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EC GASTROENTEROLOGY AND DIGESTIVE SYSTEM

Review Article

Cumulative Benefits of Physical Activity on Liver Cancer Prevention

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Received: August 26, 2019; **Published:** October 22, 2019

Abstract

Lifestyle is becoming the most important issue for human longevity and quality of life. Physical activity and a healthy diet are responsible for approximately 70 percent of our lifespan. We emphasize in this paper mostly the role of physical activity as the first step to a healthy lifestyle to prevent liver cancer. We understand the important role of a healthy diet to protect the liver against ailments or other main factors, including vaccination, treatment of hepatitis C, good hygiene procedures, particularly in health care settings, and overall public education. Limited evidence underlines the role of physical activity in prevention of hepatocellular carcinoma (HCC) named also hepatoma. Higher levels of physical activity protect human health more than moderate or leisure time activity.

Keywords: *Liver Cancer; Physical Activity; Prevention*

Introduction

Any kind of physical activity at any age is helpful to protect the human body against non-infectious chronic diseases. Even a low dose of moderate physical activity is associated with a 22 per cent reduction of mortality risk. Vigorous exercise reduces a 28 per cent risk in all-cause mortality but spending more than 3,5 hours a week being active, resulted in a 35 per cent reduction in all-causes mortality. Metabolic Equivalent of Task (MET), determines low physical activity as between 1 - 499, medium 500 - 999 and high as above 1000 minutes per week [1]. When over 30 per cent people worldwide are physically inactive, the risk of chronic non-infectious diseases increases along with more people becoming obese, having insulin resistance, chronic inflammation and being at greater risk of developing cancers. It is never too late to become physically active [1]. When researchers compared groups of leisure-time active people to sedentary ones, they found a lower risk of heart disease, all-cause mortality and several cancers, including liver cancers, in the active group [2]. Higher levels of physical activity were associated with a seven per cent lower risk of total cancers [2]. Abdominal obesity is one of the major risk factors for liver cancer and creates risk for metabolic syndrome as insulin resistance. By 2030, obesity is expected to rise, up to 50 per cent worldwide. Physical activity can reverse clinical risk factors for metabolic syndrome. Different types of exercise can reduce abdominal, subcutaneous and visceral fat [3,4].

Exercise was used as a medicine for a long time in many non-infectious chronic diseases from cardiovascular, pulmonary, cancers, psychiatric, neurological diseases to metabolic syndrome. Physical activity is significantly associated with a lower risk of diabetes mellitus type 2 (46 percent lower in the exercise group as compared to inactivity group). Exercise is able to reduce insulin secretion, alleviate visceral fat by increasing energy expenditure and induce lipolysis. Not only moderate but also vigorous physical activity is important for those who are looking for better results of health outcome, to avoid most chronic diseases. In 2030, the prevalence of type 2 diabetes will

reach over 300 million cases worldwide as compared to 170 million in 2000 [5,6]. Implementation of physical activity is probably easier to deliver for public domain than a healthy diet and prolonging exercise can help induce better eating habits. Between 30, and 60 minutes or more of exercise every day can significantly reduce the risk of cancer, mostly colon cancer, probable postmenopausal breast cancer as well as lung, pancreas, and premenopausal breast cancer [7]. Lifestyle is a key factor to avoiding major chronic non-infectious diseases, and is crucial to prevent liver cancers, diabetes, obesity, non-alcoholic steato-hepatitis (NASH), metabolic syndrome or insulin resistance. Prevention of malignant tumors, public awareness, funding for screening cancers, more comprehensive vaccination against hepatitis B, are playing a main role in reducing liver cancers risk [8]. Exercise training reduces the incidence of obesity and diabetes, which are major determinants of HCC, and further diminishes intrahepatic fat as well as free fatty acids (FFA). The best implementation of physical activity is in early childhood because obesity among children is on the rise worldwide [8-10]. The more we exercise, the more we are reducing liver cancer risk. If people implement physical activity only in moderation, like at a leisure-time, HCC risk reduction has been seen only in people who never smoked [11]. In mice, exercise significantly diminished liver tumor cell proliferation, that proved a positive link between physical training and cancer [12]. People are able to reduce the risk of HCC by 45 per cent after years of moderate-vigorous exercise. Moderate-vigorous exercise may act by lowering body mass indexes and reduction incidence of diabetes. Vigorous exercise is the most efficient way to reduce body mass index, diminish waist circumference and excessive liver fat [13]. Liver cirrhosis as a leading factor risk for liver cancer, occurs four more time in sedentary people or in people with low physical activity than in active ones. Sitting too many hours daily, particularly watching television or working on computers, could direct people toward unhealthy dietary practices [14]. Limited evidence suggests that moderate to vigorous exercise reduces the risk of liver cancer by having a beneficial effect on many other risk factors of HCC. The World Cancer Research Fund delineated strong evidence for relation of physical activity with smaller consumption of alcohol, reduction of body fatness, better glucose utilization, less chronic inflammation. Physical exercise is able to control oxidative stress responsible for inducing liver cancer [15].

HBV, HCV, fatty liver disease, type 2 diabetes and alcohol, are the greatest contributors to malignant tumors of liver. Risk factors are the same for HCC and cholangiocarcinoma [16]. In individuals who continue exercising for years, vigorous activity accounts for best prevention result, by lowering the risk of liver cancers 26- 36 per cent. Absence of obesity and preventing diabetes through physical activity, can reduce further the risk of hepatocellular cancer by 45 per cent [13,17]. It has been confirmed that higher physical activity in rats protected them against metabolic diseases. This is a very significant positive relationship between exercise and liver cancer risk factors in humans [18,19]. Clinicians have found also beneficial effects of physical activity as a treatment of the people with liver cancer. In HCC patients much more precautions are needed to decide whether we can implement moderate or vigorous training due to the development of disease. The timing and kind of surgery also impacts intensity of exercise, along with chemotherapy or radiation due to the fatigue, nausea, dizziness or other negative HCC complications. But authors found beneficial effects of physical activity among those already with liver cancer. It was reported that exercise increased HCC treatment efficacy, reduced oxidative stress, inflammation and has had a direct positive effect on tumorigenesis [20].

Mechanism of action the physical activity on cancer

We have no evidence of increased risk of premature death during and after endurance exercise in general population [5,6]. This is good news for those people who are trying to become physically active. With some recommendations from doctors and experts in physical activity, we can implement in the general population dose-response physical activity, how much and what kind of exercise is proper to conduct.

It was reported that physical activity reduces abdominal obesity, and reverse metabolic syndrome. There is a well documented positive impact of exercise on insulin resistance, chronic inflammation and oxidative stress [3,4,15,19]. Exercise diminishes intrahepatic fat, free fatty acids and fatty liver disease, responsible for diabetes [9]. Exercise training modulates nuclear factor-E2-related factor 2 (Nrf2) in skeletal muscles which is a regulator of antioxidants, defends against oxidative stress, inhibits lipid accumulation in the liver and lessens hepatic fibrosis [10,19]. Exercise reduces serum levels of estrane, estradiol and insulin. Physical activity reduces adiposity, sex steroids, insulin-like growth factors and adipokines as a promotive factors of cancer [2,10,11]. Regular vigorous physical activity alleviates excessive liver fat, inflammation and pro-inflammatory molecules like leptin and adiponectin [13]. Exercise is the single most important factor in reducing abdominal adiposity that decreases concentrations of biomarkers indicating negative changes in our body (See table 1).

Biomarkers Reduced by Physical Activity	Cytokines Reduced by Physical Activity
• Prostaglandins (PGs) • C-reactive protein (CRP) • Adiponectin • cytokines/chemokines • Growth factors	• Interleukins (IL) • Tumor necrosis factor Alpha and Beta (TNF) • Interferons (IFN) • Lymphokines • Monokines

Table 1: *The effects of physical activity on biomarkers and cytokines.*

Abdominal adiposity diminishes after regular exercise training that protects against metabolic syndrome risk [4,5]. Higher intensity physical training reduces more weight than moderate training, the risk of diabetes type 2, insulin secretion and increases muscle mass, insulin sensitivity and energy expenditure [5,6]. The pathways of damaging our DNA start early in a human's lifespan due to smoking, radiation exposure, excessive consumption of salt and preserved foods, aflatoxin, alcohol, sedentary lifestyle, and physical inactivity among others. As a result of the above mentioned circumstances, we become more prone to obesity, insulin resistance, changes in hormones, releasing cytokines, Il-6, TNF-a, and as a consequence, liver cancer can develop [7,15,16].

Discussion

In the Western hemisphere, as well as in the U.S.A. and Australia, liver cancer is on the rise and is becoming the fastest growing death rate since 1980. Liver cancer starts inside hepatocytes [13,15,16]. Hepatitis B and C significantly increase the risk of HCC [17]. Cirrhosis contributes to liver cancer approximately 90 percent, mostly because of alcohol abuse [17]. Almost 20 percent of cirrhosis patients have diabetes mellitus which promotes liver cancer. Obesity is another risk factor for liver cancer [4,8,13]. Other risk factors for HCC include tobacco use, abuses in alcohol, and aflatoxin intoxication [7,15]. Majority of above mentioned HCC risk factors are avoidable. Vaccination against HBV, curing HCV, stop smoking and drinking alcohol, reducing body weight, can significantly diminish liver cancer risk [8,9,15,16,19]. The obesity epidemic is on the rise, diabetes mellitus type 2 increases in the developed world, insufficient physical activity among men and women is spreading worldwide, as are potential risk factors for HCC. Education and the implementation of prevention programmes is necessary to change our behaviour toward a healthy lifestyle [4,5,6,14].

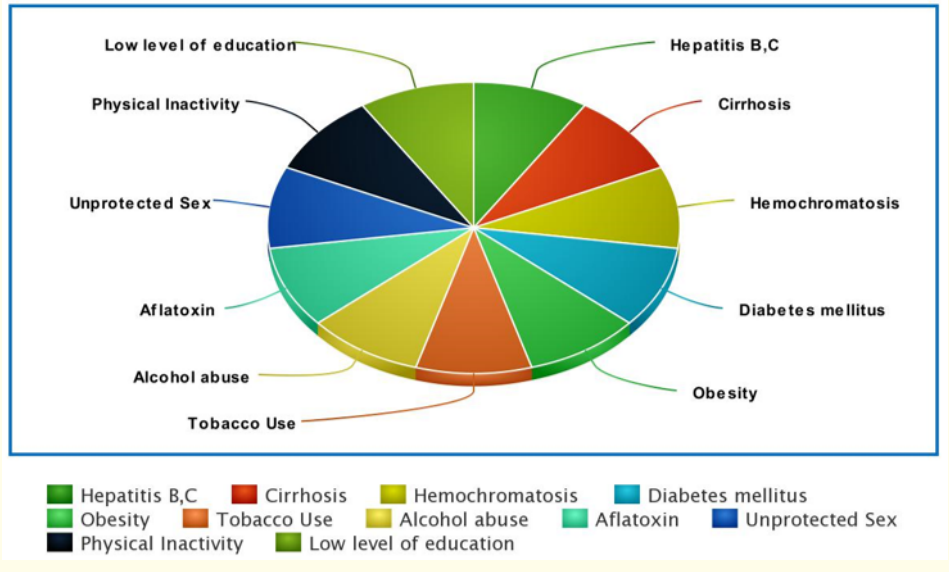

Figure: *Risk factors for liver cancer.*

Conclusion

Physical activity is as effective as pharmacological and surgical treatment and may protect humans against the development of HCC. Growing evidence suggests that effect of dose-response exercise decrease liver cancer risk about 26-36 per cent. Regular exercise for most of our lifespan is very relevant in decreasing risk of liver cancer [7,17]. Cirrhosis mostly associated with heavy alcohol excess, diabetes mellitus type 2, obesity and chronic inflammation, can be reduced by exercise [1,17]. Physical activity provides better self-esteem, better sleep, the feeling of being an athlete, which contributes to more healthy diets and improves overall health [2,8,19]. Liver cirrhosis occurs four more times in low active population, than in high active [14]. Childhood obesity worldwide continues to rise in the last decades making the prognosis of liver cancer even worse, than it is now. It was reported that even the smallest amount of exercise has been seen as beneficial in reduction of total abdominal fat, resulting further in prevention against liver cancer. The more hours of physical training per week, the greater the weight loss and lower HCC risk [3-5].

In our paper we tried to underline the physical activity as one of the most important factor in HCC prevention. Despite being inactive for months or years, it is never too late to start exercising and to increase the total amount of physical activity weeks by weeks. Because the best protection against liver cancer risk is moderate to vigorous physical activity, between 30 - 60 minutes a day, it is crucial to implement exercise properly after consultation with family doctors, specialist, trainers as liver cancer reduction has been found between 30 per cent to 45 per cent, after sustained, prolonged physical training [1,2,13,17]. It has also been well documented that healthy lifestyle matters most on HCC. Being sedentary for many hours a day as watching all kind of screens, including television, computers, etc., is an important risk factor for "alcoholic liver disease". Much worst, liver cirrhosis was four times more likely to increase in inactive people or in low activity than in active ones [14]. Experimental studies on mice have shown decreased liver tumor development and tumor cell proliferation as a result of exercise [12]. According to WHO, childhood obesity is on the rise worldwide with devastating outcomes, increasing inflammatory processes, excessive liver fat and possibility of liver cancer [13]. Abdominal obesity is a major risk factor for metabolic syndrome. Exercise can diminish abdominal fat deposits, protects against chronic inflammation, insulin resistance, diabetes type 2 [3-5]. Physical activity may reduce tumor growth, increase muscle mass, strength, mobility and psycho-social well-being [5,20].

Promoting prevention programs and increasing public awareness about the benefits of increased physical activity in society should be a lifelong efficient prevention strategy for HCC [8,9,19].

Conflict of Interest

The author declares no conflict of interest.

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Volume 6 Issue 11 November 2019