

Directed Research: Does High Dietary Intake of Glucosinolates and Isothiocyanates Reduce the Incidence of Colorectal Cancer in Adult Men and Women? A Systematic Review

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ABSTRACT

Colorectal cancer (CRC) is the third most commonly diagnosed cancer worldwide and in the United States. It is known that diet is one of the preventable lifestyle risk factors attributed to CRC and to the prevention of CRC. The purpose of this systematic literature review was to examine whether a high dietary intake of glucosinolates and isothiocyanates (ITCs) found in cruciferous vegetables (CVs) reduce the risk of CRC in adult men and women. An electronic search was conducted to identify relevant articles published through January 11, 2013 using Medline’s database; reference lists were also reviewed. Four cohort and 10 case-control studies from 7 countries were included in this review. The inconsistent results found in this review make it difficult to conclude that a high dietary intake of glucosinolates and ITCs found in CVs reduce CRC risk in adult men and women. Numerous methodological differences used in the studies most likely contribute to the inconsistent findings. A number of the studies were not adjusted for important risk factors associated with CRC risk. In order to more clearly determine CRC risk reduction with CVs intake, considerations for future research include: establish consistent confounding variables/adjustment protocol as related to CRC risk, ensure that study results are clearly differentiated between men and women, and cohort studies are recommended over case-control studies. While the results are inconclusive, registered dietitians/nutritionists should not be deterred from recommending that their clients consume CVs due to the health benefits. Eleven studies conducted in men and women combined found no association between high CVs intake with decreased CRC risk, while 5 men/women combined studies found a decreased CRC risk associated with high CVs intake. Eight studies conducted in men, and 11 studies conducted in women, found no association between CVs intake with CRC risk; however, 6 studies conducted in men, and 6 studies conducted in women, found a decreased CRC risk associated with high CVs intake. Two studies found no association between high CVs intake with increased CRC risk in men; however, 2 studies found an increased CRC risk associated with high CVs intake in men. Three studies found no association between high CVs intake and increased CRC risk in women; however, 2 studies found an increased CRC risk associated with high CVs intake in women. Finally, one men/women combined study found a positive association with high CVs intake with an increased CRC risk.

INTRODUCTION

Colorectal cancer (CRC) is the third most commonly diagnosed cancer worldwide; an estimated 1.2 million (9.7 percent) new cancer cases occurred in 2008 (1). An estimated 608,000 (eight percent) worldwide cancer deaths occurred, ranking CRC as the fourth most common cause of cancer death (1). In the United States, CRC is the third most commonly diagnosed cancer and third leading cause of cancer death in both men and women (2). CRC is primarily a “high-income countries” disease with overall proportions almost three times higher as compared to low- to middle-income countries (3). Given the world’s aging population and incessant growth, it appears likely that all current cancer rates, including CRC will continue to persist (1). It is also known that a number of preventable lifestyle risk factors are attributed to CRC and to the prevention of CRC, including diet, physical activity or inactivity, and alcohol consumption (3). In fact, thirty-three years ago, Doll and Peto (4) estimated that dietary factors contributed to as much as one third of all cancer incidents and could be prevented by a healthier diet. Similar statistics are reported today according to authoritative broad agreement (5). And, it is generally agreed that some cancer sites, especially of the colon “to be greatly or mostly affected by food and nutrition” (5). In 2011, the World Cancer Research Fund/American Institute for Cancer Research reported on CRC in its Continuous Update Project (3). The report concluded that, while limited there is evidence that certain non-starchy vegetables, fruits, and vitamin D-containing foods may protect against CRC. This paper focuses on non-starchy vegetables which are cruciferous. In particular, the chemo-protective benefits of the glucosinolates compound which are found in cruciferous vegetables (CVs) will be examined with its association in the prevention of CRC.

MATERIALS AND METHODS

Electronic and manual searches were conducted between November 20, 2012 and January 11, 2013. Selected *PubMed* MeSH terms and keywords were used and culminated in a search strategy limited to human studies and restricted to articles in English. Studies had to meet specific inclusion and exclusion criteria (see Tables 1 and 2, respectively) to be included in the systematic review. No restrictions were made on date of publication. Fourteen studies met the inclusion criteria. Figure 1 illustrates the process of identifying the studies included in this review.

This systematic review utilized the strategies adopted by the Evidence Analysis Library of the Academy of Nutrition and Dietetics as described in the *Evidence Analysis Manual: Steps in the Academy Evidence Analysis Process* (6). For each study, a data abstract worksheet was used to extract pertinent data and to examine the study’s quality. During the first round of article reviews (a total of four articles), seven health care professional reviewers (six of which were Registered Dietitian Nutritionists (RDNs); one with an undergraduate degree in Health Assessment and Promotion), independently reviewed each article. During the second round of article reviews (a total of ten articles), four of the original reviewers (all RDNs) independently reviewed each article. During both review discussions, all reviewers rated each study using the quality criteria checklist and ultimately came to a consensus on the study’s final rating.

An eighth reviewer, a statistician, evaluated the statistical analysis methods used in each of the systematic review’s 14 studies to confirm if appropriate statistical methods were followed; it was confirmed that proper statistical methods were used and that none of the articles’ ratings were affected.

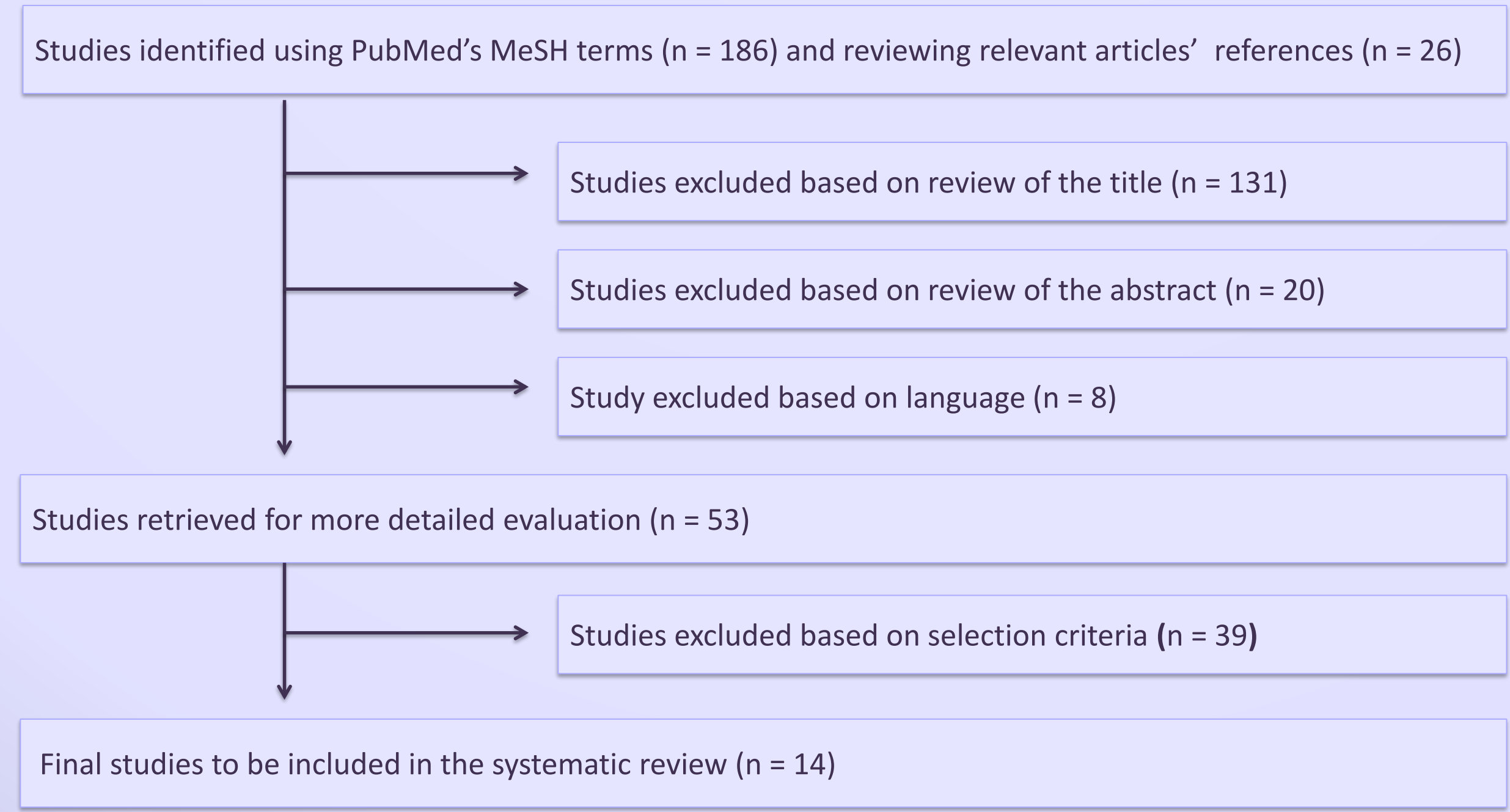
Table 1. Inclusion criteria

- 1) Colorectal cancer studies are defined as including the following: colorectal cancer/carcinoma/tumor and/or colorectum cancer/carcinoma/tumor (colorectal cancer), colon cancer, rectal and/or rectum cancer, colonic neoplasms, and colorectal neoplasms
- 2) Studies published as an original article unless unsatisfactory in conception, conduct or design
- 3) Studies in which appropriate statistical methods were followed
- 4) Studies reported in English
- 5) Studies that include adult men and women, eighteen years of age and older
- 6) Exposure of interest: glucosinolates and isothiocyanates intake from the consumption of cruciferous vegetables
- 7) Studies that report measurable dietary cruciferous vegetable intake
- 8) Outcome of interest: incidence of colorectal cancer
- 9) Studies that report various types of cancer other than colorectal cancer, only data pertaining to colorectal cancers is to be included
- 10) Studies involving human subjects

Table 2. Exclusion criteria

- 1) Studies reporting colorectal adenomas (i. e., noncancerous, benign tumors) as the outcome of interest
- 2) Observational studies that do not have control groups, such as cross-sectional studies, case series, and case report studies
- 3) Randomized clinical trials in which subjects received treatments other than dietary cruciferous vegetables intake
- 4) If duplicated data or overlapping datasets exist, then only the data from the largest or most recent publication were included

Figure 1. Flow diagram of identification of studies



RESULTS

Figure 1 shows fourteen studies included in systematic review:

- Four cohort studies (7-10) and
- Ten case-control studies (11-20). The source of case-control studies:
 - ◊ five population-based studies (11-15),
 - ◊ three hospital-based studies (16-18) and
 - ◊ two nested case-control studies (19-20).

These studies were conducted in the United States (four), Australia (three), Canada (one), China (three), Japan (one), Netherlands (one), and in the United Kingdom (one). They were published between 1987 and 2011.

RESULTS (continued)

The methods of examining CVs intake substantially varied between the qualities of the assessments used as well as the time period(s) in which the CVs were assessed. In addition, the number and selection of CVs examined varied from four (9, 11-12, 16) to as many as 11 (10). Further, one study (18) did not specify the type of CVs; in another study, it was unclear whether the investigator examined only broccoli and cabbage as the source of CVs (13).

With regard to other study characteristics, as few as two study variables (10, 15) to as many as 14 (8) study variables/adjustments were used.

- | | |
|-------------------------|------------------------------|
| • Age | • Histologically confirmed |
| • Body mass index (BMI) | • Education |
| • Gender | • Occupation |
| • Family history of CRC | • Diabetes |
| • Smoking status | • Socioeconomic status |
| • Alcohol intake | • Multivitamin use |
| • Meat intake | • Protein intake |
| • Total calorie intake | • Physical activity/exercise |

In accordance with the Evidence Analysis Library, the evidence from the seven CRC studies (11, 13, 15-16, 18-20) was assigned Grade III (6). This indicated that there was limited/weak evidence associated between decreased CRC risk and high CVs intake, given the studies of weak design and inconclusive findings. Evidence from the seven rectal cancer studies (9, 11-12, 15, 17-18, 20) was also assigned Grade III (6). Again, this indicated that there was limited/weak evidence associated between decreased rectal cancer risk and high CVs intake. The studies were of weak design and had inconsistent results. Evidence from the nine colon cancer studies (7-10, 14-15, 17-18, 20) was assigned Grade II (6). A Grade II conclusion indicated fair evidence associated between decreased colon cancer risk and high CVs intake. There were inconsistencies among the studies’ results and some of the studies were of strong design while others had weaknesses. Evidence from the four proximal colon cancer studies (9-11, 14) was also assigned Grade II (6). Yet again, this indicated fair evidence associated between decreased proximal colon cancer risk and high CVs intake. These studies were of either strong or weak design and had inconclusive findings. Evidence from the three distal colon cancer studies (10-11, 14) was assigned Grade III (6). This indicated that there was limited/weak evidence associated between decreased distal colon cancer risk and CVs intake. The majority of the studies had a weak design and reported inconsistent findings.

DISCUSSION/CONCLUSION

Inconsistent results found in this systematic literature review make it difficult to conclude that a high dietary intake of glucosinolates and ITCs found in CVs reduce the risk of CRC in adult men and women. The numerous methodological differences used in the studies most likely contribute to the inconsistent findings.

Despite the inconsistent findings, the possibility that CVs may decrease the risk of CRC is still conceivable. Cruciferous vegetables are popular in the American diet. They include broccoli, Brussels sprouts, cabbage, cauliflower, and kale, to name a few. They provide rich sources of fiber, folate, carotenoids (7, 10), flavonoids (6), and vitamin C (10); further, CVs are believed to decrease cancer risk by way of their antioxidant activity, modulation of detoxification enzymes, and stimulation of the immune system (26, 27). Moreover, CVs contain glucosinolates; certain hydrolysis products of glucosinolates, including indoles and ITCs, have shown anticarcinogenic properties. ITCs and indoles may inhibit tumorigenesis in part from their ability to repress phase I activating enzymes and induce phase II detoxification enzymes (24), thus influencing several processes related to chemical carcinogenesis (28). Phase II detoxification enzymes diminish the target tissue’s “exposure to DNA damage which exerts a ‘blocking effect’ on the initiation stage of chemical carcinogenesis” especially due to the effects of ITCs (24).

In order to more clearly determine CRC risk reduction with CVs intake, considerations for future research include: establish consistent confounding variables/adjustment protocol as related to CRC risk and ensure that study results are clearly differentiated between men and women. Cohort studies are recommended over case-control studies given their prospective design.

While results are inconclusive as to whether a high dietary intake of glucosinolates and ITCs found in CVs reduce CRC risk in adult men and women, registered dietitians/nutritionists should not be deterred from recommending that their clients consume CVs due to the health benefits discussed above. Additionally, since it is well known that a healthy diet is one of the many preventable lifestyle risk factors attributed to CRC and to the prevention of CRC, CVs can easily be incorporated in a healthy diet.

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