Reviewer #1:

1. **This is a good idea of looking into the association of the color of the vegetable and CRC. However, in the manuscript, the authors did not specifically mention about the specific vegetable for green vegetable and yellow vegetable. Is there any different between two different green color of vegetable in associate with CRC?**

   Authors' response: Vegetables and fruits were classified into 4 color groups according to Pennington & Fish's categories (e.g., green, orange/yellow, red/purple and white). The list of vegetables classified in each category for colors was presented in Table 1. In addition, we grouped orange and yellow vegetables/fruits into one category. We corrected 'orange' to' orange/yellow' throughout the manuscript.

2. **Does the way of cooking effect the outcome of your study? The data are not strong enough to back up your conclusion.**

   Authors' response: Since information on cooking methods for vegetables was not collected, we were unable to take into account the cooking methods in our analysis. We described this point as a limitation in Discussion section (Page 15, lines 332-333).

Reviewer #2:

1. **Adequacy of Abstract: Suggest that the types of 'orange' vegetables and fruits included in the category are added in brackets.**

   Authors' response: As recommended, we added types of 'orange/yellow' vegetables and fruits in the revised manuscript. (Page 4, lines 79)

2. **Methodology: OK. The limitations of the methods of data collection are stated.**
   Suggest adding that lack of accounting for processed meat intake (now confirmed as contributing to high risk of CRC) is an additional limitation of the data (unless this information is available ?).

   Authors' response: As recommended, we adjusted for processed meat in the revised manuscript (Page 8, lines 172-177). We found that additional adjustment did not change the odds ratios meaningfully.

Before revision

"Chi-square tests were used to compare the distribution of general characteristics and health related behavior factors among cases and controls. Intake levels of vegetables and fruits were categorized into sex-specific tertiles according to the distribution among control groups. The potential confounding variable considered were age, education, alcohol consumption, regular exercise, body mass index (BMI), red meat consumption, all of which were selected based on the literature [5-9] we also considered differences in the basic characteristics of the study participants."

After revision

"Chi-square tests were used to compare the distribution of general characteristics and health related behavior factors among cases and controls. Intake levels of vegetables and fruits were categorized into sex-specific tertiles according to the distribution among control groups. The potential confounding variable considered were age, education, alcohol consumption, regular exercise, body mass index (BMI), fiber intake, red meat consumption, processed meat consumption, and energy intake, all of which were selected based on the literature. After considering multi-collinearity, we finally adjusted age, education level, alcohol consumption, body mass index (BMI), regular exercise, red meat consumption, processed meat consumption, and total energy intake by residual methods."

3. **Please state if fruit intake includes fruit juice beverages?**

   Authors' response: Fruit juice beverages were included in the analysis, and we clarified it in the revised manuscript. (Page 8, lines 165).

4. **Statistical Analysis: Please define what is meant by the term 'basic characteristics' of study participants?**

   Authors' response: The basic characteristics were potential confounding variables from the literature. To avoid confusion, we deleted the sentence in the revised manuscript.

5. **Suggest adding that intake of processed meats should be considered or stated as a confounding unknown factor.**

   Authors' response: As recommended, we adjusted for processed meat in the revised manuscript.(Page 8, lines 172-177) We found that additional adjustment did not change the odds ratios meaningfully.

6. **Is it possible to break down the analysis of effect for orange plants into fruits versus vegetables,**

particularly for men?

Authors' response: As recommended, the separate results for vegetables and fruits for orange/yellow were added in Tables 3, 4, and 5.

Results section

"In the analysis of orange/yellow vegetables and fruits separately, orange/yellow fruits intake reduced the risks of colorectal cancer in women (OR: 0.64, 95%CI: 0.43-0.97). We found that higher intake of orange/yellow vegetables elevated the risks of colorectal cancer in both sexes (OR: 2.41, 95%CI: 1.83-3.16 for men. OR: 2.28, 95%CI: 1.55-3.34 for women)"

Discussion section

"This study shows that high orange/yellow vegetables intake elevates the risk of colorectal cancer. Orange/yellow vegetables include carrot, pumpkin, and ginger. In a case control study from Western Australia [10] and Prostate, Lung, Colorectal and Ovarian (PLCO) cancer screening trial study [11] reported the protective effects of dark yellow vegetables (carrot, pumpkin) for colorectal cancer risk. Gingerol and supplementation with ginger root extract inhibit colorectal carcinoma progress in vivo and humans [12, 13]. However, safrole, ingredients that generated when ginger rotted, and group 2B carcinogen classified by the IARC [14], is known to induce cancer in rodents. [15, 16] Also, the remaining chemical additives (fertilizer, preservatives, pesticide) after washing are likely to cause cancer. We have no definite explanation that orange/yellow vegetables intake increase the risk of developing colorectal cancer. More research is needed to verify this observation."

7. **Tables: Table 1. Suggest explaining what the % values refer to in the legend.**

    Authors' response: As recommended, we added explanation for percentages as followed:

    2. Proportion of color group to total vegetables and fruits.

    3. Proportion of color group to vegetables and fruits type.

8. **Table 5. Add 'P for trend' to the table column heading for the womens data section.**

    Authors' response: We revised the table as recommended.

9. **General Comments: P13, Para 1. Last sentence should be qualified as related to men and not to the total cohort**

    Authors' response: As recommended, we revised the sentence as followed:

    Before revision

"Surprisingly, a high intake from the orange vegetables and fruits color group was associated with a higher risk of colorectal cancer."

After revision

"Surprisingly, a high intake from the orange/yellow vegetables and fruits was associated with a higher risk of colorectal cancer in men."

10. **Special comments: Manuscript should have line numbers for ease of review and reference. Acknowledgements? Check for typographical errors throughout, eg, P1 first sentence of 'Data Collection section.**

Authors' response: As recommended, we added line numbers. The funding information is provided and the typographical errors were checked by a professional English editor.

Reviewer #3:

This is an interesting study, worthy of publication, but requiring some (minor) revision. Thus:

1. **Please check spelling; at least one error was found.**

   Authors' response: The typographical errors were checked by a professional English editor.

2. **What are some of the other "basic characteristics" – mentioned in "statistical analysis" of the studied group that were looked at in addition to the listed confounding factors?**

   Authors' response: The basic characteristics were potential confounding variables from the literature. To avoid confusion, we deleted the sentence in the revised manuscript.

3. **Fiber intake seems not to be a confounding variable normalized for. This needs to be mentioned in the Discussion, as it is an important variable. While in general, one can assume that increased fruit/vegetable consumption tracks with increased fiber intake, science is not about assumptions. Further, for example, sweet potatoes, not considered a vegetable in this study, contains significant fiber (as well as phytochemicals), so that is just one example of fiber intake not considered, and of course cereal/grains as well.**

Authors' response: As the reviewer suggested, there is high correlation between dietary fiber and vegetables and fruits (r=0.76) as well as total vegetables(r=0.80). Due to multicollinearity, we did not adjust for dietary fiber.

4. **On the one hand, Koreans are a useful study population, since the population is relatively homogenous and factors such as race/ethnicity are not significant confounding variables. On the other hand, whether or not these findings are generally applicable to the worldwide population is questionable and of course further studies are required. This can be touched upon in more detail in the Discussion. As one example, the different results with orange fruits in this cohort compared to other studies begs the question as to whether the findings presented here are generally applicable.**

Authors' response: As recommended, we added sentences mentioned limitation of generalizability in the discussion section as followed" (page 15, lines 318-321)

However, it is difficult to generalize to the population of many countries in the world. Because each country has its own traditional recipe and the unique vegetables and fruits that are naturally grown in each climate and topography.

5. **Readers in general may not be familiar with the details of the typical Korean diet, which may impact the results presented here. Perhaps a brief summary would be helpful: how does the diet of Koreans – and study participants of course – differ from that of other populations?**

Authors' response: As recommended, we added sentences mentioned characteristics of Korean diet as followed

"Korean diet has a unique synchronic serving method/style of which all dishes are served at one time on a table. On the other hand, Western or Chinese diet is diachronic (course meal), serving dishes at different points of time [18]. A Typical and common Korean table is set with *bap* (steamed rice), *kuk* or *chigae* (broth, stew), *banchan*(side dishes) and *kimchi* [19]. *Bap* is the main Korean dish that gives a major source of energy. *Kuk* or *chigae,* which are different than the Western soups [20] are eaten with *bap.* Usually, *banchan*(side dishes) are composed of more than three kinds of foods such as namul,

legumes, fish, meat, and *kimchi,* and are seasoned with jang, sesame or perilla seed/oil, vinegar, and herbs. Korean diet is usually well-balanced and nutritious. Based on these features, the health benefits of the Korean diet are reported in many cases of diseases [21, 22].

6.   **I understand that the Discussion noted that there is no explanation for the orange fruit differences between this and other studies with respect to colorectal cancer. Do the authors have any further speculation on this, including possibilities cited in points four and five above? How about the male vs. female difference observed within this study? Are there differences between male/female study participants in any variable not normalized for? In the general Korean population, are there differences in diet between men and women? Or are the male vs. female differences accounted for by innate biological differences between the sexes, such as hormones? I understand that the authors do not have a definitive answer - but any possibilities? Theories? Testable hypotheses?**

Authors' response:

1.   By suggestion of reviewer 2, we conducted additional analysis by splitting orange/yellow vegetables and fruits intake (tables 3, 4, and 5). Orange/yellow fruits intake observed reduced risks of colorectal cancer in women (OR: 0.64, 95%CI: 0.43-0.97). We found that higher intake of orange/yellow vegetables elevated the risks of colorectal cancer in both sexes (OR: 2.41, 95%CI: 1.83-3.16 for men. OR: 2.28, 95%CI: 1.55-3.34 for women)"

2.   For sex differences, the following sentences were added in the revised manuscript.

"Our results showed a sex difference. Although the underlying mechanism for the sex difference of our study between sexes is not clearly known, few possibilities can be considered from various aspects. Previous studies have suggested that estrogen exposure[23] and the use of oral contraception [24] prevented the development of colorectal cancer. Also, taking hormonal replacement therapy (HRT) in postmenopausal women showed reduced colorectal cancer risks in Women's Health Initiative (WHI) study [25] and a meta-analysis [26]. Another reason is that women tend to prefer vegetables and fruits than men. Because usually women are responsible in buying and cooking foods in Korean culture, they tend to have more information about beneficial health effects of vegetable/fruits and consume more of them. [27]. Other factors such as

prevalence of diabetes, physical activity, education and income levels, and lifestyle differences between sexes may influence the relationship between vegetables and fruits intake and colorectal cancer risk."

Reviewer #4:

1. **Dear Authors, Presented manuscript depicts interesting way of seeing of diet-factors impact to colorectal cancer genesis. Discrimination of vegetables and fruits according only their colour and hypothetical natural consent is substantially difficult in light of reliable statistical analysis. However, there are consistent preventive data of cruciferous vegetables, garlic or fiber-rich plants, the meaning of achieved results should be very careful. Available vegetables and fruits include diversified values of chemical additives, various preservatives and chemical fertilizers as well. Vast used, e.g. to citrus preservation, fungicides such as enilkonasol and also tiabendasol have documented pro-cancerous action. Because of that, estimation of influence of dietary plants to cancer is especially difficult in the age of chemically modified plants. It is possible that achieved OR result with orange colour in men group is a result of the above mentioned.**

Authors' response: We appreciate the reviewer's valuable comments. Vegetables and fruits were classified into 4 color groups according to Pennington & Fish's categories (e.g., green, orange/yellow, red/purple and white). The list of vegetables classified in each category for colors was presented in Table 1. In addition, we grouped orange and yellow vegetables/fruits into one category. We corrected 'orange' to' orange/yellow' throughout the manuscript. In addition, chemical additive that can cause cancer have been mentioned in the discussion (Page 14, lines 280-281).

2. **Additionally, there are possible differences between sex on field of handling with plants and preferable way of their consumption. Although, the differences with educational level and also income have been described by you, there is a consequent question – was the quality of food the same? What have been a share of other meal ingredients and their quality also? In this field is plenty factors contributed which should be counted. I realize that many factors, including diet,**

are involved in CRC genesis thus all my notes should be seen as advice for the future studies only.

Authors' response: For sex differences, the following sentences were added in the revised manuscript.

"Our results showed a sex difference. Although the underlying mechanism for the sex difference of our study between sexes is not clearly known, but few possibilities can be considered from various aspects. Previous studies have suggested that estrogen exposure[23] and the use of oral contraception [24] prevented the development of colorectal cancer. Also, taking hormonal replacement therapy (HRT) in postmenopausal women showed reduced colorectal cancer risks in Women's Health Initiative (WHI) study [25] and a meta-analysis [26]. Another reason is that women tend to prefer vegetables and fruits than men. Because usually women are responsible in buying and cooking foods in Korean culture, they tend to have more information about beneficial health effects of vegetable/fruits and consume more of them. [27]. Other factors such as prevalence of diabetes, physical activity, education and income levels, and lifestyle differences between sexes may influence the relationship between vegetables and fruits intake and colorectal cancer risk."

3. **Secondly, the authors did not consider sufficiently a contribution of inherited, diet-independent, pathway of CRC genesis. All cases with histopathological pattern suggesting MSI pathway should be excluded from the study. I think that collected material is really valuable also in potential future studying of methylation pathway, often linked with food. After all I would like to congratulate the authors a huge effort put to execute this study.**

Authors' response: We appreciate the reviewer's valuable comments. Since information on molecular characteristics of tumors, such as microsatellite Instability or CpG island methylator phenotype, was available only among limited number of colorectal cancer patients. We could not conduct further analysis by molecular characteristics, so we added the following sentence as a limitation in the Discussion section. (Page 16, lines 338).

Lastly, we could not further consider the molecular characteristics such as microsatellite Instability or CpG island methylator phenotype of colorectal cancer patients, which could be related with differential risk.