# EFFECT OF PHYSICAL EXERCISE ON COLORECTAL CANCER: SYSTEMATIC REVIEW

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## ABSTRACT

*Aerobic and resistance physical exercise can activate different molecular pathways due to different intensities, duration, and mechanical loads imposed on the muscles. The activity can result in metabolic adaptations, such as increased mitochondrial mass, oxygen supply, glucose uptake, and antioxidant capacity. The method of this systematic review followed recommendations proposed by the PRISMA Statement. Were included studies that used physical exercise as an intervention in rats and mice with induced colorectal cancer. The Studies' selection was on databases: Bireme, PubMed, Science Direct, Medline, Ibecs, Lilacs, Bdenf, Binacis, Scielo, and bibliographic references selected articles. Animal models researches showed that aerobic and resistance exercise could reduce several risk factors like oxidating stress and the tumor's pro-inflammatory status. That happens due to cytokines' regulation, thereby improve organic's defenses and reduce colon inflammation.*


**Keywords**: Colorectal cancer; Physical exercise; Mice and Rats.

## 1. INTRODUCTION

According to the World Health Organization (WHO, 2018), cancer is one of the leading causes of death globally, causing 9.6 million deaths in 2018, with colorectal cancer (CRC) responsible for 1.8 million cases. This form of cancer develops sporadically, in inherited cancer syndromes cases, or based on inflammatory bowel diseases. (Weitz et al., 2005).

Although anyone can develop colorectal cancer, several factors are associated with an increased risk for a disease. Some risk factors are modifiable like diet, obesity, lack of physical activity, tobacco use, and moderate to heavy alcohol use. (Rudy and Zdon, 2000). Colon tumors usually develop through a multiple-stage process that involves histological, morphological, and genetic changes, which accumulate over time. (Koelwyn, Wennerberg, Demaria & Jones, 2015).

Tumor progression is regulated by complex and multifaceted interactions between systemic environment (host), tumor microenvironment, and cancer cells. Whether in primary or distant ectopic sites, the tumor microenvironment is affected by increased growth factors in circulation, cytokines, angiogenic factors, hormones, and other types of cells like immune cells (Simon, 2016).

High levels of inflammatory cytokines and angiogenic factors (e.g., hepatocyte growth factor, tumor necrosis factor (TNF), interleukin 6 (IL-6), and metabolic growth hormones like insulin, glucose, leptin) are associated with higher risks of recurrence and cancer-specific mortality (Freire, 2020); (Bonatelli, 2020).

Chronic inflammation has been identified as an important risk factor for carcinogenesis. Inflammation might be linking with other factors such as increasing age, increased body fat, and neoplastic risk (Simon, 2016). Serum levels of C-reactive protein, an inflammation marker, are associated with a subsequent risk of CRC, and it is believed that inflammation might be involved in the early stage of colorectal tumor growth. (Cotti et al., 2000); (From Lima & Maio, 2012).

Genes such as adenomatous polyposis coli (APC), deleted in colorectal carcinoma (DCC), protein P53, and others, have been identified as participants in the adenoma-carcinoma sequence. That is involved

with tumor genesis based on the theory of multiple-steps, in which accumulating of genetic mutations in unstable cells is the main factor causing cancer (Souza, 2010); (Cotti et al., 2000).

The beneficial results from regular exercise can be affected by the type of activity, duration, intensity, and total time practiced per week, making it complex to understand it (Pedersen, 2009).

Resistance and aerobic exercises can activate molecular pathways because of the different frequencies and mechanical loads imposed on muscles (Neves, Gonçalves & Ramalho, 2020). Aerobic exercise results in metabolic adaptations like increasing mitochondrial mass, oxygen supply, glucose uptake, and antioxidant capacity, whereas resistance exercise mainly cause an increase in muscle mass (Ballarò, Penna, Gómez & Cabrera, 2019)

Epidemiological studies have shown that regular exercise can delay the colon and bowel cancer onsets. Indeed, long-term aerobic training protects against chemically induced colon cancer (Harriss et al., 2007).

Skeletal muscle cells secrete bioactive proteins from into the cell to the extracellular medium. Proteins secretion, which is increased in response to exercise, can regulate organs' function through autocrine, paracrine, and endocrine ways. Besides, that can mediate benefits induced by exercises like metabolic improvement, anti-inflammation, and muscle building; all this is called myokine theory (Aoi, Naito, Takagi & Yoshikawa, 2013). That provides a conceptual basis for understanding the mechanisms by which exercise can influence metabolism and have anti-inflammatory effects. Skeletal muscle contraction releases myokines that work like hormones, causing endocrine effects (Pedersen, 2009).

Physical exercise can alter polyp development by improving immune system function and consequently reduce chronic inflammation. Furthermore, it can improve some cancer risk factors like immune system dysfunction, diet, obesity, insulin action, prostaglandin levels and triglycerides, antioxidant defense mechanisms (Lira, Vancini, Silva & Nouailhetas, 2008); (Da Silva et al., 2020).

Animal research models have stood out to simulate most human tumors' characteristics (Abreu, Santiago, Abreu, Ramos, Neves & Ramalho, 2020). In vivo studies with animal models are considered critical tools required to study the molecular mechanisms of colorectal carcinogenesis, test Therapeutic Approaches, prevent and translate hypotheses derived from cell models (Johnson & Fleet, 2013).

Animal models can be used for chemoprevention studies, assess immunological, chemical, and surgical therapy regimes (Pantaleão & Luchs, 2010).

CRC rodent models can be genetically modified animals like Min/ΔAPC-mouse strains, which reproduce the tumors developing from epithelial cells initiated (mutated) to cover polyp growth through tumor progression and rarely metastases. That can also be a xenotransplant model that expresses growth tumor and its metastases when it used malignant cells, forming a tumor in animal hosts. Besides, chemical models for tumor induction can be used, in which acts on normal epithelium to form carcinomas and seldom metastases, through the multiple-stage process described above (De Robertis et al., 2011)

The 1,2-dimethylhydrazine compound (DMH) and its metabolite, azoxymethane (OMA), are the two most used carcinogens substance to induce and promote colorectal cancer in rats and mice. DMH and OMA are alkylating agents injected intraperitoneally or subcutaneously over several weeks to induce the development of distal colon tumors. (Jucá et al., 2014). Most of these tumors harbor mutations in the β-catenin (Ctnnb1) gene, which is similar to hereditary colorectal cancer without polyposis (HNPCC)

(Thaker, Shaker, Rao &Ciorb, 2012). These mutations affect the N-terminal amino acids of the β-catenin gene product, making the protein resistant to regulatory degradation, stabilizing β-catenin, and increasing WNT signal to boost the tumor's genesis (Johnson & Fleet, 2013).

Although of the broad knowledge about genetic factors involved in developing the diseases, only frequent mutations are used. Such as APC> 70%, p53> 60%, and K-ras> 40%, present in sporadic CRC; APC in familial hereditary adenomatous polyposis; MMR in hereditary non-polypus colorectal cancer (De Robertis et al., 2011). Genetically modified mice can recapitulate specific molecular precision etiologies relevant to human disease. (DE-Souza & Costa-Casagrande, 2018).

The animal model for cancer research is essential to develop new treatment strategies (Augusto Sobrinhoet al., 2019). This study investigates the physical exercise effects of physical exercise on colorectal cancer in rats and mice, which identified and analyzed the exercise results in tumor development. Based on molecular changes' hypothesis by the physical exercise related to colorectal cancer, we proposed to carry out this systematic review study in an animal model.

## 2. METHODS

This systematic review followed the recommendations proposed by the Cochrane Collaboration and by PRISMA Statement.

The Picot strategy was used to define the research question and the inclusion and exclusion criteria (an acronym for Patient, intervention, comparison, Outcomes or outcomes, and study type).

**PICO**

PATIENT: rats or mice with induced colorectal cancer

INTERVENTION: physical exercise, physical activity, aerobic exercise, anaerobic exercise, and combined exercises.

CONTROL: sedentary animals with induced colorectal cancer.

OUTCOME: result rate (positive and negative) to exercise on cancer, the result of exercise on tumor development

TYPE OF STUDY: Preclinical randomized controlled study carried out with rats and mice.

**Eligibility criteria**

Studies that assessed the resistance training effects were included based on the following criteria:

a) Animal studies with induced colorectal cancer.
b) Intervention research in which resistance and aerobic exercise training were used as a single. Intervention or as a part of the intervention.
c) Control research in which includes a group that did a physical exercise of different intensity or another form of exercise or a non-exercising control group.
d) The result from research in which have been reported results about the development of colorectal.
e) Randomized clinical trial (RCT) published on the study design.

**Exclusion criteria**

Studies that used drugs, diet or another intervention beyond physical exercise were excluded.

**Search sources**

Selection of studies was on the databases: Latin American and Caribbean Center for Health Sciences Information (Bireme), Medical Literature Analysis and Retrieval System Online (Pubmed), science direct, Medical Literature Analysis and Retrieval System Online (Medline), Spanish Bibliographic Index in Health Sciences (Ibecs), Latin American & Caribbean Health Sciences Literature (Lilacs), Nursing Database (Bdenf), Bibliografía Nacional en Ciencias de la Salud Argentina (Binacis), physiotherapy Evidence Database (Pedro) and Scientific Electronic Library Online (Scielo). Besides, it searched for references studies already published about the subject, and there was no restriction of language or year of publication.

The search was carried out until December 2019 and followed combinations of medical subject heading terms (MeSH) descriptors: Colorectal cancer; Physical exercise; Mice and Rats.

**Colorectal cancer**: (Colorectal Neoplasm) OR (Neoplasm, Colorecta)l OR (Colorectal Carcinoma) OR (Carcinoma, Colorectal) OR (Carcinomas, Colorectal) OR (Colorectal Carcinomas) OR (Colorectal Cancer) OR (Cancer, Colorectal) OR (Cancers, Colorectal) OR (Colorectal Cancers) OR (Colorectal Tumors) OR (Colorectal Tumor) OR (Tumor, Colorectal) OR (Tumors, Colorectal) OR (Neoplasms, Colorectal)

AND

**Physical exercise**: (Exercises) OR (Physical Activity) OR (Activities, Physical) OR (Activity, Physical) OR (Physical Activities) OR (Exercise, Physical) OR (Exercises, Physical) OR (Physical Exercise) OR (Physical Exercises) OR (Acute Exercise) OR (Acute Exercises) OR (Exercise, Acute)OR (Exercises, Acute) OR (Exercise, Isometric) OR (Exercises, Isometric) OR (Isometric Exercises) OR (Isometric Exercise) OR (Exercise, Aerobic) OR (Aerobic Exercise) OR (Aerobic Exercises) OR (Exercises, Aerobic) OR (Exercise Training) OR (Exercise Trainings) OR (Training, Exercise) OR (Trainings, Exercise).

AND

**Mice**: (Mus) OR (Mouse) OR (Mus musculus) OR (Mice, House) OR (House Mice) OR (Mouse, House) OR (House Mouse) OR (Mus domesticus) OR (Mus musculusdomesticus) OR (domesticus, Mus musculus) OR (Mice, Laboratory) OR ( Laboratory Mice) OR ) OR (Mouse, Laboratory) OR (Laboratory Mouse) OR (Mouse, Swiss) OR (Swiss Mouse) OR (Swiss Mice) OR (Mice, Swiss). rats (Rat) OR (Rattus) OR (Rattusnorvegicus) OR (Rats, Norway) OR (Rats, Laboratory) OR (Laboratory Rat) OR (Laboratory Rats) OR (Rat, Laboratory).

**Studies selection**

It followed two phases beyond eligibility criteria: Phase I - Two independent reviewers selected studies through reading the titles and abstracts that were selected to phase II at least one of the reviewers; Phase II – Complete selected articles analysis by both reviewers.

**Data extraction**

Two independent reviewers accomplish data extraction, using a standardized form that fills: authors, year of publication, training protocol description used on the intervention (volume, intensity, frequency, study duration), strength measures and results, alters in colorectal cancer status, comparison group description, assessment times, study results and authors' conclusions.

**Bias risk**

RoB tool for animal intervention studies (SYRCLE's RoB tool). This tool is based on the Cochrane RoB tool and has been adjusted for aspects of bias that play a specific role in animal intervention researches. The resulting RoB tool for animal studies contains ten entries:

1. Was the allocation sequence generated and appropriately applied?
2. Were the groups similar at the beginning of the study, or were they adjusted for confounding factors in the analysis?
3. Has the allocation appropriately been hidden?
4. Were the animals randomly housed during the experiment?
5. Did the caregivers and/or researchers go blind to know what intervention each animal received during the experiment?
6. Were the animals selected at random to evaluate the results?
7. Did the result appraiser go blind?
8. Were incomplete results data appropriately handled?
9. Are study reports exempt from selective results reports?
10. Was the study free of other problems that could result in a high risk of bias?

These entries are related to selection bias, report bias, detection bias, attrition bias, performance bias, and other biases (Hooijmans Rovers, De Vries, Leenaars, Ritskes, Hoitinga & Langendam, 2014).

Two independent reviewers performed the bias risk and studies' methodological quality assessments. When necessary, the reviewers' disagreements were resolved through discussion and consensus, or even through a third reviewer. The total score ranges from 0 to 10 points, with a score of 6 or higher considered high quality; RCTs with less than six were considered low quality.

**Summary measures**

Results were put in Summary Tables that contained seven entries with study data about author and year, objective, intervention group, control group, induction type, and results about tumor development comparison between treated and control groups.

## 3. RESULT

A total of 1722 studies were found through an electronic database search, of which 1225 were selected for titles and abstracts analysis, of which 1182 were excluded for not fulfill the eligibility criteria requirements. As a result, 43 abstracts were selected and assessed to a full reading. After full-text evaluations, 13 studies were selected.

Figure 1 shows the steps taken to selected and the reasons for excluding some studies.

In Tables 1 and 1.1, the Cochrane RoB Tool assesses the bias risk in the included studies by addressing the following bias types: selection bias, performance bias, attrition bias, detection bias, and reporting bias.

Bias risk graphs 1 and 1.1 show the authors' judgments about each item bias risk, represented as a percentage.

In Table 2 and 2.2, The characteristics of included studies are described, following the items: author, year of publication, study design, study subjects, division of groups, analyzed variables, and results.

**Figure 1**: Shows the steps are taken to selected and the reasons for excluding some studies.

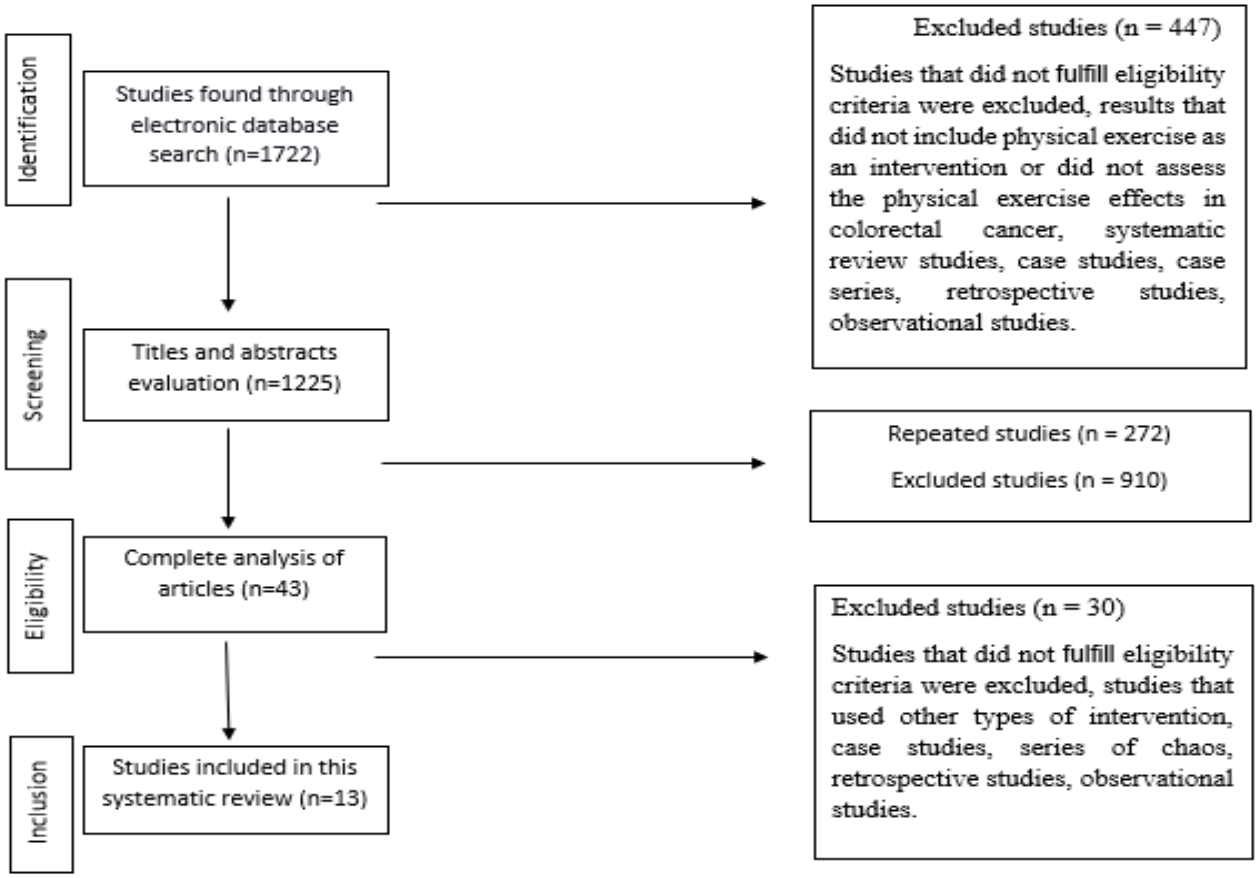
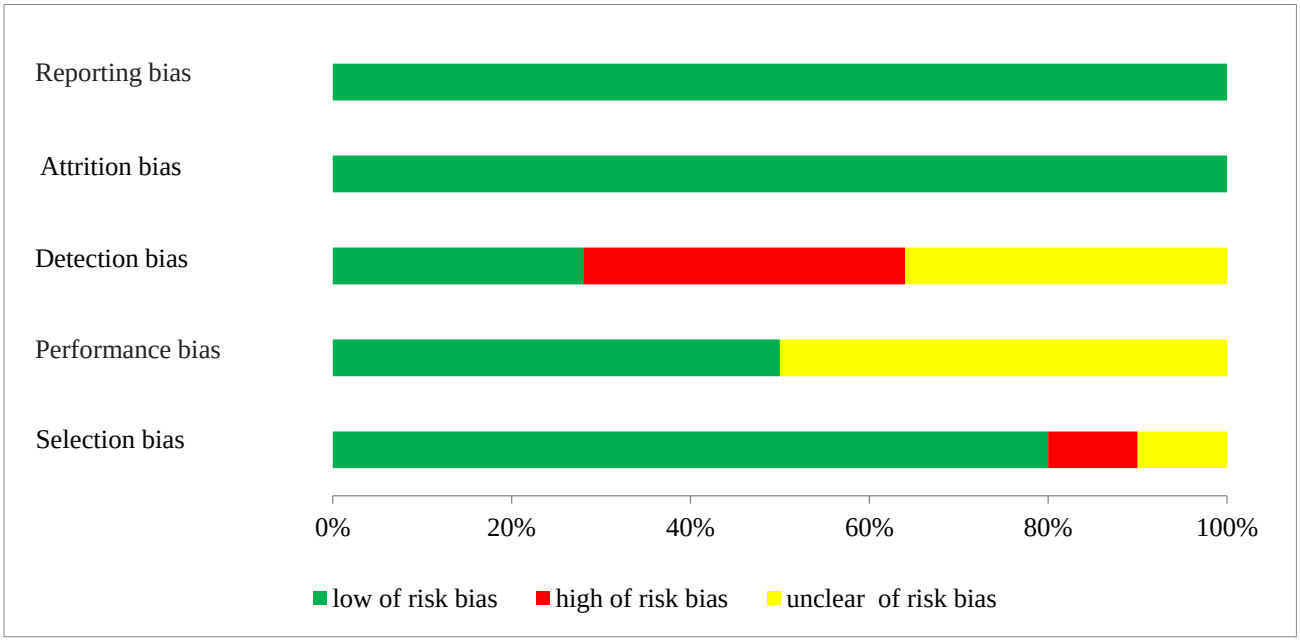


**Table 1 Summary of bias risk'**: Note the authors' judgments about each item of bias risk for each included study. Risk assessment of bias in studies with rats.

| | Study 1 | Study 2 | Study 3 | Study 4 | Study 5 | Study 6 | Study 7 |
|---|---|---|---|---|---|---|---|
| | **Lunz et al., (2008)** | **Demarzo et al., (2004)** | **Kaori et al. (2017).** | **Demarzo et al.,(2008).** | **Bandaru et al.,(1998)** | **Fuku et al,.(2007)** | **Thorling et al., (1993)** |
| **1.** | Yes | Yes | Yes | Yes | Yes | Yes | Yes |
| **2.** | Yes | Yes | Yes | Yes | Not | Yes | Yes |
| **3.** | Not | Unclear | Yes | Yes | Yes | Yes | Unclear |
| **4.** | Yes | Yes | Yes | Yes | Yes | Yes | Yes |
| **5.** | Unclear | Unclear | Unclear | Unclear | Unclear | Unclear | Unclear |
| **6.** | Yes | Yes | Unclear | Not | Not | Not | Yes |
| **7.** | Unclear | Yes | Unclear | Unclear | Not | Unclear | Not |
| **8.** | Yes | Yes | Yes | Yes | Yes | Yes | Yes |
| **9.** | Yes | Yes | Yes | Yes | Yes | Yes | Yes |
| **10.** | Yes | Yes | Yes | Yes | Yes | Yes | Yes |

**Graph 1 of bias risk**: note the authors' judgments about each item of bias risk in all included studies with rats.

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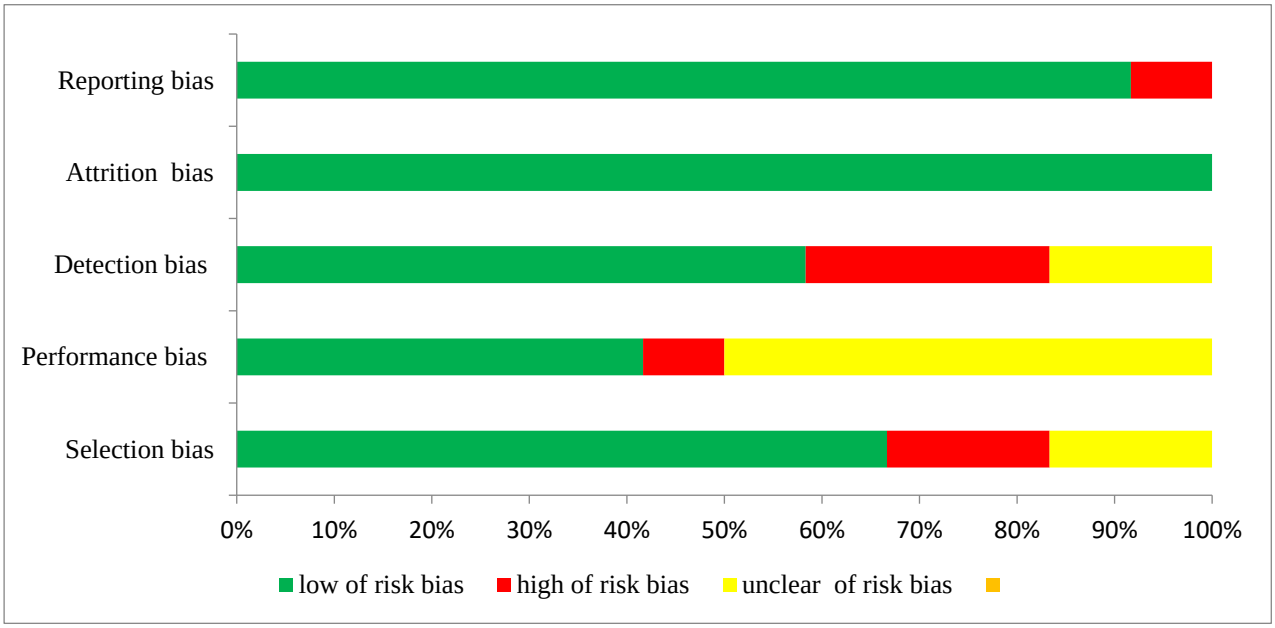
In the selection bias, study 5 didn't describe if the intervention and control groups were or weren't similar at the beginning of the experiment. Study 1, 2, and 7 didn't present enough details to set if the

intervention allocations could have been predicted before or during the subscription. In the bias of performance, all the studies presented uncertainties about the researchers blinding of knowing which intervention itch animal received. In the bias of study detection, 1 and 3 presented uncertainties, and 4, 5, and 6 didn't describe if the animals were or weren't randomly selected for results evaluation and which methods and measures were used to select the animal, for blinding the results evaluations of knowing which intervention itch animal received. In the bias of attrition, all of them described the results data integrity for the main itch result. In the bias of the report, all the studies presented selective results report and how it was examined, and what was found.

**Table 1.1 Summary of bias risk'**: Note the authors' judgments about each item of bias risk for each included study. Risk assessment of bias in studies with mice.

| | **Study1** | **Study2** | **Study3** | **Study4** | **Study5** | **Study6** |
|---|---|---|---|---|---|---|
| | **Wataru et al.,(2010)** | **Kristem et al.,(2008)** | **Kelly et al., (2017)** | **Aoi et al.,(2013)** | **Colbert et al., (2000)** | **Frajacomo et al.,(2015)** |
| **1.** | Unclear | Yes | Yes | Unclear | Yes | Yes |
| **2.** | Yes | Yes | Yes | Not | Not | Not |
| **3.** | Yes | Yes | Unclear | Yes | Yes | Yes |
| **4.** | Yes | Yes | Yes | Unclear | Yes | Yes |
| **5.** | Unclear | Unclear | Not | Unclear | Unclear | Unclear |
| **6.** | Yes | Yes | Yes | Yes | Yes | Yes |
| **7.** | Unclear | Not | Not | Unclear | Not | Yes |
| **8.** | Yes | Yes | Yes | Yes | yes | Yes |
| **9.** | Yes | Yes | Yes | Yes | Yes | Yes |
| **10.** | Yes | Yes | Yes | Not | Yes | Yes |

**Graph 1 of bias risk**: note the authors' judgments about each item of bias risk in all included studies with mice.




In the selection bias, the study 1 and 3 didn't describe how and if the groups of intervention and control were or weren't similar at the beginning of the experiment, studies 4, 5, and 6 didn't describe the criteria used to compare and judge if the intervention and control groups were or not similar at the beginning of the experiment. In the performance bias, all the studies didn't describe with clarity the measures used to blind caretakers and researchers to know which interventions itch animal received, and if the animals were or not randomly selected for results evaluation and which methods were used to select the animals if there is any. In the detection bias, studies 2, 3, 4, and 5 didn't present all the measures used to blind results evaluators of knowing which intervention itch animal received. In the attrite bias, all of the studies described the integrity of the results data for itch main result, attrite and exclusion of analyses included. In the reporting bias, all of the studies presented selective results of what was examined and found.

**Table 2**: Characteristics and results of studies included in rats in this review.

| Author, year | Objective | Subject | Intervention group | Control group | Kind of induction | Results |
|---|---|---|---|---|---|---|
| Lunz, Peluzi, Dias, Moreira, Natali, (2008). | To check the effects of aerobic training regime of long term swimming of different intensities in the colon carcinogenic process | Male Wistar rats . | 3 swimming groups in different intensities During 35 weeks by 20 min/day, 5 days/week. G1=0% of the body weight (n=12) G2=2% of the bodyweight (n=12) G3= 4% of the body weight | Sedentary control group ( N = 10) | In the second week of experiment, all the rats received 4 subcutaneous injections of 40mg/Kg of weight body of 1,2-dimethyl-hydrazine (sigma, EUA), two injections in the first week and two in the 2nd week, in nonconsecutive days | The swimming training didn't affected the tumor multiplicity (GC: 2,30 ± 0,58; GE1: 2,09 ± 0,44; GE2: 1,27 ± 0,19; GE3: 1,50 ± 0,48) or size (GC: 1,78 ± 0,24; GE1: 1,81 ± 0,14; GE2 : 1,55 ± 0,21; EG3: 2,17 ± 0,22 cm) The number of small ACF (ACF ≤3) in the EG2 also was significantly reduced compared to GC (61,00 ± 5,98 *vs.* 85,00 ± 4,73 crypts, respectively) |
| Demarzo , Garcia (2004) | To check the influence of the exhaustive exercise in colon carcinogenesis in rats not trained. | Ratos Wistar males 30 days after the birth | Swimming exercise group until the exhaustion with weight a equivalent to 2% of it (n=8) | Control (n=8) was mantained in a small chamber with 3cm of water | Only injection of 1,2-dimethyl-hydrazine (50 mg/Kg of body weight) | The number of focus in the exercise group was 10,85 ± 3,20 by microscopic field and 3,72 ± 0,70 in the control group. The LAC number increasing in the exercise group was statistically significant (P<0,01). Most of the ACF appeared in the middle and distal colon in both groups. |
| Kaori et al. (2017). | To investigate the mechanism that can explain the high-intensity physical exercise efficiency in the reduction of colon cancer, with a focus on the acid and cysteine-rich secreted protein (SPARC) | 344 Fischer male rats 4 weeks old | Training in high-intensity swimming, 12 sections of the 20s, with 16% of its body weight, a pause of 10s, between the exercise sections for five days/week during four weeks. (n=8). Swimming training of low intensity 2. | Sedentary control group (*n*=8) | Subcutaneous injection of 1,2-dimethyl-hydrazine 20mg/Kg of body weight 1 a week, for 2 weeks. | The ACF numbers were less significant in the high-intensity group compared with the control group (P<0,05). The number of LAC seem in the high intensity (14 ± 10) were significantly low compared to control groups (23 ± 14) (P<0,05). The SPARC protein levels of the high-intensity trained rats were significantly higher than the seen in the other control groups. (P<0,05) |

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|---|---|---|---|---|---|---|
| Demarzo et al., (2008). | To confirm the existence of the early inhibitory effect efficiency of the exercise against the colon carcinogenesis, studying the proliferation of the epithelial cells and check the exercise influence in the COX-2 expression. | Male Wistar rats, 30 days after the birth | Group 2 (n=8), eight weeks of swimming training, 5 days/week. Group 4 (n=8), 8 weeks. Swimming training, 5 days/week + DMH injection, first week they swam for 15 min. daily. The second week, 50 min., then 10 min. until the 6th week 90min. | Sedentary group 1 (n=8). Sedentary group 3 + DMH injections (n=8) | dimethyl-hydrazine DMH (50mg.Kg – body weight) | The physical training attenuates the increase related to DMG in the epithelial cells proliferation and in the COX-2 expression in the rat's colon mucosa. However, this increase was significantly attenuated in the training group G4 (P<0,01). Similar results were seen related to COX-2 expression. |
| Bandaru, Reddy, Sugie, Lowenfels,(1988) | To investigate the volunteer exercise effect in the colon carcinogenesis induced by OMA in male rats F344 | F344 male rats | Volunteer wheel exercise, free access + OMS (n=27) Volunteer wheel exercise (n=12) | Sedentary + OMS (*n*=27) sedentary (n=12) | OMA for 2 weeks with a doses level of 15mg/Kg. | The incidence and multiplicity of colon adenocarcinoma were significantly inhibited P < 0,05 in the exercise group when compared to the sedentary, but the incidence and multiplicity of colon adenomas weren't affected by the exercise. |
| Fuku, Ochiai, Terada, Fujimoto, Nakagama, Tabata, (2007) | We examined the running machine training effects in the induction of the aberrant crypts focus (ACF) | F344 rats, 4weeksold | Running training in the running machine (N=19) for 120 min. d- (two sections of 60 min separated by 10 min of rest, 5 days a week, for 4 weeks. | Sedentary control (*N*=19) | Subcutaneous injection of 1,2-dimethyl-hydrazine DMH, 20mg/Kg of body weight, once a week, during 2 weeks. | The number of rats ACF of the training group was significantly less than seen in the control group (P < 0,05). The total CA number was also considerably less in the training group than the control group (P < 0,05). However, the proportion of AC/total ACF, which indicates the medium size of induced ACF, didn't differ significantly between training and control groups (2,9 ± 0,2 vs. 2,9 ± 0,7, P> 0,10). |

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|---|---|---|---|---|---|---|
| Thorling, Jacobsen, Overvad, (1993). | To evaluate the exercise effect the intestine tumor development in Fischer male rats after the exposition to the azoxymethane | Fischer male rats | Exercised in the running machine, 2km a day in useful days, 38 weeks after the induction by azoxymethane | Sedentary control (n=16) | 3 subcutaneous injections of azoxymethane, 15mg/kg of body weight. | After 38 weeks, significantly fewer rats in the exercise group developed neoplasm in the colon mucosa. |

**Table 2.1**: characteristics and results of studies included in mice in this review.

| Author, year | Objective | Subject | Intervention group | Control group | Kind of induction | Results |
|---|---|---|---|---|---|---|
| Wataru et al., (2010) | To investigate the exercise effect in colon tumorigeneses associated with iNOS and COX-2 | Balb mice (8weeks old) | OMA group with running exercise (n=2-) in the running machine regular 3 weeks, during 6 weeks Speed of 15m/min until 30min to 20m/min (n=20) | Sendentary group (n=20) | Dose of 12,5mg/Kg of body weight, once a week, during 2 weeks. | Compared to the sedentary group, the exercise group presented a significant reduction in the ACF and AC number p<0,05. The injection of OMA sharply increased the expression of mRNA of iNOS in the colon, while the regular exercise suppressed this elevation. |
| Baltgalvi , Berger, Peña, Davis & Carson, (2008) | To determine if the exercise changes the polyps signaling related to inflammation and growing. | Mice $Apc^{Min/+}$ males 3,5 weeks. | Exercise (*n*= 20) run in the running machine 18 m/min; 60 min/dia; 6 days/week; 5% of degree), totalizing 9 weeks. | Sedentary control (*n*= 20) | Mice with a mutation without 850 codon sense in the gene *Apc* (*Adenomatous polyposis coli*) predispose the small and big intestine adenomas. | Nine weeks of running machine training produced a decrease of 35% in positive cells for macrophages, F4/80 in the polyps;(*P*= 0,010).The protein COX-2 total didn't change with physical training (*P*= 0,835). The exercise didn't have an effect in the accumulated by β-catenin in polyps with a low number of focus (*P*= 0,275) or in a bug number of focus (*P*= 0,420; |
| Kelly et al., (2017) | To examine the genetic background effects (tension), volunteer exercise (wheel run), and its number interaction in the intestine tumor's number and size. | Mice linage (C57BL6 A/J, C57BL6/J, C58/J, KK/HIJ, I/LNJ) With approximately 8 weeks old | G1= (n=15) female, itch one on the six lineages G2= (n=12) males A/J and (n=12) females, 5 weeks of access to a running wheel before induction, 5 weeks of access to the wheel after | Sedentary (n=x) | 2injectionsof OMA | Between exercise, conditions indicated that the access to a running wheel or whatever moment had a significant reduction statistic in the tumor numbers in relation to any exercise (P<0,03). The regression analyses revealed the distance wheel of functioning ta a significantly proportion of variance in tumor number ($R$ = -0,646,$R^2$ = 0,418,$P$ = 0,044). |

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|---|---|---|---|---|---|---|
| | | | induction. | | | |
| Aoi et al., (2013) | To identify new myosin to contribute to the prevention of colon. | Null SPARC mice (B6; 129S-Sparc $^{tm\ 1Hwe}$ / J) and savage mice. | Group 1= 6 weeks of regular exercise, Group 2 = only exercise section. | Sedentary mice. | Azoxymethane (AOM)15 μg/kg | ACF and AC were made in null SPARC mice treated with AOM of the savage mice. The exercise didn't have an inhibiting effect. More ACF and were made in null SPARC mice treated with AOM than in savage mice, and the exercise didn't have an inhibiting effect. |
| Colbert, Davis, Essig, Ghaffar, Maye, (2000). | To examine the effect of physical training in the development of the polyp in a mutant mice strain induced predispose to multiples intestine neoplasm. | Male heterozygous mice C57BL/6 J-Min/n+ and female C57BL/6 of 3 weeks old. | Running (11 males +11 females *N*= 22) exercise in the running machine 60 min in the growing speed of 18 to 21 m min, for 7 weeks. | Sedentary (10 males, 6 females n=16) | Induced with etil-nitrosureia mice, and predispose to multiples intestine neoplasm. | Combined analyses between female and male didn't revealed exercise effect over small intestine polyps effects(P= 0,50), colon (P= 0,17) or total intestine (P= 0,44). There wasn't a difference between sedentary and exercised in the female to any intestine location(P> 0,05). There was a tendency to less polyps in excited male mice in the colon(P= 0,06), small intestine (P= 0,08) and total intestine (P= 0,06). |
| Frajacomo et al., (2015) | To demonstrate that physical exercise is a protector against colon carcinogenesis. | BALB male mice with interleukin 10 (IL-10) | Aerobic group (n, MNNG=8) Aerobic group (not exposed, n=8) 5 days swimming without during 56 days, 20 min. (first week.) to 60 min (3rd week) resistance group (*n*= 8) 80 stair inclination; 1 cm space between the steps and high of 50cm) 7 climbing for 2min to recovering. | Exposed sedentary MNNG (S,*n*= 6) Not exposed sedentary (n=6). | *N*-metil-*N*'-nitro-*N*-nitrosoguanidina (MNNG).5 mg $mL^{-1}$;intrarectal deposit of 100 μL; twice by week, during 2 week. | The training with aerobic exercise was related to a significant increase in IL-10 levels between carcinogen agents exposed mice (p<0,001). The aerobic training reduced the colon dysplastic lesions in 36% of the sedentary group exposed to carcinogens agents (P<0,05). This protector effect wasn't seen between trained mice in IL-10 resistance exposed to carcinogens agents development 20% more of dysplastic lesions that its antecedents of (C57/BL6 (1,68 ± 0,91) vs IL-$10^{-/-}$ (8,69 ± 8,3 total displasm for m2 )) (*P*= 0,01,); |

## 4. DISCUSSION

The results presented that light and moderate-intensity physical exercise were capable of reducing tumor development but didn't prevent its emergence, presenting that the exercise can be an allay in colorectal cancer treatment. Found results indicated that the physical exercise generated a direct response in growing circulants factor, cytokines and angiogenic factors, hormones and several other kinds of cells which have the potential of tumor development, immune cells included, presenting possible responses of physical exercise over the tumor development.

A study of Lunz, Peluzi, Dias, Moreira, and Natali (2008) presents that different intensity of swimming exercise didn't reduce the colorectal cancer development compared to the control group; only the 2% intensity reduced the cancer development, but not against DMH induced tumors, these results sagest that the intensity of the exercise makes a central in this process, even below the anaerobic threshold.

Bandaru, Reddy, Sugie, and Lowenfels (1988) also presented in their study the volunteer wheel exercised animals when compared to the sedentary animals, the colon adenocarcinoma, induced by OMA, incidence, and multiplicity were significantly inhibited, but the colon adenoma incidence and multiplicity weren't affected b the exercise.

The exercise promotes the physiologic adaptation in the homeostatic control circuit; with it, such adaptations stimulate the systemic surroundings reprogramming, potentially characterized by availability, mobilization, recruitment, retention, and function of kinds and/or specific cell of molecule alterations. The exercise activates a diversified network of transcription factors, kinases, and coregulator proteins that culminate in genic expression alterations that raise the mitochondrial biogenesis and stimulate the skeletal muscle metabolic reprogramming (Koelwyn, Quail, Zhang, White& Jones,2017); (Brown, Winters-Stone, Lee& Schmitz,2012). Regular exercise reduces the levels of glucose and insulin, elevates the levels of corticosteroids hormones and of anti-inflammatory cytokines, and raises the receiver's expressions of insulin in the cells that fight cancer. (Spinola, Souza Manzzo& DaRocha, 2012).

Fuku, Ochiai, Terada, Fujimoto, Nakagama, Tabata, (2007). The low intensity running training inhibits the development initiation of ACF aberrant crypts focus of the DMH colon induced.

ACF aberrant crypts are the first identifiable neoplasia lesions in the carcinogenic colon model. The ACF progression to polyp and, posteriorly, to cancer is parallel to the accumulation of several biochemistry alterations and mutations, in which a small fraction of ACF evolves to colon cancer (Alrawi et al.,2006); (Gupta Pretlow & Schoen, 2006).

The exercise can change the events to the tumor initiation modifying the carcinogen activation, specifically improving the cytochrome P450 system and the selective enzymes by way of carcinogen detoxification, including, among others, transferase-S-glutathione. Besides, the exercise can reduce oxidative damage, increasing the level of an antioxidant enzyme variety, improving the DNA and intracellular proteins repair systems (Silva, Sivieri & Rossi, 2009).

Thorling, Jacobsen, and Overvad (1993) study, after 38 weeks, significantly fewer rats of the exercise group develop colon mucous neoplasia. The precocious beginning of the physical exercise execution decreases the inflammation; it protects against several kinds of cancer and increases the life expectancy of natural-age mice (Nilsson et al., 2019).

Demarzo e Garcia (2004) presented that only an exhaustive exercise section was associated with an increased number of aberrant colonic crypts in rats not trained treated with DMH when compared with the control group animals. The resisted and aerobic exercise can activate different metabolic ways due to the different intensities and mechanical loads imposed on the muscle. In fact, aerobic exercise results in different metabolic responses, resulting in an increase of mitochondrial mass, oxygen contribution, glycose capitation, and antioxidant capacity (Galle, Martella & Bresciani, 2018). Exhaustive swimming exercises originate from tissue damage, regardless of the trained condition, according documented by similar levels of muscle lipid peroxidation and mitochondria integrity loss, and reactive species found in trained and not trained exhausted rats (Ferraresso,2010).

The oxidative stress reflects an unbalance between the species production that is reactive to oxygen and adequate antioxidant defense. This adverse condition can take it to cellular and tissue damage in the components, and it is involved in different physiopathology conditions, including aging, exercise, inflammatory, cardiovascular and neurodegenerative disease, and cancer (Pingitore et al., 2015).

High oxidative stress and the function of immune depression can make de colon carcinogenesis easier. Besides the regular physical exercise have many health benefits well establish. The exercise effect over immune functions, like macrophages and lymphocytes, suggests that middle-intensity exercise get better the immune function, while exhaustive exercise promotes immune suppression (Niemane&Wentz, 2019); (Carini et al.,2017).

Kaori et al. (2017) study. It presented that the intermittent swimming of high intensity reduced the number of ACF induced bay DMH in the rat's colon, suggesting the high-intensity training can be a preventive effect in colon cancer. The results also suggest that the secreted protein, acidic and full of cysteine (SPARC), a myosin whose expression is regulated by intensity related sings of 5'-monophosphate-adenosine kinase activating protein (AMPK), can interfere in the effect of the high-intensity physical training in the prevention of colon cancer.

The SPARC, also nominated osteonectin or basement membrane-40, is a matrix-associated protein that provokes alterations in the cellular form; it inhibits the cellular cycle progression and affects extracellular matrix syntheses (Brekken, 2000). In some tissues, it seems to have tumor suppressor properties by check inhibition of some kinds of cancer growing. In the skeletal muscles, the SPARC in the colon cancer with chemotherapy reduced sensibility, and it presented that the resistant reversion to therapy could be achieved through the positive regulation of SPARC expression or of the exogenous exposure in higher levels of SPARC. (Cheetham et al., 2008); (Wang et al., 2014).

AMPK is a protein complex/Ser kinase protein/Thr highly preserved, which is another potential candidate to regulate autophagy through the maintenance of energetic homeostasis. The molecular mechanism of AMPK regulates the autophagy is usually assumed by the inhibition of the mTOR, which actuates in the initial step of autophagy, that regulates it negatively. Recent discoveries presented that the AMPK activation is critical to the biosynthetic activity maintenance of the cancer cells (Liu et al., 2019); (Hart et al., 2015).

Demarzo et al. (2008), in this exercise results, reduced the colonic expression of the cycle-oxygenase-2 (COX-2). It is known that colonic carcinogenesis is associated with the COX-2

expression increasing that takes to excessive production of prostaglandin E2. The physical training exerts notable anti-proliferative and anti-inflammatory effects in the rats' colonic mucosa, suggesting that this can be an important mechanism to explain how the exercise protects de colon cancer (Lunz, Moreira & Viana, 2006).

About 85% of the colon and rectum present elevated levels of COX-2. Literature reports suggest that the polymorphism in an only nucleotide (SNP) in the gene COX-2 could be capable of modifying the enzyme function and, this way, amplify the risk of an individual to develop colon cancer (Cossiolo, Costa, Fernandes, Laranjeira, Fernandes & Poli-Frederico, 2017).

The exercise significantly inhibits the COX-2 activity, taking to pro-inflammatory cytokines suppression and redox status alterations. The found result presented that the exercise prevented morphologic alterations triggered by high fat, reducing the COX-2 expression in the proximal and distal intestine (Campbell et al., 2016); (Eberhart, Coffey, Radhika, Giardiello, Ferrenbach, Dubois, 1994); (Lee, Yang, Huang, Huang, Kao & Chen,2015).

Chronic inflammation is connected to de development of several cancers. The intestine inflammation induces carcinogenic mutagenesis and promotes colorectal cancer beginning (Chen, Pitmon & Wang, 2017). The inflammatory environment has many similarities with the tumor microenvironment, suggesting the implication that the same mediators in the chronic intestine inflammation and in colorectal carcinogenesis. Many inflammatory mediators were found positively associated with colorectal adenomas prevalence (Lucas, Barnich & Nguyen, 2017).

The result of Wataru et al. (2010) regular exercise suppressed the genesis of aberrant crypts focus in the colon by azoxymethane. The azoxymethane injection raised the expression of nitric oxide syntheses (iNOS) in the colon, while the regular exercise suppressed this raising. The COX-2 wasn't changed by the OMA or by the exercise. The tumor necrosis factor alfa (TNFa) was reduced by the exercise in the colon and in the plasma.

INOS is an enzyme predominantly expressed during inflammatory reactions. However, the syntheses of large quantities of nitric oxide (NO) by the INOS have been demonstrated in the physiopathology process, as acute or chronic inflammation and tumorigenesis. The INOS gene expression enhanced to production is probably the mechanism that contributes to the increasing of the exercise-induced cytolysis (Gochman et al., 2012); (Bellafiore, Battaglia, Bianco & Palma, 2019).

According, the exercise increases the mRNA expression of the alpha X receptor transporter and of the ATP ligation cassette, and it reduced to inducible synthase nitric oxide (iNOS), the cyclooxygenase-2 (COX-2), the tumor necrosis factor alfa (TNFa). The protein iNOS is modulated by a moderate-intensity exercise (De Castro et al., 2019).

In the study by Kristen et al. (2008) the physical exercise reduced the macrophage number in the polyps by 35%. In relation to the apoptosis, the exercise reduced by 73% of the positive cells number to terminal marking (TUNEL). The exercise reduced the macrophage number in the polyps by 35%. The original hypothesis proposed that the macrophages were involved in the anti-tumor immunity; there is clinical and experimental substantial evidence that, in most of the cases, these macrophages associated with tumor (TAM) increase the tumor progression to malignity. The tumor-promoting functions of macrophages in the primary local include the support to angiogenesis associated with the tumor, invasion of promotion,

migration, and tumor cells intravasation, as the suppression of the anti-tumor immune response. (Rosa, Bicudo & Vaisber, 2012). The macrophages also potentiate sowing and the establishment of the metastatic cell and play a role in the tumor initiation when the inflammation is a causal factor (Qian & Pollard, 2010). The Kelly et al. (2017) volunteer exercise before or during the OMA treatment resulted in a significant reduction in the tumor numbers, but in exercise before the OMA explosion, it had no effect.

Exercise used studies as an intervention in animals as tumors presented potential changes in the tumor physiology. It was demonstrated that the exercise reduces the incidence and multiplicity and the growth of the different kinds of xenograft, chemically induced, or genetically induced, emerging mechanistic effects of exercise, including bloody vascularization and perfusion, immune function, tumor metabolism, and cross conversation between muscle and cancer (Pedersen, Christensen & Hojman 2015).; (Ruiz-Casado et al., 2017).

Aoi et al., (2013) in mice, an only exercise section increased the SPARC expression and secretion in the skeletal muscle in rats and humans. Besides that, in an azoxymethane mouse model with induced colon cancer, regular low-intensity exercise significantly reduced the crypts aberrant focus formation in savage mice, but not in SPARC-null mice. Besides that, the regular exercise improved the apoptosis in mucosa colon cells, and it increased the cleaved forms of caspase-3 and caspase-8 in savage mice, but not in SPARC-null mice.

The caspase-3 promotes the tumor growing, providing a pro-angiogenic microenvironment. Besides that, the dying cancer cells promote the restocking of tumor cells after chemotherapy. In human patients with colon cancer with low levels of activated caspase-3 had a long time of disease-free survival.

Studies presented that the caspase 3, 8, and 9 levels expression are useful prognoses factor in cancer-related to the digestive system, especially in colorectal cancer (Liu Saber & Haisma, 2019) ( Asadi et al., 2018).

Colbert, Davis, Essig, Ghaffar, Maye (2000). There were no significant effects in the exercise in males and females combined in the small intestine, colon, or total intestine polyps. When separately analyzed, however, there were total polyps in the excited male group than in the control males, although the difference hasn't been statistically meaningful. The aerobic training reduced the number of colon dysplasia lesions by 36% compared to the sedentary group exposed to cancer agents. This protector effect wasn't seen in resistance trained mice.

The exercise induces adaptations in multiples cell processes in the skeletal muscle, including metabolism, angiogenesis, and immune regulation. The depletion of the ATP and NADH levels elevate the AMP: ATP and NAD+: reasons NADH, activation several metabolic sensors, including the NAD (SIRT1) dependent sirtuin deacetylase one protein and kinases as the activate kinase protein by AMP (AMPK), ERK1/2, p38 MAPK, and kinase N-terminal (JNK) (Abreu, Leal–Cardoso & Ceccatto, 2017). These metabolic sensors activate the alpha receptor co-factor activated by one alpha peroxisome proliferator (PGC1alpha), that regulates the mitochondrial protein expression coded in nuclear and mitochondrial genomes by the interaction with several factors in the transcription, as the activated receptor by peroxisome proliferator (PPARgama), receptor alpha-related to estrogen (ERRalpha), ERRgama, nuclear respiratory

factor 1 (NRF1) and NRF2. The NRF1 also increases the mitochondrial transcription factor to tumor metabolism. (Koelwyn et al., 2017); (Yu et al., 2013).

## 5. CONCLUSION

Based on the experimental studies in found animal models, suggest that the resisted and aerobic and resistance exercise training can reduce several risk factor, as, reducing the systemic pro-inflammatory condition, induced by the tumor, reducing oxidative muscle stress and muscle damage, improving the anti-inflammatory system through the regulation of cytokine network, strengthening the defenses of the immune system and helping to keep the suitable body weight, reducing the cyclooxygenase3 expression, related to the colon inflammation. With this, it presents the practical importance of physical exercise to colorectal cancer prevention and treatment. The suggested exercise and physical activity demonstrate the need for hypothesis refinement that only will be achieved with well-directed and controlled experimental studies. Once that the colorectal cancer protection by the exercise and physical activity is considered convincing by the found evidence. It becomes fundamental that the new studies involving exercise and CC seek to explore the biologic mechanism of protection, so, this way, can be possible to understand the mechanism deeply of the exercise in colorectal cancer, and to do the prescription and practice of physical exercise that is directed specifically to colorectal cancer prevention and treatment.

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