identified as common risk factors for the most frequent CIAEs.

As reported by previous studies, HFS, CINV, nausea, and BMS were the most common types of CIAEs among CRC patients. Correlation-based clustering analysis of CIAE occurrence divided CIAEs into different clusters. There were 2 relatively large clusters, one of which comprised HFS, vomiting, nausea, and CINV (cluster I). The cluster II included anemia, leukopenia, TCP, and BMS (Figure 1C). CIAEs in the same cluster may bear similarities in pathological mechanism, including risk and protective factors from food/nutrition factors. Published studies have reported the association between mucosal toxicities involving stomatitis/mucositis, diarrhea, and HFS, as well as the association between BMS and arrested cell proliferation, which was almost consistent with our result. We hypothesize that CIAEs in cluster I (including HFS) are primarily caused by abnormal inflammatory responses, and CIAEs in cluster II (including BMS) are primarily associated with cell cycle arrest. Notably, the incidence of each CIAE from the cluster I was above 30.0%.

Based on the CIAE data we have collected, we found that HFS, CINV, and BMS were the 3 types of CIAEs with the highest incidence. We also found that eggs, milk, poultry, and dessert were associated with the most frequent CIAEs. Based on the risk and protective factors from the univariate and multivariable analyses, we suggested a potential scientific explanation of how these food/nutrition factors affected the susceptibility to CIAEs.

The most apparent factor was poultry intake, which was found to be a general protective factor for types of CIAEs including HFS, CINV, and BMS. According to published literatures and our previous metabolomic analysis, we believe that the variation in inflammation response and wound regeneration amongst individuals are potential susceptible factors for CIAEs. As nutrition deficiency is associated with poor health state, we considered it as a general risk factor for CIAEs. Therefore, poultry, as a good resource of the 3 main types of nutrition (ie, carbohydrates, proteins, and fats), can serve as a reasonably protective factor for CIAEs. What is interesting is why poultry was a better protective source of meat than the other types of meat. Marangoni et al have produced a good summary of the beneficial effects of poultry on maintaining health and well-being, but also discussed the potential scientific reason. Poultry has a variable but moderate energy content: digestible proteins, unsaturated lipids, B-group vitamins (mainly thiamin, vitamin B6, and pantothenic acid), and minerals (like iron, zinc, and copper). Epidemiological studies performed across the world have also constructed a solid association between poultry consumption on a balanced diet, and reduced risk of developing overweight and obesity, cardiovascular diseases, type 2 diabetes mellitus, and cancer risk. Therefore, we believe that the protective effects of poultry on CIAEs also come with its balanced nutrition. Particularly, compared with the red meats (pork and beef), poultry has more unsaturated fatty acids and less reactive oxygen species.

The mechanism of HFS remains elusive. The widely accepted one is considered as a type of inflammation response mediated by cyclooxygenase-2 over-expression in the palm and plantar area. Consistently, our previous work has also identified several pro-inflammatory metabolites associated with HFS susceptibility. However, a prospective study reported that pyridoxine, which suppresses inflammation, cannot effectively prevent HFS. Herein we found that milk was a risk factor for HFS. The association between milk intake and HFS was also consistent with the HFS-related plasma metabolome. A remarkably negative correlation between the milk intake and altered “lipids and lipid-like molecules” metabolites, including 2 downregulated steroid hormones (5α-dihydrotestosterone [DHT] sulfate, and epiandrosterone sulfate) in HFS group was observed (Figure 3A). As the steroid hormones are synthesized from cholesterol in human body, our result was in agreement with the well-known fact that milk intake can decrease the absorption of cholesterol. Furthermore, our recent study showed that HFS-related transcriptome changes of normal colorectal tissue had an overall suppressed inflammation profile. Our food/nutritional
Figure 2. Receiver operating characteristic (ROC) curve for the developed models using relevant food and nutrition factors to predict CIAEs. (A) to (T) show the ROC curves for the models of anemia 1-3 vs 0, BMS 1-3 vs 0, BMS 2/3 vs 0, CINV 1-3 vs 0, CINV 2/3 vs 0, constipation 1-3 vs 0, diarrhea 1-3 vs 0, diarrhea 2/3 vs 0, HFS 1-3 vs 0, HFS 2/3 vs 0, IALT 1-3 vs 0, IALT 2/3 vs 0, IAST 1-3 vs 0, IAST 2/3 vs 0, leukopenia 1-3 vs 0, nausea 1-3 vs 0, neutropenia 1-3 vs 0, neutropenia 2/3 vs 0, TCP 1-3 vs 0, TCP 2/3 vs 0, respectively. “Com” indicates the multivariate models incorporating significantly relevant nutrition predictors from univariate analysis. Abbreviations: Ca, calcium; Com, combination; DGV, dark green vegetables; FWS, food with stuffing; MM, manufactured meat; SD, sweet drinks; VA, vitamin A; VB2, vitamin B2.
findings are also in accordance with the well-established function of milk in anti-inflammation. The fat content and fermentation effect do not affect the anti-inflammation effect. In addition, DHT sulfate is a sulfate derivative of DHT. Both DHT and its precursor cholesterol have proinflammatory effect. Therefore, our results suggest that, as the overall inflammation is suppressed in patients susceptible to HFS, patients with a high risk of developing grade 2 or even more severe HFS may benefit from reducing the everyday milk consumption below 95 ml.

For BMS, it comprises 4 types of CIAEs, namely, leukopenia, neutropenia, anemia, and TCP. The direct cause of BMS is the suppressed synthesis and (or) elevated consumption of mature blood cells, which can be induced by chemotherapy and environmental stimuli. Mature blood cell formation is a complex multistep process that starts from the differentiation of pluripotent hematopoietic stem cells and ends with the formation of types of mature blood cell formation. It is tightly regulated by types of signaling mediators, growth factor receptors, and transcriptional factors.

The association between food intakes (egg, dessert, nuts, and poultry) and BMS was also consistent with the BMS-related plasma metabolome, with the largest molecular group being “lipids and lipid-like molecules.” Egg has a complicated effect on plasma lipid profile. On one hand, daily egg consumption can increase serum TC and LDL-C concentrations in women.

On the other hand, egg-yolk sphingomyelin and phosphatidylcholine had a negative effect on cholesterol absorption. Consistently, we observed that egg intake was positively related to PC(34:2) and plasmalogen(PC(36:2)), but negatively related to PC(42:9) and docosahexaenoic acid. These lipids exert influence on regulating hematopoietic stem progenitor cell. Nuts are enriched with types of lipids and lipid-like molecules. Consistently, our data showed that nut intake was positively associated with SM(d40:2), 9,10-epoxyoctadecanoic acid, and FAHFA(32:4). In addition, high dessert intake mainly affected the levels of glycerophospholipids (Figure 3B). Desserts vary in ingredient, production method, and even appearance, but sugar is always one of the most common and abundant ingredients. Glucose can suppress the plasma level of choline which is the key precursor for lipid metabolism, especially for phosphatidylcholine synthesis. Consistently, we observed that dessert intake was negatively correlated with types of phosphatidylcholines. Therefore, we speculate that food/nutrition factors may induce BMS by disrupting one’s lipid and fatty acid homeostasis, since disrupted lipid metabolism is also associated with nearly every aspect of cellular molecular functions from membrane formation to cell differentiation. Disrupted lipid metabolism is one of the main risk factors for anemia, TCP, and leukopenia.

Amongst the 4 BMS-related food (egg, dessert, nuts, and poultry), eggs were a common risk factor for all BMS-related adverse effects except neutropenia that had the lowest incidence rate (12%) amongst cluster II. Therefore, we considered eggs as the common and most important risk factor for all BMS-related adverse effects. Our result was in agreement with one previous report in which dietary egg sphingomyelin prevented aortic root plaque accumulation in apolipoprotein-E knockout mice. Excessive accumulation of platelet is one of the most important contributing factors toward aortic root plaque accumulation. Therefore, our results suggest that, as the overall disrupted lipid homeostasis is a characteristic for patients susceptible to BMS, patients with a high risk of developing grade 2 or even more severe BMS may benefit from reducing the everyday egg consumption to 105.8 g. Considering moderate discrimination in CRC patients with grade 2/3 CIAEs and the prediction model for HFS2/3 patients used in clinical practice is of greater importance, herein we focused on discussing the cut-off value of food/nutrition factors for patients at the risk of the most common CIAEs with severe grade.

The susceptibility to CIAEs is affected by various factors from internal genomic background to exogenous stimuli. Our previously developed CIEA prediction models based on urinary metabolome exhibited great potential in predicting the occurrence of 5 types of CIAEs (grade 1-3) with AUROC values higher than 0.7, namely, HFS, anemia, neutropenia, TCP, and BMS. Comparatively, based on our food/nutrition data, the constructed prediction models demonstrated good discrimination accuracies for 5 types of CIAEs (leukopenia, diarrhea, IALT, IAST, and neutropenia) with AUROC values higher than 0.7. This suggested that the direct measurement of metabolites was more relevant to the susceptibility to HFS. One reasonable explanation is

### Table 3. The Best Cut-Off Values of Food/Nutrition Factors for Predicting HFS and BMS.

| CIAEs | Food and nutrition factors (unit) | Grade 2/3 vs Grade 0 | Cut-off value |
|-------|---------------------------------|---------------------|--------------|
| HFS   | Milk (100 ml/day)               |                     | >0.950       |
| BMS   | Poultry (100 g/day)             |                     | <0.077       |
|       | Eggs (100 g/day)                |                     | >1.058       |
|       | Nuts (100 g/day)                |                     | >0.108       |
|       | Poultry (100 g/day)             |                     | <0.018       |

The normalized data by the combination of the residual method and confounding factors was used here. In brief, after applying the residual method and removeBatchEffect method to the original data, we obtained a new expression matrix, with the same dimensions as our original dataset. This new expression matrix has been adjusted for both total energy intake and potential confounding factors of age, body weight, height, BMI. Further analyses were performed on the adjusted data. Only the cut-off values of food/nutrition factors for grade 2/3 HFS and BMS were listed here. Abbreviations: BMS: bone marrow suppression; HFS: hand-foot syndrome.
Figure 3. CIAE-related food/nutrition factors and plasma metabolites. Correlations between HFS-related (A) and BMS-related (B) food/nutrition factors and plasma metabolome (left), and selected average levels of related metabolites for the CRC patients in groups 1 to 3 versus 0, and groups 2/3 versus 0 (right).

Abbreviations: DHT, 5α-dihydrotestosterone; FAHFA, fatty acid ester of hydroxyl fatty acid; LysoPC, lysophosphatidylcholines; PC, phosphatidylcholine; PE, phosphatidylethanolamine; PI, phosphatidylinositol; PS, phosphatidylserine; SM, sphingomyelin.
that metabolites are influenced by all possible HFS-related factors and food/nutrition are parts of these factors. We also tried to use blood/body parameters acquired before chemotherapy to predict CIAEs, but only the prediction model for anemia achieved AUROC higher than 0.7. Both urinary metabolites and food/nutrition factors showed much better predictive performances than body/blood parameters. Furthermore, food/nutrition factors gave an overall better prediction for more severe CIAEs (grade 2/3) compared with the onset of CIAEs (grade 1-3). We could predict 7 severe CIAEs (namely, HFS, BMS, TCP, IALT, IAST, and neutropenia) with AUROC values higher than 0.7 (Figure 2). The prediction models for patients with more severe CIAEs are of greater importance. This further confirmed that food/nutrition factors did influence the susceptibility to CIAEs, and the contribution weighted more for more severe CIAEs as such patients have a more prominent clinical phenotype and are less likely to be misjudged.

This study had several limitations. First, as the causes of CIAEs may involve types of factors ranging from intrinsic DNA mutation to exogenous material consumption, and even environmental variations. Therefore, relative factors other than food/nutrition factor should also be considered together to give the best individualized chemotherapy. Second, it was a single-center study, and the sample size was small. External validation based on a larger sample size is warranted in the future. Finally, considering this is merely an observational study, only suggestions could be given to patients to avoid CIAEs. More efforts need to be done to develop a practical individualized chemotherapy including prospective clinical trials.

Conclusions

In summary, we confirmed that food/nutrition factors were important contributing factors for types of CIAEs. Poultry intake was an overall protective factor; milk and egg intakes were risk factors for HFS and BMS, respectively. The prediction models based on food/nutrition factors were constructed with modest performance, which can provide reference for Chinese CRC patients with chemotherapy. Patients prone to HFS and BMS consumed more milk and egg than the control groups, respectively. In order to reduce the prevalence of HFS and BMS, patients with higher milk and egg intakes should be clinically instructed to control their corresponding dietary intake. Our findings advocate that dietary control may be a promising tool in personalized chemotherapy to prevent CIAEs.

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Author Contributions

Hua Wei, Mingming Li, and Houshan Yao designed and supervised the study. Jinrong Xu, Zeshuai Lin, and Jiani Chen analyzed and interpreted the data, and wrote the original draft. Jian Zhang, Wanqing Li, Rui Zhang, Jin Xing, Zhihuan Ye, Xiaoping Liu, Qianmin Gao, Xintao Chen, and Jingwen Zhai collected the data. Jinrong Xu, Zeshuai Lin, and Jiani Chen visualized the data. All authors contributed to the writing of this manuscript. All authors read and approved of the final manuscript.

Declaration of Conflicting Interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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Ethics Approval

Patients in this study were selected from a registered clinical trial (registered at www.clinicaltrials.gov, NCT03030508) at Shanghai Changzheng Hospital from January 2016 to June 2019. The ethics of this study was approved by Biomedical Research Ethics Committee of Shanghai Changzheng Hospital (No. 2016SL007).

Consent to Participate

Written informed consent was obtained from all individual participants included in the study.

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Data Availability
The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

Code Availability
All codes for data cleaning and analysis associated with the current study are available from the corresponding author on reasonable request.

Supplemental Material
Supplemental material for this article is available online.

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