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PHYSICAL ACTIVITY AND GASTROINTESTINAL CANCER RISK: A REVIEW

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Abstract. Introduction: *Western lifestyle characterized by increased consumption of red meat, fat, processed food, smoking, alcohol drinking, lower consumption of vegetables and physical inactivity has been associated with a higher gastrointestinal cancer risk. Digestive system cancers are diagnosed at late stages when they show poor response to treatment and are associated with a high mortality rate. Colorectal, gastric, esophageal and pancreatic cancers are among the most common cancers worldwide. Studies show that more than 50% of gastrointestinal cancers develop as a result of inappropriate lifestyle. An inverse association between physical activity and many chronic diseases has been proved so far. However, the association between physical activity and some gastrointestinal cancers is still controversial. This study was aimed to determine the association between physical activity and gastrointestinal cancers risk.* ***Methods:*** *We conducted a comprehensive search of English and Persian databases from February 2007 till December 2017, for studies investigating the association of physical activity and risk of gastrointestinal cancers. Finally, after reading full text of articles, 123 studies were included.* ***Results:*** *Physical activity can be helpful in reducing the risk of gastrointestinal cancer, especially colon and pancreatic cancers. The risk reduction is not similar for different types of gastrointestinal cancers and also among males and females.* ***Conclusion:*** *Different types of physical activity are associated with a lower risk of gastrointestinal cancer. However, it is unknown which type and intensity of physical activity are associated with a protective effect against gastro-intestinal cancer.*

Key words: *gastrointestinal cancer, physical activity, gastroesophageal cancer, pancreatic cancer, colorectal cancer*

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INTRODUCTION

Gastrointestinal cancers include cancers of the digestive tract (mouth, pharynx, esophagus, stomach, small intestine, colon and rectum) and cancers of supplementary organs (pancreas, gall bladder, liver) [1]. Digestive system cancers are responsible for the major part of cancer-related deaths every year. The incidence rate has increased in recent years [2-5]. Colorectal, gastric, esophageal and pancreatic cancers are the third, fourth, sixth and 12th most common cancers worldwide, respectively [6-9]. Some of these cancers such as pancreatic cancer and gastric cancer are often diagnosed

at late stages and show poor response to treatment [10, 11]. So it is necessary to determine the related risk factors for prevention of these cancers. Genetic background, family history, obesity, infectious agent, lifestyle factors such as diet, physical activity, smoking, alcohol consumption, tobacco use and some underlying diseases such as type 2 diabetes are associated with an increased risk of digestive system cancers [4, 12-14]. In contrast to non-modifiable risk factors, lifestyle is a modifiable risk factor and its improvement is associated with a reduced risk of digestive system cancers [15]. Based on the World Health Organization's (WHO) definition, lifestyle is "a way of living based on identifiable patterns of behavior which are determined by the interplay between the individual personal characteristics, social interactions, and socioeconomic and environmental living conditions" [16]. Western lifestyle characterized by increased consumption of red meat, fat and processed food, lower consumption of fiber and vegetables, higher calorie intake, smoking, increased alcohol drinking and physical inactivity is responsible for increased incidence of digestive system cancers, especially in developed countries [17-19].

Based on the WHO's definition, physical activity is "any bodily movement produced by the skeletal muscles that requires energy expenditure" [20]. The inverse association between physical activity and risk of many chronic diseases and some cancers has been certainly proved. However, results from the studies that examined the association between physical activity and other cancers are inconsistent [9, 18, 20, 21].

In this review, we discuss the association between physical activity and digestive system cancer risk and some related mechanisms.

METHODS

We conducted a comprehensive search of PUBMED, Google Scholar, Scopus, SID, IranMedex and IranDoc databases from February 2007 to December 2017, for studies that investigated the association of physical activity and risk of gastrointestinal cancers. The search consisted of terms related to physical activity (including "exercise', "physical activity", "motor activity", "sport", "cardiorespiratory fitness", "cardiovascular fitness", "aerobic", "anaerobic", "leisure activities", "occupational activities", "recreational activities", "transport activities") in combination with terms for cancer sites of interests (including "stomach", "gastric", "cardia", "esophagus", "esophageal", "pancreas", "pancreatic", "rectum", "rectal", "colorectal", "colon", "bowel", "gut", "right colon", "right-sided colon", "left colon", "left-sided colon", "proximal colon", "distal colon") using an AND operator, and in combination with terms for cancer description (including "cancer", "neoplasm", "carcinoma", "tumor", "malignancy") using an AND operator. A manually search of reference list of included articles also was performed for additional studies. After eliminating duplicate articles, the titles and abstracts of remaining articles were screened. Studies were excluded if: 1) they were not published in English, 2) there was no abstract or full text available for them, 3) they had evaluated the effects of physical activity in management and treatment of the digestive system cancers and 4) they were conducted on animal models. Finally after reading full text of all remaining articles, 123 studies were included.

RESULTS OF THE SEARCH AND DISCUSSION

Physical activity

Based on the WHO's definition, "physical activity is any bodily movement produced by the skeletal muscles that requires energy expenditure". Physical activities are divided into four categories including occupational, household, transportation and recreational (leisure-time) physical activities. Occupational physical activities refer to activities which are related to work and are performed in about eight hours per work day. Household activities refer to activities which are performed in the household. Transportation activities refer to activities which are performed for going somewhere. Recreational activities refer to activities which are performed during leisure-time [20]. Different physical activities are characterized by intensity, duration and frequency [22].

Industrialization and new technologies together with occupations demanding lesser physical activity have made people more inactive during their life. Nowadays 31% of the world population is inactive (20, 23). Studies demonstrated that nearly 25% of cancers around the world develop as a result of increased body weight, physical inactivity and sedentary lifestyle [24].

Metabolic equivalent of task (MET) is used to measure energy expenditure during physical activity. So in this scale, metabolic rate during a physical activity is compared to a standard resting metabolic rate during quiet sitting. A MET is equivalent to 4.184 $kJ \bullet kg^{-1}$ body $weight \bullet h^{-1}$ kilojoules for an adult which is equal to uptake 3.5 ml of $oxygen \bullet kg^{-1}$ body $weight \bullet min^{-1}$ [25-27].

Based on MET level, activities are divided into four categories:

1. Sedentary: MET score 1-1.6, these activities don't result in significant changes on heart and

breathing rate compared to resting level and demand less than 40% of maximum heart rate.

2. Light: MET score 1.6-3, these activities result in minor changes on heart rate and breathing rate compared to resting level and demand 40-55% of maximum heart rate. Their duration should be at least 60 min.
3. Moderate: MET score 3-6, these activities increase maximum heart rate from 55 to 70%. Their duration should be between 30-60 min.
4. Vigorous: MET score ≥ 6, these activities increase maximum heart rate from 70 to 90%, in this situation anaerobic metabolism is needed to provide enough energy. Their duration should be up to 30 min [25, 27, 28].

A systematic review and meta-analysis of 126 articles carried out by Li Liu et al., found that as stated in the WHO recommendation, participating in moderate aerobic exercise for at least 2.5 hours, vigorous aerobic exercise for 1.25 hours or a combination of moderate and vigorous aerobic exercise is associated with a 7% risk reduction for cancers [29]. World Cancer Research Fund recommends moderate physical activity for at least 30 minutes every day to have a healthy life [30].

The inverse association between physical activity and risk of many chronic diseases such as hypertension, type 2 diabetes, cardiovascular, pulmonary and musculoskeletal diseases, and some cancers such as colon, prostate and breast cancer, has been clearly proved [9, 18, 20, 31]. Steven C. Moore et al., in a study which reviewed 12 prospective articles reported that recreational physical activity is associated with 20% reduced risk of 13 different types of cancers [23]. However, results from the studies that examined the association between physical activity and other cancers are inconsistent.

Esophageal cancer

Esophageal cancer is the sixth most common cancer around the world [32]; nearly 460 000 new cases of esophageal cancer are diagnosed every year [8, 33]. The incidence is 2-3 folds greater in men than in women and has increased 300 percent among women and 500 percent among men in Western countries [4, 34].

Esophageal cancer is associated with a high mortality rate and poor response to treatment in advanced stages [8]. Studies demonstrated that the 5-year survival rate of esophageal cancer patients was 17% [35]. Esophageal cancer is the sixth leading cause of cancer related deaths around the world [5].

Esophageal cancers include esophageal squamous cell carcinoma and esophageal adenocarcinoma [5, 12, 33]. In contrast with reduced incidence of esophageal squamous cell carcinoma in recent years, the incidence of esophageal adenocarcinoma has increased in developed countries. However, esophageal squamous cell carcinoma is the most common type of esophageal cancers in most countries around the world such as central Asian countries [5, 12, 36].

Gastro-esophageal reflux is one of the main risk factors for developing esophageal adenocarcinoma. Chronic reflux damages normal esophageal epithelial squamous cells and leads to Barrett's metaplasia. Thereafter dysplasia occurs in esophageal epithelium and finally esophageal adenocarcinoma develops [4, 36, 37]. Patients with Barrett's esophagus have 30-40 fold greater risk for developing esophageal adenocarcinoma, which is at least 5 times greater among men than women [34]. Hiatal hernia, smoking, long persistent diseases, higher body weight, body mass index and waist circumference are among the risk factors which can promote Barrett's esophagus developing to esophageal adenocarcinoma [37]. Although some studies found that moderate to vigorous physical activity reduces the risk of esophageal adenocarcinoma, results from the studies that examined the association between physical activity and esophageal squamous cell carcinoma risk are inconsistent [4, 23, 32-36, 38]. Studies demonstrated that both recreational and occupational physical activity are associated with reduced esophageal cancer risk [39] and even low physical activity against physical inactivity is helpful in esophageal cancer risk reduction [33].

Gastric cancer

Gastric cancer is the fourth most common cancer and second leading cause of cancer- related deaths worldwide [40]. Gastric cancers often are diagnosed in late stages when treatment strategies can't be helpful [8, 13]. The 5-year survival rate of gastric cancer is 28% [35]. Gastric cancer has greater incidence among men than women, for example gastric cardia cancer incidence is five times greater among men [40]. Nearly 900 000 new cases of gastric cancer are diagnosed every year [3, 8, 33] and most cases are intestinal-type adenocarcinomas [41]. Although the incidence of gastric non-cardia and gastro-esophageal junction cancers has increased especially in high income countries, the incidence of gastric non-cardia adenocarcinomas has been reduced [3]. Gastric cancer incidence shows geographical variations, with the highest incidence in Asian countries and the lowest rate in African countries [42]. Nearly two-thirds of gastric cancer cases occur in developing countries [7]. Infection with Helicobacter pylori, smoking, alcohol drinking, tobacco use, excessive amount of salt consumption and physical inactivity can increase

gastric cancer risk [7, 13, 43]. Studies found that healthy lifestyle is associated with a 50% risk reduction of gastric cancer [44]. Risk factors of gastric cancer show variations depend on cancer type and anatomic site, for example infection with Helicobacter pylori is associated with an increased risk of gastric cardia and non-cardia adenocarcinoma but chronic reflux is only associated with an increased risk of gastric cardia adenocarcinoma [33], also some risk factors are similar between gastric cardia cancers and esophageal malignancies [40]. Studies demonstrated that physical activity is associated with a reduced risk of gastric cancers, however these results are inconsistent. A prospective study carried out by Jose´ Marı´a Huerta et al., found that high levels of physical activity was associated with 25-38% reduced risk of gastric adenocarcinoma, particularly gastric noncardia adenocarcinoma but there was no significant association between recreational physical activity and risk of gastric adenocarcinoma [3]. Another study carried out by Peter T. Campbell demonstrated that recreational physical activity with high intensity is associated with almost 20-40% reduced risk of stomach cancer and the risk reduction was different during several periods of lifelong [45]. Furthermore they found no significant association between occupational or moderate intensity physical activity and risk of gastric cancer. A systematic review and meta-analysis of 16 studies carried out by Siddharth Singh et al., reported that the risk of both cardia and noncardia gastric cancers among the most active people was 21% lower than the least active people [46]. A recent case-control study carried out by Jose M. Huerta in the MCC-Spain reported that household physical activity is strongly associated with reduced risk of gastric adenocarcinoma. Also they found that recreational physical activity is associated with gastric adenocarcinoma and the association was stronger for non-cardia tumors [47]. Another recent systematic review and meta-analysis of 22 studies carried out by Theodora Psaltopoulou reported that any type of physical activities was associated with reduced risk of gastric cancer and the risk reduction was 19% among persons with the highest levels of physical activity [30]. Some other studies also reported an inverse association between physical activity and gastric cancer risk [8, 23, 35, 40, 48]. Studies demonstrated that moderate or vigorous recreational physical activity is associated with 50 % reduced risk of gastric cancer [49].

Pancreatic cancer

Pancreatic cancer is the 12th most common cancer and seventh leading cause of cancer related deaths worldwide and fourth leading cause of cancer related deaths in developed countries [9, 50, 51]. It seems that this geographical variation is due to the Western lifestyle, excessive consumption of foods containing more fat and energy, less fiber consumption and low physical activity in developed countries. Pancreatic cancer incidence shows geographical variation which is similar to prostate, breast and colon cancer incidence pattern, with the highest incidence in North America, Europe, some countries of South America and the lowest incidence in Asia and Africa [19]. Approximately 250 000 cases die due to pancreatic cancer each year [52]. Pancreatic cancer often occurs at older ages and is diagnosed in late stages [10, 50]. Pancreatic cancer has a rapid growth and early metastasis and shows poor response to treatment strategies [10, 53]. Most cases of pancreatic cancer occur in exocrine glands and the most common type of pancreatic cancers is ductal adenocarcinoma cancer. The 1-year survival rate of pancreatic cancer is 26% and the 5-years survival rate is 7% [50, 53]. Smoking is the most important risk factor for pancreatic cancer [53], moreover high body mass index, low physical activity, age, some infectious agents such as *Helicobacter pylori* and hepatitis virus, chronic pancreatitis, cholecystectomy, chemical exposure, family history, insulin resistance, hyperglycemia, obesity and inappropriate dietary habits are associated with an increased risk of pancreatic cancer [9, 14, 51, 52, 54-57]. Studies demonstrated that physical activity offers a protective effect against pancreatic cancer development [19, 50, 54, 58]. A systematic review of 30 studies carried out by Gundula Behrens et al., found that physical activity was associated with a weak risk reduction of pancreatic cancer. The risk reduction was greater in case-control studies than cohort studies (22% against 7%) [51]. In another systematic review of 26 studies by Megan S.Farris et al., they found that participation in recreational physical activity was associated with 11% reduced risk of pancreatic cancer. The risk reduction was greater in case-control studies than in cohort studies (31% against 9%) [9]. Some other recent studies also reported that regular recreational physical activity can reduce pancreatic cancer risk [14, 50, 53] and increase in intensity and frequency of physical activity can reduce pancreatic cancer risk up to 50% [14]. However some studies reported no significant inverse association between physical activity and pancreatic cancer risk [10, 28, 55, 57, 59, 60].

Colorectal cancer

Colorectal cancer accounts for 10% of all cancer cases around the world and is the third most common cancer among men after pulmonary and prostate cancer, the second most common cancer among women after breast cancer and the third most common can-

cer worldwide [2, 6, 15-17, 61]. The risk of colorectal cancer is 2 times higher in men than in women [62]. Colorectal cancer incidence shows geographical variations with the lowest incidence in central Africa, Asia and South America and the highest incidence in industrialized countries such as Japan, United States, Canada, Australia and New Zealand [17, 18, 63, 64]. In addition to lifestyle variations, differences in races are also responsible for colorectal cancer incidence variations among different countries [65].

One million new cases of colorectal cancer are diagnosed each year and nearly 500000 subjects die due to colorectal cancer [18, 66, 67]. Colorectal cancer mortality accounts for 8% of cancer related mortalities around the world [2, 18] and is the fourth leading cause of cancer related deaths [68].

Economic developments have been associated with lifestyle changes in recent decades. Two-thirds of colorectal cancer cases occur in developed countries [17, 69]. Studies demonstrated that more than 50% of colorectal cancer cases develop as a result of environmental factors, inappropriate lifestyle, dietary habits and other modifiable risk factors [2, 15, 17, 70-72]. Among these factors, physical inactivity is the most important risk factor in colorectal cancer development [68].

Colorectal cancer can occur in different anatomic sites such as the proximal (ascending) colon, distal (descending) colon and sigmoid colon which are associated with different incidence risk. For example, older ages and female sex are associated with a higher incidence of proximal colon cancer, but distal colon cancer shows higher incidence rate among men and young people [73]. In addition to embryonic, morphological and physiological differences between different parts of colon, the cancers which rise from different anatomic sites are also different in morphological, molecular and genetic aspects [73, 74], so it is probable that different risk or protective factors may exert their effect with different intensity on different parts of colon [27, 73, 75-77]. Ji Hyun Song et al., in a cross sectional study on 1400 subjects in Korea found that participation in vigorous physical activity per week was associated with reduced risk of distal colon adenomas and was greater for advanced and high risk adenomas. In contrast, they didn't find any significant association between physical activity and proximal colon adenomas [78]. However some studies reported that physical activity results in similar risk reduction among different anatomic sites of colon [22, 74, 79, 80]. In a systematic review of 21 studies carried out by Terry Boyle et al., they found that physical activity was associated with 25% reduced risk of cancer in all different parts of colon [73].

Most colorectal cancers develop from polyps [81]. Polyps are produced by mucus proliferation [82]. Studies found that some lifestyle factors can affect the process of polyp development to colorectal cancer [83]. In a meta-analysis of 20 studies, KY Wolin et al., found that high levels of physical activity was associated with 16% reduced risk of colon polyp and was nearly 35% for large and advanced polyps. This effect was same among males and females [84]. In contrast, the meta-analysis of 55 studies carried out by Harindra Jayasekara et al., found no significant association between lifestyle factors such as physical activity and reduced risk of colon polyps [85]. Tanvir R Haque et al., in a review study reported that there was no significant association between physical activity and the risk of serrated polyp development [86]. However it seems that effect of physical activity on colon polyp risk is dependent on type of polyps [15].

Several studies demonstrated that physical activity is associated with a 10-70% reduced risk of colorectal cancer [16, 62, 71, 72, 87-92]. It seems that different physical activities exert different effects on colorectal cancer risk [61]. For example, in a case-control study carried out by Golshiri et al., they found that recreational physical activity was associated with 27% reduced risk of colorectal cancer. In contrast, they found no significant inverse association between occupational physical activity and colorectal cancer risk [63]. A prospective cohort study carried out in Japan by Hideko Takashi et al., reported that even daily walking was associated with reduced colon cancer risk among men but not women [93]. They also found no association between daily walking and risk of rectal cancer. Santhana Krishnan Iswarya et al., in a case-control study in India found that physical activity can't reduce colorectal cancer risk at all. It seems that this result found because of small study population (94 subjects) and bias as a result of several changes in patient's lifestyle after cancer development [2]. Also in a case-control study by Valentina Rosato et al., carried out in Italy they found that there wasn't any inverse association between physical activity and colorectal cancer risk during ages 30-39 [94], so it is possible that physical activity exerts different effects on biological mechanisms which are related to cancer development during lifelong [39]. There are a few studies which examined the association between participation in physical activity at specific ages and risk of colon cancer. So the appropriate age period at which person should participate in physical activities, is not clear. Some studies reported that participation in physical activity at any ages older than 20 years, is associated with colon cancer risk reduction. Also they found that physical activity performed at age 30-50

years has the strongest association with colon cancer risk reduction [95]. Further studies are needed to explore the exact association between age-specific physical activity and colon cancer risk.

Some studies reported that physical activity is associated with different risk reduction among males and females [6, 26, 31, 76, 80, 95, 96]; it seems that this difference is due to different biological profiles of the two sexes such as different amounts and types of secreted hormones, different lifestyles and also different incidence of colorectal cancer [26, 93]. In contrast some studies reported that effects of physical activity on colorectal cancer are similar between males and females [73, 84, 87].

In contrast with consistent result which confirmed an inverse association between physical activity and colon cancer risk [9, 23, 31, 96-107], results from the studies that examined the association between physical activity and rectal cancer risk are inconsistent [6, 22, 23, 74, 76, 78, 96, 97, 103, 108, 109]. However, Colinda C. J. M. Simons et al., in a case-control study carried out on 120 000 subjects in Netherland found that regular participation in recreational physical activity such as daily walking and riding bicycle reduced rectal cancer risk among women but not among men [110]. A prospective study carried out by Anna M. Gorczyca on 74 870 women in USA, reported that there was an inverse association between recreational physical activity and risk of rectal cancer [111]. Regan A. Howard et al., in a cohort study found that only vigorous physical activity was associated with a reduced risk of rectal cancer among men [26].

Age is the most important risk factor in colorectal cancer development [112]. In addition obesity, impaired glucose tolerance, hyperinsulinemia, hyperlipidemia, hypertension, dietary habits such as low fiber consumption and high meat consumption, smoking, drinking alcohol, excessive consumption of bread, sugar and processed cereals, low consumption of vitamin C and D, fibre, fruit, garlic, calcium and folate are among the other risk factors which increase colorectal cancer risk [17, 94, 112, 113].

Mechanisms

Exact underlying mechanisms linking physical activity to digestive system cancers are unknown. However there are some suggested mechanisms which are discussed below.

High levels of physical activity prevent positive balance of energy [26, 114, 115] leading to loss of weight and ventral adipose tissue. Studies show that obesity plays an important role in cancer development via different pathways, for example it alters steroid metabolism, increases insulin resistance and therefor increases insulin, glucose and insulin like growth factor 1 (IGF-1) levels which are associated with carcinogenesis [116]. Physical activity also has a role in the regulation of hormones released from adipose tissue such as leptin and adiponectin. Physical activity reduces leptin and increases adiponectin levels in the serum. Leptin acts as a mitogen. It is also an anti-apoptotic factor and responsible for promoting angiogenesis. In contrast adiponectin has anti-leptin and anti-inflammatory effects. Also excess visceral fat can lead to hyperinsulinemia and increased level of IGF-1 [11], so physical activity may play an important role in regulating hormones in blood circulation via change in visceral adipose tissue. For example physical activity increases insulin entry into skeletal muscles, therefor reduces blood insulin and C-peptide levels, improves its sensitivity and reduces insulin resistance. Reduction of insulin release increases IGF-1 binding protein and therefor reduces bioavailable IGF-1. Insulin like growth factor 1 has mitogenic and anti-apoptotic effects and also reduces p53 expression which causes DNA repair impairment, continuous cell cycle and prevents apoptosis [4, 33, 46, 55, 59, 117].

Physical activity modulates the immune system function, for example it can promote the anti-tumor function of natural killer cells and increases their inhibitory effects on tumors as well as an increase of the free scavenger system activity [49, 116]. Physical activity can also reduce the production of IL-6 and TNF-α leading to increased lipolysis in adipose tissue. TNF-α induces inflammation and chronic inflammation promotes carcinogenesis via different pathways such as altering some specific DNA methylation [4, 118]. TNF-α is also responsible for increased proliferation of some specific cells [4, 119]. Pro-inflammatory factors lead to activation of cyclooxygenase2 enzyme which generates prostaglandin E2 [1, 120]. Physical activity alters amount of prostaglandins. For example, it can reduce prostaglandin E2 in colon mucosa which is responsible for tumor proliferation and metastasis by suppressing tumor suppressor and DNA repairing genes. It can also reduce gut motility. Physical activity also increases prostaglandin F2α which inhibits cell proliferation and increases colon motility [17, 76, 93, 105, 120]. Increased colon motility leads to reduced risk of constipation, waste particles transit time and therefor reduced risk of colon exposure to carcinogens. Also it can reduce colon contact with bile acids [78].

Several studies found that water intake may play a role in reduction of some digestive cancer risks. Exercise leads to increased water intake, so people who participate in physical activities have more water intake. Water plays a role in softening gut content, increasing waste particle transit time and diluting carcinogens, all decrease the risk of colorectal cancer development [121].

Physical activity alters hormone secretion in the stomach, intestine and pancreas [17] and regulates secretion of sex hormones. Physical activity increases sex hormone binding protein levels via different mechanisms, for example by reduction of insulin and IGF-1 levels which can stimulate synthesis of sex hormones. Increased sex hormone binding protein levels reduces steroid bioavailability [116, 122]. Some sex hormones lead to excessive proliferation of cells and some have a negative effect on tumor growth [11, 50, 123]. Some studies also reported that high levels of estrogen – an important sex hormone – reduces natural killer cell activity which can lead to increased risk of cancer development [116]. Moreover, people with high levels of physical activity have higher levels of vitamin D in their blood circulation because they have more exposure to sunlight; vitamin D regulates cellular signaling cascades which have role in cell proliferation [32, 78].

Physical activity promotes anti-oxidant defense which leads to reduced endogenous oxidative stress and therefor more DNA repair and less DNA injury [25, 123]. Physical activity reduces chromosomal instability, rearrangement and mutations in genes which are involved in cancer development such as p53 and K-ras [17]. Also physical activity can alter expression of B-cell lymphoma-2-associated protein and apoptotic-regulating protein B-cell lymphoma-2 [110].

Physical activity increases myokines which are released from muscles in response to activity and have role in metabolism improvement and inflammatory prevention (Table 1) [120].

Table 1. Biological mechanisms relating physical activity to digestive cancer risk

Risk Factor	Mechanism	Physical activity effect
Obesity	Increase in insulin resistance, change in steroid metabolism	Decrease
Body fat	Adipokines secretion, insulin resistance	Decreases
Leptin	Promotion of angiogenesis, prevention of apoptosis, mitogenic effects exertion, prevention of adiponectin secretion	Decreases
Adiponectin	Prevention of angiogenesis, inhibition of inflammation, inhibition of mitogenesis	Increases
Insulin resistance	Reduction in Insulin like growth factor 1 (IGF-1) binding protein, stimulation of sex hormones synthesis	Decreases
IGF-1 binding protein	Binding to IGF-1, reduction in IGF-1 bioavailability	Increases
IGF-1	Mitogenic effect exertion, prevention of apoptosis, reduction in p53 expression, stimulation of sex hormones synthesis	Decreases
Sex hormone binding protein	Binding to sex hormones, reduction in sex hormones bioavailability	Increases
Sex hormones	Increase in cell proliferation, change in immune system function	Decreases
Vitamin D	Regulation of cell proliferation signaling	Increases
Immune system function	Improvement in Immune cell function	Increases
Anti-tumor NK cells function	Eradication of Cancer cells	Increases
IL-6 secretion	Inhibition of Lipolysis, inhibition of adiponectin secretion	Decreases
TNFα secretion	Inhibition of Lipolysis, inhibition of adiponectin secretion, induction of inflammation, promotion of cell proliferation	Decreases
Inflammation	Promotion of carcinogenesis, change in specific gene expression	Decreases
Cyclooxygenase-2 activity	Prostaglandin E2 generation	Decreases
Prostaglandin E2	Promotion of cell proliferation, promotion of cancer cell metastasis, Reduction in colon motility	Decreases
Prostaglandin F2α	Inhibition of cell proliferation, Increase in colon motility	Increases
Colon motility	Reduction in stool transit time, reduction in constipation risk	Increases
Stool transit time	Reduction in colonic carcinogen exposure, reduction in colonic bile acid exposure	Decreases
Anti-oxidant defense	Reduction in Oxidative stress	Increases
Oxidative stress	Cell injury, DNA mutations	Decreases
Gene mutation	Change in cancer promoter or suppressor gene expression	Decreases
Myokines	Metabolism improvement, inhibition of inflammation	Increases
Water intake	Softening gut content, increase in stool transit time, dilution of carcinogens	Increases

CONCLUSION

A number of studies demonstrated that avoiding sedentary lifestyle and participating in physical activities can be helpful in reducing the risk of cancers of the digestive system. This effect seems to be most apparent for colon and pancreatic cancers other than gastric and esophageal cancers, but results for rectal cancers are inconsistent. However, it is unknown which type and intensity of physical activity is associated with a protective effect against digestive system cancer.

Further studies with sufficient size, no bias, exact physical activity assessment, considering different types and intensities of physical activity, are needed to explore the effects of physical activity on the reduction of cancer risk of the digestive system.

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Conflict of interest disclosures

The authors declare that they have no conflict of interest.

REFERENCES

1. Keum N, Bao Y, Smith-Warner SA et al. Association of Physical Activity by Type and Intensity With Digestive System Cancer Risk. JAMA oncology. 2016;2(9):1146-53.
2. Iswarya SK, Premarajan KC, Kar SS et al. Risk factors for the development of colorectal carcinoma: A case control study from South India. World J Gastrointest Oncol. 2016;8(2):207-14.
3. Huerta JM, Navarro C, Chirlaque MD et al. Prospective study of physical activity and risk of primary adenocarcinomas of the oesophagus and stomach in the EPIC (European Prospective Investigation into Cancer and nutrition) cohort. CCC. 2010;21(5):657-69.
4. Winzer BM, Paratz JD, Reeves MM, Whiteman DC. Exercise and the Prevention of Oesophageal Cancer (EPOC) study protocol: a randomized controlled trial of exercise versus stretching in males with Barrett's oesophagus. BMC cancer. 2010;10:292.
5. Yang CS, Chen X, Tu S. Etiology and Prevention of Esophageal Cancer. Gastrointestinal tumors. 2016;3(1):3-16.
6. Spence RR, Heesch KC, Brown WJ. A systematic review of the association between physical activity and colorectal cancer risk. Scand J Med Sci Sports. 2009;19(6):764-81.
7. Wen XY. Salt taste sensitivity, physical activity and gastric cancer. APJCP. 2010;11(6):1473-7.
8. Chen Y, Yu C, Li Y. Physical activity and risks of esophageal and gastric cancers: a meta-analysis. PloS one. 2014;9(2):e88082.
9. Farris MS, Mosli MH, McFadden AA et al. The Association between Leisure Time Physical Activity and Pancreatic Cancer Risk in Adults: A Systematic Review and Meta-analysis. Cancer Epidemiol, Biomarkers Prev. 2015;24(10):1462-73.
10. Nothlings U, Wilkens LR, Murphy SP et al. Body mass index and physical activity as risk factors for pancreatic cancer: the Multiethnic Cohort Study. CCC. 2007;18(2):165-75.
11. Shephard RJ. Cancers of the Esophagus and Stomach: Potential Mechanisms behind the Beneficial Influence of Physical Activity. Clini J Sport Med. 2017;27(4):415-21.
12. Etemadi A, Golozar A, Kamangar F et al. Large body size and sedentary lifestyle during childhood and early adulthood and esophageal squamous cell carcinoma in a high-risk population. Ann Oncol. 2012;23(6):1593-600.
13. Lee YY, Derakhshan MH. Environmental and lifestyle risk factors of gastric cancer. Arch Irani Med. 2013;16(6):358-65.
14. Brenner DR, Wozniak MB, Feyt C et al. Physical activity and risk of pancreatic cancer in a central European multicenter case-control study. CCC. 2014;25(6):669-81.
15. Bailie L, Loughrey MB, Coleman HG. Lifestyle Risk Factors for Serrated Colorectal Polyps: A Systematic Review and Meta-analysis. Gastroenterology. 2017;152(1):92-104.
16. Mahfouz EM, Sadek RR, Abdel-Latief WM et al. The role of dietary and lifestyle factors in the development of colorectal cancer: case control study in Minia, Egypt. Central Eur J Publ Health. 2014;22(4):215-22.
17. Watson AJ, Collins PD. Colon cancer: a civilization disorder. Digestive diseases (Basel, Switzerland). 2011;29(2):222-8.
18. Gingras D, Beliveau R. Colorectal cancer prevention through dietary and lifestyle modifications. Cancer Microenviron. 2011;4(2):133-9.
19. Zhang J, Dhakal IB, Gross MD et al. Physical activity, diet, and pancreatic cancer: a population-based, case-control study in Minnesota. Nutr Cancer. 2009;61(4):457-65.
20. Leitzmann M, Powers H, Anderson AS et al. European Code against Cancer 4th Edition: Physical activity and cancer. Cancer Epidemiol. 2015;39 Suppl 1:S46-55.
21. Knight JA. Physical inactivity: Associated diseases and disorders. Ann Clin Laboratory Sci. 2012;42(3):320-37.
22. Namasivayam V, Lim S. Recent advances in the link between physical activity, sedentary behavior, physical fitness, and colorectal cancer. F1000Research. 2017;6.
23. Moore SC, Lee IM, Weiderpass E et al. Association of Leisure-Time Physical Activity With Risk of 26 Types of Cancer in 1.44 Million Adults. JAMA Int Med. 2016;176(6):816-25.
24. Cook MB, Matthews CE, Gunja MZ et al. Physical activity and sedentary behavior in relation to esophageal and gastric cancers in the NIH-AARP cohort. PloS one. 2013;8(12):e84805.
25. Kruk J, Czerniak U. Physical activity and its relation to cancer risk: updating the evidence. APJCP. 2013;14(7):3993-4003.
26. Howard RA, Freedman DM, Park Y et al. Physical activity, sedentary behavior, and the risk of colon and rectal cancer in the NIH-AARP Diet and Health Study. CCC. 2008;19(9):939-53.
27. Wolin KY, Lee IM, Colditz GA et al. Leisure-time physical activity patterns and risk of colon cancer in women. Int J Cancer. 2007;121(12):2776-81.
28. Stolzenberg-Solomon RZ, Adams K, Leitzmann M et al. Adiposity, physical activity, and pancreatic cancer in the National Institutes of Health-AARP Diet and Health Cohort. Am J Epidemiol. 2008;167(5):586-97.
29. Liu L, Shi Y, Li T et al. Leisure time physical activity and cancer risk: evaluation of the WHO's recommendation based

on 126 high-quality epidemiological studies. British J Sports Med. 2016;50(6):372-8.
30. Psaltopoulou T, Ntanasis-Stathopoulos I, Tzanninis IG et al. Physical Activity and Gastric Cancer Risk: A Systematic Review and Meta-Analysis. Clin J Sport Med. 2016;26(6):445-64.
31. Nunez C, Bauman A, Egger S et al. Obesity, physical activity and cancer risks: Results from the Cancer, Lifestyle and Evaluation of Risk Study (CLEAR). Cancer Epidemiol. 2017;47:56-63.
32. Singh S, Devanna S, Edakkanambeth Varayil J et al. Physical activity is associated with reduced risk of esophageal cancer, particularly esophageal adenocarcinoma: a systematic review and meta-analysis. BMC Gastroenterology. 2014;14:101.
33. Leitzmann MF, Koebnick C, Freedman ND et al. Physical activity and esophageal and gastric carcinoma in a large prospective study. Am J Prev Med. 2009;36(2):112-9.
34. Winzer BM, Paratz JD, Whitehead JP et al. The feasibility of an exercise intervention in males at risk of oesophageal adenocarcinoma: a randomized controlled trial. PLoS One. 2015;10(2):e0117922.
35. Behrens G, Jochem C, Keimling M et al. The association between physical activity and gastroesophageal cancer: systematic review and meta-analysis. Eur J Epidemiol. 2014;29(3):151-70.
36. Castro C, Peleteiro B, Lunet N. Modifiable factors and esophageal cancer: a systematic review of published meta-analyses. J Gastroenterol. 2017:1-15.
37. Realdon S, Antonello A, Arcidiacono D et al. Adherence to WCRF/AICR lifestyle recommendations for cancer prevention and the risk of Barrett's esophagus onset and evolution to esophageal adenocarcinoma: results from a pilot study in a high-risk population. Eur J Nutr. 2016;55(4):1563-71.
38. Balbuena L, Casson AG. Physical activity, obesity and risk for esophageal adenocarcinoma. Future oncology (London, England). 2009;5(7):1051-63.
39. Parent ME, Rousseau MC, El-Zein M et al. Occupational and recreational physical activity during adult life and the risk of cancer among men. Cancer Epidemiol. 2011;35(2):151-9.
40. Abioye AI, Odesanya MO, Abioye AI, Ibrahim NA. Physical activity and risk of gastric cancer: a meta-analysis of observational studies. Br J Sports Med. 2015;49(4):224-9.
41. Den Hoed CM, Kuipers EJ. Gastric Cancer: How Can We Reduce the Incidence of this Disease? Current Gastroenterol Rep. 2016;18(7):1-8.
42. Baroudi O, Chaaben AB, Mezlini A et al. Impact of lifestyle factors and nutrients intake on occurrence of gastrointestinal cancer in Tunisian population. Tumor Biology. 2014;35(6):5815-22.
43. De Jonge PJF, Wolters LMM, Steyerberg EW et al. Environmental risk factors in the development of adenocarcinoma of the oesophagus or gastric cardia: A cross-sectional study in a Dutch cohort. Alimen Pharmacol Ther. 2007;26(1):31-9.
44. Buckland G, Travier N, Huerta JM et al. Healthy lifestyle index and risk of gastric adenocarcinoma in the EPIC cohort study. Int J Cancer. 2015;137(3):598-606.
45. Campbell PT, Sloan M, Kreiger N. Physical activity and stomach cancer risk: The influence of intensity and timing during the lifetime. Eur J Cancer. 2007;43(3):593-600.
46. Singh S, Varayil JE, Devanna S et al. Physical activity is associated with reduced risk of gastric cancer: A systematic review and meta-analysis. Cancer Prev Res. 2014;7(1):12-22.
47. Huerta JM, Chirlaque MD, Molina AJ et al. Physical activity domains and risk of gastric adenocarcinoma in the MCC-Spain case-control study. PLoS ONE. 2017;12(7).
48. Yun YH, Lim MK, Won YJ et al. Dietary preference, physical activity, and cancer risk in men: national health insurance corporation study. BMC cancer. 2008;8:366.
49. Sjodahl K, Jia C, Vatten L et al. Body mass and physical activity and risk of gastric cancer in a population-based cohort study in Norway. Cancer Epidemiol, Biomarkers Prev. 2008;17(1):135-40.
50. Barone E, Corrado A, Gemignani F, Landi S. Environmental risk factors for pancreatic cancer: an update. Arch Toxicol. 2016;90(11):2617-42.
51. Behrens G, Jochem C, Schmid D et al. Physical activity and risk of pancreatic cancer: a systematic review and meta-analysis. Eur J Epidemiol. 2015;30(4):279-98.
52. Noor NM, Banim PJ, Luben RN et al. Investigating Physical Activity in the Etiology of Pancreatic Cancer: The Age at Which This Is Measured Is Important and Is Independent of Body Mass Index. Pancreas. 2016;45(3):388-93.
53. O'Rorke MA, Cantwell MM, Cardwell CR et al. Can physical activity modulate pancreatic cancer risk? a systematic review and meta-analysis. Int JCancer. 2010;126(12):2957-68.
54. Calton BA, Stolzenberg-Solomon RZ, Moore SC et al. A prospective study of physical activity and the risk of pancreatic cancer among women (United States). BMC cancer. 2008;8:63.
55. Heinen MM, Verhage BA, Goldbohm RA et al. Physical activity, energy restriction, and the risk of pancreatic cancer: a prospective study in the Netherlands. Am J Clin Nut. 2011;94(5):1314-23.
56. Maisonneuve P, Lowenfels AB. Risk factors for pancreatic cancer: A summary review of meta-analytical studies. Int J Epidemiol. 2015;44(1):186-98.
57. Lin Y, Kikuchi S, Tamakoshi A et al. Obesity, physical activity and the risk of pancreatic cancer in a large Japanese cohort. Intl J Cancer. 2007;120(12):2665-71.
58. Kushi LH, Doyle C, McCullough M et al. American Cancer Society guidelines on nutrition and physical activity for cancer prevention: Reducing the Risk of Cancer with Healthy Food Choices and Physical Activity. CA Cancer J Clin. 2012;62(1):30-67.
59. Bao Y, Michaud DS. Physical activity and pancreatic cancer risk: a systematic review. Cancer Epidemiol. 2008;17(10):2671-82.
60. Stevens RJ, Roddam AW, Spencer EA et al. Factors associated with incident and fatal pancreatic cancer in a cohort of middle-aged women. Int J Cancer. 2009;124(10):2400-5.
61. Sehdev A, O'Neil BH. The Role of Aspirin, Vitamin D, Exercise, Diet, Statins, and Metformin in the Prevention and Treatment of Colorectal Cancer. Curr Treat Options oncol. 2015;16(9):43.
62. Aran V, Victorino AP, Thuler LC, Ferreira CG. Colorectal Cancer: Epidemiology, Disease Mechanisms and Interventions to Reduce Onset and Mortality. Clin Colorectal Cancer. 2016;15(3):195-203.
63. Golshiri P, Rasooli S, Emami M, Najimi A. Effects of Physical Activity on Risk of Colorectal Cancer: A Case-control Study. Int J Prev Med. 2016;7:32.
64. Mohandas KM. Colorectal cancer in India: Controversies, enigmas and primary prevention. Indian J Gastroenterol. 2011;30(1):3-6.
65. Sanchez NF, Stierman B, Saab S et al. Physical activity reduces risk for colon polyps in a multiethnic colorectal cancer screening population. BMC research notes. 2012;5:312.
66. Qasim A, O'Morain C. Primary prevention of colorectal cancer: Are we closer to reality? Eur J Gastroenterol Hepatology. 2010;22(1):9-17.

67. Lieberman D. Screening, Surveillance, and Prevention of Colorectal Cancer. Gastrointest Endosc Clin N Am. 2008;18(3):595-605.
68. Omran S, Barakat H, Muliira JK, McMillan S. Dietary and Lifestyle Risk Factors for Colorectal Cancer in Apparently Healthy Adults in Jordanian Hospitals. J Cancer Educ. 2015.
69. Crosara Teixeira M, Braghiroli MI, Sabbaga J, Hoff PM. Primary prevention of colorectal cancer: myth or reality? World J Gastroenterol. 2014;20(41):15060-9.
70. Wei EK, Colditz GA, Giovannucci EL et al. Cumulative risk of colon cancer up to age 70 years by risk factor status using data from the nurses' health study. Am J Epidemiol. 2009;170(7):863-72.
71. Erdrich J, Zhang X, Giovannucci E, Willett W. Proportion of colon cancer attributable to lifestyle in a cohort of US women. Cancer Causes Control. 2015;26(9):1271-9.
72. Huxley RR, Ansary-Moghaddam A, Clifton P et al. The impact of dietary and lifestyle risk factors on risk of colorectal cancer: A quantitative overview of the epidemiological evidence. Int J Cancer. 2009;125(1):171-80.
73. Boyle T, Keegel T, Bull F et al. Physical activity and risks of proximal and distal colon cancers: a systematic review and meta-analysis. J Nat Cancer Inst. 2012;104(20):1548-61.
74. Robsahm TE, Aagnes B, Hjartaker A et al. Body mass index, physical activity, and colorectal cancer by anatomical subsites: a systematic review and meta-analysis of cohort studies. Eur J Cancer Prev. 2013;22(6):492-505.
75. Nilsen TI, Romundstad PR, Petersen H et al. Recreational physical activity and cancer risk in subsites of the colon (the Nord-Trondelag Health Study). Cancer Epidemiol, biomarkers Prev. 2008;17(1):183-8.
76. Lee KJ, Inoue M, Otani T et al. Physical activity and risk of colorectal cancer in Japanese men and women: the Japan Public Health Center-based prospective study. Cancer causes & control: CCC. 2007;18(2):199-209.
77. Odegaard AO, Koh WP, Yuan JM. Combined lifestyle factors and risk of incident colorectal cancer in a Chinese population. Cancer Prev Res. 2013;6(4):360-7.
78. Song JH, Kim YS, Yang SY et al. Physical activity and other lifestyle factors in relation to the prevalence of colorectal adenoma: a colonoscopy-based study in asymptomatic Koreans. CCC. 2013;24(9):1717-26.
79. Mai PL, Sullivan-Halley J, Ursin G et al. Physical activity and colon cancer risk among women in the California Teachers Study. Cancer Epidemiol, Biomarkers Prev. 2007;16(3):517-25.
80. Eaglehouse YL, Koh WP, Wang R et al. Physical activity, sedentary time, and risk of colorectal cancer: the Singapore Chinese Health Study. Eur Jo Cancer Prev. 2017.
81. Wang FW, Hsu PI, Chuang HY et al. Prevalence and risk factors of asymptomatic colorectal polyps in Taiwan. Gastroenterol Res Practice. 2014;2014.
82. Øines M, Helsingen LM, Bretthauer M, Emilsson L. Epidemiology and risk factors of colorectal polyps. Best Practice and Research: Clin Gastroenterol. 2017;31(4):419-24.
83. Fu Z, Shrubsole MJ, Smalley WE et al. Lifestyle factors and their combined impact on the risk of colorectal polyps. Am J Epidemiol. 2012;176(9):766-76.
84. Wolin KY, Yan Y, Colditz GA. Physical activity and risk of colon adenoma: a meta-analysis. Br J Cancer. 2011;104(5):882-5.
85. Jayasekara H, Reece JC, Buchanan DD et al. Risk factors for metachronous colorectal cancer or polyp: A systematic review and meta-analysis. J Gastroenterol Hepatol (Australia). 2017;32(2):301-26.
86. Haque TR, Bradshaw PT, Crockett SD. Risk Factors for Serrated Polyps of the Colorectum. Dig Dis Sci. 2014;59(12):2874-89.
87. Wolin KY, Yan Y, Colditz GA, Lee IM. Physical activity and colon cancer prevention: a meta-analysis. Br J Cancer. 2009;100(4):611-6.
88. Tayyem RF, Shehadeh IN, Abumweis SS et al. Physical inactivity, water intake and constipation as risk factors for colorectal cancer among adults in Jordan. APJCP. 2013;14(9):5207-12.
89. Naing C, Lai PK, Mak JW. Immediately modifiable risk factors attributable to colorectal cancer in Malaysia. BMC Public Health. 2017;17(1).
90. Thrumurthy SG, Thrumurthy SSD, Gilbert CE et al. Colorectal adenocarcinoma: Risks, prevention and diagnosis. BMJ (Online). 2016;354.
91. White V, Miller R. Colorectal cancer: prevention and early diagnosis. Medicine. 2007;35(6):297-301.
92. Johnson CM, Wei C, Ensor JE et al. Meta-Analyses of colorectal cancer risk factors. Cancer Causes Control. 2013;24(6):1207-22.
93. Takahashi H, Kuriyama S, Tsubono Y et al. Time spent walking and risk of colorectal cancer in Japan: The Miyagi Cohort Study. Eur J Cancer Prev. 2007;16(5):403-8.
94. Rosato V, Bosetti C, Levi F et al. Risk factors for young-onset colorectal cancer. CCC. 2013;24(2):335-41.
95. Boyle T. Physical Activity and Colon Cancer: Timing, Intensity, and Sedentary Behavior. Am J Lifestyle Med. 2012;6(3):204-15.
96. Moradi T, Gridley G, Björk J et al. Occupational physical activity and risk for cancer of the colon and rectum in Sweden among men and women by anatomic subsite. Eur J Cancer Prev. 2008;17(3):201-8.
97. Harriss DJ, Atkinson G, Batterham A et al. Lifestyle factors and colorectal cancer risk (2): a systematic review and meta-analysis of associations with leisure-time physical activity. Colorectal dis. 2009;11(7):689-701.
98. Wolin KY, Patel AV, Campbell PT et al. Change in physical activity and colon cancer incidence and mortality. Cancer Epidemiol, Biomarkers Prev. 2010;19(12):3000-4.
99. Halle M, Schoenberg MH. Physical activity in the prevention and treatment of colorectal carcinoma. Dtsch Arztebl Int. 2009;106(44):722-7.
100. Alazzeh AY, Azzeh FS. Active lifestyle patterns reduce the risk of colorectal cancer in the Mecca region, Saudi Arabia: a case–control study. Eur J Cancer Prev. 2017.
101. Fang JY, Shi YQ, Chen YX et al. Chinese consensus on the prevention of colorectal cancer (2016, Shanghai). J Dig Dis. 2017;18(2):63-83.
102. Hang J, Cai B, Xue P et al. The Joint effects of lifestyle factors and comorbidities on the risk of colorectal cancer: A large Chinese retrospective case-control study. PLoS ONE. 2015;10(12).
103. Mehta M, Shike M. Diet and physical activity in the prevention of colorectal cancer. JNCCN. 2014;12(12):1721-6.
104. Azeem K, Ševčíková J, Kyselý Z et al. Primary and secondary prevention of colorectal cancer in the Czech Republic. Prz Gastroenterol. 2016;11(1):1-5.
105. Marshall JR. Prevention of Colorectal Cancer: Diet, Chemoprevention, and Lifestyle. Gastroenterol Clin N Am. 2008;37(1):73-82.
106. Chan AT, Giovannucci EL. Primary Prevention of Colorectal Cancer. Gastroenterol. 2010;138(6):2029-43.e10.

107. Roncucci L, Mariani F. Prevention of colorectal cancer: How many tools do we have in our basket? Eur J Int Med. 2015;26(10):752-6.
108. Boyle T, Bull F, Fritschi L, Heyworth J. Resistance training and the risk of colon and rectal cancers. Cancer Causes and Control. 2012;23(7):1091-7.
109. Parkin DM, Olsen AH, Sasieni P. The potential for prevention of colorectal cancer in the UK. Eur J Cancer Prev. 2009;18(3):179-90.
110. Simons CC, Hughes LA, van Engeland M et al. Physical activity, occupational sitting time, and colorectal cancer risk in the Netherlands cohort study. Am J Epidemiol. 2013;177(6):514-30.
111. Gorczyca AM, Eaton CB, LaMonte MJ et al. Association of physical activity and sitting time with incident colorectal cancer in postmenopausal women. Eur J Cancer Prev. 2017.
112. Yarnall JM, Crouch DJM, Lewis CM. Incorporating non-genetic risk factors and behavioural modifications into risk prediction models for colorectal cancer. Cancer Epidemiol. 2013;37(3):324-9.
113. Ranadive IN, Sussman DA. Prevention of colorectal cancer: The future is now. Curr Colorectal Cancer Rep. 2014;10(1):84-93.
114. Brenner DR. Cancer incidence due to excess body weight and leisure-time physical inactivity in Canada: Implications for prevention. Prev Med. 2014;66:131-9.
115. Dahham SS, Majid AMA. The impact of life style and nutritional components in primary prevention of colorectal cancer. J Appl Pharm Sci. 2016;6(9):237-44.
116. Miles L. Physical activity and the prevention of cancer: A review of recent findings. Nutrition Bulletin. 2007;32(3): 250-82.
117. Rasool S, Kadla SA, Rasool V, Ganai BA. A comparative overview of general risk factors associated with the incidence of colorectal cancer. Tumor Biology. 2013;34(5):2469-76.
118. Hughes LAE, Simons CCJM, van den Brandt PA et al. Body size, physical activity and risk of colorectal cancer with or without the CpG island methylator phenotype (CIMP). PLoS ONE. 2011;6(4).
119. Durko L, Malecka-Panas E. Lifestyle Modifications and Colorectal Cancer. Curr Colorectal Cancer Reports. 2014;10:45-54.
120. Schoenberg MH. Physical Activity and Nutrition in Primary and Tertiary Prevention of Colorectal Cancer. Vis Med. 2016;32(3):199-204.
121. Trojian TH, Mody K, Chain P. Exercise and colon cancer: Primary and secondary prevention. Curr Sports Med Reports. 2007;6(2):120-4.
122. Fuemmeler BF, Pendzich MK, Tercyak KP. Weight, dietary behavior, and physical activity in childhood and adolescence: Implications for adult cancer risk. Obesity Facts. 2009;2(3):179-86.
123. Friedenreich CM, Neilson HK, Lynch BM. State of the epidemiological evidence on physical activity and cancer prevention. Eur J Cancer (Oxford, England: 1990). 2010;46(14):2593-604.