Diet and Colorectal Cancer Risk in Asia - a Systematic Review

Salman Azeem, Syed Wasif Gillani, Ammar Siddiqui, Suresh Babu Jandrajupalli, Vinci Poh, Syed Azhar Syed Sulaiman

Abstract

Diet is one of the major factors that can exert a majorly influence on colorectal cancer risk. This systematic review aimed to find correlations between various diet types, food or nutrients and colorectal cancer risk among Asian populations. Search limitations include Asian populations residing in Asia, being published from the year 2008 till present, and written in the English language. A total of 16 articles were included in this systematic review. We found that red meats, processed meats, preserved foods, saturated/animal fats, cholesterol, high sugar foods, spicy foods, tubers or refined carbohydrates have been found by most studies to have a positive association with colorectal cancer risk. Inversely, calcium/dairy foods, vitamin D, general vegetable/fruit/fiber consumption, cruciferous vegetables, soy bean/soy products, selenium, vitamins C,E and B12, lycophene, alpha-carotene, beta-carotene, folic acid and many other vitamins and minerals play a protective role against colorectal cancer risk. Associations of fish and seafood consumption with colorectal cancer risk are still inconclusive due to many varying findings, and require further more detailed studies to pinpoint the actual correlation. There is either a positive or no association for total meat consumption or white meats, however their influence is not as strong as with red and processed meats.

Keywords: Colorectal cancer - diet - food - Asia - risk - correlation

Introduction

Cancer is one of the major causes of morbidity and death globally, and colorectal cancer is among the top 5 cancers most commonly diagnosed in both men and women alike (WHO, 2015; Talaiezadah et al., 2013). In 2008 alone, there has been more than 1.2 million newly diagnosed cases and 608,700 deaths caused by colorectal cancer. There is a higher incidence of colorectal cancer in economically developed countries compared to economically developing countries, and comparatively, more males develop colorectal cancer compared to the fairer sex (Barouni et al., 2012; Morrison et al., 2013; WHO, 2015).

While there are many factors that can alter the risk of getting colorectal cancer, dietary factors are known to be closely correlated with any type of cancer, and its link with colorectal cancer in particular is extremely profound (Jemal et al., 2011, Xue-Yan and Xin-Em Huang, 2015; Wu, Huang, 2015; WHO, 2015). Numerous studies over the years have studied and analyzed different dietary aspects and their link to colorectal cancer to try and find the correlation and reasoning behind these links, and generally have found that intake of red meats and processed meats, consuming meats cooked at high temperatures, high dietary animal fats and high dietary sugars potentially increase risk, while high fruit and vegetable consumption, fish consumption and high intake of certain nutrients such as selenium, calcium, vitamin D and folate may have a protective effect against colorectal cancer (Jemal et al., 2011; Magaji et al., 2014; ACS, 2015; CR-UK, 2015; WHO, 2015). However, a majority of these studies were done in countries where colorectal cancer was historically prevalent, mostly Western countries. In Asia, where colorectal cancer has comparatively recently became a more prominent problem, less studies have been conducted on the impact of diet on colorectal cancer among Asians. While it is true that many Asian countries are experiencing increasing ‘Westernization’ in their dietary patterns (Yusoff, 2012; Suh et al., 2013; Tashan, Andsoy, Iyugun, 2013; Lai et al., 2014; WHO, 2015), the amount, patterns, variations and cooking methods of their diet still differ substantially, and there may be notable difference in bodily response of the Asian population towards different diet components compared to the Western population (CDC, 2014; WHO, 2015; Li Li et al., 2015; Ersin Ozaslan et al., 2015).

Of the studies available that were done on the link of diet and colorectal cancer among the Asian population, there are varied conclusions to the effect of these dietary components towards colorectal cancer risk. Hence, this systematic review aims to compile the available data to
**Table 1. Study Findings on Various Diets/Foods/Nutrients**

<table>
<thead>
<tr>
<th>Diet/Food/Nutrient</th>
<th>Conclusion</th>
<th>Articles</th>
<th>Remarks</th>
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<tbody>
<tr>
<td>Fish/Seafood</td>
<td>Positive association</td>
<td>Lee et al (2009)</td>
<td>-positive association for cholesterol rich fish (eel, shrimp, shellfish)</td>
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<td></td>
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<td>Ganesh et al (2009)</td>
<td>-positive association for ‘dried fish’ among men, due to salting, drying and preserving</td>
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<td></td>
<td>Inverse association</td>
<td>Ganesh et al (2009)</td>
<td>-inverse association for fresh fish</td>
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<td></td>
<td>Mahfouz et al (2014)</td>
<td>-inverse association for seafood</td>
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<td></td>
<td>No association</td>
<td>Pham et al (2013)</td>
<td>-no association in cohort studies</td>
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<td></td>
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<td>Sugawara et al (2009)</td>
<td>-weak inverse association in case-control studies</td>
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<td></td>
<td></td>
<td>Lee et al (2009)</td>
<td>-may be due to comparatively high daily fish consumption</td>
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<td>-no association for total fish intake</td>
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<td>-lack of inverse association may be caused by raising seafood in polluted waters</td>
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<td></td>
<td></td>
<td>Nayak et al (2009)</td>
<td>-inverse but insignificant association for daily fish consumption</td>
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<td>Total meat</td>
<td>Positive association</td>
<td>Takachi et al (2011)</td>
<td>-positively associated in men (distal colon cancer)</td>
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<td></td>
<td></td>
<td>Ganesh et al (2009)</td>
<td>-positive association in women</td>
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<td></td>
<td>Inverse association</td>
<td>Lee et al (2009)</td>
<td>-may be due to overall low meat consumption</td>
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<td></td>
<td>No association</td>
<td>Butler et al (2008)</td>
<td>-no association of meat-based diet pattern</td>
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<td>-</td>
<td>-results may be affected by cooking methods</td>
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<tr>
<td>Red meat</td>
<td>Positive association</td>
<td>Mahfouz et al (2014)</td>
<td>-positively associated among women (proximal colon cancer)</td>
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<td></td>
<td></td>
<td>Pham et al (2014)</td>
<td>-increased colorectal adenoma risk but not colorectal carcinoma risk</td>
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<td></td>
<td></td>
<td>Takachi et al (2011)</td>
<td>-associated with high temperature cooking method</td>
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<td></td>
<td>Ramadas et al (2009)</td>
<td>-beef</td>
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<td></td>
<td>Nayak et al (2009)</td>
<td>-positive association regardless of consumption quantity</td>
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<td>Nashar et al (2008)</td>
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<td>Arafa et al (2011)</td>
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<td>Inverse association</td>
<td>Takachi et al (2011)</td>
<td>-No association for rectal cancer</td>
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<td>No association</td>
<td>Mahfouz et al (2014)</td>
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<td>Nashar et al (2008)</td>
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<tr>
<td>White meat</td>
<td>Positive association</td>
<td>Lee et al (2009)</td>
<td>-slight but insignificant positive association</td>
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<tr>
<td></td>
<td>Inverse association</td>
<td>Ramadas et al (2009)</td>
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attempt to reach a consensus on their influence towards colorectal cancer, and for the studies that report otherwise, to attempt to explain what lead to their findings.

**Materials and Methods**

Literature search was done on the influence of various...
dietary components, food types or nutrients on colorectal risk. No study design limitations were implemented. Search limitations were confined to studies done on Asian populations residing in Asia, being published from the year 2008 till present, and written in the English language. However, systematic reviews and meta-analyses done in Asia but did not limit their article search to Asian populations residing in Asia were excluded. Search terms were linked using the Boolean operator ‘and’. Primary search was done using databases and individual journal websites, like Pubmed, ResearchGate, Google Scholar, Wiley Online Library, British Journal of Cancer, Cancer Epidemiology, The American Journal of Clinical Nutrition, Asian Pacific Journal of Cancer Prevention and so forth. After primary search, a secondary search was done on the reference lists of the articles found.

Primary screening focused mainly on a quick scan of the title, abstract and discussion sections. Articles that passed primary screening are then read fully in detail as secondary screening.

**Results**

A total of 16 articles matched the aforementioned criteria and were included for review. 7 articles were from Japan, 2 each from Malaysia and India, and 1 each from Egypt, China, Singapore, Jordan and Saudi Arabia. As seen, a majority of the studies were conducted in Japan, which is not surprising as incidences in Japan has been increasing drastically and have exceeded peak rates of countries that were previously among those with the highest incidence rates, such as the United States of...
America, Australia and New Zealand (Center et al., 2009; Cetin et al., 2012; Bozkurt et al., 2014).

Some articles studied on a single type of diet whereas some tackled multiple diet areas. The table below summarizes the findings of the articles on each diet type. A positive association means an increase in colorectal cancer risk, whereas an inverse association means a decrease in colorectal cancer.

In summary, most studies found that fish and seafood consumption has no association. There is either a positive or no association for total meat consumption or white meats. There is a positive association for red meats, processed meats, preserved foods, saturated/animal fats, cholesterol, high sugar foods, spicy foods,
Discussion

Fish and seafoods are well-known for having high n-3 fatty acid content, and it has been long believed that n-3 fatty acids, more popularly known as omega-3 fatty acids, are capable of preventing carcinogenesis via multiple pathways (Pham et al., 2013). According to Cockbain et al, omega-3 fatty acids are capable of reducing mucosal epithelial cell proliferation and have anti-inflammatory properties (Cockbain et al., 2012). However, more and more studies show conflicting findings on the efficacy of omega-3 fatty acids towards cancer prevention, and a re-analysis of past research suggested that there may not be any reduction of cancer risk after all (ACS, 2013; Dirican et al., 2014). Then again, interpretation of these studies have been difficult due to numerous differences in study design and lack of control of variables. Type of fish, whether the fish consumed is fresh or processed, method of preparation and differences of unit of reporting outcome measures have made it challenging to come up with accurate results (cockbain et al., 2012). A meta-analysis that attempted to navigate these variables managed to find that consumption of fish does inhibit colorectal carcinogenesis (Geelen et al., 2007; He et al., 2014). Other than omega-3 fatty acids, fish are also known to contain vitamin D and selenium, which are also known to have anti-cancer properties (Pham et al., 2013). The World Cancer Research Fund and American Institute for Cancer Research (WCRF/AICR) also voiced agreement in the role of fish in colorectal cancer prevention, though they did clarify that their findings are based on limited evidence (CR-UK, 2015).

Of the 6 articles included in this review that discussed the link between fish or seafood with colorectal cancer, 4 have concluded that there is no association. The systematic review by Pham et al. (2013) found no association in the cohort studies but a weak inverse association in case-control studies, but also noted that the case-control studies are prone to recall and selection bias due to a tendency of selecting controls among those who have undergone a health screening, and did not adjust for meat consumption and other potential confounding factors. This being said, the 2 studies that reported that fish has a protective effect against colorectal cancer were both case-control studies, also having picked their controls from an oncology center and hospital respectively. Of the 2 articles that reported an increase in colorectal risk by fish consumption, one was reporting on ‘dry fish’, and hence the increase in risk may be attributable to other factors such as the fish being a preserved food item, which is found to increase colorectal cancer risk (Ganesh et al., 2009; Mahfouz et al., 2014). The other paper by Lee et al. (2009) found positive association in cholesterol rich fish, and cholesterol is also found to increase the risk of colorectal cancer. The other 3 papers that reported no association each attempted to explain possible factors that lead to a difference in results of their findings compared to those that reported otherwise, with Sugawara et al stating that it may be due to the comparatively high fish consumption of their study cohort and the different species of fish consumed (Sugawara et al., 2009); Lee et al. (2009) explained on the possible effects of consuming seafood raised in polluted waters in Shanghai, where the study was conducted; Nayak SP et al. (2009) reported on the formation of heterocyclic amines (HCA) on fish meat when cooked which can be carcinogenic, though also stating that fish consumption is safe but does not significantly reduce colorectal cancer risk. Hence, it may be said that instead of having no association at all with colorectal cancer risk, it may be said that results are inconclusive, and further more detailed studies are required to pinpoint the actual association.

Regarding the effect of meats towards colorectal cancer risk, less studies are done on total meat consumption and white meats as they are not identified to be major risks of colorectal cancer, and this is mirrored in our findings. Most studies focus more on red meats and processed meats, which are well known for a long time to play an important role in increasing colorectal cancer risk. Numerous large scale studies conducted in countries with high red meat and processed meat consumption have confirmed this link (Harvard Medical School, 2008). The same has been found in this systematic review, with 7 out of 9 studies supporting the positive association of red meats and colorectal cancer risk and 3 out of 4 studies supporting the link regarding processed meats.
Red meat has high amounts of heme iron, which can not only damage DNA, but also catalyze genotoxic and cytotoxic aldehyde formation and increase multisite carcinogens known as N-nitroso compounds (NOCs). NOCs are also formed in the making of processed meats. Meats are also commonly cooked at high temperature, and this leads to the formation of HCAs and polycyclic aromatic hydrocarbons (PAHs) that are carcinogens as well (Takachi et al., 2011; Pham et al., 2014). In the study done by Lee et al. (2009) which studies on the effects of Chinese cooking methods towards colorectal cancer risk, only the ‘smoking’ method, which exposes the meat to heat for a long period of time, showed a link. NOCs, PAHs and HCAs are capable to interact with our genes and alter the risk of forming colorectal adenomas. Nayak et al. (2009) explained that beef, a commonly consumed red meat, can increase colorectal cancer risk irrespective of HCA content, meaning that HCA is not concentration dependent and just the involvement of beef in one’s diet can increase risk of getting colorectal cancer. They also stated that meat consumption can increase bile acid production which can promote mitosis. Interestingly, Ramadas et al. (2009) reported that red meat can increase the risk of developing colorectal adenomas but does not affect carcinoma risk. Nevertheless, this is still of concern as carcinomas can easily develop from existing adenomas.

4 out of 5 studies confirmed a positive association of saturated or animal fats and cholesterol with colorectal cancer risk, though none gave detailed explanations on the mechanism. However Lee et al. (2009) did mention that cholesterol plays a role as co-carcinogen in cancer development, though a brief search revealed that most studies reporting this finding are animal studies. A number of other mechanisms have also been proposed, including the link between a high fat diet, bile acid and cancer. High fat diets lead to higher bile acid production, and this leads to a higher generation of reactive nitrogen species (RNS) and reactive oxygen species (ROS). Exposure of colonic cells to RNS and ROS can lead to DNA damage and cell mutation. Additionally, long term exposure to RNS and ROS can reduce cell apoptosis capabilities, increasing mutagenesis risk (Bernstein et al., 2009; Ozdemir et al., 2014).

Takachi et al. (2009) studied on the effects of sodium and preserved foods on colorectal cancer risk. They found that while overall high sodium consumption does not have an association, preserved foods with high salt content does have a positive link. Being a Japanese study they singled out salted fish roe and dried fish as examples. They explained that it was not primarily due to the salt content that caused the link, but due to the curing process by the salt that lead to carcinogen formation similar to that mentioned above regarding the cooking and curing of meats. Ganesh et al. (2009) also reported the increase in colorectal cancer risk by ‘dry fish’ consumption, due to the involvement of salting and drying of the fish for preservation purposes.

Both studies that studied on the effects of sugar consumption to colorectal cancer risk found a positive association, with Mahfouz et al specifically mentioning artificial sweeteners and soft drinks, while Nayak et al. (2009) mentioned overall heavy sugar consumption. Nayak et al. (2009) also stated a positive association of refined carbohydrates with the risk (Mahfouz et al., 2014). High carbohydrate and sugar content can lead to excess insulin production, and not only so, such a diet can lead to accumulation of visceral adipose tissue and hence obesity, and this in turn is also associated with high insulin production. Insulin, being a growth factor in the colon, can enhance colonic cell proliferation and increase the risk of development of colorectal cancer (Schioen et al., 1999; Levy, 2012).

Spices are commonly included in various Asian cuisine, so not surprisingly there are a couple of studies that try to find the link between spicy food and colorectal cancer. Both studies found a positive link, with Nayak et al. (2009) specifying on pungent spices, such as chilies. There seems to be conflicting findings on the effects of capsaicin, the alkaloid that gives chilies their pungency, on cancer; some reported it to be anti-carcinogenic, while others reported it to be otherwise. There are no human studies so far. But findings in their study alone found that long term consumption of pungent spices can lead to colorectal cancer. Mahfouz et al. (2014) also mentioned similar findings and quoted Nayak et al. (2009) in their study.

Calcium has been frequently mentioned as a protective nutrient against colorectal cancer. Calcium is capable of acting at multiple tiers of colonic cell organization by manipulating a complex series of signaling events, preventing colorectal carcinogenesis. Proliferation of colonic epithelial cells is reduced, and recurrence of adenomas is also likewise reduced (Cho et al., 2004). Calcium can also enhance colonic cell apoptosis (Miller, 2005). Vitamin D also plays a role in colorectal cancer prevention as not only does it aid in the absorption of calcium, it itself also exerts anti-cancer properties by regulating apoptosis, proliferation and differentiation of cells and inhibits angiogenesis (Mizoue et al., 2008). 4 studies in our review support the inverse association of calcium and 1 study supports the role of vitamin D. Some studies also mentioned the role of other nutrients in dairy products that also have anti-carcinogenic properties, such as conjugated linoleic acid (Mizoue et al., 2008). However, Mizoue et al. (2008) has noted that only milk exerts this protective effect, and that other dairy products actually can increase colorectal cancer risk. Different dairy products contain different compositions and are produced differently; hence more studies need to be conducted to explain the association. Findings by Nahsar et al. (2008) on the positive correlation between whole fat dairy products and colorectal cancer risk may be attributed to the fat contents of the product, which mentioned previously is positively linked to colorectal cancer risk. As for Ishihara et al that does not find an association of dietary vitamin D with colorectal cancer risk, it may be due to the relatively low calcium intake among the study population, therefore without sufficient calcium vitamin D cannot exert its influence on calcium fully, and hence the association may not be so pronounced (Ishihara et al., 2008).

High vegetable and fruit intake has always been viewed as beneficial to health and an important element in cancer.
prevention, due to rich fiber content, vitamins, minerals and antioxidants (Nayak et al., 2009). This is mirrored in our findings where 6 out of 8 studies supported the inverse association towards colorectal cancer risk, and none reported positive associations. Nashar et al. (2008) stated several potential protective mechanisms by vegetables and fruits, including shortening of feces transit time by fiber, which reduces contact time with the colonic wall and hence less exposure to potential carcinogens; production of short chain fatty acids when fiber is fermented in the colon, which has apoptotic and antiproliferative, antifibrotic and differentiating properties (Hinnebusch et al., 2002); the action of selenium, which is present in cereals, which acts as a cofactor for glutathione peroxidase that prevents oxidative tissue damage and hence suppresses cancer cell proliferation; folic acid from fruits, which not only helps in DNA repair and replication, but also aids in production of S-adenosylmethionine (SAM), which is important for DNA methylation and can act in the suppression of viral repetitive DNA (Ulrich, 2007); and the provision of anticarcinogens such as protease inhibitors, resveratrol, carotenoids, flavonoids, vitamin C, isothiocyanates and organosulfides. Ramadas et al. (2010) has noted a stronger preventive role by vegetable consumption for the prevention of adenoma to carcinoma conversion, compared to the initial formation of adenomas. A family of vegetables, known as cruciferous vegetables, have been of particular interest as they are not only rich in nutrients such as folate, minerals, various vitamins and carotenoids, they also contain glucosinolates that are broken down during food preparation and consumption to biologically active nitriles, indoles, isothiocyanates and thiocyanates. Isothiocyanates and indoles exhibit anticancer properties, such as inducing apoptosis, anti-inflammatory effects, inactivate carcinogens and protect from DNA damage, among others (NCI, 2012).

Tubers, despite also being rich in fibers, have been found to have a positive correlation with colorectal cancer risk, as found by Ramadas et al. (2009) and Nayak et al. (2009). Nayak et al. (2009) also mentioned tapioca in particular as this is a staple food among their study population in Kerala, South India. They attributed the increase in colorectal cancer link to the presence of toxins such as cyanide derivatives and linamarin. These toxins require processing to be removed, but tapioca was found to have a positive correlation with colorectal cancer risk, as found by Ramadas et al. (2009) and none of the studies supported the inverse association to colorectal cancer risk. Association of fish and seafood consumption with colorectal cancer risk is still inconclusive due to many varying findings, and requires further more detailed studies to pinpoint the actual correlation. There is either a positive or no association for total meat consumption or white meats, however their influence is not as strong as red and processed meats. Several diet/food types require more or further investigation on their influence, particularly foods that are frequently consumed in the Asian population. Studies that focus more on the influence of such foods towards the Asian genetics and physique in particular are scarce, and more studies in this area may unearth new findings that can be helpful towards the prevention of colorectal cancer in Asia.

References

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