Cancer Epidemiology 56 (2018) 38–45

Contents lists available at ScienceDirect

Cancer Epidemiology

journal homepage: www.elsevier.com/locate/canep

Preventable fractions of colon and breast cancers by increasing physical activity in Brazil: perspectives from plausible counterfactual scenarios

Leandro Fórnias Machado de Rezende[a,*], Leandro Martin Totaro Garcia[b], Grégore Iven Mielke[c,d], Dong Hoon Lee[e], Kana Wu[e], Edward Giovannucci[e,f,g,1], José Eluf-Neto[a,1]

[a] Departamento de Medicina Preventiva, Faculdade de Medicina FMUSP, Universidade de Sao Paulo, Sao Paulo, SP, Brazil
[b] UKCRC Centre for Diet and Activity Research, MRC Epidemiology Unit, University of Cambridge School of Clinical Medicine, Cambridge, United Kingdom
[c] School of Human Movement and Nutrition Sciences, University of Queensland, Brisbane, Australia
[d] Postgraduate Program in Epidemiology, Federal University of Pelotas, Brazil
[e] Department of Nutrition, Harvard T.H. Chan School of Public Health, Boston, Massachusetts, United States
[f] Department of Epidemiology, Harvard T.H. Chan School of Public Health, Boston, Massachusetts, United States
[g] Channing Division of Network Medicine, Brigham and Women's Hospital and Harvard Medical School, Boston, Massachusetts, United States

ARTICLE INFO

Keywords:
Epidemiology
Population attributable fraction
Physical activity
Cancer

ABSTRACT

Background: Physical activity is associated with lower risk of colon and breast cancers. Herein we estimated preventable fractions of colon and breast cancers in Brazil by increasing population-wide physical activity to different counterfactual scenarios.
Methods: We used data from a representative national survey in Brazil and corresponding relative risks of colon and postmenopausal breast cancers from a meta-analysis. Estimated cancer incidence was retrieved from GLOBOCAN and Brazilian National Cancer Institute. Five counterfactual scenarios for physical activity were considered: (i) theoretical minimum risk exposure level (≥8,000 metabolic equivalent of tasks-minute/week – MET-min/week); (ii) physical activity recommendation (≥600 MET-min/week); (iii) a 10% reduction in prevalence of insufficient physical inactivity (< 600 MET-min/week); (iv) physical activity level in each state equals the most active state in Brazil; (v) closing the gender differences in physical activity.
Results: About 19% (3,630 cases) of colon cancers and 12% (6,712 cases) of postmenopausal breast cancers could be prevented by increasing physical activity to ≥8,000 MET-min/week. Plausible counterfactual scenarios suggested the following impact on cancer prevention: reaching physical activity recommendation: 1.7% (1,113 cases) of breast and 6% (1,137 cases) of colon; 10% reduction in physical inactivity prevalence: 0.2% (111 cases) of breast and 0.6% (114 cases) of colon; most active state scenario: 0.3% (168 cases) of breast and 1% (189 cases) of colon; reducing gender differences in physical activity: 1.1% (384 cases) of breast and 0.6% (122 cases) of colon.
Conclusions: High levels of physical activity are required to achieve a sizable impact on breast and colon cancer prevention in Brazil.

1. Introduction

Convincing evidence supports the association between physical activity and lower risk of colon and breast cancers [1–3]. Potential protective effect of physical activity on other cancer sites has been recently suggested [4–14], yet the evidence is less consistent and dose-response shape unknown [1]. Physical activity may exert major influences on cancer risk mainly through weight management and adiposity level [15,16], and additionally *via* direct effects on hormones and inflammatory markers [17–19]. To obtain these health benefits the World Health Organization (WHO) recommends at least 600 metabolic equivalents of tasks-minute per week (MET-min/week) of total physical activity, which has been translated as 150 min/week in activities with moderate intensity (3–6 MET) or 75 min/week in vigorous activities (> 6 MET) [20]. However, higher levels of total physical activity (*i.e.*, ≥8000 MET-min/week) have been recently suggested to provide optimum risk reduction returns in non-communicable diseases (NCDs), especially for breast and colon cancers [21].

* Corresponding author at: Av Dr Arnaldo 455, 2nd floor. Sao Paulo, SP, 01246-903, Brazil.
E-mail address: lerezende@usp.br (L.F.M.d. Rezende).
[1] These authors contributed equally to this paper.

https://doi.org/10.1016/j.canep.2018.07.006
Received 17 February 2018; Received in revised form 20 June 2018; Accepted 3 July 2018

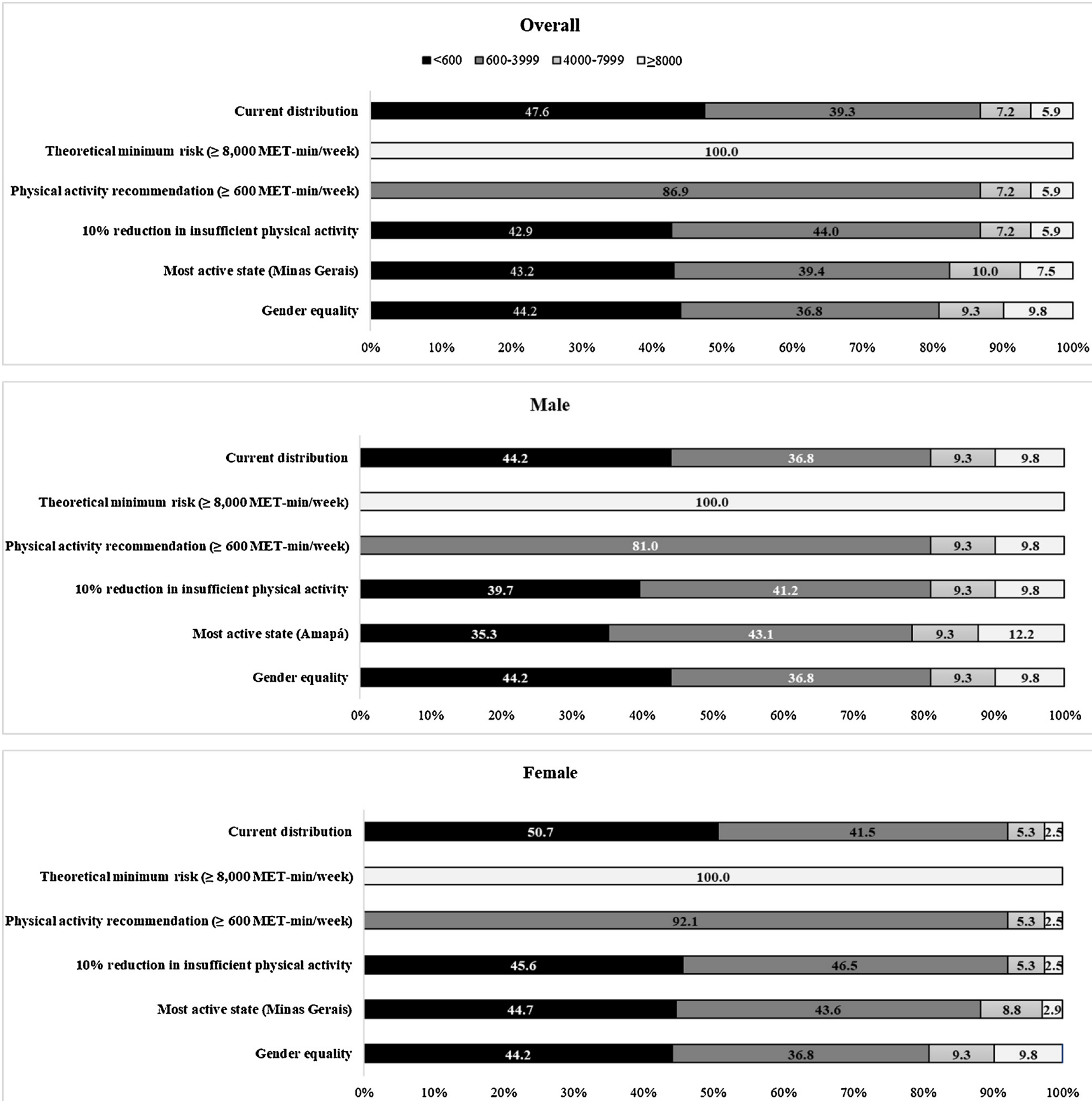

Fig. 1. Current and counterfactual scenarios of physical activity (PA) among Brazilian adults, by sex.

Globally, lack physical activity accounts for, on average, 12% of breast cancer and 18% of colon cancer [22]. To calculate the fraction of cancers due to lack of physical activity, both the distribution of physical activity at the population level (*e.g.*, prevalence of exposure) and the relative risk (RR) of cancer are required [23,24]. Frequently, studies have obtained RR from meta-analyses comparing the most and the least active groups, which is heterogeneously defined across primary studies. Therefore, the definition of lack of physical activity cannot be consistently used to estimate the exposure level at the target population.

Studies on preventable fractions usually report the proportion of cancer that could be potentially avoided if exposure to a certain risk factor were eliminated (*i.e.*, theoretical minimum risk exposure level) [23,24]. Notwithstanding informative, this scenario is unlikely to be reached at the population level. On the other hand, alternative scenarios considering plausible reductions in exposure level are sparse in the literature, despite its importance to inform policy makers and cancer prevention strategies. For instance, the WHO Global Action Plan for the Prevention and Control of NCDs (WHO 25 × 25) targeted a 10% reduction in the prevalence of insufficient physical activity for 2025 [25]. Reducing gender inequality in physical activity is also important [26,27]. Globally, the prevalence of insufficient physical inactivity is, on average, 20% lower in women than in men [27]. There are also great disparities in insufficient physical activity within countries. For instance, prevalence of insufficient physical activity ranges from 41% to 58% in Brazilian states [28]. Reducing disparities in physical activity between gender and geographic areas may have a positive impact on population levels of physical activity. However, the extent to which these alternative scenarios of physical activity could potentially reduce the burden of cancer is unknown.

Herein we estimated preventable fractions of colon and breast cancer cases in Brazil by increasing population-wide physical activity to five different counterfactual scenarios: (i) reaching the theoretical minimum risk exposure level (≥ 8,000 MET-min/week), (ii) reaching the WHO recommendation for physical activity (≥ 600 MET-min/week)

[20] (iii) a 10% reduction in prevalence of insufficient physical activity [25], (iv) increasing physical activity in each Brazilian state to levels observed in the most active state in Brazil, and (v) reducing gender differences in physical activity by increasing physical activity in women.

2. Methods

2.1. Data input

2.1.1. Physical activity data: current distribution and counterfactual scenarios

We used data from the National Health Survey (*Pesquisa Nacional de Saúde* – PNS, 2013), the most recent nationally representative survey in Brazil, including 60,202 individuals aged 18 years and older. Further information about PNS has been reported elsewhere [29,30]. In this study, we used information from 57,962 adults aged 20 years or older that responded the physical activity questionnaire.

Weekly frequency and duration (hours and minutes) of recreational, occupational, commuting (walking or cycling) to work, commuting to other daily activities, and household activities in a typical week were self-reported. The most frequent type of recreational activity (*e.g.*, walking, cycling, running, soccer) was also collected. We assigned MET for each domain of physical activity (recreational, occupational, commuting and household) according to 2011 compendium of physical activities (Table S1) [31]. To obtain the total volume of physical activity, we summed-up MET-min/week across domains of physical activity. We estimated total physical activity by sex, age-group (20–34, 35–44, 45–54, 65–74, and ≥75 years), and federative units in Brazil (*e.g.*, 26 states and 1 federal district). Total physical activity was categorized into four groups (< 600, 600–3,999, 4,000–7,999, and ≥8,000 MET-min/week) according to cut-offs used in the RR estimates.

We calculated the following counterfactual scenarios of physical activity (Fig. 1):

i) Theoretical minimum risk exposure level: everyone reaches ≥8,000 MET-min/week [21];
ii) WHO recommendation for physical activity: everyone achieves ≥600 MET-min/week [20];
iii) WHO 25 × 25: a 10% reduction in the prevalence of insufficient physical activity (< 600 MET-min/week) [25];
iv) Most active state: physical activity level in each federative unit equals the most active state in Brazil (Minas Gerais for women and Amapá for men);
v) Gender equality: physical activity level is equal between women and men (reference group). Physical activity level in women was increased to levels observed in men.

2.1.2. Cancer data: relative risk and estimated Cancer incidence

We included in our study only types of cancer with strong or highly suggestive evidence to be associated with physical activity, namely breast cancer in women (postmenopausal) and colon cancer [1–3]. We extracted RR and 95% confidence intervals from a recent dose-response meta-analysis of prospective cohort studies (35 studies for breast cancer and 19 studies for colon cancer) [21,32] synthesizing the associations of total physical activity (< 600, 600 to 3,999, 4000 to 7,999, and ≥8000 MET-min/week) with breast cancer (postmenopausal) and colon cancer (Table S2).

Estimated number of colorectal and breast cancer cases diagnosed in Brazil in 2012 by sex and age-group (20–34, 35–44, 45–54, 65–74, and ≥ 75 years) were retrieved from the GLOBOCAN project [33]. Estimated cancer cases for each federative unit in 2012 by sex was obtained from the Brazilian National Cancer Institute [34]. Both sources have been used to inform cancer prevention strategies in Brazil. Details about these estimated cancer incidence data have been published elsewhere [33,34]. To obtain colon cancer cases only, we applied the proportion of this subtype by sex to total number of colorectal cancer cases (*i.e.*, colon, rectum, and anus) as reported in Cancer in Five Continents Volume X [35]. Breast cancer (postmenopausal) was defined as cases in women aged ≥45 years as reported in the GLOBOCAN 2012 [33] (Table S3).

2.2. Data analysis

Preventable fractions of colon and breast cancers by sex and age-group were estimated for country and by sex for each federative unit using the following potential impact fraction (PIF) equation [23,24]:

$$PIF = \frac{\sum_{i=1}^{n} P_i RR_i - \sum_{i=1}^{n} P'_i RR_i}{\sum_{i=1}^{n} P_i RR_i}$$

where P_i is the proportion of the population at the level i of physical activity, P'_i is the proportion of the population at the level i of physical activity in the counterfactual scenario, and RR_i is the relative risk of postmenopausal breast cancer and colon cancer at the level i of physical activity. Levels i of physical activity were < 600, 600 to 3,999, 4,000–7,999, and ≥8,000 MET-min/week (reference group). PIF for the theoretical minimum risk exposure level scenario will be referred hereinafter as population attributable fraction (PAF), a special case of PIF where the exposure is eliminated [23,24].

To calculate the number of avoidable cancer cases in each counterfactual scenario of physical activity, we applied PIF estimates to total number of postmenopausal breast cancer cases and colon cancer cases in 2012. We summed up number of avoidable breast and colon cancer cases and divided by total number of cancer cases (excluding non-melanoma skin cancer) to obtain preventable fraction of all cancer cases due to increase in population-wide physical activity in the corresponding counterfactual scenario.

Recent studies on preventable fractions of cancer due to lack of physical activity have considered about 10-year latency period to account for population aging and time since exposure (Table S4). We performed sensitivity analysis using number of new cancer cases projected for 2025 in Brazil by sex from GLOBOCAN [33]. Projections of cancer incidence were calculated by multiplying age-specific cancer incidence in 2012 by the population structure expected for 2025 [33].

Data analysis was performed in Stata version 15.0. Data input and scripts used in our study are available at https://osf.io/5ut4z/.

3. Results

3.1. Current distribution and counterfactual scenarios of physical activity

Nearly half (47.6%) of the Brazilian adults did not achieve the WHO recommendation of 600 MET-min/week, with a higher proportion of women (50.7%) than men (42.7%). Only 6% were engaged in ≥8,000 MET-min/week, the reference group used in our study to represent the theoretical minimum risk exposure level. The prevalence of ≥8,000 MET-min/week in men was almost 4 times as high as the prevalence in women (Fig. 1). Counterfactual scenarios of physical activity by sex are presented in the Fig. 1.

3.2. Theoretical minimum risk exposure level scenario

We estimated that 12.3% (6,712 cases) of postmenopausal breast cancers and 19.0% (3,630 cases) of colon cancers could be potentially avoided in Brazil in 2012 by reaching ≥8,000 MET-min/week. In women, preventable fractions of colon (19.6%) and postmenopausal breast cancers (12.3%) represented about 8,645 avoidable cancer cases. In men, preventable fractions of colon cancer (18.5%) represented 1,697 avoidable cancer cases. Avoidable cancer cases represented around 4.1% and 0.8% of all cancer cases diagnosed in 2012 in women and men, respectively (Table 1). The highest PAFs for all cancers were

Table 1
Theoretical minimum risk exposure level (≥8,000 MET-min/week of physical activity): population attributable fraction (PAF) and number of avoidable cancer cases in Brazil in 2012, by sex, age, and cancer site.

Sex & age	Breast, postmenopausal			Colon			All Cancers*		
	Cases (n)	PAF (%)	Avoidable cases (n)	Cases (n)	PAF (%)	Avoidable cases (n)	Cases (n)	PAF (%)	Avoidable cases (n)
Overall									
Total	54,598	12.29	6712	19,063	19.04	3,630	429,657	2.41	10,342
20 to 34	NA	NA	NA	538	16.55	89	23,066	0.39	89
35 to 44	NA	NA	NA	1,049	16.97	178	30,920	0.58	178
45 to 54	17,739	11.75	2,084	2,991	17.22	515	70,777	3.67	2,599
55 to 64	15,986	12.12	1,937	4,266	18.10	772	99,762	2.72	2,709
65 to 74	11,314	12.65	1,432	4,942	19.57	967	102,793	2.33	2,399
75+	9,559	13.17	1,259	5,277	21.02	1,109	102,339	2.31	2,368
Men									
Total	NA	NA	NA	9,189	18.47	1697	219,026	0.77	1,697
20 to 34	NA	NA	NA	261	15.31	40	7,285	0.55	40
35 to 44	NA	NA	NA	421	16.29	69	9,766	0.70	69
45 to 54	NA	NA	NA	1,462	16.51	241	29,154	0.83	241
55 to 64	NA	NA	NA	2,266	17.53	397	54,248	0.73	397
65 to 74	NA	NA	NA	2,459	19.14	471	61,143	0.77	471
75+	NA	NA	NA	2,320	20.66	479	57,429	0.83	479
Women									
Total	54,598	12.29	6,712	9,874	19.58	1,933	210,631	4.10	8,645
20 to 34	NA	NA	NA	277	17.82	49	15,780	0.31	49
35 to 44	NA	NA	NA	628	17.38	109	21,154	0.52	109
45 to 54	17,739	11.75	2,084	1,529	17.89	273	41,623	5.66	2,357
55 to 64	15,986	12.12	1,937	2,000	18.75	375	45,514	5.08	2,312
65 to 74	11,314	12.65	1,432	2,483	19.99	497	41,650	4.63	1,928
75+	9,559	13.17	1,259	2,957	21.30	630	44,910	4.21	1,889

* PAF and avoidable cases accounting only for postmenopausal breast cancer in women and colon cancer; PAF: population attributable fraction; NA: not applicable.

found in the richest states of Brazil, namely Rio de Janeiro (0.8% in men; 2.6% in women), São Paulo (0.9% in men; 2.4% in women) and Distrito Federal (0.8% in men; 3.8% in women) (Fig. 2, Table S5-S7).

3.3. Plausible counterfactual scenarios

Plausible counterfactual scenarios of physical activity suggested number of avoidable cancer cases 5 to 46-fold lower than the theoretical minimum risk exposure level scenario. By achieving the physical activity recommendation, about 1.7% (1,113 cases) of postmenopausal breast cancers and 6% (1,137 cases) of colon cancers could be potentially avoided in 2012. Other plausible counterfactual scenarios of physical activity showed modest impact on cancer prevention. Eliminating gender differences in physical activity by increasing physical activity in women to levels observed in men could have avoided 1.1% (384 cases) of postmenopausal breast cancers and 0.6% (122 cases) of colon cancers. Increasing physical activity levels in Brazil to levels observed in the most active state could have avoided 0.3% (168 cases) of postmenopausal breast cancers and 1% (189 cases) of colon cancers. The WHO 25 × 25 goal for physical activity was the scenario with the worst performance, suggesting that about 0.2% (111 cases) of postmenopausal breast cancers and 0.6% (114 cases) of colon cancers could be potentially avoided (Table 2).

3.4. Sensitivity analysis

Sensitivity analysis using number of new cancer cases projected for 2025 showed preventable fractions of breast and colon slightly lower than in the primary analysis. In the theoretical minimum risk exposure level scenario, avoidable cancer cases represented 1.0% and 5.6% of all cancer cases projected for 2025 in men and women, respectively. We estimated that increasing physical activity could potentially avoid 14,076 cancer cases in 2025, compared to 10,342 cancer cases estimated in the primary analysis (Table 3).

4. Discussion

In this study we estimated preventable fractions of breast and colon cancer in Brazil by increasing population-wide physical activity to different counterfactual scenarios. About 12% of breast post-menopausal cancers and 19% of colon cancers in 2012 could be potentially avoided by reaching ≥8000 MET-min/week. When plausible counterfactual distributions of physical activity were considered, number of avoidable cancer cases were 5 to 46-fold lower than the aforementioned estimates. At best, about 1.3% of breast cancers and 6% colon cancers could be avoided by achieving the physical activity recommendation. Other counterfactual scenarios showed modest impact on cancer prevention.

Previous studies suggested that, on average, 12% of breast cancers and 18% of colon cancers are attributable to lack physical activity [22,36–51]. These results are similar to our PAF estimates, although comparing results is challenging due to methodological heterogeneity between studies (Table S4). Three different equations have been used to estimate PIF/PAF, but Levin's formula [52] has been most frequently used. Friedenreich and colleagues' study was the only one that estimated potential impact of different counterfactual scenarios of physical activity (*i.e.*, ≥3,000 MET-min/week and ≥600 MET-min/week) on cancer prevention [46]. Achieving the WHO recommendation for physical activity is the most frequent threshold used to define the theoretical minimum risk exposure level. Prevalence of total and leisure-time physical activity have been used to estimate the proportion of the population exposed to lack of physical activity (*i.e.*, below theoretical minimum risk exposure level). In this study, we used several categories of total physical activity (< 600, 600-3,999, 4,000–7,999, and ≥8,000 MET-min/week) to estimate preventable colon and breast cancer cases. Importantly, additional benefits of physical activity on cancer prevention were found far beyond the recommended level of 600 MET-min/week.

Cancer sites included in previous studies are also a concern. PAF estimates underlies a causal relationship assumption that physical activity decreases the risk of cancer. While the association between

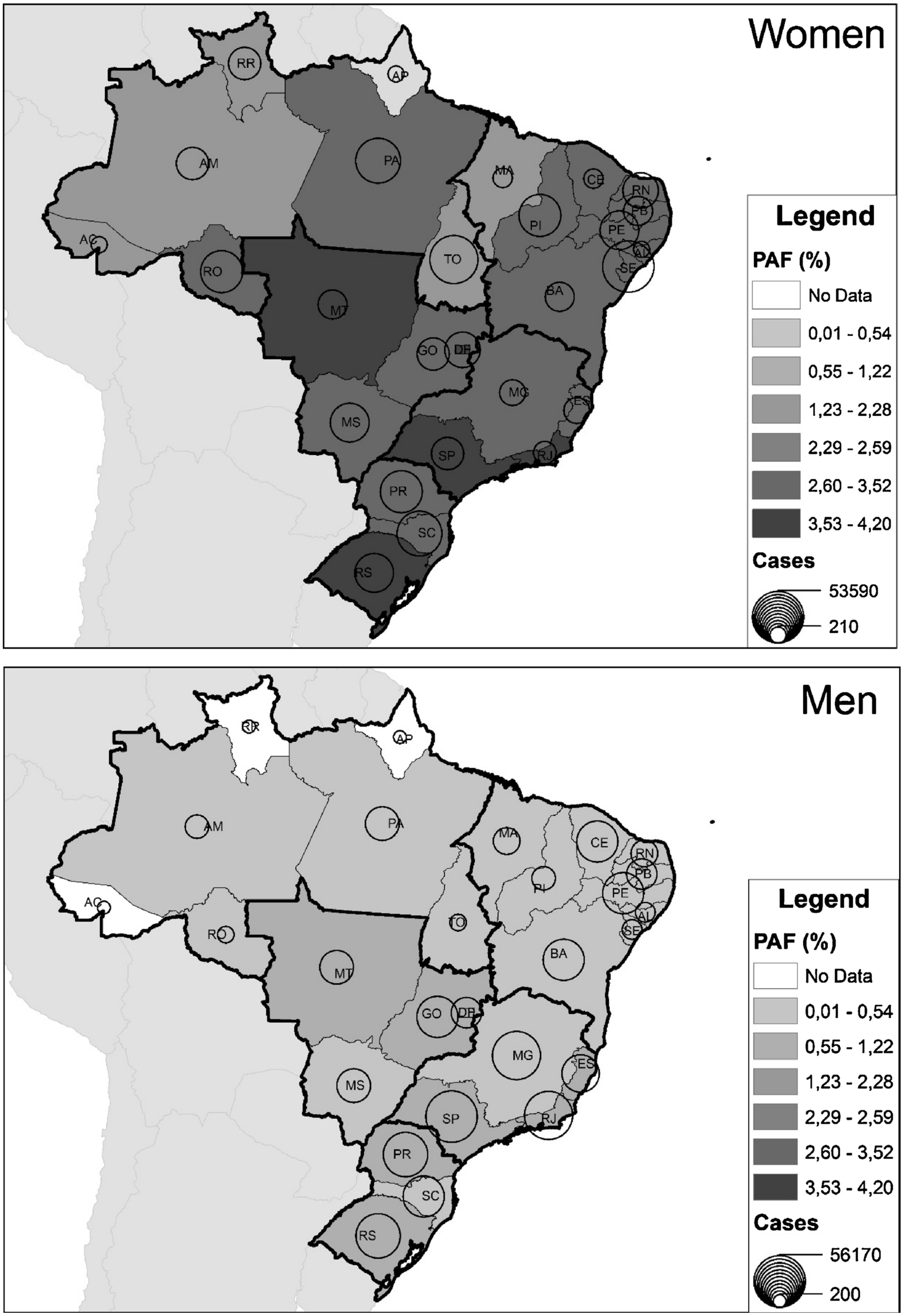

Fig. 2. Estimated cancer cases and its preventable fractions by increasing physical activity in Brazil in 2012.
Footnote:
- PAF of all cancers in Brazil by increasing physical activity to theoretical minimum risk exposure level (everyone reaches ≥8,000 MET-min/week);
- 27 Federative units: AC, Acre; AL, Alagoas; AP, Amapá; AM, Amazonas; BA, Bahia; CE, Ceará; DF, Distrito Federal; ES, Espírito Santo; GO, Goiás; MA, Maranhão; MT, Mato Grosso; MS, Mato Grosso do Sul; MG; Minas Gerais; PA; Pará; PB, Paraíba; PR, Paraná; PE, Pernambuco; PI, Piauí; RJ, Rio de Janeiro; RN, Rio Grande do Norte; RS, Rio Grande do Sul; RO, Rondônia; RR, Roraima; SC, Santa Catarina; SP, São Paulo; SE, Sergipe; TO, Tocantins;
- Region-level: Bold lines represents five regions: North (AC, RO, AM, RR, AP, PA, TO), Northeast (MA, PI, CE, RN, PB, PE, AL, SE, BA), Mid-west (MT, MS, GO, DF), Southeast (MG, SP, ES, RJ), and South (PR, SC, RS)

Table 2
Preventable fractions of cancers and number of avoidable cancer cases in Brazil in 2012 by increasing physical activity, according to sex, cancer site, and scenario.

Cancer site & Sex	Cases (n)	TMREL (≥8,000 MET-min/week)		PA recommendation (≥600 MET-min/week)		10% reduction in insufficient PA**		Most active state#		Gender equality ±	
		PAF (%)	Avoidable cases (n)	PIF (%)	Avoidable cases (n)	PIF (%)	Avoidable cases (n)	PIF (%)	Avoidable cases (n)	PIF (%)	Avoidable cases (n)
Breast, postmenopausal											
Overall	54,598	12.29	6,712	1.74	1,113	0.17	111	0.33	168	1.09	384
Men	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
Women	54,598	12.29	6,712	1.74	1,113	0.17	111	0.33	168	1.09	384
Colon											
Overall	19,063	19.04	3,630	5.97	1,137	0.60	114	0.99	189	0.64	122
Men	9,189	18.47	1,697	5.72	525	0.57	53	1.15	105	0.00	0
Women	9,874	19.58	1,933	6.20	612	0.62	61	0.85	84	1.23	122
All Cancers*											
+ Overall	429,657	2.41	10,342	0.52	2,250	0.05	225	0.08	358	0.12	505
Men	219,026	0.77	1,697	0.24	525	0.02	53	0.05	105	0.00	0
Women	210,631	4.10	8,645	0.82	1,725	0.08	173	0.12	252	0.24	505

* PIF and avoidable cases accounting only for postmenopausal breast cancer and colon cancer. ** Insufficient physical activity defined as < 600 MET-min/week. # physical activity levels in Brazil as observed in the most active federative unit (Minas Gerais for women and Amapá for men); ± physical activity level in women was increased to levels observed in men (reference group).
PA: physical activity; PAF: population attributable fraction; PIF: population impact fraction. TMREL: theoretical minimum risk exposure level; NA: not applicable.

physical activity and colon cancer and breast cancer are unanimous in the PAF literature, other cancer sites, such as endometrial, lung, ovary, gastric-esophagus, bladder, and prostate have also been included in some studies (Table S4). Currently, the World Cancer Research Fund consider convincing the evidence for the association between physical activity and colon cancer; and probable for breast and endometrial cancers [3]. The last statement from the International Agency for Research on Cancer support the association for colon and breast cancers only [2]. Recently, a pooled analysis from 12 cohort studies [4] and several systematic reviews suggested that high physical activity is associated with lower risk of bladder [5], breast [21,53,54], colon [21,55,56], endometrial [6], oesophageal [7], gastric [7,8], glioma [9], kidney [10], lung [11], ovarian [12], pancreas [13] and prostate [14]. Although physical activity could be confirmed with convincing protective effect on these cancers in the future, it's also likely presence of bias in the literature favoring studies showing "positive results" [57]. In fact, a recent umbrella review of literature on physical activity and cancer found hints of reporting bias (*i.e.*, small study effect and excess of significance bias) in about 15% of these meta-analyses [1]. Consequently, only associations between physical activity and colon and breast cancers were supported by strong and highly suggestive evidence, respectively [1]. Evidence of association with other cancer sites were not statistically significant (bladder, chronic/small lymphocytic lymphoma, diffuse large B-cell lymphoma, follicular lymphoma, gastric, glioma, Hodgkin and non-Hodgkin's lymphoma, kidney, leukaemia, multiple myeloma, ovary, rectum, and thyroid) or were considered less consistent (endometrial, oesophageal, meningioma, lung, and pancreas) due to hints of uncertainty and/or bias in literature [1].

We included in our estimates only cancer sites with convincing evidence to be associated with physical activity, as well with available estimates of dose-response relationship. These criteria may have underestimated the overall contribution of physical activity on cancer prevention if associations with other cancer sites turn out to be confirmed genuine. Triangulation of evidence from multiple methodologies, approaches, and disciplines may help to strengthen causal inference on physical activity and cancer [58,59]. Further results on type,

Table 3
Preventable fractions of cancers and number of avoidable cancer cases in Brazil in 2025§ by increasing physical activity, according to sex, cancer site, and scenario.

Cancer site & Sex	Cases (n)	TMREL (≥8,000 MET-min/week)		PA recommendation (≥600 MET-min/week)		10% reduction in insufficient PA**		Most active state#		Gender equality ±	
		PAF (%)	Avoidable cases (n)	PIF (%)	Avoidable cases (n)	PIF (%)	Avoidable cases (n)	PIF (%)	Avoidable cases (n)	PIF (%)	Avoidable cases (n)
Breast, postmenopausal											
Overall	76,115	11.91	9,060	1.75	1,325	0.17	132	0.32	253	0.81	832
Men	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
Women	76,115	11.91	9,060	1.75	1,325	0.17	132	0.32	253	0.81	832
Colon											
Overall	28,737	17.54	5,016	5.03	1,364	0.50	136	1.20	313	0.73	299
Men	13,789	16.89	2,287	4.85	615	0.48	61	1.65	173	0.00	0
Women	14,948	18.15	2,729	5.20	749	0.52	75	0.79	140	1.41	299
All Cancers*											
Overall	639,763	3.28	14,076	0.63	2,688	0.06	269	0.13	566	0.26	1,131
Men	333,843	1.04	2,287	0.28	615	0.03	61	0.08	173	0.00	0
Women	305,920	5.60	11,789	0.98	2,074	0.10	207	0.19	393	0.54	1,131

* PIF and avoidable cases accounting only for postmenopausal breast cancer and colon cancer. ** Insufficient physical activity defined as < 600 MET-min/week. # physical activity levels in Brazil as observed in the most active federative unit (Minas Gerais for women and Amapá for men); ± physical activity level in women was increased to levels observed in men (reference group).
PA: physical activity; PAF: population attributable fraction; PIF: population impact fraction. TMREL: theoretical minimum risk exposure level; NA: not applicable.
§We used projected cancer cases for 2025 to account for about 10-year latency period between physical activity and breast and colon cancers.

intensity, and volume of physical activity from The Physical Activity Collaboration of the National Cancer Institute's Cohort Consortium [4]; cohort studies with repeated measures of physical activity over time; and studies exploring biological mechanisms linking physical activity and cancer may play an important role on appraisal of the evidence.

Our study has several limitations and assumptions. RR estimates for the association between physical activity and cancer in the Brazilian population are inexistent. We used RR derived from a recent dose-response meta-analysis using data from cohort studies conducted mainly in US and European countries. These estimates might not be applicable to Brazil, especially if the prevalence of effect modifiers differs between settings [[60]]. Some RR estimates included in this meta-analysis were adjusted by body mass index. Therefore, our preventable fractions estimates are likely to be underestimated by not considering the overall effect of physical activity mediated through adiposity, which is an established risk factor for breast and colon cancers [61,62].

In our study, physical activity level was self-reported and therefore misclassification may have occurred. However, the PNS questionnaire showed reasonable reliability and validity compared to the Global Physical Activity Questionnaire, a validated questionnaire for physical activity surveillance recommended by the WHO [63]. Participants were asked about frequency and duration of physical activity in a typical week, but the questionnaire did not include information about intensity of activities. To define intensity of activities, we used a standard method by applying MET (Table S1) related to each domain of physical activity as described in the 2011 compendium of physical activities [31]. Questionnaires assessing physical activity level in the typical week tend to overestimate total energy expenditure compared to objective-measures (*e.g.,* doubly labelled water) [64]. Therefore, our estimates of preventable fractions due to physical activity may be underestimated. We used prevalence data from the most recent representative population-based survey conducted in Brazil in 2013, assuming that trends of physical activity have remained unchanged over time. In fact, leisure-time physical activity slightly increased in the 27 federative units in Brazil over the past few year, while a decrease in transportation physical activity was also observed [65]. Whether these changes affected total physical activity level in the whole country remains unknown and a matter of future studies.

Finally, attributable cancer cases were estimated using cancer cases from 2012 in Brazil. However, physical activity may not have an immediate impact on breast and colon cancers given the relatively long latency period of cancer. Therefore, we performed sensitivity analysis using projected cancer cases for 2025 in Brazil. Considering about 10-year latency period between physical activity and cancers, we estimated that about 3.3% (14,000 cases) of all cancers could be potentially avoided.

In conclusion, our estimates suggest that physical activity may play an important role in cancer prevention strategies by avoiding up to 12% of postmenopausal breast cancers and 19% of colon cancers in Brazil. Alternative scenarios considering plausible increases in physical activity level showed limited to moderate impact on cancer prevention, suggesting that high levels of physical activity are required to obtain a sizable impact on breast and colon cancer prevention in Brazil.

Authorship contribution statement

LFMR, LMTG, GIM, DHL, KW, EG, and JEN conceived and designed the study. LFMR, LMTG, GIM, DHL acquired and collated the data. LFMR analyzed the data. All authors drafted and critically revised the manuscript for important intellectual content and gave final approval of the version to be published.

Funding

Leandro Fórnias Machado de Rezende receives a doctoral scholarship from Sao Paulo Research Foundation (FAPESP), grant #2014/25614-4 and #2016/21390-0. Leandro Martin Totaro Garcia has undertaken this work under the auspices of the Centre for Diet and Activity Research (CEDAR), a UKCRC Public Health Research Centre of Excellence which is funded by the British Heart Foundation, Cancer Research UK, Economic and Social Research Council, Medical Research Council, the National Institute for Health Research, and the Wellcome Trust.

Conflict of interest

None.

Acknowledgment

None.

Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.canep.2018.07.006.

References

[1] L.F.M. Rezende, T.H. Sa, G. Markozannes, J.P. Rey-Lopez, I.M. Lee, K.K. Tsilidis, J.P.A. Ioannidis, J. Eluf-Neto, Physical activity and cancer: an umbrella review of the literature including 22 major anatomical sites and 770 000 cancer cases, Br. J. Sports Med. 52 (13) (2017) 826–833.

[2] International agency for research on cancer (IARC), weight control and physical activity, IARC Handbook of Cancer Prevention 6 IARC press, Lyon, 2002.

[3] World Cancer Research Fund/American Institute for Cancer research, Continuous Update Project Expert Report 2018. Physical Activity and Risk of Cancer, (2018) dietandcancerreport.org.

[4] S.C. Moore, I.M. Lee, E. Weiderpass, P.T. Campbell, J.N. Sampson, C.M. Kitahara, S.K. Keadle, H. Arem, A. Berrington de Gonzalez, P. Hartge, H.O. Adami, C.K. Blair, K.B. Borch, E. Boyd, D.P. Check, A. Fournier, N.D. Freedman, M. Gunter, M. Johannson, K.T. Khaw, M.S. Linet, N. Orsini, Y. Park, E. Riboli, K. Robien, C. Schairer, H. Sesso, M. Spriggs, R. Van Dusen, A. Wolk, C.E. Matthews, A.V. Patel, Association of leisure-time physical activity with risk of 26 types of Cancer in 1.44 million adults, JAMA Intern. Med. 176 (6) (2018) 816–825.

[5] M. Keimling, G. Behrens, D. Schmid, C. Jochem, M.F. Leitzmann, The association between physical activity and bladder cancer: systematic review and meta-analysis, Br. J. Cancer 110 (7) (2014) 1862–1870.

[6] D. Schmid, G. Behrens, M. Keimling, C. Jochem, C. Ricci, M. Leitzmann, A systematic review and meta-analysis of physical activity and endometrial cancer risk, Eur. J. Epidemiol. 30 (5) (2015) 397–412.

[7] G. Behrens, C. Jochem, M. Keimling, C. Ricci, D. Schmid, M.F. Leitzmann, The association between physical activity and gastroesophageal cancer: systematic review and meta-analysis, Eur. J. Epidemiol. 29 (3) (2014) 151–170.

[8] T. Psaltopoulou, I. Ntanasis-Stathopoulos, I.G. Tzanninis, M. Kantzanou, D. Georgiadou, T.N. Sergentanis, Physical activity and gastric Cancer risk: a systematic review and meta-analysis, Clin. J. Sport Med. 26 (6) (2016) 445–464.

[9] T. Niedermaier, G. Behrens, D. Schmid, I. Schlecht, B. Fischer, M.F. Leitzmann, Body mass index, physical activity, and risk of adult meningioma and glioma: A meta-analysis, Neurology 85 (15) (2015) 1342–1350.

[10] G. Behrens, M.F. Leitzmann, The association between physical activity and renal cancer: systematic review and meta-analysis, Br. J. Cancer 108 (4) (2013) 798–811.

[11] D.R. Brenner, D.H. Yannitsos, M.S. Farris, M. Johansson, C.M. Friedenreich, Leisure-time physical activity and lung cancer risk: A systematic review and meta-analysis, Lung Cancer 95 (2016) 17–27.

[12] S. Zhong, L. Chen, M. Lv, T. Ma, X. Zhang, J. Zhao, Nonoccupational physical activity and risk of ovarian cancer: a meta-analysis, Tumour Biol. 35 (11) (2014) 11065–11073.

[13] M.S. Farris, M.H. Mosli, A.A. McFadden, C.M. Friedenreich, D.R. Brenner, The association between leisure time physical activity and pancreatic Cancer risk in adults: a systematic review and meta-analysis, Cancer Epidemiol. Biomarkers Prev. 24 (10) (2015) 1462–1473.

[14] Y. Liu, F. Hu, D. Li, F. Wang, L. Zhu, W. Chen, J. Ge, R. An, Y. Zhao, Does physical activity reduce the risk of prostate cancer? A systematic review and meta-analysis, Eur. Urol. 60 (5) (2011) 1029–1044.

[15] J.E. Donnelly, S.N. Blair, J.M. Jakicic, M.M. Manore, J.W. Rankin, B.K. Smith, M. American College of Sports, American College of Sports Medicine Position Stand, Appropriate physical activity intervention strategies for weight loss and prevention of weight regain for adults, Med. Sci. Sports Exerc. 41 (2) (2009) 459–471.

[16] E. Giovannucci, An integrative approach for deciphering the causal associations of physical activity and Cancer risk: the role of adiposity, J. Natl. Cancer Inst. 110 (9) (2018) djy091.

[17] E. Giovannucci, A framework to understand diet, physical activity, body weight, and cancer risk, Cancer Causes Control 29 (1) (2017) 1–6.

[18] G.J. Koelwyn, D.F. Quail, X. Zhang, R.M. White, L.W. Jones, Exercise-dependent

regulation of the tumour microenvironment, Nat. Rev. Cancer 17 (10) (2017) 545–549.
[19] A. McTiernan, Mechanisms linking physical activity with cancer, Nat. Rev. Cancer 8 (3) (2008) 205–211.
[20] World Health Organization (WHO), Global Recommendations on Physical Activity for Health, World Health Organization, Geneva, 2010.
[21] H.H. Kyu, V.F. Bachman, L.T. Alexander, J.E. Mumford, A. Afshin, K. Estep, J.L. Veerman, K. Delwiche, M.L. Iannarone, M.L. Moyer, K. Cercy, T. Vos, C.J. Murray, M.H. Forouzanfar, Physical activity and risk of breast cancer, colon cancer, diabetes, ischemic heart disease, and ischemic stroke events: systematic review and dose-response meta-analysis for the Global Burden of Disease Study, BMJ 354 (2016) (2013) i3857.
[22] D.C. Whiteman, L.F. Wilson, The fractions of cancer attributable to modifiable factors: A global review, Cancer Epidemiol. 44 (2016) 203–221.
[23] L.F. Rezende, J. Eluf-Neto, Population attributable fraction: planning of diseases prevention actions in Brazil, Rev. Saude Publica 50 (2016) 1–6.
[24] C.J.L. Murray, M. Ezzati, A.D. Lopez, A. Rodgers, S. Vander Hoorn, Comparative quantification of health risks: conceptual framework and methodological issues, Popul. Health Metr. 1 (1) (2003) 1.
[25] World Health Organization (WHO), Global Status Report on Noncommunicable Diseases 2014, WHO press, Geneva, 2014.
[26] T. Althoff, R. Sosic, J.L. Hicks, A.C. King, S.L. Delp, J. Leskovec, Large-scale physical activity data reveal worldwide activity inequality, Nature 547 (7663) (2017) 336–339.
[27] G.I. Mielke, I.C.M. da Silva, T.L. Kolbe-Alexander, W.J. Brown, Shifting the physical inactivity curve worldwide by closing the gender gap, Sport. Med. 48 (2) (2017) 481–489.
[28] G.I. Mielke, P.C. Hallal, G.B.A. Rodrigues, C.L. Szwarcwald, F.V. Santos, D.C. Malta, Physical activity and television viewing among Brazilian adults: national Health Survey 2013, Epidemiologia e Serviços de Saúde 24 (2015) 277–286.
[29] C.L. Szwarcwald, D.C. Malta, C.A. Pereira, M.L. Vieira, W.L. Conde, P.R. Souza Junior, G.N. Damacena, L.O. Azevedo, E.S.G. Azevedo, M.M. Theme Filha, S. Lopes Cde, D.E. Romero, S. Almeida Wda, C.A. Monteiro, National Health Survey in Brazil: design and methodology of application, Cien. Saude Colet. 19 (2) (2014) 333–342.
[30] Instituto Brasileiro de Geografia e Estatística, Pesquisa Nacional De Saúde 2013: Percepção Do Estado De Saúde, Estilo De Vida E Doenças Crônicas. Brasil, Grandes Regiões E Unidades Da Federação, (2013) (Accessed 03 April 2017), http://www.ibge.gov.br/home/estatistica/populacao/pns/2013/.
[31] B.E. Ainsworth, W.L. Haskell, S.D. Herrmann, N. Meckes, D.R. Bassett Jr, C. Tudor-Locke, J.L. Greer, J. Vezina, M.C. Whitt-Glover, A.S. Leon, Compendium of Physical Activities: a second update of codes and MET values, Med. Sci. Sports Exerc. 43 (8) (2011) 1575–1581 2011.
[32] GBD Risk Factors Collaborators, Global, regional, and national comparative risk assessment of 79 behavioural, environmental and occupational, and metabolic risks or clusters of risks, 1990-2015: a systematic analysis for the Global Burden of Disease Study 2015, Lancet 388 (10053) (2016) 1659–1724.
[33] S.I. Ferlay J, M. Ervik, R. Dikshit, S. Eser, C. Mathers, M. Rebelo, D.M. Parkin, D. Forman, F. Bray, GLOBOCAN 2012 v1.0, Cancer Incidence and Mortality Worldwide: IARC CancerBase No. 11 [Internet], (2013) (Accessed 24 March, 2017), http://globocan.iarc.fr.
[34] Instituto Nacional de Câncer José Alencar Gomes da Silva, Coordenação Geral De Ações Estratégicas. Coordenação De Prevenção E Vigilância, Estimativa 2012 : Incidência De Câncer No Brasil, INCA, Rio De Janeiro, (2011).
[35] D. Forman, F. Bray, D. Brewster, C. Gombe Mbalawa, B. Kohler, M. Piñeros, E. Steliarova-Foucher, R. Swaminathan, J. Ferlay, Cancer Incidence in Five Continents, Vol. X (electronic version), (2013) (Accessed 11 May 2017), http://ci5.iarc.fr.
[36] I.M. Lee, E.J. Shiroma, F. Lobelo, P. Puska, S.N. Blair, P.T. Katzmarzyk, Effect of physical inactivity on major non-communicable diseases worldwide: an analysis of burden of disease and life expectancy, Lancet 380 (9838) (2012) 219–229.
[37] J. Hayes, A. Richardson, C. Frampton, Population attributable risks for modifiable lifestyle factors and breast cancer in New Zealand women, Intern. Med. J. 43 (11) (2013) 1198–1204.
[38] D.R. Brenner, Cancer incidence due to excess body weight and leisure-time physical inactivity in Canada: implications for prevention, Prev. Med. 66 (2014) 131–139.
[39] D.R. Brenner, A.E. Poirier, A. Grundy, F. Khandwala, A. McFadden, C.M. Friedenreich, Cancer incidence attributable to inadequate physical activity in Alberta in 2012, CMAJ Open 5 (2) (2017) E338–E344.
[40] C.M. Olsen, L.F. Wilson, C.M. Nagle, B.J. Kendall, C.J. Bain, N. Pandeya, P.M. Webb, D.C. Whiteman, Cancers in Australia in 2010 attributable to insufficient physical activity, Aust. N. Z. J. Public Health 39 (5) (2015) 458–463.
[41] D.M. Parkin, 9. Cancers attributable to inadequate physical exercise in the UK in 2010, Br. J. Cancer 105 (Suppl 2) (2011) S38–41.
[42] G. Azevedo e Silva, L. de Moura, M.P. Curado, Fd.S. Gomes, U. Otero, L.F.Md. Rezende, R.P. Daumas, R.M. Guimarães, K.C. Meira, Id.C. Leite, J.G. Valente, R.I. Moreira, R. Koifman, D.C. Malta, M.Sd.C. Mello, T.W.G. Guedes, P. Boffetta, The fraction of Cancer Attributable to ways of life, infections, occupation, and environmental agents in Brazil in 2020, PLoS One 11 (2) (2016) e0148761.
[43] L.F. de Rezende, F.M. Rabacow, J.Y. Viscondi, C. Luiz Odo, V.K. Matsudo, I.M. Lee, Effect of physical inactivity on major noncommunicable diseases and life expectancy in Brazil, J. Phys. Act. Health 12 (3) (2015) 299–306.
[44] M. Inoue, N. Sawada, T. Matsuda, M. Iwasaki, S. Sasazuki, T. Shimazu, K. Shibuya, S. Tsugane, Attributable causes of cancer in Japan in 2005–systematic assessment to estimate current burden of cancer attributable to known preventable risk factors in Japan, Ann. Oncol. 23 (5) (2012) 1362–1369.
[45] S. Park, Y. Kim, H.R. Shin, B. Lee, A. Shin, K.W. Jung, S.H. Jee, D.H. Kim, Y.H. Yun, S.K. Park, M. Boniol, P. Boffetta, Population-attributable causes of cancer in Korea: obesity and physical inactivity, PLoS One 9 (4) (2014) e90871.
[46] C.M. Friedenreich, H.K. Neilson, B.M. Lynch, State of the epidemiological evidence on physical activity and cancer prevention, Eur. J. Cancer 46 (14) (2010) 2593–2604.
[47] F. Islami, A. Goding Sauer, K.D. Miller, R.L. Siegel, S.A. Fedewa, E.J. Jacobs, M.L. McCullough, A.V. Patel, J. Ma, I. Soerjomataram, W.D. Flanders, O.W. Brawley, S.M. Gapstur, A. Jemal, Proportion and number of cancer cases and deaths attributable to potentially modifiable risk factors in the United States, CA. Cancer J. Clin. 68 (1) (2017) 31–54.
[48] M.A. Charafeddine, S.H. Olson, D. Mukherji, S.N. Temraz, G.K. Abou-Alfa, A.I. Shamseddine, Proportion of cancer in a Middle eastern country attributable to established risk factors, BMC Cancer 17 (1) (2017) 337.
[49] C. Naing, P.K. Lai, J.W. Mak, Immediately modifiable risk factors attributable to colorectal cancer in Malaysia, BMC Public Health 17 (1) (2017) 637.
[50] W.A. van Gemert, C.I. Lanting, R.A. Goldbohm, P.A. van den Brandt, H.G. Grooters, E. Kampman, L. Kiemeney, F.E. van Leeuwen, E.M. Monninkhof, E. de Vries, P.H. Peeters, S.G. Elias, The proportion of postmenopausal breast cancer cases in the Netherlands attributable to lifestyle-related risk factors, Breast Cancer Res. Treat. 152 (1) (2015) 155–162.
[51] D. Wang, W. Zheng, S.M. Wang, J.B. Wang, W.Q. Wei, H. Liang, Y.L. Qiao, P. Boffetta, Estimation of cancer incidence and mortality attributable to overweight, obesity, and physical inactivity in China, Nutr. Cancer 64 (1) (2012) 48–56.
[52] M.L. Levin, The occurrence of lung cancer in man, Acta Unio Int. Contra Cancrum 9 (3) (1953) 531–541.
[53] H.K. Neilson, M.S. Farris, C.R. Stone, M.M. Vaska, D.R. Brenner, C.M. Friedenreich, Moderate-vigorous recreational physical activity and breast cancer risk, stratified by menopause status: a systematic review and meta-analysis, Menopause 24 (3) (2017) 322–344.
[54] C. Pizot, M. Boniol, P. Mullie, A. Koechlin, M. Boniol, P. Boyle, P. Autier, Physical activity, hormone replacement therapy and breast cancer risk: A meta-analysis of prospective studies, Eur. J. Cancer 52 (2016) 138–154.
[55] T. Boyle, T. Keegel, F. Bull, J. Heyworth, L. Fritschi, Physical activity and risks of proximal and distal colon cancers: a systematic review and meta-analysis, J. Natl. Cancer Inst. 104 (20) (2012) 1548–1561.
[56] K.Y. Wolin, Y. Yan, G.A. Colditz, I.M. Lee, Physical activity and colon cancer prevention: a meta-analysis, Br. J. Cancer 100 (4) (2009) 611–616.
[57] P. Boffetta, J.K. McLaughlin, C. La Vecchia, R.E. Tarone, L. Lipworth, W.J. Blot, False-positive results in cancer epidemiology: a plea for epistemological modesty, J. Natl. Cancer Inst. 100 (14) (2008) 988–995.
[58] M.R. Munafo, G.D. Smith, Robust research needs many lines of evidence, Nature 553 (7689) (2018) 399–401.
[59] D.A. Lawlor, K. Tilling, G. Davey Smith, Triangulation in aetiological epidemiology, Int. J. Epidemiol. 45 (6) (2016) 1866–1886.
[60] K.J. Rothman, Causes, Am. J. Epidemiol. 104 (6) (1976) 587–592.
[61] B. Lauby-Secretan, C. Scoccianti, D. Loomis, Y. Grosse, F. Bianchini, K. Straif, Body fatness and Cancer–Viewpoint of the IARC working group, N. Engl. J. Med. 375 (8) (2016) 794–798.
[62] World Cancer Research Fund/American Institute for Cancer research, Continous Update Project Expert Report 2018. Body Fatness and Weight Gain and the Risk of Cancer, (2018) dietandcancerreport.org.
[63] A.D. Moreira, R.M. Claro, M.S. Felisbino-Mendes, G. Velasquez-Melendez, Validity and reliability of a telephone survey of physical activity in Brazil, Rev. Bras. Epidemiol. 20 (1) (2017) 136–146.
[64] K.P. Dowd, R. Szeklicki, M.A. Minetto, M.H. Murphy, A. Polito, E. Ghigo, H. van der Ploeg, U. Ekelund, J. Maciaszek, R. Stemplewski, M. Tomczak, A.E. Donnelly, A systematic literature review of reviews on techniques for physical activity measurement in adults: a DEDIPAC study, Int. J. Behav. Nutr. Phys. Act. 15 (1) (2018) 15.
[65] G.I. Mielke, P.C. Hallal, D.C. Malta, I.M. Lee, Time trends of physical activity and television viewing time in Brazil: 2006-2012, Int. J. Behav. Nutr. Phys. Act. 11 (101) (2014).