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MINI-REVIEW

High salt and fat intake, inflammation, and risk of cancer

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BACKGROUND: Inflammatory conditions are involved in the pathophysiology of cancer. Recent findings have revealed that excessive salt and fat intake is involved in the development of severe inflammatory reactions.
METHODS: A literature search was performed on various online databases (PubMed, Scopus, and Google Scholar) regarding the roles of high salt and fat intake in the induction of inflammatory reactions and their roles in the etiopathogenesis of cancer.
RESULTS: The results indicate that high salt and fat intake can induce severe inflammatory conditions. However, various inflammatory conditions have been strongly linked to the development of cancer. Hence, high salt and fat intake might be involved in the pathogenesis of cancer progression via putative mechanisms related to inflammatory reactions.
CONCLUSION: Reducing salt and fat intake may decrease the risk of cancer.

Keywords cancer, inflammation, nutrition, salt, fat

Introduction

Inflammatory responses play crucial roles in tumor progression and responses to cancer chemotherapy (Grivennikov et al., 2010). Interestingly, the development of inflammatory conditions is linked to dietary patterns. Recent studies indicated the role of excess dietary salt and fat in the development of severe inflammatory reaction (Binger et al., 2015; Catta-Preta et al., 2012; Dutheil et al., 2016). Moreover, epidemiological studies revealed the role of high dietary salt and fat intake as a risk factor for cancer (D'Elia et al., 2012; Han et al., 2015). Therefore, important questions arise: does high salt and fat intake increase the risk of cancer via putative mechanisms related to inflammatory reactions?

Theory

i) Cancer is associated with inflammatory conditions.

ii) High salt and fat intake induces severe inflammatory reactions.

iii) High salt and fat intake may contribute to cancer progression via induction of inflammatory reactions.

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Inflammation and cancer

Inflammation has been linked to cancer development or exacerbation (Coussens and Werb, 2002; Lin and Karin, 2007). Chronic inflammation also increases the risk of cancer (Grivennikov et al., 2010). A systematic review of clinical studies demonstrated that the concentrations of cytokines TNFα, IL-6, IL-8, IL-10, IL-18, and TGFβ were increased in cancer patients (Lippitz, 2013). However, the role of Th17 cells and IL-17 in cancer development is controversial because these cells and cytokines can have a dichotomous role as tumor suppressor and tumor promoter depending on the cancer type (Alizadeh et al., 2013; Guéry and Hugues, 2015; Hemdan, 2013).

Nutrition and cancer

Epidemiological studies revealed that a healthy diet containing fruits, vegetables, whole grains, fish, low fat, and less red meat, which is also known as "Mediterranean" diet, has been associated with decreased inflammatory conditions (Barbaresko et al., 2013; Eichelmann et al., 2016; Schwingshackl and Hoffmann, 2014). Conversely, a "Western" diet, which is high in fat, protein, sodium, and sugar, has been associated with increased inflammatory conditions (Barbaresko et al., 2013; Manzel et al., 2014). Hence, dietary patterns may be associated with an increase or decrease cancer risk (Wicki and Hagmann, 2011). In this regard, the results of a recent meta-

analysis revealed that the Mediterranean diet significantly decreased the risk of the overall cancer mortality/incidence (Schwingshackl and Hoffmann, 2014). Another meta-analysis revealed that the Western dietary pattern is associated with an increased risk of colorectal cancer (Yusof and Shah, 2012).

High salt intake induces inflammatory reactions: implication for cancer progression

High salt intake-induced inflammation

Salt is an essential macronutrient that plays multifunctional roles in physiologic conditions (Kotchen et al., 2013). Excessive salt intake is a major cause of hypertension and stroke (Mozaffarian et al., 2014). Interestingly, different studies revealed that high salt intake induces severe inflammatory reactions, but inhibits regulatory T cell development and anti-inflammatory cytokine production (Binger et al., 2015). On the one hand, excessive salt intake augments T helper-17 pathway and inflammatory cytokines such as IL-17, IL-23, TNF-α, IL-2, and nuclear factor-κB (NF-κB) in a mouse model of multiple sclerosis (experimental autoimmune encephalomyelitis (EAE)) (Kleinewietfeld et al., 2013; Wu et al., 2013; Krementsov et al., 2015; Hucke et al., 2016; Jörg et al., 2016). On the other hand, high salt treatment not only inhibits the suppressive function of regulatory T cells, but also stimulates these cells to secrete IFNγ (Hernandez et al., 2015). Furthermore, high salt intake reduces the ability of macrophages to secrete anti-inflammatory cytokines IL-4 and IL-13 (Binger et al., 2015). A high salt diet also exacerbates blood-brain barrier disruption in a mouse model of cerebral ischemia (Zhang et al., 2015) and experimental colitis in mice (Monteleone et al., 2016). Clinical investigations showed that a salt-enriched diet enhances the disease activity of multiple sclerosis, an inflammatory autoimmune disorder (Farez et al., 2015). Yi et al. (2015) reported that healthy individuals with high dietary salt intake had a higher number of monocytes than those with normal salt intake. Remarkably, decreased concentrations of inflammatory cytokines and increased production of anti-inflammatory cytokine IL-10 were observed after reducing salt intake. Therefore, high dietary salt intake induces inflammatory conditions.

Linking high salt intake and cancer

Several evidences showed that excessive salt intake is an important risk factor for gastric cancer (Nagini, 2012). A meta-analysis of case control studies demonstrated that high salt intake is significantly associated with increased risk of gastric cancer (D'Elia et al., 2012). Faeh et al. (2014) compared the cancer mortality among 17,733 Swiss men and women who added salt to their prepared meals. Results revealed that cancer mortality risk increased by 30% in people who always added salt to their meals than those who never added salt (Faeh et al., 2014). Previous studies reported that *Helicobacter pylori* infection induces gastric carcinogenesis. Interestingly, different studies showed that high salt intake enhances *H. pylori* colonization (Fox et al., 1999), exacerbates *H. pylori*-induced gastric carcinogenesis (Gaddy et al., 2013; Kato et al., 2006; Nozaki et al., 2002; Xu et al., 2015), and increases gastric inflammation (Gaddy et al., 2013; Loh et al., 2015) associated with increased gastric pH (Gaddy et al., 2013) and oxidative stress (Loh et al., 2015). Furthermore, in vitro studies revealed that a high NaCl treatment for breast cancer induces inflammatory cytokines (IL-17, IL-6 and TNF-α), increases the activities of nitrogen and oxygen (RNS/ROS) species, enhances the expression of vascular endothelial growth factor (VEGF)-A, and promotes cancer (Amara et al., 2016; Amara et al., 2016). These data suggest that a high salt intake can induce inflammatory reactions and lead to cancer progression.

High fat intake induces inflammatory reactions: implication for cancer progression

High fat intake induced inflammation

A high fat diet is a major cause of obesity and other related disorders (Teodoro et al., 2014). Fats, especially one with saturated fats and trans-fats, is associated with increased risk of mortality of different diseases (Wang et al., 2016). A high fat diet is also associated with increased inflammatory conditions. In this regard, Catta-Preta et al. (2012) found that a high fat diet increases the levels of resistin (also known as adipose tissue-specific secretory factor (ADSF)), leptin and IL-6 in mice. Gulhane et al., (2016) demonstrated that a high fat diet induces obesity, disrupts mucosal barrier integrity, and exacerbates colitis in mice. Moreover, they noted an increase in the oxidative stress and enhancement of the mRNA expression of inflammatory cytokines (TNF-α, IL-1β, and IL-17) in the colon of mice that were fed an enriched fat diet (Gulhane et al., 2016). Timmermans et al. (2014) studied the effects of a high fat diet on the course of EAE in mice. Results showed that a high fat diet exacerbates the severity and neuroinflammation of EAE in mice that were fed a high fat diet compared with those in the control group (Timmermans et al., 2014). Dutheil et al. (Dutheil et al., 2016) reported that a high fat diet induces anxiety and anhedonic behaviors associated with increased inflammatory cytokines (e.g., IL-6, IL-1β, TNF-α) corticosterone levels in rats. Another study demonstrated that age affects the inflammatory response to a high fat diet, while Kim et al. (2016) found that aged mice had higher expression levels of inflammatory cytokines (TNF-α, IL-1β, IL-6, IL-12, IL-17A), monocyte chemoattractant protein-1 (MCP-1), and TLR4, associated with increased

oxidative stress in their liver and kidney due to old age, than middle-aged mice (Kim et al., 2016). Moreover, a high fat diet exacerbates collagen-induced arthritis (Jhun et al., 2012), IBD (Paik et al., 2013), and trinitrobenzenesulfonic acid-induced colitis (Okada et al., 2013) in mouse models. It is worth noting that not only high dietary fat induces inflammation. Internal adipose tissues secrete inflammatory cytokines that act as mediators of obesity-associated cancer development (reviewed in (Howe et al., 2013)).

Link between high fat intake and cancer

Different investigations demonstrated that high dietary fat intake increases the risk of cancer. The result of a meta-analysis of observational studies revealed that high total fat intake is positively associated with increased risk of gastric cancer (Han et al., 2015). Furthermore, a high fat intake is associated with increased risk of mortality among men with non-metastatic prostate cancer (Richman et al., 2013) and women with breast cancer (Kroenke et al., 2013). In mouse models, a high fat diet promoted the development of prostate cancer, improved the levels of cytokines and chemokines, and decreased the survival rate (Cho et al., 2015). In a rat model of colon carcinoma, a high fat diet promoted azoxymethane-induced colon carcinogenesis (Reddy and Maeura,1984). Another study found that a high fat diet enhances mammary tumor growth and increases the levels of inflammatory cytokines (e.g., IL-6 and MCP1) and leptin in a mouse model of breast cancer (Cowen et al., 2015). Taken together, a high fat intake induces inflammatory reactions and may lead to cancer development.

Concluding remarks

There are strong links between inflammation and cancer. High salt and fat intake induced inflammatory reactions, which subsequently led to the progression of cancer. The synergistic effects of high salt and high fat intake need further consideration. Thus, reducing salt and fat intake may decrease the risk of cancer.

Compliance with ethics guidelines

Amir Abdoli declares that he has no conflict of interest.
This manuscript is a review article and does not involve a research protocol requiring approval by the relevant institutional review board or ethics committee.

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