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Bidirectional Influences between Colorectal Cancer and Exercise - A Review

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Abstract

Colorectal cancer is one of the cancers where physical activity is of paramount importance, either in primary prevention or as a part of rehabilitation strategies during or after medical or surgical treatments. In fact, colorectal cancer is regarded as one of the most preventable types of cancer through lifestyle measures. Treatments of this particular type of cancer may easily refrain patients from practicing physical activities. Direct physical limitations or psychological aspects along with frequent wrong beliefs or misconceptions are behind this deleterious effect. We intent to present a bidirectional influence between cancer and exercise: cancer as a strong restrictor to the practice of physical activity and exercise as an efficient primary preventer but also a booster for quick recovery. Biological mechanisms are also mentioned according to recent literature. To our knowledge, this is the first review where all this aspects are covered in a single article.

Introduction

Each year, 14.1 million people are expected to develop cancer, according to the last World Cancer Report. Colorectal cancer is the third most frequent cancer in men and the second most frequent in women. One third of all cases originate in rectum [1].

Colorectal cancer is currently seen as one of the most preventable types of cancer through lifestyle measures [2]. It is also one of the most killing cancers. Primary treatment modality is margin-free surgical resection. However, adjuvant treatment is frequently administered due to spreading disease or residual carcinoma [3].

Stage III colon cancer requires postoperative chemotherapy as well as stage II cases with high risk features (perforation, bowel obstruction, poorly differentiated or venous involvement). Concerning rectal cancer, high risk stage II and stage III cancers imply preoperative radiation along with chemotherapy as a downsize strategy allowing sphincter preserving surgeries [4-6]. Recent advances in chemotherapy modalities have emerged, with a shift to platinum-based therapies (FOLFOX, CapeOx, XELOX) [5].

However, treatment of colorectal cancer with or without surgery can be debilitating. It is now consensual that QOL and exercise and closely attached. As colorectal cancer is a disease of aging, various barriers also present in general population can limit physical conditioning. Significant side-effects of treatments add more barriers to the normal aging process which has strong deleterious consequences to the quality of life and undeniable impact on overall well-being [7-10].

Concerning surgical strategies, stomas are frequently a part of the solution but also a part of the problem with strong impact in the quality of life (QOL) [11].

Thereby, individual QOL measurements provide leading strategies to weight harms and benefits of colorectal cancer treatments. There is a substantial inter individual difference in QOL perceptions that must comprise physical, functional, psychological social and emotional aspects altogether. Patient's satisfaction is directly related with expectations, preoperative conceptions and postoperative handling of what is perceived as possible or ideal [12-14].

Search Strategy

English language studies (all types) where included in this review due to the paucity of literature

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in this particular field. We performed a research in PubMed database of all articles covering the topic "colorectal cancer and exercise", published between 1980 and 2019. The rarity of large studies made unaccepted all kinds of studies, as meta-analysis and systematic reviews are of very little number.

QOL is inextricably intertwined with exercise. More and more evidence supports exercise in cancer settings, with numerous physiological processes that explain better overall survival with better QOL. Effects on tumor physiology and metabolism are now being revealed, albeit mostly in rodent model studies [15].

Cancer as a Barrier to Exercise

It is now clear that colorectal cancer treatment (surgery with or without chemotherapy or radiotherapy) causes detrimental effects in the practice of physical activity. The first year after diagnosis seems to be one of the most important periods where sensitizing actions should be implemented [16].

First step: understanding the barriers

Promoting physical activity in people in cancer should be considered a priority. In order to incentive to exercise, perceived barriers need to be addressed. They may directly stem from disease itself but also from medical and surgical treatments, co morbidities, aging process and others (fear, commitments, lack of time or motivation, etc).

Questionnaires have shown that the most common barrier is fatigue. Stomial bag related barriers are also frequently cited as well as COPD or breathlessness. Patients also frequently mention generalized aches and age per si as barriers [17,18].

Few patients understand that exercise may improve their fatigue. Educational strategies should be implemented to make patients realize that this barrier can soon disappear if exercise is done [18].

A Canadian study shown that 69.5% of colorectal cancer survivors identify improved fitness as a perceived benefit of exercise. Such studies could help guiding medical staff to promote physical activity while targeting beliefs of this particular population [19].

Stoma as a barrier to physical activity

Stoma creation may be lifesaving and yet is also responsible for very frequent complications. Fear of pouch leakage, odor, clothing problems and depression are the most frequent stoma-related complications, with strong psychosocial impact. Problems such as skin irritation or stoma-related sexual activity limitations also have a strong impact in physical activity [20].

Sleep problems are also frequent cited with stomal patients. Frequent awakening to empty the bag or worrying about rolling onto it help to explain daily fatigue and reluctance to exercise practicing. Trial and error strategies with different devices help to lessen these complications over time [21].

Lack of preoperative informative preparation may lead to disastrous misconceptions that will impeach the patient to rapidly recover from surgery, psychologically speaking. Participation in exercise after the creation of a stoma is advisable and its benefits are well documented [20,21].

A systematic review showed that physical capacity deteriorates among colorectal cancer survivors after treatment. Thereby, medical staff can generally assume with few exceptions that reestablishing physical conditioning is needed, irrespective of the chosen treatment approach [16].

The importance of shifting process

Adapting to cancer or a stoma might be a very difficult step. There seems to be a period of reconceptualization at the middle of the adaptation process, where the patients start to shift towards acceptation of stomial bag and related issues. It is also clear that misconceptions and discrepancy between post operative difficulties and perceived preoperative difficulties play a strong role in the shifting process. In this process, recalibration of standards of quality of life takes place with changing of the actual meaning of what is perceived as average quality of life. Patients are particularly susceptible to lifestyle changes in this period, and strategies need to be implemented to individually predict this moment and act once the moment comes [21].

Biological mechanisms of exercise benefits

It is now well known that exercise reduces the risk of colorectal cancer, as well as many other cancers. Risk reduction in colorectal cancer approaches -23%, one of the most spectacular risk reductions amid all cancers. It appears that between 3.5 and 4 hours of weekly vigorous exercise are needed to optimize protection [22].

Hypothesis of decreased gastrointestinal transit time

Several mechanisms are evoked that could explain how exercise may exert its protection against colorectal cancer. The most well documented mechanism is the hypothesis of gastrointestinal time. The defenses of this mechanism argue that a decreased gastrointestinal time observed in people involved in moderate level activities reduces exposition of the intestinal lumen to carcinogens [2]. Strenuous exercises might increase levels of PGF2a and decrease levels of PGE2. The latter decreases colonic motion and increases cell proliferation rates, mainly neoplasic cells [2,15].

A decreased Body Mass Index (BMI) among physically active people could also partially explain the protective effect [23,24].

Preventing proliferative signaling

Another possible explanation concerns insulin sensitivity. Studies have shown that exercise is associated with better insulin sensitivity and down regulation of IGF1. One study using mouse models proved that p53 related regulators might be involved in this inhibition. Both insulin and IGF1 are strong mitogens of carcinomatous colonic cells. On the other hand, exercise could be responsible for metabolic shifting from glycolytic metabolism to oxidative phosphorylation. The former is a widespread phenomenon in most malignancies while the latter could efficiently restrain tumor growth [2,15,25].

Growth suppressor pathway and apoptosis regulation

Recently, the PI3K signaling pathway as been explored as one of the potential targets of exercise. This pathway is dysregulated in almost all cancers, with important repercussions in cellular transcriptions, growth and survival. Inhibition of this pathway was proved through GenMAPP software in rodents that experiment weight loss [26,27].

Physical activity can interfere with p53 tumoral suppressor gene. Its inactivation may be responsible for the development of colon cancer. Data suggest that Western life style may induce p53 mutations [28].

In rodent studies, it was demonstrated that mouse that exercise have increased tumor growth suppression and apoptosis. Caspase-3 activity measurements were determinant to explain this difference.

Levels of prop apoptotic proteins as Bax and Bak may also play an important role in this settings, with one study proving higher levels in exercise rodents [29-31].

Immune escaping pathway

Immune responses after exercise could also play a protective role in physically active patients. Regular acute exercise increases the basal level of NK cell activity which constitutes an important defense against tumor spreading. Several studies have shown that enhanced NK cell cytotocicity is accompanied by reductions in tumor growth [2,15,32].

Inducing angiogenesis

There is currently solid evidence that hypoxia and poor blood supply promote cancer progression and is an important barrier to effective antineoplasic therapies [33].

Interference of exercise in tumoral blood supply was hypothesized as one of the mechanisms that could explain some antineoplasic protection, notably through the liberation of Hypoxia Inducible Factor (HIF) [15].

Exercise promotes a shifting in vascular normalization, increasing tumoral perfusion allowing for antineoplastic drugs to act. Increasing VEGF along with HIF-1a seems to be crucial pathways in this process [34-36].

Preventing tumoral invasion and metastasis

Primary tumors easily invade adjacent structures and even distant ones. Intratumoral B-catenin and e-cadherin glycoprotein are involved in such disseminating processes. Voluntary exercise in mice decreases intratumoral levels of E-cadherin, regarded as the glue between epithelial cells favoring locally or distant invasion [37].

Myokines theory

Studies in rodents appear to show that extracts from exhausted muscles might inhibit tumor growth. This myokine pathway could explain some skeletal muscle induced protection against cancer through liberation of muscle derived protective factors. Such factors have anti-inflammatory and insulin sensitizing effects. Some myokines could actually trigger apoptosis in specific tumors (osteonectin in the case of colon cancer). This constitutes perhaps the most recent field of investigation with a recent bulk of literature approaching this theory. Despite excitement, most remains to be proven [38-40].

General Benefits of Exercise

Other general benefits of exercise are well documented in literature. Most are particularly important in the context of cancer and go far beyond colorectal cancer.

Bone loss may occur as a consequence of metastasis or treatments. There is very good quality evidence that exercise will improve bone quality, stimulating bone formation and promoting structural positive modifications [41-44].

Sarcopenia and weight imbalance may also take place due to antineoplastic therapies or the cancer itself. Exercise can act on muscle strength and reducing fat mass. Cachexia can also be prevented with exercise, along with nutritional therapies [45-49].

Peripheral neuropathy may stem from anti-cancer treatment or may appear as a paraneoplasic syndrome. Drugs such as platinum drugs, Microtubule-Targeting agents, proteasome inhibitors and angiogenesis inhibitors play a role in peripheral nerve damage. Despite conflicting evidence, exercise appears to be safe and effective for people with peripheral neuropathy and reduce axonal degeneration [50-52].

Exercise may also help in cases of lymph edema as high BMI is a significant risk factor for this condition [48,53].

Pain is also a common symptom in cancer patients either due to compression/invasion of surrounding structures by cancer itself or induced by antineoplastic treatments. Exercise is able to induce hypoalgesia through some unknown mechanisms. One of them, known as conditioned pain modulation which implies negative pain modulation is well described in the literature [53-56].

Exercise prevents depression, anxiety and sleep problems, frequently intertwined [57,58]. It seems that practicing exercise considerably reduces perceived barriers to physical activity. Among sedentary patients, the number of perceived barriers is considerably higher [17,59].

Special Consideration about Parastomal Hernia

The incidence of parastomal hernia varies between 7-50%. Impact of exercise on the incidence of parastomal hernia and consequences of such a diagnosis in the practice of physical exercise merit special attention. It is now consensual that an optimal body mass index reduces the incidence of parastomal hernia as well as wearing of garments. Nurse advice about abdominal exercise should take place systematically as strengthening of abdominal wall is effective reducing hernia incidence. Advice to restrain from physical activities actually increases the risk of parastomal hernia [60].

Surgical correction may be necessary. Open techniques with or without stoma transposition are well described in the literature. Laparoscopic correction or hybrid approaches are also well studied. The gold standard procedure implies reinforcement of abdominal wall with prosthetic material. However, in cases of local septic process, prosthesis is contra-indicated [61].

The use of a prophylactic mesh when creating a colostomy is not recommended. A recent randomized controlled trial did not show any differences in the incidence of parastomal hernias between patients with or without prophylactic mesh procedures [62].

Post-operative exercises can be initiated as soon as 3-4 days after surgery. However, nursing specialists are frequently not aware of this recommendation. Pilates-style training with reinforcement of pelvic floor and controlled contraction of transverse abdominals are good examples of core exercises that can be implemented [60].

Conclusions

There is no doubt that exercise and cancer have a closed connection that must be further studied. Protective role of physical activity as primary prophylaxis of cancer or as adjuvant therapy is of undeniable importance. Unfortunately, there is no universal consensus or guidelines on this topic. Therefore, patients are currently advised based on professional's individual experiences. Many of the biological mechanisms are hypothesized in rodent studies and extrapolation to humans is difficult. While this pathways are being scrutinized, regular physical activity should be advised to every colorectal cancer survivor. Misconceptions must be dissolved from the beginning of the process with appropriate counseling with interdisciplinary interventions without forgetting inter individual variability.

What is already known?

Colorectal cancer can be prevented with regular sports actives.

Neoplastic treatments are a strong limitation to the practice of exercise.

Most hypothesized biological mechanisms stem from rodent models.

What are the new findings?

Patient's expectations directly influence recovery and rehabilitation.

The shifting point must be recognized and explored to boost recovery.

Understanding stomal limitations to exercise is of paramount importance.

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Contributor ship-AM and CM: study conception/design, data acquisition and revision of manuscript. TP and LF: manuscript revision, critical revision and bibliography selection.

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1. Colorectal cancer cannot be prevented with regular exercise.
2. After neoplastic treatments patient's compliance to exercise is increased.
3. Stomial bag related barriers to exercise are frequently cited by patients.
4. Patient's expectations before treatments have little impact in the recovery process.
5. An exercise program should be implemented two years after diagnosis.

Correct answer 3

1. The shifting process refers to the moment when patient realizes his cancer is not curable.
2. The aging process reduces the barriers against exercise.
3. The impact of exercise in colorectal cancer was mostly studied in humans.
4. The most frequently cited mechanism of exercise benefits is the decreased gastrointestinal time.
5. Pain is a rare symptom in patients with colorectal cancer

Correct answer 4

1. Exercise increases the risk of parastomial hernia.
2. Surgical correction of parastomial hernia is never necessary.
3. Pilates-style exercises should be avoided in patients with a stoma.
4. Restrain from physical activities may increase the risk of parastomial hernia.
5. Post operative exercises after stoma creation should not take place before a month.

Correct answer 4

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