

# Physical Activity and Colorrectal Cancer: Case-Control Study in the City of Pelotas

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*Atividade Física e Câncer Colorretal: Estudo de Caso-Control no Município de Pelotas*

*Actividad Física y Cáncer de Colorretal: Estudio de Caso-Control en la Ciudad de Pelotas*

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## ABSTRACT

**Introduction:** Neoplasms are one of the main prevalent health problems. Colorectal cancer (CRC) has a high incidence in Brazil, the treatment of the disease consists in helping the immune system to fight the malignant cells, and the practice of exercises can help its prevention. Studies addressing the risk factors for CRC found consistent data about inadequate diet, physical inactivity, obesity, alcohol, and tobacco use, but it was not possible to find data on the history of physical activity (PA) of patients diagnosed with CRC in Brazil.

**Objective:** The aim of this study was to evaluate whether physical activity (PA) during the lifespan can influence the likelihood of developing the disease. **Method:** A case-control study was carried out. Cases were obtained from oncologic health centers in Pelotas, Brazil. Two controls were found for each case in the same health center. Both groups were age-matched ( $\pm 5$  years), 82 cases and 165 controls participated in the study. **Results:** Based in the raw and adjusted analyzes for the confounding factors, PA in its four domains and total PA performed throughout life were not associated with the outcome. **Conclusion:** The results analyzed in this study were, mostly, contrary to those found in the literature, with possible explanations being the profile of PA of the population studied, the characteristics of occupational physical activity and the sample size.

**Key words:** Colorectal Neoplasms; Exercise; Risk Factors; Case-Control Studies.

## RESUMO

**Introdução:** Neoplasias são um dos principais problemas de saúde prevalentes. O câncer colorretal (CCR) apresenta alta incidência no Brasil, o tratamento da doença consiste em auxiliar o sistema imunológico a combater as células malignas, e a prática de exercícios pode auxiliar em sua prevenção. Na busca de fatores de risco para CCR, pesquisas obtiveram dados consistentes quanto a: alimentação inadequada, inatividade física, obesidade, consumo de álcool e tabaco, mas ainda não foi possível encontrar dados sobre o histórico de atividade física (AF) dos pacientes diagnosticados com CCR. **Objetivo:** Avaliar se a prática de AF durante toda a vida pode influenciar no desenvolvimento da doença. **Método:** Estudo caso-control. Os casos foram obtidos nos centros oncológicos de Pelotas, Brasil. Dois controles de cada caso foram detectados no mesmo centro de saúde. Ambos os grupos foram pareados por idade ( $\pm 5$  anos). Ao todo, participaram do estudo 82 casos e 165 controles. **Resultados:** A partir das análises brutas e ajustadas para os fatores de confusão, a AF em seus quatro domínios e a AF total, realizadas durante toda a vida, não estiveram associadas ao desfecho. **Conclusão:** Os resultados analisados neste estudo foram contrários, em sua maior parte, ao encontrado na literatura; as possíveis explicações foram o perfil de AF na população estudada, as características da AF ocupacional e o tamanho amostral.

**Palavras-chave:** Neoplasias Colorretais; Exercício Físico; Fatores de Risco; Estudos de Casos e Controles.

## RESUMEN

**Introducción:** Neoplasias son uno de los principales problemas de salud prevalentes. Cáncer colorrectal (CCR) tiene una alta incidencia en Brasil, el tratamiento consiste en ayudar al sistema inmunológico en la defensa de las células malignas y la práctica de ejercicios puede ayudar en su prevención. Búsqueda de factores de riesgo para CCR, investigación ha obtenido datos consistentes sobre dieta inadecuada, inactividad física, obesidad, consumo de alcohol y tabaco, pero aún no ha sido posible encontrar datos brasileños sobre la historia de actividad física (AF) de los pacientes diagnosticado con CCR. **Objetivo:** El estudio tuvo como objetivo evaluar si la práctica de AF a lo largo de la vida puede influir en la probabilidad de desarrollar la enfermedad. **Método:** Realizó un estudio de casos y controles. Los casos fueron reclutados en centros de oncología en Pelotas, Brasil. Cada caso tuvo dos controles, que se encuentran en el mismo centro de salud. Ambos grupos fueron emparejados por edad ( $\pm 5$  años), 82 casos y 165 controles participaron en el estudio. **Resultados:** Análisis crudos y ajustados para los factores de confusión, AF en sus cuatro dominios y AF total realizada durante toda la vida no se asociaron con el resultado. **Conclusión:** Resultados analizados en este estudio fueron contrarios, en su mayor parte, a los encontrados en la literatura, siendo posibles explicaciones el perfil de actividad física en la población estudiada, las características de la AF ocupacional y el tamaño de la muestra.

**Palabras clave:** Neoplasias Colorrectales; Ejercicio Físico; Factores de Riesgo; Estudios de Casos y Controles.

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## INTRODUCTION

In Brazil, the progressive process of industrialization and globalization changed the paradigms of mortality. In the beginning of the twentieth century, the infectious contagious diseases appeared as the leading public health problems responsible for elevated rates of childhood mortality and low perspective of life of the population<sup>1</sup>. Nowadays, cancer is the main public health problem worldwide because of ageing, population growth, change of the distribution and prevalence of cancer risk factors, specially associated with socioeconomic development. There was a drop of cancer-associated infections and growth of cancers associated with the improvement of socioeconomic conditions with urbanization-related habits and behaviors (sedentarism, incorrect feeding among others)<sup>2</sup>.

Among the main incident neoplasms, colorectal cancer (CRC) is the development of malignant tumors in the colon and/or rectum. Its symptoms are little perceptible and when they appear, it is at an advanced stage. Epidemiological data show its high incidence in Brazil where, according to the population-base information in 2015, there were 151/100 thousand inhabitants new cases. Per GLOBOCAN 2008, the world incidence reveals that colorectal cancers are ranked third with 1.2 million new cases and 680 thousand deaths<sup>3</sup>. The 2020 estimates of CRC in the State of Rio Grande do Sul indicate high raw rates of incidence (1,300/100 thousand inhabitants in males and 1,240/100 thousand inhabitants in females), it is the fourth most frequent type of cancer in this region for both sexes<sup>2</sup>.

However, there are still difficulties in finding solutions to prevent neoplasms with frequent deaths for that cause in many countries. The treatment consists in helping the immune system in defending against malignant cells and physical activity can support this process<sup>4</sup>. The literature affirms that CRC is a multifactorial disease influenced by genetic, environmental factors associated with lifestyle<sup>5,6</sup>.

Regular physical activity (PA) can prevent and help to control heart diseases, type 2 diabetes, and cancer (bladder, breast, colon, endometrium, adenocarcinoma, esophageal and kidneys) that cause nearly three quarters of deaths worldwide<sup>7</sup>.

According to world recommendations, adults should do at least 150 to 300 minutes of moderate-intensity aerobic activity weekly or at least 75 to 150 minutes of vigorous-intensity aerobic activity<sup>7</sup>, figures far from the reality of most Brazilian capitals<sup>8</sup>. In developed countries, the high incidence of CRC is associated with the lifestyle and factors as hypercaloric and rich in red meat diet.

However, the body weight within regular standards (body mass index – BMI 20-25), PA and healthy diet can diminish the risk of CRC in 60% to 80%.

Several studies showed a relation between PA and development of CRC<sup>10-17</sup>. But in developing countries, this subject was poorly addressed, and the lifestyle of this population is dissimilar in many aspects. Considering the potential impacts of the disease and its epidemiological data, it is essential that health professionals are guided on potential variables that can help to prevent it. The objective of this study was to investigate the association of PA practice during the lifetime and incidence of CRC in Brazil's South.

## METHOD

A case-control design study. The cases were patients of either sex, older than 18 years of age diagnosed with CRC and controls, individuals treated in the same health service and their companions but affected by other infirmities. The design allowed a retrospective approach of the sample about the variables analyzed. The main variable of exposure investigated was PA practiced during the lifetime in the domains: leisure, occupational, household, and commuting. The study proposed the analysis of the association of PA practice and occurrence of CRC. The data of the cases were obtained in public and private oncologic health services in the city of Pelotas. The interviews were conducted after selection of the cases from charts provided by the institutions. The questionnaires were applied during the chemotherapy session or hospital admission and from them, two controls of the same health service of the cases were chosen paired by sex and age ( $\pm 5$  years). Only individuals affected by primary incident and prevalent CRC were included in the sample. Individuals with secondary cancer were excluded.

The cases and controls responded to the questionnaire with questions about sociodemographic characteristics, sex, age and skin color, anthropometric variables (height and weight), marital status, education, behavioral aspects (diet, tobacco and alcohol use and PA) and family history of cancer. The variable "physical activity for the lifetime" was evaluated through the questionnaire proposed by Friedenreich et al.<sup>18</sup> (Division of Epidemiology, Prevention and Screening, Alberta Cancer Board, Canada) called "*The lifetime total physical activity questionnaire*" which encompassed the four domains of PA addressing household, occupational, leisure and commuting activities during the lifetime. In addition, frequency (times per week), duration (time) and intensity (multiple equivalent metabolic – MET) of each activity with a score of activity for the lifetime were measured.

The instrument provided the quantification of PA as MET, one MET is equal to the number of calories a body intakes while at rest<sup>19</sup>. MET are boosted as the activity intensity grows. The score of PA includes the number of months/years the individual did this activity accounting the regular values of weekly frequency, duration, and type of activity, being possible to associate to MET expenditure.

The variables about the main risk factors for CRC – sociodemographic characteristics, diet, obesity, PA and sedentary behavior, alcohol, and tobacco – were chosen from a literature review. Data on preventive tests, as colonoscopy were not collected because the history of the sample was investigated.

The sociodemographic characteristics were reviewed, the socioeconomic level determined by the assets index of the participants (analysis of the main components of an inventory of domestic utensils) and skin color defined by the investigator after observation. Data about education, anthropometric variables (height and weight), marital status, behavioral characteristics, cancer family history, sex, and age were collected. The behavioral and anthropometric variables were drawn through the questionnaire and self-report of weight and height and for the cases, the mean of weight before and after the disease. The diet was elaborated by the analysis of the intake, of the monthly frequency and during the lifetime: beef, poultry, pork, fish, fried food, legumes, vegetables, fruits, sweets, canned fruit juices and soda.

Data were collected from October 2018 to May 2019, amounting to 82 cases and 165 controls obtained from health services. Data were keyed in Excel spreadsheet (Microsoft Excel® 2010) and the statistical analysis, with Stata 15.0 for Windows (Stata Corporation). PA and MET scores were created and bivariate analysis by logistic regression followed by multivariable analysis by conditional logistic regression (paired by sex and age) to control possible confounding factors.

The variables were tested one by one to measure their association with the outcome. Variables with value of  $p$  lower than 0.20 migrated to the regression model and excluded when  $p$  was higher than 0.20 post-adjustment. After the formation of the model of final regression, the variables of PA were tested one by one (regardless of its value in the raw analysis) to measure the association of the domains of PA adjusted for potential confounding factors.

The sample size obtained associated with the characteristics of the participants' PA ensured a statistical power below 50%, calculated after the analyzes.

The Institutional Review Board of the “*Escola Superior de Educação Física da Universidade Federal de Pelotas*” (CAEE 94588318.6.0000.5313) approved the study.

The interviewees were asked to consent verbally to have their information collected followed by the signature of the Informed Consent Form confirming their voluntary decision to join the study and any participant could withdraw whenever they wanted.

## RESULTS

Personal, sociodemographic, behavioral, and anthropometric characteristics were reviewed to compare cases and controls. Mostly, the participants were white, married, and mean age of 59 years old ( $\pm 12.95$ ). No significant difference among cases and controls was found regarding sex, age, skin-color, marital status, education, socioeconomic level (assets index) alcohol and tobacco use, BMI. As characteristics of the sample, most of the cases were ex-smokers with high percentage of overweight (according to BMI) (Table 1).

In the raw analysis of the risk factors of sociodemographic, behavioral, and anthropometric aspects for CRC, the sociodemographic, behavioral variables and BMI were not associated with the outcome, but the variables of the diet as soda ( $p=0.04$ ) and fish ( $p=0.001$ ) intake were associated with the outcome, increasing the risk of cancer.

In relation to the profile of PA of the sample in the domain leisure, 25% of the individuals were inactive for the lifetime and 85.8% reported household PA; in PA of commuting, 44.5% did active coming and going and in the domain occupational, 95.9% were physically active, and 32% reported burdensome farming activity and exposure to pesticides. Table 2 presents data of the raw and adjusted analysis of PA. For both analyzes, PA in the four domains (leisure, household, commuting and occupational) and PA total were not associated with the outcome.

## DISCUSSION

The sociodemographic and behavioral variables were not associated with the study outcome, as opposed to the literature regarding tobacco, alcohol use and red meat for the development of CRC which presented significant differences in several studies<sup>20-23</sup>; another case-control study did not find significant difference for CRC risk increase in relation to tobacco, alcohol and fibres<sup>24</sup>, which makes these variables inconsistent with the disease investigated. In relation to BMI, no significant association was encountered, but in a case-control study, the BMI of obese men was analyzed with positive association with the risk of developing CRC<sup>25</sup>.

There was a significant difference in the intake of soda ( $p=0.04$ ) and fish ( $p=0.001$ ) during the lifetime in the raw

**Table 1.** Description of the sociodemographic and behavioral characteristics of the sample. Pelotas, 2019 (n=247)

Characteristics	Total sample (%)	Cases (%)	Value of p
<b>Sex</b>			0.96 <sup>2</sup>
Male	50.2	33.1	
Female	49.8	33.3	
<b>Age (years)</b>			0.47 <sup>1</sup>
19-50	23.5	31.0	
51-65	40.9	31.7	
66-88	35.6	36.4	
<b>Skin color</b>			0.70 <sup>2</sup>
White	63.5	34.4	
Black	13.8	35.3	
Brown	22.7	28.6	
<b>Marital status</b>			0.41 <sup>2</sup>
Married	68.0	30.4	
Single	8.9	31.8	
Divorced	11.3	39.3	
Widow/widower	11.8	44.8	
<b>Education (years)</b>			0.99 <sup>1</sup>
Until 5	55.1	33.1	
6-10	17.0	38.1	
11-15	25.1	27.4	
16-19	2.8	57.1	
<b>Assets Index (quartile)</b>			0.08 <sup>1</sup>
1 <sup>st</sup> (poorer)	25.1	24.2	
2 <sup>nd</sup>	25.1	30.7	
3 <sup>rd</sup>	25.1	41.9	
4 <sup>th</sup> (richer)	24.7	36.1	
<b>History of tobacco use</b>			0.15 <sup>2</sup>
Smokers	8.1	20.0	
Never smoked	42.5	29.5	
Ex-smokers	49.4	38.5	
<b>Alcohol use</b>			0.42 <sup>2</sup>
Yes	87.9	26.7	
No	12.1	34.1	
<b>Body Mass Index (kg/m<sup>2</sup>)</b>			0.36 <sup>1</sup>
Regular weight	43.3	29.9	
Overweight	35.6	35.2	
Obesity grade 1	21.1	36.5	

(1) Chi-square test of linear tendency.

(2) Chi-square test of heterogeneity.

analysis of the diet with more odds of developing CRC. For fish intake, several studies differed from the findings of the present study, with significant reduction of risk of CRC<sup>16,26</sup>; however, it is possible that the preparation of fish (usually deep fried) has some bearing on this association. No studies addressing soda intake were found, but some authors encountered association with elevated intake of

highly glycemic food, which could partially explain this association<sup>27,28</sup>.

The main exposure variable measured was PA in its four domains and total and after the adjusted analysis for confounding factors, no significant association was found with the study outcome. Despite the effect measures indicate odds ratio of protection for the domains of

**Table 2.** Raw and adjusted analysis of colorectal cancer according to the domains of physical activity during the lifetime. Odds ratio and confidence interval of 95% obtained by conditional logistic regression paired by sex and age. Pelotas, 2019 (n=247)

Physical Activity (quartiles)	OR <sub>raw</sub> (CI95%)	Value of p	OR* <sub>adjusted</sub> (CI95%)	Value of p
<b>Leisure</b>		0.53		0.55
1 <sup>st</sup> (less active)	1.0		1.0	
2 <sup>nd</sup>	1.49 (0.67-3.30)		1.30 (0.51-3.30)	
3 <sup>rd</sup>	1.09 (0.49-2.42)		0.95 (0.39-2.32)	
4 <sup>th</sup> (more active)	1.61 (0.64-3.24)		1.56 (0.58-4.20)	
<b>Household</b>		0.51		0.64
1 <sup>st</sup> (less active)	1.0		1.0	
2 <sup>nd</sup>	0.46 (0.21-1.04)		0.55 (0.22-1.33)	
3 <sup>rd</sup>	0.40 (0.30-1.65)		0.48 (0.18-1.26)	
4 <sup>th</sup> (more active)	0.71 (0.30-1.65)		0.78 (0.29-2.08)	
<b>Commuting</b>		0.44		0.38
1 <sup>st</sup> (less active)	1.0		1.00	
2 <sup>nd</sup>	0.96 (0.29-3.12)		1.16 (0.32-4.22)	
3 <sup>rd</sup>	0.68 (0.34-1.37)		0.46 (0.20-1.06)	
4 <sup>th</sup> (more active)	0.86 (0.43-1.73)		0.96 (0.42-2.22)	
<b>Occupational</b>		0.69		0.61
1 <sup>st</sup> (less active)	1.0		1.0	
2 <sup>nd</sup>	2.43 (0.97-6.05)		2.56 (0.90-7.27)	
3 <sup>rd</sup>	1.30 (0.52-3.22)		1.30 (0.46-3.68)	
4 <sup>th</sup> (more active)	1.83 (0.71-4.73)		2.04 (0.64-6.45)	
<b>PA total</b>		0.83		0.91
1 <sup>st</sup> (less active)	1.0		1.0	
2 <sup>nd</sup>	0.59 (0.26-1.36)		0.69 (0.27-1.77)	
3 <sup>rd</sup>	0.91 (0.42-1.98)		0.90 (0.35-2.30)	
4 <sup>th</sup> (more active)	0.76 (0.33-1.73)		0.83 (0.31-2.28)	

**Captions:** OR = Odds ratios; CI95% = Confidence Interval of 95%.

(\*) Variables of physical activity adjusted for confounding factors as assets index, tobacco use, pork meat intake, sweets, fruits, soda, and fish during the lifetime.

commuting, household and total activities during lifetime, no significant association was found among any PA domain and CRC outcome.

Some of the speculations about these findings are based in the specific characteristics of the sample with low level of PA, apparently a quite inactive population and great load of occupational activity which can influence health outcomes substantially.

The limitations are inherent to case-control studies, a design that calls for recollection of events and behaviors of a long gone past with biases of remembrance, information, and possible classification. Regardless of this limitation, it is the most indicated for this type of association because of the long inducive and latency of the outcome.

Meta-analyzes about PA and cancer found different results compared with the present study<sup>14,29,30</sup>. Liu

et al.<sup>29</sup> estimated the risk of cancer and LPA (leisure physical activity) in 126 studies. The week-hours of LPA reported were multiplied by 8 MET for vigorous activities; 6 MET for moderate to vigorous activities showing that the total risk of cancer was reduced in 10% for individuals with more time of LPA as compared to those who did the least<sup>29</sup>. Different joint analysis of data about LPA in 12 prospective US studies and European cohort studies obtained LPA level of 8 MET-h/week, the equivalent to 150 minutes/week of PA with moderate intensity associated with lower risk for 13 types of cancer, especially colon cancer with 16% of protection (hazard ratio – HR=0.84; CI0.77-0.91) when more and less active individuals were compared<sup>31</sup>.

A cohort study concluded that PA above 21 MET-hours/week was associated with reduction of CRC risk

in 39% (HR=0.61;  $p < 0.0001$ ) and colon cancer in 45% (HR=0.55;  $p < 0.0001$ )<sup>20</sup>. A cohort of the Nurses' Health Study found protective results for LPA (leisure physical activity). In the adjusted analysis, while relating the highest versus the lowest level of PA, there was reduction for CRC risk in LPA in 29% (HR=0.7; CI95% 0.49-1.28;  $p=0.03$ ) but the other domains of PA failed to present significant value<sup>32</sup>.

The current article was based in a sex-paired analysis. Some studies reported dissimilar results among men and women, for instance, Keum et al.<sup>33</sup> reviewed the reduction of cancer risk with PA in a prospective cohort which followed up 43,479 men and investigated the association of PA and risk of cancer in the digestive tract: the results indicated that higher levels of PA were associated with 26% (HR=0.74 for  $\geq 63.0$  vs.  $\leq 8.9$  MET-hours/week; CI95% 0.59-0.93) of protection against cancer. Aerobic activity (approximately 30 MET-hours/week  $-1$  MET, or the metabolic equivalent corresponds to oxygen consumption of 3.5 mL of oxygen for each kg of body mass per minute) reached 32% protection (HR=0.68; CI95% 0.56-0.83) against cancer of the digestive system<sup>33,34</sup>.

Another cohort study concluded that men with low PA (8.3 MET-h/week) increased the risk of CRC in 31% (HR=0.69; CI95% 1.00-1.70) in comparison with participants with high PA ( $>16.6$  MET-h/week), but no association was found with cancer incidence among women<sup>35</sup>. Similar results were encountered in a prospective cohort study where no associations between the level of PA and risk of colon cancer were found comparing women with PA level 1-2 with those with PA 5-6 (baseline: HR=0.90; CI95% 0.66-1.23;  $p=0.76$ ; repeated measures: HR=0.78; CI95% 0.55-1.10;  $p=0.27$ ). The results were the same when PA level 9-10 was compared with the reference level (baseline: HR=0.80; CI95% 0.56-1.12;  $p=0.76$ ; repeated measures: HR=0.82; CI95% 0.58-1.16;  $p=0.27$ )<sup>36</sup>. In a different study, women who practiced PA at level 21 MET-hours/week reduced the risk in 49% in comparison with women who practiced only 2 MET-hours of activity per week<sup>22</sup>. According to these studies, PA protects against CRC in men, but it is not possible to affirm for women because the results are controversial.

Many biological mechanisms have been suggested to explain the association between PA and CRC. One of them is the capacity of physical inactivity to increase the prevalence of colon cancer through elevated insulin levels in the blood, which in the long-run can result in insulin resistance – a known risk factor for cancer. In addition, it can cause higher levels of IGF-1 (growth factor similar to insulin 1 in the bloodstream, exposing the fast return in the epithelium of the colon at higher levels of anabolic hormone associated with more incidence of colon

cancer)<sup>11,12</sup>. PA can directly influence the risk of cancer as it diminishes the time of intestinal transit, reducing the exposure to fecal carcinogenic in the surface of the colon mucosa<sup>13</sup>. Another preventive mechanism may be related to the levels of prostaglandins and bile acids – factors involved in the proliferation and growth of colon cells – suggesting the PA can regulate beneficially the levels of these factors<sup>37,38</sup>.

## CONCLUSION

The present study concluded that after raw and adjusted analyzes for confounding factors, PA in its four domains (leisure, household, occupational and commuting) and total PA performed during lifetime were not associated with the outcome. This study reached opposite results compared with the literature mostly; possible explanations were the profile of PA of the population investigated, the characteristics of occupational PA and sample size.

## CONTRIBUTIONS

All the authors contributed substantially for the study design, data collection and/or interpretation, wording, critical review and approved the final version to be published.

## DECLARATION OF CONFLICT OF INTERESTS

There is no conflict of interests to declare.

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