Cruciferous vegetables consumption and lung cancer prevention: epidemiological studies and molecular mechanisms

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Abstract: During the last decades cancer has become a global concern and it is currently considered as one of the leading causes of death worldwide. Lung cancer (LC), which is the first and foremost cause of cancer death, is mostly caused by airborne carcinogens exposures, such as cigarette smoke (CS), automobile exhaust, and coal combustion, that lead to DNA damage and mutation. Various cellular systems have been evolved to counteract this destructive process, including DNA repair and the programmed cell death machineries. However, the growing level of exposure to environmental insults of modern life requires additional protection against diseases like cancer, such as found in a daily consumption of fruits and vegetables. Here, we review studies that show LC chemopreventive effects of cruciferous vegetables and their phytochemicals, and describe the molecular mechanisms potentially involved in its prevention.

Keywords: Lung cancer (LC); cruciferous vegetables; cigarette smoke (CS); microRNA (miRNA); estrogen

Received: 28 December 2018; Accepted: 10 April 2019; published: 21 May 2019.
doi: 10.21037/jxym.2019.04.01
View this article at: http://dx.doi.org/10.21037/jxym.2019.04.01

Introduction

The increasing number of people living with cancer and the resulting millions of deaths each year makes it a growing global epidemic (1,2). Lung cancer (LC) is the most commonly diagnosed cancer, and the leading cause of cancer death worldwide (3). The etiology of LC is mainly related to harmful chemicals found in cigarette smoke (CS), such as polycyclic aromatic hydrocarbons (PHAs) and nicotine-derived nitrosamine ketone (NNK) (4). However, growing epidemiological evidences suggest rather consistently that general ambient air pollution may be responsible for increased rates of LC (5-10). According to The International Agency for Research on Cancer (IARC) the carcinogenicity of outdoor air pollution as a complex mixture of particulates [particulate matter (PM)] seems to be consistent with the increased risk of LC in epidemiological research studies and in experimental animals (8,9). LC can also be the result of an endogenous metabolic process, such as in the case of estrogen [17β-estradiol (E2)] and estrogen receptors (ERs) alteration by CS or chemicals with estrogenic activity (6,11). Exposure to environmental pollutants is also associated with changes in the expression of genes involved in DNA damage and repair, inflammation, immune and oxidative stress response, as well as altered telomere length and epigenetic effects such as DNA methylation (12,13). During the initiation stage of carcinogenesis, chemical and physical agents bind and form adducts with DNA. This damage can then be converted into mutations by error-prone repair, which in turn may cause inactivation of tumor suppressor genes or activation of proto-oncogenes and initiate the carcinogenic process (14). One of the most typical DNA adducts is 8-hydroxy-2'-deoxyguanosine (8-OHdG) which is an oxidative product of damage done to the guanine (G) nucleobase (15) that has lower oxidation potential and most easily oxidized among the four nucleobases (16). Several cellular mechanisms repair DNA damage and thereby help to prevent cancer (17), including the base excision repair (BER) system used to repair oxidative lesions such as 8-OHdG (18). However, modern life constantly exposes us to many stressors that lead to the development of chronic illnesses like cancer, and therefore the importance of disease prevention is gaining increasing recognition. In recent years, epidemiological studies have shown that daily fruit and vegetable consumption confers effective protection against various types of cancer, and the preventive effects of their dietary phytochemicals are also well documented (19,20). Among them, the cruciferous (also known as brassica) vegetables have been extensively studied and are especially known for their cancer chemopreventive function (21,22). The cruciferous family, whose name is derived from the cross-shaped flowers, includes several vegetable members with different edible parts, such as; seeds (mustard), flowers (broccoli, cauliflower), leaves (cabbage, brussels sprouts, kale, rocket, watercress), stem (kohlrabi) and roots (radish, turnip). Here, we summarize recent published information about cruciferous vegetables, and describe epidemiological and molecular studies showing their LC prevention properties.

Cruciferous vegetables and LC prevalence: epidemiological studies

Several studies have previously shown an inverse association between cruciferous vegetables consumption and the prevalence of different types of cancer (21-23). The study of Bosetti *et al.* have analyzed data from a series of case–control studies conducted in Italy and Switzerland between the years 1991 and 2009, that included 11,493 controls and 12,469 cases of 12 different cancer types (24). Using a 78-item food frequency questionnaire (FFQ), which included a specific question on weekly consumption of cruciferous vegetables, the investigators could evaluate the consumption of vegetables at least once a week as compared with no/occasional consumption. The results found a significant reduced risk for developing cancers of the digestive track (oral cavity and pharynx, esophagus, colorectum), breast and kidney, for people who consumed at least one portion (~125 grams) of cruciferous weekly. Moreover, although not statistically significant, the odds ratio (OR) of all the other investigated cancer types (stomach, liver, pancreas, larynx, endometrium, ovary, prostate) were below unity (24). Similar results were also shown in a large number of epidemiological studies that investigated the association of cruciferous vegetable consumption with LC. In the meta-analysis of 31 observational studies, cruciferous vegetable intake was shown to be inversely associated with LC risk (25). A systematic review, which included 19 studies, indicated that cruciferous vegetable intake is inversely associated with LC risk, and that the strongest inverse association was among individuals with homozygous deletion for glutathione S-transferase M1 (GSTM1) and T1 (GSTT1) genotypes (26). Interestingly, this kind of polymorphism seems to be important since individuals with GSTM1/GSTT1 null genotypes metabolize compounds produced by cruciferous vegetables less efficiently, therefore permitting them to remain biologically active for a longer period (27,28). A recent large-scale population-based prospective study found a similar inverse association of cruciferous vegetables intake and LC among current nonsmokers in Japan (29). The study used a 5-years follow-up survey for 82,330 participants who responded to a 138-item FFQ that contained cruciferous vegetables and also included information on smoking. The results found that cruciferous vegetable intake was significantly inversely associated with LC risk among both never and past smokers, however, no such association was observed in current smokers (29). A previous case–control study by Tang *et al.* using 948 primary LC cases and 1,743 control cases, investigated the association between cruciferous vegetables intake and LC risk among smokers (30). A 44-item FFQ was used to assess usual diet in the years before diagnosis, including raw and cooked cruciferous vegetables, and also requested detailed information on cigarette smoking status. Conversely, the results of this study showed a significant inverse correlation between cruciferous vegetables intake and the risk of developing LC, among smokers, indicating that when more cruciferous vegetables are consumed the resulted OR is lower (30). For cooked cruciferous, the lowest OR (0.59) was for the consumption of >25 servings (1 serving =0.5 cup) per month, while for raw cruciferous, the lowest OR (0.58) was for the consumption of >10 servings per month. Therefore, intake of raw cruciferous vegetables was more strongly inversely associated with LC risk (30).

Phytochemicals of cruciferous vegetables and LC prevention: molecular mechanisms

The plant enzyme myrosinase that forms biologically active compounds hydrolyzes glucosinolates, the sulfur-containing compounds that are responsible for the spicy taste and pungent aromas of cruciferous vegetables (23).

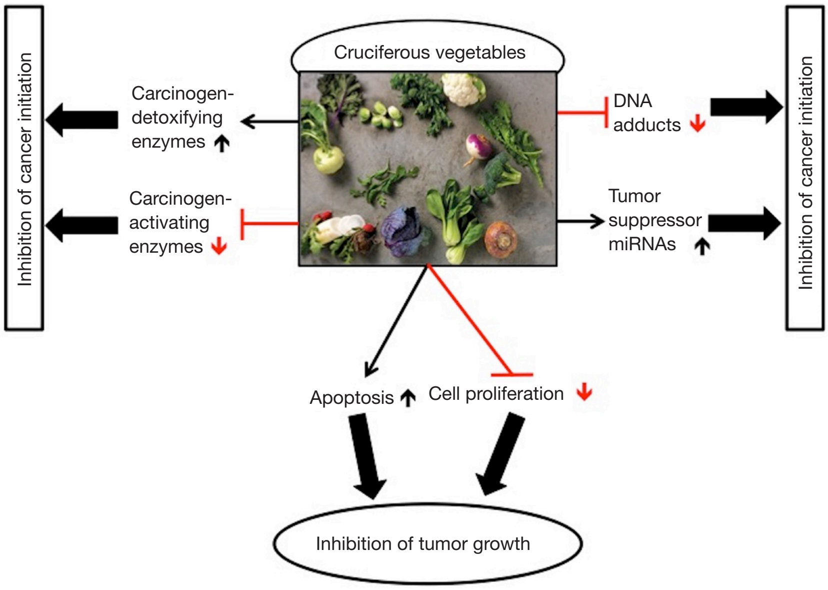

Figure 1 Cancer chemopreventive functions of cruciferous vegetables and their phytochemicals.

The degradation products of glucosinolates precursors include; indoles, such as indole-3-carbinol (I3C), and isothiocyanate (ITC), such as phenethyl isothiocyanates (PEITC), allyl isothiocyanate (AITC), benzyl isothiocyanate (BITC), and sulforaphane (SFN), which are some of the most studied components of cruciferous vegetables, and proved to possess anti-cancer properties (23). Numerous studies have revealed the contribution of ITC for various cellular processes used against carcinogenesis, such as inhibition of cell cycle progression and proliferation, and induction of apoptosis (31) (*Figure 1*). It has been recently suggested that ITC effects against cancer are also related with the activity of nuclear factor-kappaB (NF-κB) transcription factor, which is an active player in human cancers (32). PEITC was shown to be most effective agent in inhibition of CS-related cytogenetic damage, transcriptome alterations, and lung tumorigenesis (33-36). Furthermore, PEITC was shown to significantly inhibit the formation of the xenoestrogen bisphenol A (BPA)-induced DNA adducts (37), and SFN-induced protective phase II enzymes activity, resulted in reduction of E2-induced DNA damage (38). In addition, I3C and its condensation product 3,3'-diindolylmethane (DIM) exhibited potent antitumor activities in a wide range of human cancer cells, including LC (39,40), and SFN was shown to suppress LC through an epigenetic effect (41). Another suggested mechanism for the SFN anti-cancer effects is by modulating microRNA (miRNA) expression (42,43). MiRNAs are endogenous small RNA molecules with diverse biological functions that have been implicated in various human diseases, including LC (44-46). Global downregulation of miRNAs expression was observed in different human cancer types (47-49) after exposure to CS (50-52) or to the hormone E2 (53-56). Izzotti *et al.* evaluated miRNA expression in the lungs of rats exposed to CS and treated with several cancer chemopreventive agents. Administration of the dietary agents PEITC and I3C attenuated the CS-induced down-regulation of miRNA expression (57). In the case of the combined treatment with PEITC and I3C, they had profound effects on almost all CS- down-regulated miRNAs and their expression even exceeded the baseline situation (57). We have previously suggested that this effect may be related to the observed anti-estrogenic functions of PEITC and I3C (58-61). Recently, we described an association between the comprehensive miRNA repression observed in cancer and after E2 exposure, with G enrichment in the terminal loops of their precursors (62,63), which was also associated with their tendency to act as tumor suppressor miRNAs in lung and breast cancers (64). Thus, it is plausible that the effect of cruciferous dietary phytochemicals on miRNA expression may also involve the aforementioned mechanism (65,66).

Conclusions

The studies described above show that phytochemical compounds, such as those found in cruciferous vegetables, can help attenuate the molecular effects of carcinogenic substances such as CS and E2, and potentially reduce the risk of developing LC and other types of cancer. A potential application for these results may be the use of cruciferous phytochemicals as cancer preventive agents (e.g., as nutritional supplements). It is well established, however, that increasing cruciferous vegetables intake in the diet can be a simple and effective way for cancer prevention.

Acknowledgments

Funding: None.

Footnote

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at http://dx.doi.org/10.21037/jxym.2019.04.01). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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doi: 10.21037/jxym.2019.04.01
Cite this article as: Cohen A, Burgos-Aceves MA, Bar-Ziv N, Smith Y. Cruciferous vegetables consumption and lung cancer prevention: epidemiological studies and molecular mechanisms. J Xiangya Med 2019;4:21.

