LEANDRO FÓRNIAS MACHADO DE REZENDE

**Atividade física e câncer:
evidências epidemiológicas e perspectivas para prevenção do
câncer no Brasil**

Tese apresentada à Faculdade de Medicina da Universidade

de São Paulo para obtenção do título de Doutor em Ciências

Programa de Saúde Coletiva

Orientador: Prof. Dr. José Eluf Neto

São Paulo

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Dados Internacionais de Catalogação na Publicação (CIP)

Preparada pela Biblioteca da
Faculdade de Medicina da Universidade de São Paulo

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Rezende, Leandro Fórnias Machado de
Atividade física e câncer : evidências epidemiológicas e perspectivas para
prevenção do câncer no Brasil / Leandro Fórnias Machado de
Rezende. -- São Paulo, 2018.
Tese(doutorado)--Faculdade de Medicina da Universidade de São Paulo.
Programa de Saúde Coletiva.
Orientador: José Eluf Neto.

Descritores: 1.Atividade física 2.Neoplasias 3.Prevenção de doenças
4.Epidemiologia 5.Saúde pública 6.Causalidade

USP/FM/DBD-486/18

Responsável: Erinalva da Conceição Batista, CRB-8 6755

DEDICATÓRIA

À minha família

AGRADECIMENTOS

Ao meu orientador, José Eluf Neto, pela confiança, dedicação e incentivo.

Aos meus queridos pais, pelo amor, pelos valores e ensinamentos preciosos e as oportunidades proporcionadas.

Ao meu irmão, Guilherme, meu orgulho e admiração.

À Ju, pelo amor, parceria e por estar sempre ao meu lado, mesmo quando a distância se fez presente.

Ao Ringo, pelo amor incondicional e os lambeijos, todos os dias.

Aos professores Alicia Matijasevich Manitto, Victor Wünsch Filho e Moyses Szklo, pelas preciosas contribuições no exame de qualificação de doutorado.

Aos amigos/co-orientadores/conselheiros Renata Levy, Maria Fernanda, Marcia Couto, Catarina Azeredo, Thiago de Sá, Leandro Garcia, Maria Carolina Borges, Fernando Adami, Juan Pablo Rey-López, Rafael Claro, Alexandre Grangeiro, Olinda Luiz e Euclides Castilho.

Aos colaboradores dos manuscritos que compuseram esta tese.

Ao CELAFISCS, especialmente ao Dr. Victor Matsudo, onde tudo começou.

Aos amigos e colegas Edward Giovannucci, Donghoon Lee, NaNa Keum, Kana Wu e Mingyang Song, pela recepção, experiência e aprendizados em Boston.

A todos alunos, professores, pesquisadores e funcionários do Departamento de Medicina Preventiva da Faculdade de Medicina da Universidade de São Paulo, pelos valiosos aprendizados e oportunidades.

Às amigas Maria Laura, Giovanna, Camila, Priscila, Carla, Maria, e Larissa, pelos aprendizados, ajudas e celebrações.

Aos membros do Núcleo de Pesquisas Epidemiológicas em Nutrição e Saúde, pelos aprendizados acadêmicos

À Fundação de Amparo à Pesquisa do Estado de São Paulo (FAPESP), pela bolsa de doutorado no país (processo nº 2014/25614-4) e pela bolsa de estágio de pesquisa no exterior (processo nº 2016/21390-0).

Death in old age is inevitable, but before old age is not

Richard Doll, 1994

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Abreviaturas dos títulos dos periódicos de acordo com *List of Journals Indexed in Index Medicus*.

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RESUMO

Rezende LFM. *Atividade física e câncer: evidências epidemiológicas e perspectivas para prevenção do câncer no Brasil* [tese]. São Paulo: Faculdade de Medicina, Universidade de São Paulo; 2018.

Câncer é a segunda maior causa de morte no Brasil e no mundo. Esse cenário tende a se agravar devido ao crescimento e envelhecimento populacional e ao aumento da prevalência das causas de câncer na população. Compreender o papel da atividade física na redução do risco de câncer é de grande interesse na literatura epidemiológica. Os objetivos deste estudo foram (i) avaliar a associação entre atividade física e o risco de câncer na população; (ii) estimar a potencial contribuição da atividade física na prevenção e controle do câncer no Brasil. Cinco manuscritos compuseram essa tese. O primeiro apresentou revisão de literatura sobre a consistência da evidência epidemiológica sobre a associação entre atividade física e 22 tipos de câncer. Os resultados indicaram que a atividade física em adultos está associada com menor risco de sete tipos de câncer. No entanto, houve evidência consistente apenas para os cânceres de cólon e mama pós-menopausa. Evidência para outros tipos de câncer apresentou indícios de viés e heterogeneidade na literatura. O segundo manuscrito avaliou a associação entre atividade física durante a adolescência e risco de adenoma colorretal, um precursor de câncer colorretal. Os resultados indicaram que a atividade física durante a adolescência também pode contribuir para menor risco de câncer colorretal, independentemente da atividade física na fase adulta. Mulheres que praticaram mais atividade física na adolescência apresentaram menor risco de adenoma colorretal do que aquelas que praticaram menos atividade física. O terceiro manuscrito investigou a influência do tipo e intensidade da atividade física para redução de biomarcadores inflamatórios e de resposta à insulina relacionados ao risco de câncer. A atividade física foi associada com menor concentração desses biomarcadores. As associações foram mais fortes em participantes que praticaram atividade física aeróbica e de força combinadas. Não houve benefício adicional de atividades físicas de intensidade vigorosa, comparado com atividades moderadas. O quarto e o quinto avaliaram, respectivamente, a preventabilidade de câncer mediante o aumento da atividade física no Brasil; a magnitude dessa preventabilidade *vis-à-vis* a redução de fatores de risco

relacionados ao estilo de vida. Aproximadamente 10 mil casos de câncer (12% dos casos de câncer de mama pós-menopausa e 19% dos casos de câncer de cólon) poderiam ser prevenidos por ano mediante o aumento da atividade física. No entanto, tabagismo ainda é a principal causal de câncer no Brasil, seguido de excesso de peso/obesidade e consumo de álcool. A redução de todos fatores de risco relacionados ao estilo de vida (tabagismo, excesso de peso, consumo de álcool, falta de atividade física, e alimentação não saudável) poderia prevenir até 27% de todos os casos de câncer e 34% de todas as mortes por câncer no Brasil. Em conclusão, atividade física, desde a infância até a fase adulta, pode reduzir o risco de alguns tipos de câncer. Mecanismos biológicos corroboram essas associações e indicam maior benefício para atividades aeróbicas e de força combinadas. Resultados das estimativas de preventabilidade de câncer mediante aumento da atividade física podem ser úteis para estratégias de prevenção e controle do câncer no Brasil.

Descritores: atividade física; neoplasias; prevenção de doenças; epidemiologia; saúde pública; causalidade

ABSTRACT

Rezende LFM. *Physical Activity and cancer: epidemiological evidence and perspectives for cancer prevention in Brazil*. [thesis]. São Paulo: “Faculdade de Medicina, Universidade de São Paulo”; 2018.

Cancer is the second leading cause of death in Brazil and worldwide. This scenario has an aggravating effect due to expected population aging and growth and the increasing prevalence of cancer causes. To understand the role of physical activity in reducing the risk of cancer is of high interest in epidemiological literature. The objectives of this study were: (i) to evaluate the association between physical activity and risk of cancer in the population; (ii) to estimate the potential contribution of physical activity for cancer prevention and control in Brazil. Five manuscripts composed this thesis. The first presented a review of the literature on the consistency of epidemiological evidence between physical activity and 22 types of cancer. The results showed that physical activity in adults was associated with a lower risk of seven types of cancer. However, only breast post-menopausal and colon cancers were supported by convincing evidence. Evidence for the other types of cancer presented hints of bias and heterogeneity in the literature. The second manuscript examined the association between physical activity during the adolescence and risk of colorectal adenomas, a precursor of colorectal cancer. Physical activity during the adolescence was associated with lower the risk of colorectal cancer, independent of physical activity during adulthood. Women with high physical activity during adolescence presented lower risk of adenomas later in life compared to those with lower physical activity. The third manuscript investigated the influence of type and intensity of physical activity with cancer biomarkers of inflammatory and insulin response. High physical activity was associated with favorable concentration of cancer biomarkers. Associations were stronger for combined aerobic and resistance training. There were no additional benefits of engaging in vigorous physical activity over moderate activities. The fourth and fifth manuscripts evaluated, respectively, the preventability of cancer by increasing physical activity in Brazil; and the magnitude of this preventability *vis-à-vis* the reduction of other lifestyle risk factors. About 10 thousand cancer cases per year (12% of postmenopausal cancers and 19% of colon cancers) could be avoided by increasing population-wide physical activity in

Brazil. However, smoking is still the major cause of cancer in Brazil, followed by overweight/obesity and alcohol consumption. The reduction of all lifestyle risk factors (smoking, overweight/obesity, alcohol consumption, lack of physical activity and unhealthy diet) could potentially avoid up to 27% of all cancer cases and 34% of all cancer deaths in Brazil. In conclusion, physical activity, from childhood to adulthood, may reduce the risk of some types of cancer. Biological mechanisms corroborate these associations and indicate more favorable outcomes for combined aerobic and resistance training. Our findings on preventability of cancer by increasing population-wide physical activity may be useful for cancer prevention strategies in Brazil.

Descriptors: physical activity; neoplasms; disease prevention; epidemiology; public health; causality

APRESENTAÇÃO

Desde os idos de 1920, a epidemiologia, ciência responsável por identificar as causas das doenças e condições de saúde em populações, avalia o efeito putativo da atividade física na redução do risco do câncer. Naquele contexto, já se reconhecia que, se os achados preliminares de fato refletissem uma relação de causa e efeito, a atividade física poderia contribuir com a prevenção dessa doença: *“If muscular activity has an intimate relationship to carcinoma, the value of it will be most apparent in prophylaxis, the field which to date promises the most in the attack on this malady”* (Sivertsen; Dahlstrom, 1922, p. 365-6). Doravante, compreender essa relação é ainda mais necessário. Atualmente, a carga do câncer é alta, e tende a se agravar nas próximas décadas tendo vista o aumento e envelhecimento populacional projetados para as próximas décadas, especialmente em países de baixa e média renda. Ademais, populações modernas, altamente urbanizadas e industrializadas, têm apresentado modos de vida com baixos níveis de atividade física no cotidiano. No Brasil, por exemplo, aproximadamente metade da população pratica menos de 30 minutos de atividade física por dia.

Posto isto, essa pesquisa, iniciada em 2014 com meu ingresso no doutorado junto ao Departamento de Medicina Preventiva da Faculdade de Medicina da Universidade de São Paulo, forjou-se na (i) investigação da evidência epidemiológica sobre atividade física e câncer; (ii) quantificação de casos e mortes por câncer potencialmente preveníveis mediante o aumento da atividade física no Brasil. Pretendo com isso, contribuir com o conhecimento e o debate científicos acerca do efeito protetor da atividade física no risco de câncer, e, consecutivamente, fornecer elementos que embasem estratégias de prevenção e controle do câncer no Brasil.

No primeiro capítulo, exponho o contexto científico em que essa pesquisa está inserida. Apresento, inicialmente, um panorama geral da magnitude do problema, isto é, “a carga do câncer no Brasil e no mundo” em termos de incidência e mortalidade. O cenário é alarmante. Em 28 países do mundo, o câncer já é a principal causa de morte. Em outros, como países de baixa e média renda, ambas taxas de incidência e mortalidade por câncer são altas - porém menores do que países de alta renda - e o

acesso ao tratamento adequado é escasso, de modo que a prevenção se configura como a maneira mais realista e efetiva para o controle da doença. Nesse sentido, identificar e intervir nas principais causas que aumentam o risco de câncer na população é imperativo.

Nas seções de “causas do câncer e inferência causal em epidemiologia” e “preventabilidade do câncer” apresento os principais fatores que atuariam no processo complexo, não linear e de múltiplas etapas da carcinogênese. Seriam a má sorte e os fatores hereditários os principais fatores envolvidos no risco de câncer? Fatores ambientais e de estilo de vida também importam? Como e em que medida a epidemiologia contribuiu para a identificação das causas do câncer na população? É possível estimar a proporção e número de casos de câncer potencialmente preveníveis, isto é, que não teriam acontecido ou aconteceriam tardiamente, mediante a redução das causas do câncer? São alguns dos tópicos que procurei abordar nessas seções.

Na seção “atividade física e câncer: antecedente e justificativas” apresento um breve histórico dos estudos epidemiológicos sobre atividade e câncer. A *International Agency for Research on Cancer*, o *World Cancer Research Fund International* e dezenas de publicações realizadas por grupos independentes de pesquisadores ao redor do mundo, apontam uma possível relação causal entre atividade e a diminuição de alguns tipos de câncer. Mas quais são os principais mecanismos biológicos pelos quais a atividade física poderia reduzir o risco de câncer? Existem explicações alternativas à causalidade que poderiam explicar as associações observadas nesses estudos epidemiológicos? Espero responder essas inquietações ao final desse tópico.

Finalmente, destaco as perguntas de pesquisa que motivaram e nortearam o desenvolvimento dessa pesquisa, e que, ao meu ver, tem recebido pouco destaque na literatura. Essas perguntas de pesquisa compuseram os objetivos da tese (Capítulo 2), concretizados em cinco manuscritos, brevemente apresentados a seguir.

O capítulo 3 consiste no manuscrito intitulado “*Physical activity and cancer: an umbrella review of the literature including 22 major anatomical sites and 770,000 cancer cases*”, que avaliou a consistência da evidência epidemiológica, bem como indícios de viés na literatura, que, por ventura, favoreceriam a publicação de “resultados positivos” sobre o efeito da atividade física nos diferentes tipos de câncer.

O capítulo 4 trata-se do manuscrito “*Physical activity during adolescence and risk of colorectal adenoma in women*”, que avaliou o possível papel da atividade física

no início da vida para redução o risco de câncer na fase adulta. Nesse manuscrito investigamos a associação entre atividade física na adolescência e risco de adenoma colorretal, um precursor do câncer colorretal, utilizando dados da coorte *Nurses' Health Study II*. Esse trabalho foi produto do estágio de pesquisa no exterior realizado no Departamento de Nutrição da *Harvard T.H. Chan School of Public Health* no ano de 2017/2018, sob supervisão do Professor Edward Giovannucci.

O capítulo 5 trata-se do manuscrito “*Association of type and intensity of physical activity with plasma biomarkers of inflammation and insulin response*”, que avaliou a influência do tipo e intensidade da atividade física para redução de biomarcadores inflamatórios e de resposta à insulina relacionados ao risco de câncer. Avaliamos ainda se essas associações diferem segundo padrão de alimentação e adiposidade dos indivíduos. Nesse trabalho, também fruto do estágio de pesquisa descrito anteriormente, utilizamos dados do *Health Professionals Follow-up Study*.

Nos capítulos 6 e 7, numa tentativa de traduzir os conhecimentos obtidos nos capítulos anteriores para a prática, procurei utilizar o instrumental da epidemiologia para gerar informações potencialmente úteis para gestão em saúde pública. Explico. Nos manuscritos “*Preventable fractions of colon and breast cancers by increasing physical activity in Brazil: perspectives from plausible counterfactual scenarios*” e “*Proportion of cancer cases and deaths attributable to lifestyle risk factors in Brazil*” estimei o potencial de prevenção de câncer (preventabilidade) no Brasil mediante o aumento da atividade física na população. Posteriormente, comparei essas estimativas de preventabilidade *vis-à-vis* a outros fatores de risco relacionados ao aumento do risco de câncer (tabagismo, consumo de álcool, excesso de peso/obesidade e alimentação não saudável). Para isso, foram utilizadas informações de pesquisas com amostras representativas do Brasil, informações do risco relativos do câncer e estimativas de casos e mortes por câncer no Brasil.

No capítulo de considerações finais, discuto as principais implicações dos achados dessas pesquisas para o avanço do conhecimento acerca do efeito protetor da atividade física no risco de câncer e para estratégias de prevenção do câncer no Brasil.

1. INTRODUÇÃO

1.1. A CARGA DO CÂNCER NO BRASIL E NO MUNDO

Cancer is costly. First and foremost, there is the human cost, comprising the uncertainty and suffering that a diagnosis of cancer brings in its wake. Behind each statistic of a new cancer case is an individual face, accompanied by the faces of family and friends drawn into this singular event. The harrowing experience of a cancer diagnosis is a truly universal one, played out in every community worldwide, every day (Wild, 2014a, p. x).

O último levantamento da Agência Internacional de Pesquisa em Câncer (*International Agency for Research on Cancer - IARC*) estimou que, em 2018, ocorreram 18,1 milhões casos de câncer (excluindo câncer de pele não-melanoma) e 9,6 milhões de mortes por câncer no mundo. A taxa de incidência de câncer, ajustada por idade, foi aproximadamente 20% maior em homens (218,6 casos por 100 000) do que em mulheres (182,6 casos por 100 000). Em homens, observou-se grande variação nas taxas de incidência de câncer entre os continentes, com maiores taxas na Oceania (509,9 por 100 000) e menores taxas na África (121,9 por 100 000). Em mulheres, houve menor variação nas taxas de incidência de câncer entre os continentes, com maiores taxas na Oceania (335,2 por 100 000) e menores taxas na África (139,2 por 100 000) (Bray et al., 2018; Ferlay et al., 2018). Vale ressaltar que, as diferenças nas taxas de incidência segundo os continentes, pode ser explicada tanto pela distribuição das causas dos diferentes tipos de câncer, quanto pela disponibilidade de programas e serviços de detecção da doença, que por sua vez se refletem na qualidade dos registros de câncer.

Em relação às taxas de mortalidade por câncer, houve menor variação segundo os diferentes continentes. Em homens, a taxa de mortalidade por câncer variou de 90,2 por 100 000 na África a 144,0 por 100 000 na Europa. Em mulheres, a taxa de mortalidade por câncer variou de 80,0 por 100 000 na Ásia a 86,9 por 100 000 na Oceania (Figura 1) (Bray et al., 2018; Ferlay et al., 2018).

Figura 1 - Taxas de incidência e mortalidade por câncer, segundo sexo e continentes do mundo, 2018

Taxas padronizadas por idade por 100.000 habitantes. Excluindo câncer de pele não melanoma. Fonte: Ferlay J, Ervik M, Lam F, Colombet M, Mery L, Piñeros M, Znaor A, Soerjomataram I, Bray F (2018). Global Cancer Observatory: Cancer Today. Lyon, France: International Agency for Research on Cancer. Disponível em <https://gco.iarc.fr/today>, acessado em 17/09/2018.

Diferenças nas taxas de mortalidade por câncer entre regiões podem estar relacionadas tanto com a incidência de câncer quanto com a sobrevivência de pacientes. Portanto, não apenas a distribuição das causas do câncer e dos programas e serviços de rastreamento podem explicar a variabilidade das taxas de mortalidade por câncer, como também o acesso ao tratamento adequado da doença (Ezzati et al., 2018).

As taxas de incidência e mortalidade por câncer, ajustadas por idade, são de 2 a 3 vezes maiores em países de alta renda comparado aos países de baixa e média renda. Apesar de países de baixa e média renda representarem mais de 80% da população mundial, apenas 43% dos casos diagnosticados e 65% das mortes por câncer ocorrem nesses países (Bray et al., 2018; Ferlay et al., 2018). Entretanto, a carga do câncer tende a se agravar em países de baixa e média renda devido a mudança na composição demográfica – crescimento e envelhecimento populacional (Bray; Moller, 2006). Estimativas apontam que entre 2018 e 2040 haverá um aumento de 63% no total de casos de câncer diagnosticados no mundo, com maior magnitude de aumento em países de baixa e média renda (Bray et al., 2018; Ferlay et al., 2018). Na América do Sul, por exemplo, estima-se um aumento de 76% (85,5% em homens e 67,4% nas mulheres) no total de casos de câncer diagnosticados no período (Bray et al., 2018; Ferlay et al., 2018).

Em relação aos tipos de câncer, no mundo, os tumores de pulmão/brônquios/traqueia e mama foram os tipos mais frequentemente diagnosticados e as principais causas de morte por câncer em homens e mulheres, respectivamente. Além desses, os tumores de próstata, colorretal e estômago também apresentaram altas taxas de incidência e mortalidade em homens. Em mulheres, destacaram-se ainda os cânceres colorretal, pulmão e colo de útero (Figura 2) (Bray et al., 2018; Ferlay et al., 2018).

Figura 2 - Incidência e mortalidade por câncer no mundo, segundos sexo e tipos de câncer, 2018

Taxas padronizadas por idade por 100.000 habitantes. Fonte: Ferlay J, Ervik M, Lam F, Colombet M, Mery L, Piñeros M, Znaor A, Soerjomataram I, Bray F (2018). Global Cancer Observatory: Cancer Today. Lyon, France: International Agency for Research on Cancer. Disponível em <https://gco.iarc.fr/today>, acessado em 17/09/2018.

No Brasil, ocorreram aproximadamente 560 mil casos de câncer em 2018 (excluindo câncer de pele não-melanoma), dos quais 279 mil em homens e 281 mil em mulheres (Tabela 1). Em homens, os tipos de câncer mais frequentemente diagnosticados foram próstata, cólon e reto e pulmão. Em mulheres, câncer de mama, colo do útero e colorretal foram os mais frequentes. Em relação à mortalidade por câncer, aproximadamente 244 mil mortes ocorreram em 2018, das quais mais da metade (129 mil) em homens. As maiores taxas de mortalidade segundo tipos de câncer foram pulmão, próstata e colorretal em homens, e mama, pulmão e colorretal em mulheres (Ferlay et al., 2018).

Tabela 1 - Incidência e mortalidade por câncer no Brasil, 2018

Indicador	Masculino	Feminino	Ambos sexos
<i>População</i>	103 599 314	107 268 645	210 867 959
<i>Incidência</i>			
Número de novos casos de câncer	278 607	280 764	559 317
Taxa de incidência padronizada por idade*	240,9	201,5	217,2
Tipos de câncer mais frequentes	Próstata Colorretal Pulmão Estômago Bexiga	Mama Colorretal Tireoide Colo do útero Pulmão	Mama Próstata Colorretal Pulmão Tireoide
<i>Mortalidade</i>			
Número de mortes por câncer	129 134	114 454	243 588
Taxa de mortalidade padronizada por idade*	109,7	77,9	91,3
Tipos de câncer mais frequentes	Pulmão Próstata Colorretal Estômago Esôfago	Mama Pulmão Colorretal Colo do útero Pâncreas	Pulmão Colorretal Mama Próstata Estômago

*Taxa padronizada por idade por 100.000 habitantes. Excluindo câncer de pele não melanoma. Adaptado e traduzido de Ferlay J, Ervik M, Lam F, Colombet M, Mery L, Piñeros M, Znaor A, Soerjomataram I, Bray F (2018). Global Cancer Observatory: Cancer Today. Lyon, France: International Agency for Research on Cancer. Disponível em <https://gco.iarc.fr/today>, acessado em 17/09/2018.

Em síntese, altas taxas de incidência e mortalidade por câncer acometem a população mundial. Os cânceres de pulmão e mama são os mais frequentes em homens e mulheres, respectivamente, mas existe grande variação na incidência e mortalidade dos tipos de câncer segundo regiões. Aproximadamente 40% dos casos e 65% das mortes por câncer ocorrem em países de baixa e média renda, justamente onde os casos

de câncer são detectados em estádios mais avançados e o acesso ao tratamento da doença é escasso. Ainda que tais recursos estivessem disponíveis, como ocorre em alguns países de alta renda, o “custo humano e social” do câncer é alto (Wild, 2014a). Portanto, identificar, compreender e intervir nas principais causas que aumentam o risco de câncer é necessário para prevenção e controle da doença na população.

1.2. CAUSAS DO CÂNCER E INFERÊNCIA CAUSAL EM EPIDEMIOLOGIA

Is there any other way of explaining the set of facts before us, is there any other answer equally, or more, likely than cause and effect? (Hill, 1965, p. 299)

A epidemiologia é a ciência responsável por identificar as causas das doenças e das condições de saúde em populações. O processo de inferência causal, isto é, de sugerir relações de causa e efeito para ocorrência da doença na população, sofreu mudanças substanciais ao longo da história. Do miasma ao modelo de multicausalidade das doenças, foram muitos os estudiosos que problematizaram, revisaram e propuseram novas formas de compreensão da causalidade, cada qual contribuindo com o debate à luz dos conhecimentos vigentes e dos problemas e condições de saúde enfrentados à época (Susser, 1991).

Em epidemiologia, entende-se por causa um fator, característica ou condição que, necessariamente precede, e contribui para a ocorrência da doença em alguns indivíduos da população (Rothman, 1976). Outra maneira de conceitualizar causa é por meio da abordagem de desfechos potenciais ou desfechos contrafactuais. Esse conceito tem sido abordado por pensadores e pesquisadores de diversas áreas desde, pelo menos, o filósofo David Hume:

We may define a cause to be an object, followed by another, and where all objects, similar to the first, are followed by objects similar to the second. Or in other words, where, if the first object had not been, the second never had existed (Hume, 1748 apud Lewis, 1973, p. 556).

Nesse contexto, dizemos que há uma relação de causa e efeito se o desfecho (doença = 1) fosse diferente em alguns indivíduos da população (doença = 0) tivesse o fator, característica ou condição sido diferente (causa = 0) do que foi (causa = 1). Esse conceito foi formalizado na literatura estatística por Neyman (1923), no contexto de experimentos randomizados em agricultura, Rubin (1974), em estudos epidemiológicos observacionais, e mais recentemente por Robins (1986) e Pearl (1995) em teoria de diagramas causais ou gráficos acíclicos direcionados (VanderWeele, 2015).

Essa relação de causa e efeito deve ser entendida em termos probabilísticos, uma vez que são raras, se existentes, as causas que contribuem isoladamente para ocorrência da doença. Se assim o fosse, essa causa poderia ser considerada suficiente e necessária. Entende-se por causas suficientes, fatores que produzem inevitavelmente a ocorrência de uma doença. Em seu modelo de causas suficientes e causas componentes (*Rothman's Pie model*), Rothman define causa suficiente como constelação de fenômenos, ou causas componentes, que quando acumulados produzem a doença (Rothman, 1976). Por exemplo, pessoas que fumam apresentam, em média, risco de desenvolver câncer de pulmão 23 vezes maior do que pessoas que não fumam (Carter et al., 2015). Entretanto, o tabagismo não é causa suficiente do câncer de pulmão, uma vez que nem todos indivíduos que fumam terão a doença. Portanto, o hábito de fumar deve ser entendido como uma causa componente importante, presente em diversas, mas não em todas, causas suficientes que produzem o câncer de pulmão. Por fim, algumas pessoas que não fumam ao longo da vida também desenvolvem câncer de pulmão e, portanto, o hábito de fumar não é causa necessária da doença (Keyes; Galea, 2014).

Causa necessária pode ser entendida como uma causa componente que está presente em todas as causas suficientes que produzem a doença (Rothman, 1976). Um exemplo de causa necessária em epidemiologia do câncer é o papiloma vírus humano (*Human papillomavirus* – HPV), pois este estaria presente em todas as causas suficientes do câncer de colo do útero. Em outras palavras, todas as mulheres com câncer de colo do útero teriam sido infectadas pelo HPV antes da ocorrência da doença. Caso o HPV fosse eliminado, 100% dos casos de câncer de colo do útero seriam evitados. Entretanto, o HPV não é capaz de influenciar de forma isolada a ocorrência do câncer de colo do útero (não é causa suficiente), pois a grande maioria das mulheres infectadas pelo vírus não desenvolvem a doença (Lagiou et al., 2008).

Identificar todas as causas componentes, apesar de importante para compreensão da etiologia, é desnecessário do ponto de vista da prevenção das doenças. Para atuar na prevenção das doenças, Rothman (1976) argumenta que bastaria intervir nas principais causas componentes da doença, ou seja, nas causas componentes que estão presentes em diversas causas suficientes. Dessa forma, removendo ou reduzindo essas causas, o conjunto das demais causas componentes seria insuficiente para produzir a doença (Rothman, 1976). Richard Peto define essas causas componentes como “as grandes causas”, e argumenta que “*a moderate reduction in a big cause can prevent far more deaths than a big reduction in a small cause*” (Peto et al., 2014; The, 2016, p. 414). Esse conceito é especialmente relevante no modelo de multicausalidade das doenças, atualmente utilizado na compreensão da etiologia do câncer.

Entendemos que a ocorrência do câncer (efeito) se deve a diversos fatores, características e condições (causas componentes), acumulados ao longo da vida, que iniciam e promovem mutações genéticas de células normais, até que uma causa suficiente seja completada e ocorra a formação e progressão do tumor maligno (Rothman, 1976; Hanahan; Weinberg, 2011). Com efeito, a realidade é mais complexa do que isso. A carcinogênese é um processo complexo, não linear e de múltiplas etapas (iniciação, promoção e progressão), em que células normais sofrem alterações genéticas e adquirem fenótipos malignos. Câncer é um grupo de doenças heterogêneas, que ocorrem em diferentes tecidos, e que apresentam biologia, características e etiologia distintas. Até mesmo tumores que ocorrem em um mesmo sítio (câncer de mama) apresentam heterogeneidade biológica marcante. Não obstante, algumas “marcas registradas” (*The Hallmarks of Cancers*) - capacidades biológicas desenvolvidas pelas células tumorais ao longo do processo de carcinogênese - auxiliam na definição desse grupo de doenças. São elas: a capacidade de i) sustentar sinais de proliferação; ii) evitar supressão do crescimento; iii) evitar destruição pelo sistema imune; iv) permitir imortalidade replicativa; v) ativar sinais de invasão e metástase; vi) induzir angiogênese; vii) resistir a sinais de morte celular; e viii) desregulação energética da célula. Essas capacidades são facilitadas por duas características do tumor, desenvolvidas durante o processo de carcinogênese: i) instabilidade genética e mutação e ii) inflamação pró-tumorigênese (Hanahan; Weinberg, 2011).

São três os principais grupos de causas descritos na literatura que atuam na iniciação e promoção dessas mutações genéticas: processos estocásticos, fatores genéticos/hereditários e fatores ambientais e de estilo de vida (Song et al., 2018).

Recentemente publicada por Tomasetti e Vogelstein (2015), a teoria de processos estocásticos na causação do câncer sugere que o risco de diferentes tipos de câncer está associado com o número total de divisões de células tronco que ocorrem no sítio ao longo da vida. O conceito por de trás dessa teoria é que mudanças genômicas ocorreriam aleatoriamente durante o processo de replicação do ácido desoxirribonucleico (*deoxyribonucleic acid* - DNA). Portanto, as taxas de mutação das células tronco nos diferentes tecidos explicariam a variação da incidência de câncer entre os órgãos. Segundo os autores, esse modelo sugere que a maioria dos casos de câncer (65%) seria atribuível ao acaso. Essa teoria tem importantes implicações na compreensão da etiologia e prevenção do câncer, uma vez que, se genuína, apenas um terço dos casos de câncer seria atribuível às demais causas – hereditariedade e fatores ambientais e estilo de vida.

O efeito da susceptibilidade hereditária no risco de câncer está bem documentado na literatura. Em meados do século passado, estudos indicavam agregados de casos de câncer em famílias grandes, nomeada síndrome do câncer hereditário, corroborando com a hipótese de que fatores genéticos estão presentes na causação do câncer (Lynch et al., 1966). Famílias afetadas por essas síndromes apresentavam características peculiares, como casos de câncer raros, ocorrência de câncer em idades mais jovens, múltiplos tipos de câncer num mesmo indivíduo, câncer em ambos pares de órgãos e câncer infantil em irmãos (ACS, 2014). A partir da década de 80, com o desenvolvimento da biologia molecular, diversos genes de câncer inerentes (*inherited cancer genes*) foram identificados. Análises de *linkage*, em que membros familiares são categorizados quanto à presença ou ausência de determinados genes, permitiram identificar mutações em oncogenes e genes supressores de tumor que estariam associadas com a ocorrência do câncer (Cavenee et al., 1983). No entanto, essa relação entre a mutação genética e a ocorrência de câncer depende da presença de outros genes, bem como de fatores ambientais e de estilo de vida que poderiam influenciar o risco do câncer. Portanto, a presença de uma mutação genética inerente não deve ser entendida como causa suficiente do câncer (Fearon, 1997; ACS, 2014).

Além das mutações de alguns genes, a herança de outros genes raros e que apresentam menor risco para câncer (com menor penetração) também fornecem evidências sobre a susceptibilidade hereditária como causa de câncer. O conhecimento acerca da relação desses genes raros e a ocorrência de câncer foi obtido por meio dos *genomewide studies* (GWAS), em que milhares de polimorfismos de nucleotídeo único (*single-nucleotide polymorphisms* – SNPS) são investigados simultaneamente (Foulkes, 2008). Entretanto, esses estudos sugerem que apenas 5 a 10% dos tipos de câncer apresentariam algum componente hereditário (ACS, 2014).

Estudos sobre divisão de células tronco nos diferentes tecidos ao longo da vida e da susceptibilidade hereditária têm contribuído para o entendimento da etiologia do câncer. No entanto, esses estudos são, por vezes, interpretados e comunicados de maneira isolada, negligenciando evidências extensas sobre o papel de fatores de risco ambientais e de estilo de vida para câncer. Por exemplo, o estudo de Tomasetti e Vogelstein foi amplamente divulgado pela mídia, que por sua vez enalteceu que 65% dos casos de câncer são atribuíveis à má sorte/acaso, sendo apenas o complemento (35%) potencialmente prevenível (Tomasetti; Vogelstein, 2015; Davey Smith et al., 2016). A repercussão desses achados foi prontamente replicada por epidemiologistas que destacaram que diferenças nas taxas de câncer ao longo tempo e entre populações, bem como mudanças nas taxas de incidência de câncer em migrantes semelhantes às da população local, sugerem fortemente papel etiológico de fatores ambientes e de estilo de vida (Wild et al., 2015). Claramente, a mudança na má sorte não deve explicar essas diferenças nas taxas segundo pessoa, tempo e espaço (Davey Smith et al., 2016). Para estimar a proporção de casos de câncer que poderia ser potencialmente prevenida é necessário comparar as taxas de incidência de câncer entre as populações com diferentes padrões de fatores de risco (alto risco versus baixo risco), ao invés de comparar taxas de incidência de câncer em diferentes tecidos de um mesmo indivíduo (Doll; Peto, 1981; Song; Giovannucci, 2015). Isso porque as causas do câncer em indivíduos são distintas das causas do câncer nas populações (Rose, 1985; Davey Smith et al., 2016).

Além disso, é incorreta a afirmação de que 65% das diferenças das taxas de incidência de câncer entre as localizações são atribuíveis ao processo de divisão de células tronco ao longo dos anos e, portanto, apenas 35% dos casos estariam relacionados às demais causas (Tomasetti; Vogelstein, 2015). Ao afirmar isso, os

autores presumem que a fração da doença atribuível ao conjunto de causas componentes deve somar 100%. Entretanto, as doenças na população são causadas por diversas causas componentes, que se sobrepõem nas diferentes causas suficientes possíveis. Portanto, a soma da fração atribuível de cada fator causal (causa componente) pode ser maior que a unidade (Rothman, 1976; Song; Giovannucci, 2015).

A compreensão de que o câncer pode ser prevenido e controlado não é recente. A primeira referência que se tem notícia sobre a possibilidade de controle do câncer surgiu em 1913 com a criação da *American Society for the Control of Cancer*, que posteriormente se tornaria a *American Cancer Society*. Na época, o conceito de controle do câncer estava voltado às intervenções médicas, principalmente cirúrgicas, a fim de remover o tumor em estádios precoce da doença (Hiatt; Rimer, 2006). Já em novembro de 1963, o *World Health Organization Expert Committee on the Prevention of Cancer* já evidenciava o potencial de prevenção do câncer por meio da mudança do ambiente e do estilo de vida (WHO, 1964):

The potential scope of cancer prevention is limited by the proportion of human cancers in which extrinsic factors are responsible. These include all environmental carcinogens (whether already identified or not) as well as “modifying factors” that favour neoplasia of apparently intrinsic origin (e.g., hormonal imbalances, dietary deficiencies and metabolic defects). The types of cancer that are thus influenced, directly or indirectly, by extrinsic factors include many tumors of the skin and mouth, the respiratory, gastro-intestinal and urinary tracts, hormone-dependent organs (such as the breast, thyroid and uterus), haematopoietic and lymphopoietic systems - which, collectively, account for more than three-quarters of human cancers. It would seem, therefore, that the majority of human cancer is potentially preventable (WHO, 1964 apud Doll; Peto, 1981, p. 1197).

Atualmente existem evidências convincentes sobre o papel de diversos fatores ambientais e de estilo de vida que atuam na causação do câncer. A IARC já catalogou mais de 400 fatores de risco (Quadro 1), entre fatores ambientais, químicos, exposições ocupacionais, agentes físicos e biológicos, que apresentam evidência convincente ou provável sobre carcinogenicidade (IARC, 1971-2015):

Quadro 1 - Evidência de fatores ambientais potencialmente carcinogênicos segundo a Agência Internacional de Pesquisa em Câncer (IARC, 1971-2015)

Evidência sobre potencial carcinogênico	Número de agentes cancerígenos classificados
Grupo 1 - Agente cancerígeno para humanos: evidências suficientes de carcinogenicidade para humanos	120
Grupo 2A - Agente provavelmente cancerígeno para humanos: evidências limitadas de carcinogenicidade para humanos, mas evidências suficientes em animais	82
Grupo 2B - Agente possivelmente cancerígeno para humanos: evidências limitadas de carcinogenicidade em humanos e evidências insuficientes em animais	299
Grupo 3 - Agente não classificável em relação ao potencial cancerígeno para humanos: evidências de carcinogenicidade são inadequadas em humanos e insuficientes em animais.	502
Grupo 4 - Agente provavelmente não cancerígeno para humanos: evidências sugerindo que não há efeito cancerígeno em humanos e em animais	1

A epidemiologia teve um papel central na identificação dessas causas do câncer, ainda que a interpretação dos resultados dos estudos seja inerentemente desafiadora. O pressuposto de comparabilidade (*exchangeability*) entre os grupos exposto e não exposto à causa putativa é essencial no processo de inferência causal. Utilizando o conceito de desfecho contrafactual descrito anteriormente, seria possível identificar relações de causa e efeito, bem como estimar a magnitude do efeito causal no risco de câncer na população, se fosse possível comparar: (a) as taxas de incidência de câncer quando todos indivíduos da população são expostos ao fator causal com (b) as taxas de câncer que seriam observadas se os mesmos indivíduos da população não tivessem sido expostos a esse fator; mantendo os demais causais estáveis. Se as taxas de câncer obtidas nessas duas situações fossem diferentes, poderíamos dizer que há uma relação de causa e efeito entre a exposição e o câncer (Greenland et al., 2008; Hernán et al., 2004).

Em estudos epidemiológicos, no entanto, conseguimos comparar taxas de câncer em grupos diferentes (grupo exposto v.s. grupo não exposto) relativamente à exposição sob investigação. Dizemos que há uma associação quando a probabilidade de ocorrência da doença é diferente entre os grupos comparados. O contraste das taxas de câncer entre os grupos, expressa em diferenças absolutas ou relativas das taxas de câncer, é chamada de medida de associação. Quando há diferença entre a (real) magnitude do efeito causal da exposição no câncer e a magnitude de associação obtida no estudo, dizemos que associação $\neq$ causação. Em outras palavras, há viés na magnitude de associação encontrada no estudo (Greenland et al., 2008; Hernán et al., 2004).

Nesse sentido, ensaios clínicos randomizados, estudo de intervenção em que dois ou mais grupos de pessoas são alocados de forma aleatória (randomização) para receber (grupo intervenção) ou não receber (grupo controle) determinada intervenção relacionada ao potencial fator causal, forneceriam a melhor evidência sobre causalidade. Pelo processo de randomização, os grupos intervenção e controle se tornariam comparáveis no que diz respeito à distribuição de outras causas (conhecidas e desconhecidas) da doença. Portanto, a diferença no risco da doença entre os grupos estaria relacionada apenas à exposição/intervenção sob investigação (Lagiou et al., 2008). No entanto, em diversos contextos, ensaios clínicos randomizados não podem ser conduzidos por questões éticas e/ou logísticas e, portanto, estudos observacionais são frequentemente utilizados para investigar as causas da doença.

Em estudos observacionais, a interpretação causal das associações observadas torna-se mais difícil, devido a erros aleatórios, sistemáticos e confundimento. Ao passo que erros aleatórios podem ser solucionados com o aumento do tamanho da amostra e, consequentemente, da precisão das estimativas, vieses e confundimento ocorrem por insuficiência do delineamento do estudo durante a seleção dos participantes (viés de seleção), a coleta das informações sobre exposição e desfecho (viés de informação) e a análise e apresentação dos resultados (Lagiou et al., 2008; Rothman et al., 2008; Szklo; Nieto, 2014a).

Confundimento é particularmente preocupante em estudos observacionais. Entende-se por confundimento um efeito aparente da exposição na doença distorcido pelo efeito de uma outra variável - variável de confusão ou confundidor (Rothman et al., 2008; Szklo; Nieto, 2014b). A mistura de efeitos introduzida pela variável de confusão

pode distorcer a estimativa do efeito da exposição no desfecho, que pode ser inclusive nula, conforme apresentado na Figura 3.

Figura 3 - Diagrama causal representando associação espúria entre exposição (E) e desfecho (D) devido à confundimento (C)

Essa distorção da medida de associação dependerá da direção das associações entre a variável de confusão e exposição/desfecho, conforme apresentado abaixo na Tabela 2 (Rothman et al., 2008; Szklo; Nieto, 2014b):

Tabela 2 - Impacto do confundimento na associação entre exposição e desfecho segundo direção das associações entre variável de confusão e exposição e desfecho

Associação entre exposição e variável de confusão	Associação entre variável de confusão e desfecho	Mudança esperada na medida de efeito
Positiva	Positiva	$RR_{\text{bruto}} > RR_{\text{Ajustado}}$
Positiva	Negativa	$RR_{\text{bruto}} < RR_{\text{Ajustado}}$
Negativa	Negativa	$RR_{\text{bruto}} > RR_{\text{Ajustado}}$
Negativa	Positiva	$RR_{\text{bruto}} < RR_{\text{Ajustado}}$

Associação positiva: a presença da variável de confusão está associada com aumento na probabilidade da exposição/desfecho; Associação negativa: a presença da variável de confusão está associada com a diminuição na probabilidade da exposição/desfecho; RR: risco relativo. Fonte: Szklo M, Nieto J. Identifying Noncausal Associations: Confounding. In: Szklo M, Nieto J. Epidemiology: Beyond the Basics. 3rd edition. Jones & Bartlett Learning: Burlington; 2014b

Frequentemente, essas limitações (vieses e confundimento) não conseguem ser superadas em estudos epidemiológicos, gerando associações espúrias entre exposições e câncer. Entende-se que há viés na literatura quando o conjunto de estudos que investigam determinada relação entre exposição e desfecho apresentam resultados que, em média, diferem da real magnitude de efeito (Szklo; Nieto, 2014a).

O viés na literatura também ocorre por más práticas ao longo do processo hipotético-dedutível de produção do conhecimento científico: hipótese → delineamento do estudo → coleta dos dados → análise dos dados e teste de hipótese → interpretação

dos resultados → publicação. Análise dos dados com fins a mostrar resultados estatisticamente significante (*P-hacking*), conflitos de interesse e viés de publicação são alguns exemplos dessas práticas que podem impactar a validade e credibilidade da literatura (Munafò et al., 2018). O viés de publicação ocorre quando fatores outros, que não a qualidade metodológica dos estudos, influenciam a probabilidade da publicação dos achados. A presença de resultados estatisticamente significantes ($P < 0,05$) ou clinicamente favoráveis é um exemplo desses fatores que influenciam a disseminação e publicação dos estudos. Esse processo torna estimativas de efeito disponíveis na literatura enviesadas e, conseqüentemente, podem sugerir tomadas de decisões clínicas e em saúdes públicas incorretas (Dickersin, 1990; Young; Ioannidis, 2008; Munafò et al., 2018; Rezende et al., 2018).

Viés de publicação em estudos sobre causas do câncer tem sido investigado, identificado e problematizado na literatura. Por exemplo, resultados dos primeiros estudos sobre o potencial efeito de poluentes em câncer de mama, bem como exposição ocupacional à acrilonitrila em câncer de pulmão, não foram replicados em estudos subsequentes (Boffetta et al., 2008). De fato, os primeiros estudos em determinado campo de investigação tendem a superestimar a magnitude do efeito da exposição no desfecho em comparação aos estudos subsequentes. Esse fenômeno de regressão à média das estimativas de efeito pode ser explicado, entre outros fatores, pela diminuição do viés de publicação ao longo do tempo (Fanelli et al., 2017).

Diversas revisões de literatura têm identificado indícios de viés de publicação em meta-análises sobre associação entre alimentação, diabetes tipo 2, biomarcadores e o risco de câncer (Tsilidis et al., 2012; 2015; Schoenfeld; Ioannidis, 2013). O estudo publicado por Schoenfeld e Ioannidis (2013) é um exemplo particularmente interessante dessas revisões de literatura. Nesse estudo, foram obtidas informações a respeito das conclusões, significância estatística e reprodutibilidade na literatura sobre alimentos específicos e risco de câncer por meio de uma “revisão sistemática de livros de receitas”. Foram selecionados de forma aleatória 50 ingredientes de receitas e, posteriormente, uma revisão da literatura sobre a relação desses ingredientes com o risco de câncer foi conduzida. Aproximadamente 80% dos ingredientes selecionados tinham artigos na literatura sugerindo a relação com risco de câncer. Desses artigos ($n=264$), 72% ($n=191$) concluíram que o ingrediente estava associado com aumento ($n=103$) ou diminuição ($n=88$) no risco de câncer. A mediana e intervalos interquartis

das medidas de associação (riscos relativos) obtidas nos estudos variou de 2,20 (1,60 a 3,44) a 0,52 (0,39 a 0,66), sugerindo magnitude de efeito implausível quando comparadas com a síntese meta-analítica obtida em revisões sistemáticas sobre a mesma pergunta de pesquisa. Os resultados reportados nos resumos desses estudos apresentaram, com maior frequência, resultados estatisticamente significantes do que na seção de resultados do artigo. Esses achados sugerem o favorecimento da publicação de estudos com resultados estatisticamente significantes e com efeitos superestimados da alimentação no risco de câncer (Schoenfeld; Ioannidis, 2013). Portanto, é prudente analisar a possível influência de viés de publicação durante a investigação e interpretação da evidência sobre as possíveis causas do câncer na população.

Considerando que diversos vieses podem interferir na validade e credibilidade dos resultados de estudos epidemiológicos, diversos critérios têm sido utilizados para avaliação e interpretação da evidência. Os nove pontos de vista (ou critérios), descritos por Austin Bradford Hill para distinguir associação de causação, são os mais comumente utilizados e difundidos em epidemiologia (Tabela 3). Hill (1965) reconhece, no entanto, que nenhum desses critérios é condição *sine qua non* para discernir associações espúrias de causalidade, mas esses podem oferecer elementos importantes durante a avaliação da evidência.

Tabela 3 - Critérios de Austin Bradford Hill para discernir associação de causação, 1965

Critérios	Definição
Força de associação	Quanto maior a magnitude da associação, maior a evidência de que o fator é causal. A magnitude da associação pode ser medida pela razão da ocorrência do desfecho (efeito) entre grupo exposto e não exposto ao fator causal (risco relativo)
Consistência	Resultados evidenciados de forma semelhante em diferentes populações e circunstâncias reforçam a hipótese de causalidade
Especificidade	Quando o fator está associado especificamente a um determinado efeito (tipo de câncer), é mais provável que o mesmo seja um fator causal
Temporalidade	A causa deve necessariamente preceder o efeito
Gradiente biológico	Aumento na frequência ou intensidade da causa produz um aumento na ocorrência do desfecho (efeito). O gradiente pode ser medido pela função da relação dose-resposta entre causa e efeito
Plausibilidade	Evidências sobre a biologia da doença corroboram com a hipótese de causalidade
Coerência	A interpretação da relação de causa e efeito não deve ser conflitua com o estado da arte sobre a biologia e a distribuição da doença na população e no tempo
Experimento	Evidência experimental com intervenção no fator causal modifica a ocorrência da doença (efeito)
Analogia	Existência de uma analogia que ajude a explicar a associação, reforça a hipótese de causalidade

Os critérios de Hill têm sido utilizados, por exemplo, pela IARC para avaliação da evidência de possíveis agentes cancerígenos para humanos (IARC, 2016). Além desses critérios, a IARC avalia estudos em humanos segundo (1) o tipo de estudo epidemiológico (coorte, caso-controle, ecológicos e ensaios clínicos randomizados); (2) qualidade metodológica dos estudos com ênfase no risco de vieses, confundimento e erro aleatório na interpretação dos resultados; (3) síntese meta-analítica das medidas de associação dos estudos (revisões sistemáticas e meta-análises) e meta-análise de dados individuais de participantes (*meta-analysis of individual participant data*); (4) análise detalhada da temporalidade das relações entre as causas e o câncer; e (5) resultados de

estudos epidemiológicos sobre biomarcadores moleculares e celulares do câncer. Além desses critérios, a IARC também considera evidências oriundas de estudos experimentais com animais e outros estudos mecanísticos sobre carcinogênese (IARC, 2006). Entretanto, vale ressaltar que a avaliação de vieses na literatura oriunda de práticas que favorecem a publicação de resultados estatisticamente significantes (viés de publicação), não faz parte dos critérios utilizados pela IARC para classificação de agentes cancerígenos para humanos, apesar da clara implicação desses vieses na validade e credibilidade da evidência.

Em síntese, identificar e compreender as causas do câncer é essencial para informar tomadas de decisão clínica e em saúde pública, bem como comunicar adequadamente o potencial de intervenções voltadas à prevenção de câncer. As causas do câncer diferem a nível individual e populacional. Processos estocásticos, fatores genéticos/hereditários, ambientais e de estilo de vida atuam em conjunto ao longo da vida, alterando o risco de desenvolver e morrer por câncer na população. O processo de inferência causal em epidemiologia do câncer é complexo. Erros aleatórios e sistemáticos em estudos epidemiológicos, bem como práticas que favorecem a disseminação e publicação de resultados estatisticamente significantes, podem distorcer a evidência científica sobre causas do câncer. Essas limitações devem ser levadas em consideração durante a interpretação da evidência.

1.3. PREVENTABILIDADE DE CÂNCER

Relative risk is only for researchers; decisions call for absolute measures (Rose, 1992, p.19).

Identificar as causas do câncer na população é um dos objetivos centrais da epidemiologia. No entanto, mais informações são necessárias para que esses conhecimentos sobre etiologia sejam aplicados para a prevenção e o controle da doença. Por exemplo, estimar a relação dose-resposta entre fatores de risco e câncer é crítico. O formato da curva dose-resposta (exemplo: linear, exponencial, em “U”, em “J”) implica

diretamente nas ações de políticos, gestores e tomadores de decisão (Rose, 1992). A relação linear entre tabagismo e câncer de pulmão sugere que não há nível seguro de consumo de cigarro e que, portanto, políticas públicas devem focar na cessação do tabaco para diminuição do risco de câncer de pulmão (Carter et al., 2015). A estimativa da relação dose-resposta é usualmente calculada em termos relativos, uma vez que o risco (incidência ou taxa) da doença é estimado segundo estratos da exposição de interesse e comparado a um grupo de referência não exposto ou com baixos níveis de exposição. Exemplos dessas medidas de associação baseadas em diferenças relativas são risco relativo e *odds ratio* (Greenland et al., 2008).

Outra informação relevante para planejamento de ações em prevenção é a distribuição da população segundo estratos da exposição, dado que, uma alta magnitude do risco relativo da doença pode ter um baixo impacto populacional se o fator de risco em questão for raro. Por outro lado, riscos relativos de menor magnitude podem refletir em grande impacto populacional quando a exposição é mais frequente na população. Este célebre axioma da medicina preventiva, conhecido como paradoxo da prevenção, foi descrito por Geoffrey Rose em 1985: “*A large number of people at small risk may give rise to more cases of disease than a small number of people at high risk*” (Rose, 1985, p.37). Com efeito, medidas de associação baseadas em diferenças absolutas da ocorrência da doença são necessárias para estimar o excesso do risco da doença associado à exposição (Rose, 1992). Essas oferecem a possibilidade de estimar o potencial de prevenção (preventabilidade) da doença por meio da redução/eliminação do fator de risco na população (Greenland et al., 2008).

Estudos sobre a preventabilidade de câncer são importantes para informar políticas públicas e intervenções voltadas ao controle da doença. Conforme descrito anteriormente, a preventabilidade pode ser estimada por meio de medidas de associação baseadas em diferenças absolutas do risco de câncer. Por exemplo, comparando populações com altas taxas de câncer com populações com baixas taxas de câncer. Diferenças entre as taxas seriam, portanto, atribuíveis a diferenças no padrão de exposição à fatores de risco ambientais e estilo de vida entre as populações (Song; Giovannucci, 2015; Davey Smith et al., 2016). Um exemplo clássico da aplicação desse método foi publicado pelos eminentes epidemiologistas, Richard Doll e Richard Peto. Doll e Peto (1981) estimaram a proporção de mortes por câncer que seria potencialmente evitável nos Estados Unidos da América (EUA) comparando as taxas de

mortalidade por câncer do país com as de Connecticut - população de referência com baixas taxas de mortalidade por câncer. Eles encontraram que, aproximadamente, 75% a 80% das mortes por câncer nos EUA em 1970 poderiam ser potencialmente evitadas. O tabagismo foi o fator de risco modificável que contribuiu com maior fração das mortes por câncer nos EUA, apesar de estimativas apontarem para uma fração equivalente, porém menos precisa, aos fatores relacionados à alimentação (Tabela 4) (Doll; Peto, 1981).

Tabela 4 - Proporções (%) de mortes por câncer atribuíveis a diferentes fatores. Estados Unidos, 1978*

Fatores ou classe de fatores	Melhor estimativa	Variação aceitável das estimativas
Tabagismo	30	25 – 40
Álcool	3	2 – 4
Dieta	35	10 – 70
Aditivos alimentares	<1	-5 ^a – 2
Reprodutivos e sexuais	7	1 – 13
Ocupacionais	4	2 – 8
Poluição	2	<1 – 5
Produtos Industriais	<1	<1 – 2
Procedimentos médicos e medicamentos	1	0,5 – 3
Geográficos ^b	3	2 – 4
Infecções	10 ?	1 - ?

*Adaptação e tradução da Tabela 20 do artigo “Doll R, Peto R. The causes of cancer: quantitative estimates of avoidable risks of cancer in the United States today. *J Natl Cancer Inst.* 1981;66(6):1191-308”. ^a Assumindo a possibilidade de efeitos protetores de antioxidantes e outros preservantes.

^b Apenas 1%, e não 3%, pode ser razoavelmente descrito como evitável. Fatores geográficos também causam uma grande proporção de câncer não letal (até 30% de todos os casos de câncer, dependendo da miscigenação étnica e latitude) por causa da importância dos raios UV na causação de carcinoma basocelular e escamoso em peles expostas à luz solar.

Recentemente, a preventabilidade de câncer tem sido calculada pelo método de fração atribuível populacional (Olsen et al., 1997; Bofetta et al., 2009; Inoue et al., 2012; Whiteman et al., 2015; Azevedo e Silva et al., 2016; Islami et al., 2017; 2018; Brown et al., 2018). A fração atribuível populacional fornece estimativa da proporção dos casos de câncer potencialmente prevenível caso determinado fator causal fosse eliminado. No Apêndice A apresento uma breve descrição de como as estimativas de

fração atribuível populacional podem ser calculadas por meio de dados secundários, bem como nuances metodológicos e pressupostos dessas análises, a fim de fornecer importantes elementos para planejamento de ações de prevenção e controle de doenças. Brevemente, esse método depende de informações disponíveis sobre i) evidência convincente de que o fator causal aumenta/diminui o risco de câncer; ii) distribuição do fator causal na população; iii) magnitude do risco relativo do câncer associado ao fator causal, ajustado por potenciais variáveis de confusão; iv) número de casos e mortes por câncer na população de interesse (Rezende; Eluf-Neto, 2016).

Por meio desse método, a preventabilidade de câncer foi estimada na Finlândia, Noruega França, Reino Unido, Japão, China, EUA, Austrália e Brasil (Olsen et al., 1997; Boffetta et al., 2009; Inoue et al., 2012; Whiteman et al., 2015; Azevedo e Silva et al., 2016; Islami et al., 2017; 2018; Brown et al., 2018). Nesses países, a proporção do total de casos câncer atribuível à fatores de risco modificáveis variou de 27% em países Nórdicos (Finlândia e Noruega) (Olsen et al., 1997) a 42% nos Estados Unidos (Islami et al., 2018), enquanto a fração das mortes variou de 35% na França (Boffetta et al., 2009) a 52% na China (Islami et al., 2017).

No tocante ao estudo conduzido no Brasil, a fração do total de casos e mortes por câncer atribuível a fatores de risco modificáveis foi estimada para o ano de 2020. Para tanto, foram considerados 25 tipos de câncer e 32 exposições pertencentes às seguintes categorias: tabagismo, uso de álcool, alimentação, excesso de peso e obesidade, falta de atividade física, infecções, histórico reprodutivo, riscos ocupacionais e ambientais. Aproximadamente 34% e 42% dos casos e mortes por câncer, respectivamente, que ocorrerão em 2020 são atribuíveis a fatores de risco modificáveis citados. Dentre esses fatores, tabagismo, infecções, alimentação, falta de atividade física e obesidade são os principais responsáveis pela carga do câncer no país (Azevedo e Silva et al., 2016).

Em conclusão, investigar as causas do câncer é uma função central da epidemiologia. Medidas de associação baseadas em diferenças relativas das taxas de câncer entre subgrupos da população são utilizadas para estudo da etiologia do câncer. Medidas de associação baseadas em diferenças absolutas das taxas de câncer, como a fração atribuível populacional, fornecem informações sobre a preventabilidade de câncer na população. Essas informações são importantes para planejamento de intervenções e políticas públicas voltadas à prevenção da doença.

1.4. ATIVIDADE FÍSICA E CÂNCER: ANTECEDENTES E JUSTIFICATIVAS

We believe that the carcinoma problem may also be simplified by the recognition of the value of muscular activity in those periods of life most affected by carcinoma, those periods of life when we are prone to “let down” and check our pace. If muscular activity has an intimate relationship to carcinoma, the value of it will be most apparent in prophylaxis, the field which to date promises the most in the attack on this malady (Sivertsen; Dahlstrom, 1922, p. 365-6).

A relação entre atividade física e a diminuição no risco de câncer foi aventada por Bernardino Ramazzini (1633-1714). Ramazzini acreditava que os casos de câncer em trabalhadores estavam associados com a exposição aos materiais tóxicos, e eram acelerados por movimentos violentos ou irregulares e posturas não naturais ao corpo. Por isso, recomendava que trabalhadores interrompessem posturas prolongadas com caminhadas e exercícios físicos (Dishman et al., 2013).

No entanto, apenas em 1922, foram realizados os primeiros estudos epidemiológicos que avaliaram a associação entre atividade física e o risco de câncer. Em artigo intitulado “*A theory of cancer*”, o australiano Cherry (1922) reportou maior mortalidade por câncer entre indivíduos com menor intensidade de atividade muscular no trabalho em comparação àqueles com maior atividade física. De maneira semelhante, no mesmo ano, em Minnesota, EUA, Sivertsen e Dahlstrom publicaram artigo intitulado “*The relation of muscular activity to carcinoma: a preliminary report*”, que apresentou resultados semelhantes ao estudo australiano¹ (Sivertsen; Dahlstrom, 1922). Nesse estudo, os autores agruparam as atividades ocupacionais comuns à época segundo níveis de exigência de atividade muscular da seguinte maneira: (1) atividade muscular alta: pedreiros, ferreiros, caldeiros e moldadores; (2) atividade muscular moderada: carpinteiros, marceneiros, pedreiros e encanadores; (3) Atividade muscular média:

¹ Apesar dos estudos terem sido desenvolvidos de forma independente, Sivertsen e Dahlstrom tinham conhecimento dos achados de Cherry, e citam em sua publicação: “*It is interesting to us to find that in another part of the world similar ideas have been advanced almost simultaneously. Cherry, of Melbourne, on March 1, 1922, read a paper on A Theory of Cancer in which he attributes the recent increase of cancer to deficient muscular activity, overnutrition, arid lessened skin activity, as a result of modern living conditions of civilized peoples.*” (Sivertsen; Dahlstrom, 1922).

capatazes, moleiros e cervejeiros; (4) Atividade muscular baixa: professores e atividades de escritório; (5) atividade muscular sazonal: fazendeiros; (6) Sem atividade profissional remunerada: desempregados, aposentados e hospitalizados. Em geral, a taxa de mortalidade por câncer foi menor em trabalhadores com maior atividade muscular no trabalho comparado aos trabalhadores com menor atividade muscular. É interessante notar ainda que os autores descreveram que a presença de uma relação dose-resposta entre atividade muscular e mortalidade por câncer reforça a hipótese de causalidade (Tabela 5).

Tabela 5 - Atividade ocupacional segundo nível de atividade muscular e mortalidade por câncer, 1922*

Nível de atividade muscular	Número de pessoas	Número de Mortes	Taxa mortalidade**	Risco relativo
Atividade muscular alta	46 736	20,0	43,0	1
Atividade muscular moderada	168 460	128,0	75,8	1,7
Atividade muscular média	84 523	77,0	91,1	2,1
Atividade muscular baixa	211 824	213,9	100,8	2,3
Atividade ocupacional sazonal	170 483	267,7	156,6	3,6
Sem atividade profissional remunerada	64 503	330,0	510,0	11,8

* Adaptado de Sivertsen e Dahlstrom. The relation of muscular activity to carcinoma. A preliminary report. J Cancer Res. 1922;6,365-78; ** Por 100.000 homens

Após a publicação dos estudos pioneiros de Cherry, Sivertsen e Dahlstrom, o tema atividade física e câncer praticamente desaparece do cenário científico internacional. Somente na década 1980, o tema volta a chamar a atenção de pesquisadores que, a partir de então, produzem grande quantidade de estudos epidemiológicos (Lee; Oguma, 2006).

Atualmente, devido ao grande volume de estudos publicados, os grupos consultivos da IARC e da *World Cancer Research Fund International* (WCRF) avaliam periodicamente a consistência da evidência sobre as possíveis causas do câncer, incluindo o possível efeito protetor da atividade física em câncer. Em 2002, a IARC publicou o primeiro relatório voltado especificamente à avaliação da evidência de estudos epidemiológicos e experimentais sobre peso corporal, atividade física e câncer. Nesse relatório, a IARC concluiu que há evidência suficiente em humanos sobre o efeito protetor da atividade física na redução do risco de câncer de mama pós-menopausa e o câncer de cólon, além de evidência limitada para o câncer de endométrio e o câncer de

próstata. Essas associações poderiam ocorrer independentemente da redução do peso corporal/adiposidade. Para os demais tipos de câncer, no entanto, a evidência foi considerada insuficiente/inadequada para assumir causalidade (IARC, 2002).

A WCRF (2018), de modo semelhante, em seu último projeto de atualização da avaliação da evidência, concluiu que existe evidência consistente de que atividade física está associada com diminuição do risco de câncer de cólon, e evidência provável para redução do risco de câncer de mama pós-menopausa e câncer de endométrio. Ainda, há evidência limitada/sugestiva para associação entre atividade física e redução do risco de câncer de esôfago, fígado, pulmão e mama pré-menopausa.

Além desses documentos, estudos independentes, incluindo diversas revisões sistemáticas, apontaram uma possível relação entre a atividade física e a diminuição do risco de diversos tipos de câncer: próstata, rim, bexiga, estômago/gástrico, esôfago, ovário, endométrio, glioma, meningioma, pâncreas, pulmão, cólon e reto, mama, leucemias e linfomas (Liu et al., 2011; Behrens et al., 2013; 2014; 2015; Keimling et al., 2014; Zhong et al., 2014; Schmid et al., 2015; Niedermaier et al., 2015; Brenner et al., 2016). Caso essas associações sejam causais, o aumento da atividade física na população pode contribuir substancialmente com a diminuição da carga do câncer. Por outro lado, há pelo menos 5 explicações alternativas à causalidade para que estudos epidemiológicos observacionais reportem essas associações: (1) câncer causa inatividade física; (2) chance; (3) viés de seleção; (4) viés de informação; (5) confundimento (Rothman et al., 2008).

Portanto, para melhor interpretação da evidência epidemiológica em atividade física e câncer é oportuno compreender, entre outros aspectos: (1) Por quais mecanismos biológicos a atividade física poderia reduzir o risco desses tipos de câncer? (2) Quais vieses poderiam explicar as associações observadas entre atividade física e esses tipos de câncer?

1.4.1. Mecanismos biológicos entre atividade física e câncer

A redução da adiposidade é um mecanismo central do possível efeito da atividade física na prevenção de câncer (Figure 4) (Giovannucci, 2018a; 2018b). Ambas IARC e WCRF concluem que há evidências consistentes na literatura mostrando que o excesso de peso e a obesidade estão associados com aumento do risco de diversos tipos

de câncer: estômago, pâncreas, vesícula biliar, fígado, colorretal, mama pós-menopausa, ovário, endométrio, próstata (estádio avançado apenas), rim, tireoide, mieloma múltiplo e adenocarcinoma de esôfago (Lauby-Secretan et al., 2016; WCRF, 2018). Os principais mecanismos biológicos pelos quais a redução da adiposidade poderia prevenir o risco desses tipos de câncer são: 1) redução de fatores pró-inflamatórios; 2) alteração de adipocitocinas; 3) redução de insulina e fatores de crescimento semelhantes à insulina (*insulin-like growth fator*, IGF); 4) redução de hormônios sexuais; 5) e melhora da função imune (McTiernan et al., 2008; Renehan et al., 2015). Vale ressaltar que, embora a atividade física possa auxiliar na manutenção do peso (Donnelly et al., 2009), ensaios clínicos randomizados de longa duração têm mostrado que 150 a 250 minutos de atividades aeróbicas por semana produzem apenas reduções modestas de peso corporal (Thorogood et al., 2011). Apenas treinamento aeróbico e de força muscular combinados, acompanhado de alimentação saudável, têm se mostrado efetivos na perda de peso e melhora da composição corporal (aumento da massa magra e redução da adiposidade) (Miller et al., 2013; Romieu et al., 2017). No entanto, exercício físico pode reduzir a gordura visceral, um forte preditor de doenças crônicas não transmissíveis e mortalidade, independentemente da mudança no índice de massa corporal (IMC)/peso corporal (Verheggen et al., 2016).

Figura 4 - Mecanismos biológicos para a associação entre atividade física e risco de câncer

A inflamação tem se mostrado um importante fator pelo qual células normais adquirem as características marcantes (*Hallmarks of cancer*) de fenótipos malignos. A inflamação está envolvida na iniciação e/ou promoção de fenótipos malignos de células por meio da bioativação de moléculas no microambiente tumoral responsáveis pela proliferação celular, apoptose celular, angiogênese, invasão e metástase (Hanahan; Weinberg, 2011). Com efeito, estudos epidemiológicos têm encontrado associação entre níveis elevados de fatores pró-inflamatórios - proteína C-reativa, interleucina 6 (IL-6), fator de necrose tumoral alpha (TNF- α) - e o aumento no risco de câncer. A atividade física, por sua vez, quando praticada de forma regular, está associada com redução dos níveis sistêmicos desses fatores pró-inflamatórios, direta e indiretamente pela redução da adiposidade (McTiernan et al., 2008).

O eixo insulina/IGF é outro importante mecanismo biológico pelo qual a atividade física poderia prevenir o risco de diversos tipos de câncer. Células tumorais expressam receptores de insulina e IGF-1, que por sua vez estão associados com múltiplas vias de sinalização intracelular. Uma vez ativadas, essas vias podem estimular a proliferação celular, inibição da apoptose, invasão e metástase (Giovannucci et al., 2001; 2010). Por exemplo, insulina e IGF sinalizam vias de sinalização celulares como PI3K-AKT, MAPK e MYC, responsáveis pela absorção de nutrientes que auxiliam a proliferação celular (Koelwyn et al., 2017). Além disso, a hiperinsulinemia está associada ao aumento da disponibilidade biológica de hormônios sexuais relacionados ao aumento do risco de alguns tipos de câncer (McTiernan et al., 2008; Giovannucci et al., 2001; 2010). Ambas *American Diabetes Association* e *American Cancer Society* sugerem que há evidências consistentes sobre a associação entre diabetes tipo 2 e aumento do risco de câncer de mama, cólon, endométrio, bexiga, fígado, pâncreas e próstata (Giovannucci et al., 2010). A atividade física, por sua vez, está fortemente associada à redução da resistência à insulina e do risco de diabetes tipo 2 (Smith et al., 2016).

Níveis elevados de hormônios sexuais estão associados a um aumento no risco de alguns tipos de câncer (McTiernan et al., 2008). Estudos com mulheres atletas sugerem que a atividade física pode influenciar no atraso da idade da menarca, amenorreia e baixos níveis de progesterona e estrogênio. No entanto, o efeito da atividade física no *milieu* hormonal de mulheres pré-menopausadas não tem sido consistentemente reproduzido por ensaios clínicos randomizados (McTiernan et al.,

2008). De fato, estudos epidemiológicos sobre atividade física em mulheres pré-menopausadas e risco de câncer de mama e endométrio não tem apresentado resultados consistentes na literatura (IARC, 2012; WCRF, 2018). Por outro lado, atividade física pós-menopausa está associada a uma menor concentração de hormônios sexuais. No período após a menopausa, a principal fonte de estrogênio é oriunda do tecido adiposo. Ensaio clínicos randomizados têm mostrado que mulheres pós-menopausadas envolvidas em atividades físicas de intensidade moderada à vigorosa apresentam redução nos níveis de hormônios sexuais após um ano de intervenção. Esse efeito foi observado principalmente em mulheres que tiveram redução no percentual de gordura, reforçando a hipótese de que a redução da adiposidade é um mecanismo central do possível efeito da atividade física na prevenção de câncer (McTiernan et al., 2008; Giovannucci et al., 2018a; 2018b).

Outro possível efeito da atividade física na prevenção do câncer seria mediado pela melhora da função imune. A atividade física aumentaria em número e função células do sistema imune que, por sua vez, teriam uma função supressora de tumor, reconhecendo e eliminando células com fenótipos malignos. No momento, resultados de ensaios clínicos randomizados sobre esse mecanismo ainda são inconclusivos (McTiernan, 2008; Koelwyn et al., 2017).

1.4.2. Vieses em estudos epidemiológicos sobre atividade física e câncer

As evidências epidemiológicas sobre a relação entre atividade física e câncer são eminentemente oriundas de estudos observacionais. Conforme abordado anteriormente, a falta de validade da evidência de estudos epidemiológicos observacionais pode emergir de vieses e confundimento. A teoria de diagramas causais ou gráficos acíclicos direcionados (*directed acyclic graphs* – DAGs) é uma ferramenta útil para apresentação e análise das possíveis fontes de viés e incerteza nos resultados de estudos epidemiológicos. Os DAGs são representações gráficas, hipotéticas e qualitativas sobre os processos causais que, em última instância, dão origem aos dados e às associações observadas nos estudos. Esses diagramas são construídos a partir do conhecimento prévio das relações sobre as variáveis e, portanto, são importantes para a formalização das hipóteses e pressupostos sobre os quais associações observadas nos dados referem-se a causalidade e/ou vieses. Diversos artigos metodológicos e capítulos de livro têm

abordado a teoria dos DAGs detalhadamente (Greenland et al., 1999; Hernán et al., 2004; Glymour; Greenland, 2008; Cortes et al., 2016). Apresento abaixo algumas noções básicas necessárias para o entendimento de DAGs, com o objetivo de exemplificar situações em que associações entre atividade física e câncer poderiam ser atribuíveis, parcial ou inteiramente, a vieses.

Os DAGs são gráficos compostos por variáveis (vértices), medidas ou não pelo estudo, e setas que denotam relações entre variáveis. A seta representa um efeito causal direto (*direct causal effect*) entre duas variáveis, denominadas em teorias dos gráficos de variáveis ancestral/pai e descendente/filha. O caminho entre variáveis é representado por um conjunto de setas, usualmente, mas não necessariamente, apresentado de maneira temporal, da esquerda (passado) para a direita (futuro). O caminho entre variáveis é indireto quando há uma variável intermediária, também chamada de mediadora, entre a variável ancestral e a descendente. Na Figura 4, por exemplo, o caminho atividade física → adiposidade → câncer é indireto, uma vez que a variável adiposidade (mediadora) está entre as variáveis atividade física e câncer. Quando, num mesmo caminho causal, uma variável recebe duas ou mais setas de variáveis ancestrais, essa recebe o nome de colisor (*collider*). A ausência de setas entre variáveis implica em conhecimento prévio suficiente sobre ausência de causalidade e, consequentemente, pressuposto de independência entre variáveis no modelo estatístico (Greenland et al., 1999; Hernán et al., 2004; Glymour; Greenland, 2008; Cortes et al., 2016).

Além de estruturas causais, os DAGs são representações de associações estatísticas entre variáveis, que serão observadas quando uma ou mais das seguintes “estruturas causais” estiverem presentes (Hernán et al., 2004):

- a) Causa e efeito: se a exposição causa o desfecho, ou vice e versa, essas variáveis estarão estatisticamente associadas (Figura 5a).
- b) Causas comuns: se exposição (E) e desfecho (D) compartilharem uma causa comum (L), esses estarão estatisticamente associados mesmo que não haja uma estrutura de causa e efeito entre E e D (Figura 5b).
- c) Efeitos comuns: Se exposição (E) e desfecho (D) exercerem um efeito comum numa terceira variável (C), esses estarão estatisticamente associados quando a análise for computada segundo estratos da variável C ou de uma variável descendente de C (Figura 5c).

Figura 5 – Associação estatística entre exposição e desfecho produzidas por 3 estruturas causais: (a) causa e efeito; (b) causas comuns; (c) efeitos comuns

Chance é outra fonte de associações estatísticas encontradas em estudos epidemiológicos. No entanto, conforme descrito anteriormente, o erro aleatório é reduzido na medida em que aumenta o tamanho da amostra e, nesse cenário, erros sistemáticos tornam-se a principal fonte de associações espúrias. Assumindo tamanho de amostra infinito (erro padrão = 0) e variáveis do estudo mensuradas perfeitamente (não há viés de informação), associação $\neq$ causalidade se um ou mais os seguintes vieses estiverem presentes no estudo (Hernán et al., 2004):

- 1) Causalidade reversa: se o desfecho (D) causar a exposição (E), ao invés do contrário, esses estarão associados e haverá viés na medida de associação entre exposição e desfecho.
- 2) Causas comuns: se exposição (E) e desfecho (D) compartilharem uma causa comum (L), e a análise não for computada segundo estratos da variável L, haverá viés na medida de associação. Em epidemiologia, esse viés na medida de associação é chamado de confundimento.
- 3) Condicionamento por efeitos comuns: Se a exposição (E) e desfecho (D) exercerem um efeito comum numa terceira variável (C), e a análise for computada segundo estratos de C ou de uma variável descendente de C, haverá viés na medida de associação. Em epidemiologia, esse viés é chamado de viés de seleção ou estratificação por variável colisor (*Collider stratification bias*).

Apresento abaixo exemplos em que a associação entre atividade física e câncer pode ser devida à causalidade reversa, causas comuns (confundimento) e condicionamento por efeitos comuns (viés de seleção).

Causalidade reversa em atividade física e câncer

Câncer é uma doença de longo período de latência, tempo que corresponde à exposição a causa suficiente (acumulo de causas componentes) e a manifestação da doença (Rothman, 1976). Durante esse período, condições pré-clínicas podem causar mudanças no estado nutricional e hábitos alimentares, entre outros fatores, antes do diagnóstico da doença. Por exemplo, a perda de peso não intencional antes do diagnóstico de alguns tipos de câncer está bem documentada na literatura. Estudos observacionais sobre obesidade e câncer têm reportado um aparente paradoxo nas associações observadas, uma vez que indivíduos com menor IMC apresentam maior risco de câncer comparados aos indivíduos com alto IMC (“paradoxo da obesidade”). No entanto, esse resultado se dá pelo fato de que o grupo de referência (baixo IMC) inclui, de maneira desproporcional, indivíduos com perda de peso não intencional causada pelo câncer - essa perda de peso pode ocorrer até 16 anos antes do diagnóstico do câncer (Yu et al., 2017). Consequentemente, a causalidade reversa tende a distorcer a medida de associação do estudo - IMC alto associado (de maneira espúria) com diminuição do risco de câncer (Park et al., 2018).

Estudos epidemiológicos sobre atividade física e câncer também estão sujeitos à causalidade reversa, no entanto, o impacto do viés na medida de associação tende a ser mais sutil. É plausível que durante o período pré-clínico do câncer, ocorra, por exemplo, aumento de fadiga e diminuição do nível de atividade física causados pela doença (Figura 6) (Bower, 2014).

Figura 6 - Causalidade reversa e a associação entre atividade física e câncer

Esse viés tenderá a superestimar a magnitude de associação entre atividade física e diminuição no risco de câncer. Nesse caso, ao contrário do paradoxo da obesidade, o grupo de referência incluirá, de maneira desproporcional, pessoas com baixo nível de atividade física causado pelo câncer. Consequentemente, a magnitude da associação encontrada no estudo será maior do que o (real) efeito causal. Estudos de coorte com curto período de seguimento e com apenas uma medida de atividade física ao longo do

tempo, estão mais sujeitos a esse tipo de viés. Em estudos caso-controle, a causalidade reversa tende a se “manifestar” na forma de viés de informação, especificamente, erro de classificação diferencial. Devido ao diagnóstico do câncer, casos tendem a reportar menor nível de atividade física do que controles nos anos anteriores ao diagnóstico da doença (*recall bias*). Não obstante, parte do efeito da diminuição do nível de atividade física no grupo de casos foi causado pelo próprio câncer.

Causas comuns da atividade física e câncer

Confundimento é uma preocupação importante em estudos sobre atividade física e câncer, de modo que ajustar pelas causas comuns da exposição e desfecho é condição *sine qua non* para estimar efeitos causais. Por exemplo, para estimar o efeito da atividade física no risco de câncer de pulmão é necessário computar a associação ajustada do tabagismo, uma vez que fumantes (1) tendem a praticar menos atividade física por diminuição da capacidade respiratória (Brenner et al., 2016); (2) e têm maior risco de câncer de pulmão (Carter et al., 2015), comparado aos indivíduos que nunca fumaram (Figura 7).

Figura 7 - Confundimento por tabagismo na associação entre atividade física e câncer

Assumindo que não há outras fontes de viés, seria possível estimar o efeito causal da atividade física no câncer de pulmão computando a associação ajustada por tabagismo. O problema é que, na maioria das vezes, o pressuposto de ausência de outros vieses é irrealista. Viés de informação é ubíquo em estudos epidemiológicos (o impacto desse viés é descrito mais à frente). Portanto, mesmo após ajuste, a estimativa de associação entre atividade física e câncer de pulmão pode estar enviesada devido à confundimento residual por tabagismo. De fato, estudos epidemiológicos que analisaram a associação entre atividade física e risco de câncer de pulmão em indivíduos que nunca fumaram - análise menos sujeita a viés de informação e

confundimento residual por tabagismo - encontraram associação nula (Moore et al., 2016). Esse resultado sugere fortemente que a estrutura causal que produziu a associação observada entre atividade física e câncer de pulmão foi a presença de uma causa comum (Figura 5b), ao invés de existência de uma relação de causa e efeito (Figura 5a). Esse DAG foi simplificado a título de exemplo, de modo que uma miríade de outras causas comuns não observadas/conhecidas poderia enviesar a associação entre atividade física no risco de câncer de pulmão. O problema é ainda mais complexo, posto que as causas comuns tendem a diferir por tipos de atividade física (atividade física no lazer v.s. atividade física no trabalho) e de câncer (câncer de pulmão v.s. câncer de cólon). Portanto, uma análise detalhada das causas comuns da atividade física e dos diversos tipos de câncer é desejável para obtenção de estimativas de associação corretas (não enviesada).

Condicionamento por efeitos comuns da atividade física e do câncer

Viés de seleção é uma distorção das associações observadas em estudos epidemiológicos decorrente dos procedimentos utilizados na seleção, bem como de fatores que influenciam a participação/retenção, e, em última instância, na análise dos dados dos participantes do estudo. São exemplos de viés de seleção a seleção inapropriada de controles em um estudo caso-controle, perda de seguimento diferencial em estudos de coorte, viés do voluntário (*volunteer bias*) e viés do trabalhador saudável (*healthy worker bias*) (Hernán et al., 2004; Rothman et al., 2008). Em diagramas causais, esses tipos de viés de seleção podem ser sintetizados mediante a definição de “condicionamento por efeitos comuns”, descrita anteriormente.

Na Figura 8 apresento exemplo hipotético de estudo caso-controle de base hospitalar sobre o efeito putativo da atividade física de transporte no risco de câncer de ovário. Em estudos caso-controle, idealmente, a seleção dos controles deve cumprir os seguintes critérios: (1) os controles devem ser selecionados da mesma população que deu origem aos casos e (2) segundo estratos das variáveis que serão utilizadas para estratificação na análise, os controles devem ser selecionados independentemente do status da exposição, de modo que o processo de amostragem dos controles não varie com a exposição (Rothman et al., 2008). Quando isso não ocorre, a seleção inadequada de controles pode produzir estimativas incorretas do efeito da atividade física no câncer,

mesmo em contextos em que o efeito causal é nulo (*selection bias under the null*) (Hernán et al., 2004).

Figura 8 - Viés de seleção devido a seleção inadequada de controles em estudo caso-controle sobre atividade física e risco de câncer de ovário

Nesse exemplo, assume-se que o efeito da atividade física de transporte no câncer de ovário é nulo – não há seta entre atividade física e câncer de ovário. A seta entre as variáveis câncer de ovário e seleção indicam que casos tem maior probabilidade de serem selecionados para o estudo do que controles, característica inerente ao desenho caso-controle. Casos de câncer de ovário foram selecionados do Instituto do Câncer do Estado de São Paulo e controles do Instituto de Traumatologia e Ortopedia do Hospital das Clínicas da Faculdade de Medicina da Universidade de São Paulo. Consequentemente, a fratura óssea é mais frequente em controles do que em casos, representado na Figura 8 pela seta entre fratura óssea e seleção. O retângulo ao redor da variável seleção significa que a associação entre atividade física de transporte e câncer de ovário foi computada apenas em participantes selecionados para o estudo (condicionada à seleção para o estudo). Por fim, há uma seta indicando que atividade física de transporte aumenta o risco de fratura óssea em decorrência de acidentes de trânsito. Nesse exemplo, o condicionamento por um efeito comum da atividade física de transporte e do câncer de ovário - seleção dos participantes do estudo - produzirá uma estimativa de efeito causal enviesada. Em outras palavras, devido ao processo de seleção dos participantes do estudo, controles têm maior probabilidade de fratura óssea do que os casos. Uma vez que a atividade física de transporte está associada com aumento no risco de fratura óssea, controles apresentam, em média, maior nível de atividade física de transporte do que os casos. Nesse exemplo, a associação inversa entre atividade física de transporte e câncer de ovário diferirá do real efeito causal (nulo).

Viés de informação em estudos de atividade física e câncer

Viés de informação é ubíquo em estudos epidemiológicos. Esse viés ocorre quando há erro na mensuração das variáveis de interesse do estudo (Rothman et al., 2008). No contexto de estudos epidemiológicos que visam investigar relações de causa e efeito, assumindo ausência de confundimento e viés de seleção, há viés de informação quando a associação entre exposição e desfecho, mensurados no estudo com erro, diferir do verdadeiro efeito da real exposição no real desfecho (Hernán; Cole, 2009). Esse viés não foi apresentado anteriormente porque não há uma única “estrutura causal” (Figura 5) capaz de representar o viés de informação. Isso porque viés de informação decorre da presença de erro de classificação da exposição e do desfecho, e há quatro formas (definições) distintas de erro de classificação: (1) não diferencial e independente, (2) não diferencial e dependente, (3) diferencial e independente, e (4) diferencial e dependente (Rothman et al., 2008; Hernán; Cole, 2009). Detalhes metodológicos sobre diagramas causais e viés de informação foram descritos em outras publicações (Hernán; Cole, 2009; VanderWeele; Hernán, 2012). Abaixo apresento uma breve definição de atividade física e métodos de mensuração. Em seguida, apresento exemplos de viés de informação em estudos sobre atividade física e câncer. Por simplicidade, considerarei apenas a definição de erro de classificação diferencial e não diferencial, assumindo que os erros de mensuração da exposição e do desfecho são independentes (não correlacionados).

Medir a atividade física em populações é uma tarefa particularmente difícil, em que erros de mensuração são inevitáveis. O desafio se inicia pela definição do construto atividade física. Classicamente, atividade física é definida por movimento corporal realizado pelo músculo esquelético que aumenta o gasto energético acima dos níveis de repouso (Caspersen et al., 1985). O volume ou quantidade dessas atividades pode ser caracterizado por três componentes: frequência (número de seções – ex: dias/semana), duração (tempo) e intensidade (gasto energético por unidade de tempo). A intensidade é frequentemente expressa em equivalentes metabólicos (*metabolic equivalent of tasks* – MET), que corresponde à razão do consumo de oxigênio da atividade física pelo consumo de oxigênio em repouso ($3,5 \text{ ml/quilo/min} = 1 \text{ MET}$). Dessa maneira, as atividades são classificadas com intensidade leve (1,6 a 2,9 MET), moderada (3,0 a 5,9 MET) e vigorosa ($\geq 6 \text{ MET}$). Além dos componentes descritos acima, usualmente utiliza-se 4 categorias/domínios de atividades físicas para descrever o contexto em que

estas ocorrem: lazer, transporte, ocupacionais e domésticas (Leitzmann et al., 2015). Vale ressaltar, no entanto, que essa definição de atividade física baseada em gasto energético é bastante restrita, e utilizada apenas como um indicador desse comportamento multidimensional e complexo, composto por múltiplas facetas (motivações, significados, padrões, etc.) (Silva et al., 2017).

Para medir a atividade física na população, dois métodos principais para coleta de dados têm sido utilizados: métodos subjetivos e métodos objetivos. Dentre os métodos subjetivos destacam-se os questionários de atividade física, como, por exemplo, o *International Physical Activity Questionnaire* (IPAQ) e *Global Physical Activity Questionnaire* (GAP), além dos recordatórios e diários de atividades realizadas no passado (na última semana, mês ou ano). Pedômetros, acelerômetros e métodos de mensuração do gasto energético (água duplamente marcada) são exemplos de métodos objetivos para mensuração da atividade física. Métodos objetivos permitem medir a atividade física em condições do dia a dia (*free-living*), além de apresentarem melhor acurácia do que métodos subjetivos. No entanto, esses métodos são raramente utilizados em estudos epidemiológicos dado o alto custo e difícil logística para utilização dessas ferramentas (Leitzmann et al., 2015).

Métodos subjetivos são mais frequentemente utilizados em estudos epidemiológicos sobre a atividade física e câncer. Em estudos de coorte, em que a atividade física é medida por questionário décadas antes da ocorrência do câncer, é plausível assumir que o erro de classificação não diferencial da atividade física seja mais frequente do que o erro de classificação diferencial (Figura 9). Este tipo de viés de informação é particularmente relevante pois, ao contrário dos demais tipos descritos anteriormente, a direção do viés na estimativa de efeito frequentemente tenderá à nulidade. Ainda, este tipo de viés não produz associação espúria quando o verdadeiro efeito causal sob investigação é nulo (Hernán; Cole, 2009; VanderWeele; Hernán, 2012). Consequentemente, o impacto do viés de informação nos resultados obtidos em estudos de coorte tenderá a subestimar o efeito da atividade física nos diferentes tipos de câncer.

Figura 9 - Erro de classificação não diferencial em estudo de coorte sobre a relação entre atividade física e câncer

Em estudos caso-controle, em que casos e controles reportam de maneira retrospectiva a presença/ocorrência da exposição no passado, o erro de classificação da atividade física pode ser diferencial (Figura 10) (Rothman et al., 2008). Isso porque o erro na classificação da atividade física pode ser dependente do status da doença, de modo que a sensibilidade e a especificidade da classificação da exposição são diferentes entre casos e controles. O erro de classificação diferencial pode distorcer a associação tanto em direção quanto ao contrário da nulidade (Rothman et al., 2008). Por exemplo, se casos de câncer de cólon reportarem menor nível de atividade física do que controles, justamente por terem a doença - possivelmente por terem pesquisado as causas do câncer de cólon após receberem o diagnóstico da doença - a associação entre atividade física e câncer de cólon será superestimada em relação ao real efeito causal. Dessa maneira, o impacto do viés de informação em estudos caso-controle pode superestimar o real efeito da atividade física nos diferentes tipos de câncer. Além disso, espera-se maior heterogeneidade nas associações entre estudo caso-controle, uma vez que a direção do viés (difícil de prever) resultará de uma relação complexa entre sensibilidade, especificidade e prevalência da exposição nas diferentes populações estudadas (Szklo; Nieto, 2014a).

Figura 10 - Erro de classificação diferencial em estudo caso-control sobre a relação entre atividade física e câncer

1.4.3. Incertezas na literatura em atividade física e câncer: motivações e perguntas norteadoras dessa pesquisa

Compreender e quantificar o papel da atividade física na prevenção do câncer é uma tarefa complexa e multidisciplinar. Contudo, a epidemiologia, por meio de suas ferramentas metodológicas e analíticas, tem contribuído sobremaneira para tal. Desde os primeiros estudos conduzidos nos idos de 1920, estudos epidemiológicos têm investigado o efeito causal da atividade física no risco de diversos tipos de câncer. Atualmente, no entanto, há consenso de que a atividade física *em adultos* reduz apenas o risco de câncer de mama pós-menopausa e câncer de cólon (IARC, 2002; WCRF, 2018). É possível que a atividade física também exerça um efeito protetor em uma dezena de outros tipos de câncer (próstata, rim, bexiga, estômago/gástrico, esôfago, ovário, endométrio, glioma, meningioma, pâncreas, pulmão, cabeça e pescoço, fígado, leucemia mieloide, mieloma múltiplo). Revisões sistemáticas de estudos observacionais e diversos mecanismos biológicos descritos na literatura corroboram a hipótese de causalidade. Não obstante, inúmeras incertezas sobre o efeito da atividade física no risco de câncer permanecem, dentre as quais, resalto as que motivaram o desenvolvimento dessa pesquisa.

1) Vieses na literatura favorecem a publicação de “resultados positivos” sobre o efeito da atividade física nos diferentes tipos de câncer?

Vieses podem afetar a validade e credibilidade dos resultados de estudos epidemiológicos. Numa perspectiva teórica, descrevi anteriormente que vieses e confundimento poderiam afetar a validade dos estudos epidemiológicos sobre atividade física e câncer. É incerto, no entanto, em que medida há viés na literatura decorrente do favorecimento da publicação de estudos com resultados estatisticamente significantes e/ou efeitos superestimados da atividade física no risco de câncer. Quantificar a magnitude desses vieses é importante para avaliar a validade e credibilidade do conjunto de evidência disponível na literatura.

2) Atividade física na adolescência está associada com redução no risco de câncer colorretal na fase adulta?

Considerando o longo período de latência do câncer, é plausível que exposições no início da vida modifiquem o risco de câncer na população. No entanto, atualmente, por motivos metodológicos, financeiros e logísticos, a maioria dos estudos epidemiológicos sobre atividade física e câncer utilizou dados de adultos de meia idade e idosos (Moore et al., 2016). É possível, por exemplo, que a atividade física durante a adolescência reduza o risco de câncer de cólon, uma vez que há evidência consistente dessa relação em adultos (IARC, 2002; WCRF, 2018). No entanto, extrapolar associações entre exposições em adultos e risco de câncer para populações mais jovens não é apropriado, uma vez que a fisiologia humana modifica substancialmente ao longo da vida (IOM, 2000). Compreender o papel da atividade física nos diferentes estágios da vida na redução do risco de câncer pode fornecer elementos importantes para formulação de intervenções e políticas públicas para prevenção de câncer.

3) Qual a influência do volume, tipo, e intensidade da atividade física para redução de marcadores biológicos relacionados ao risco de câncer? As associações entre atividade física e marcadores biológicos relacionados ao risco de câncer diferem segundo padrão de alimentação e adiposidade dos indivíduos?

A atividade física está associada com redução de biomarcadores metabólicos e endócrinos envolvidos na carcinogênese. Há evidência consistente na literatura, inclusive de ensaios clínicos randomizados, sobre o papel da atividade física na redução

de fatores pró-inflamatórios e de resposta à insulina (Giovannucci, 2018a; WCRF, 2018). Entretanto, é desconhecida a importância de componentes específicos da atividade física (volume, tipo e intensidade), bem como a presença de interações entre atividade física, alimentação e adiposidade nos biomarcadores relacionados ao risco de câncer. Compreender essas nuances é importante para implementação de intervenções efetivas de atividade física em indivíduos e populações.

4) Quantos casos e mortes por câncer poderiam ser evitados no Brasil mediante o aumento da atividade física na população? Qual a magnitude dessa prevenção vis-à-vis a redução de outros fatores de risco relacionados ao estilo de vida?

Atualmente, há evidência consistente de que a atividade física reduz o risco de câncer de mama pós-menopausa e cólon, além de informação detalhada do formato da curva dose-resposta oriunda de dezenas de estudos de coorte (IARC, 2002; Kyu et al., 2016; WCRF, 2018). Estimar a preventabilidade de câncer mediante o aumento da atividade física na população pode fornecer informações úteis para planejamento de ações de promoção da atividade física para prevenção de câncer no Brasil. Outrossim, comparar a magnitude dessa preventabilidade de câncer *vis-à-vis* a redução de outros fatores de risco relacionados ao estilo de vida é importante para planejamento e priorização de ações e recursos para prevenção de câncer no país.

1.5. REFERÊNCIAS

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2. OBJETIVO

O objetivo desta pesquisa foi avaliar a associação entre atividade física e o risco de câncer, bem como estimar a potencial contribuição da atividade física na prevenção dos casos e mortes por câncer no Brasil.

OBJETIVOS ESPECÍFICOS

- 1) Avaliar a consistência da evidência epidemiológica sobre a associação entre atividade física e risco de desenvolver e morrer por diferentes tipos de câncer, bem como indícios de viés e incerteza na literatura.
- 2) Avaliar a associação entre atividade física durante a adolescência e risco de adenoma colorretal na fase adulta.
- 3) Investigar a associação entre diferentes tipos e intensidades de atividade física com biomarcadores de inflamação e resposta à insulina relacionados com risco de câncer.
- 4) Estimar a preventabilidade de câncer mediante o aumento da atividade física no Brasil.
- 5) Comparar a preventabilidade de câncer mediante aumento da atividade física com a redução de demais fatores de risco relacionados ao estilo de vida no Brasil.

3. AVALIAÇÃO DA EVIDÊNCIA E INDÍCIOS DE VIÉS NA LITERATURA EPIDEMIOLÓGICA SOBRE ATIVIDADE FÍSICA E CÂNCER

Este capítulo apresenta o artigo “*Physical activity and cancer: an umbrella review of the literature including 22 major anatomical sites and 770,000 cancer cases*” de autoria de Leandro Fórnias Machado de Rezende, Thiago Hérick de Sá, George Markozannes, Juan Pablo Rey-López, I-Min Lee, Konstantinos K Tsilidis, John P. A. Ioannidis e José Eluf-Neto. O artigo foi originalmente publicado na revista *British Journal of Sports Medicine* e pode ser acessado gratuitamente no link <https://bjsm.bmj.com/content/52/13/826>. Essa publicação apresenta material suplementar extenso, disponível apenas no link da revista.

Para citação: Rezende LFM, Sá TH, Markozannes G, Rey-López JP, Lee IM, Tsilidis KK, Ioannidis JPA, Eluf-Neto J. Physical activity and cancer: an umbrella review of the literature including 22 major anatomical sites and 770,000 cancer cases. *Br J Sports Med*. 2018;52(13):826-833. doi: 10.1136/bjsports-2017-098391

ABSTRACT

Objective: To provide an overview of the breadth and validity of claimed associations between physical activity and risk of developing or dying from cancer.

Design: Umbrella review.

Data Sources: We searched Medline, Embase, Cochrane Database, and Web of Science.

Eligibility criteria for selecting studies: Systematic reviews about physical activity and cancer incidence and cancer mortality in different body sites among general population.

Results: We included nineteen reviews covering 22 cancer sites, 26 exposure-outcome pairs comparisons, and 541 original studies. Physical activity was associated with lower risk of seven cancer sites (colon, breast, endometrial, lung, esophageal, pancreas, and meningioma). Only colon (a protective association with recreational physical activity) and breast cancer (a protective association with overall physical activity) were supported by strong evidence and highly suggestive evidence, respectively. Evidence from endometrial, lung, esophageal, pancreas, and meningioma presented hints of uncertainty and bias in the literature (e.g., not reaching P values $<10^{-6}$), showing large between-study heterogeneity, and/or not demonstrating a definite direction for the effect when 95% prediction intervals were considered). Four of the 26 meta-analyses showed small study effects and 4 showed excess significance.

Conclusion: Physical activity is associated with a lower risk of several cancers, but only colon and breast cancer associations were supported by strong or highly suggestive evidence, respectively. Evidence from other cancer sites was less consistent, presenting hints of uncertainty and/or bias.

3.1. INTRODUCTION

Physical activity has been traditionally linked with lower risks of colon and breast cancer (IARC, 2002; WCRF, 2018; Wolin et al., et al. 2009; Boyle et al., 2012; Neilson et al., 2016; Pizot et al., 2016). Annually, thousands of new epidemiological studies are conducted and published to examine whether physical activity may also decrease risk of other types of cancer. Recently, prospective cohort studies (Keum et al., 2016; Moore et al., 2016) and meta-analyses have claimed that physical activity might be additionally associated with cancer of bladder (Keimling et al., 2014), endometrial (Schmid et al., 2015), esophageal (Behrens et al., 2014), gastric (Psaltopoulos et al., 2016), glioma (Niedermaier et al., 2015), kidney (Behrens; Leitzmann, 2013), lung (Behrens et al., 2016), meningioma (Niedermaier et al., 2015), ovarian (Zhong et al., 2014), pancreas (Behrens et al., 2015), and prostate (Liu et al., 2011). If these associations are causal, a substantial burden of cancer could be avoided worldwide given the high prevalence of physical inactivity (Hallal et al., 2012).

Another possibility is that some claimed associations about physical activity and cancer could be explained by biases in the literature. There is strong evidence that studies showing positive and significant results are more likely to be published than studies with negative and non-significant findings (Dwan et al., 2013). These sorts of publication bias and outcome reporting bias threat validity of scientific evidence (Ioannidis, 2005; Young et al., 2008) causes general public anxiety and skepticism (Taubes, 1995), and misguide clinical and public health decisions. In fact, bias has been suspected in cancer epidemiology literature about presumed risk and prognostic factors, biomarkers, and multiple carcinogens (Kyzas et al., 2007; Bofetta et al., 2008; Tsilidis et al., 2012; Schoenfeld; Ioannidis, 2013; Ioannidis et al., 2014, Tsilidis et al., 2015, Markozannes et al., 2016, Kyrgiou et al., 2017). Nevertheless, neither the international organizations (e.g., International Agency for Research on Cancer – IARC; World Cancer Research Fund – WCRF) nor the most comprehensive systematic reviews and meta-analyses on physical activity and cancer have considered the array of analytical procedures available to detect hints of uncertainty and bias in the body of evidence to state their conclusions (Table S1).

We performed an umbrella review of systematic reviews and meta-analyses to provide an overview of the breadth and validity of claimed association between physical

activity and risk of developing or dying from cancer. We comprehensively evaluated the robustness of evidence between physical activity and cancer, appraising hints of uncertainty and bias in the body of literature.

3.2. METHODS

Literature Search

We searched Medline, Embase, Cochrane Database of systematic reviews, and Web of Science for systematic reviews published up to 22th November 2016, aiming to investigate the association between physical activity and risk of cancer incidence and cancer mortality. Table S2 in the appendix shows the search strategy. We also reviewed the references list of the eligible reviews.

Selection of reviews and methodological quality assessment

We only selected systematic reviews (irrespective of performing meta-analyses) evaluating the association between physical activity and cancer among the general (healthy) population. Whenever more than one eligible systematic review addressed the association between physical activity and the same cancer site, we selected the review with the largest number of studies included. We selected more than one review per cancer site whenever the reviews with the largest number of individual studies were restricted by study design or cancer subsite. In these cases (i.e., breast, colon, and rectum cancers), data analyses were performed separated by review to avoid overlap of studies. We excluded systematic reviews of prognostic studies, reviews that did not systematically search the literature, and reviews that did not provided comprehensive data from individual studies (specifically information listed in the data extraction section). Two researchers (LFMR and JPRL) independently selected the eligible reviews after screening consequently titles, abstracts and full texts. A third researcher (THS) settled disagreements between authors. The list of included and excluded reviews is available in the Table S3 in the appendix.

We assessed the methodological quality of the included reviews using the AMSTAR tool (Shea et al., 2007) and gathering data on statistical analyses used to assess hints of uncertainty and bias in the body of evidence.

Data extraction

We extracted author's name, year of publication, number of studies included (by study design), physical activity domains (e.g., recreational, occupational, total), and maximally-adjusted summary estimates from the systematic reviews. For each individual study in a systematic review, we extracted authors, year of publication, study design (case-control or cohort), sex, physical activity domain, period in life which of physical activity was measured, number of cases and controls (for case-control studies), number of cases and sample size (for cohort studies), cancer indicator (incidence, mortality, or incidence and mortality), maximally-adjusted measure of association and its respective 95% confidence intervals (95% CI) comparing high versus low categories of physical activity. Data extraction was independently performed by two researchers (LFMR and JPRL), with discrepancies solved by a third researcher (THS).

Statistical analysis

Primary analysis

The primary analysis in this umbrella review focused on two approaches to evaluate the association between physical activity and cancer. 1) 'Any physical activity': if individual study presented multiple measures of association by physical activity domains, we selected one based on the following order: total physical activity, multiple physical activity domains, recreational, commuting, occupational, and household physical activity. We considered 'total physical activity' any estimate with all four physical activity domains, and 'multiple physical activity' an estimate with a combination of at least two, but not all, domains. The 'any physical activity' approach was the most comprehensive analysis since it included the largest number of estimates per meta-analysis; 2) Recreational physical activity: we performed data analysis using all individual studies presenting recreational physical activity estimates. Recreational physical activity is the most studied and the more easily modifiable physical activity in comparison to other domains.

Both approaches used in the primary analysis included only cohort studies (i.e. case-control results were considered in the stratified and subgroup analyses) and one measure of association per individual study. Whenever a measure of association was not available for the total sample in an individual study (e.g., men and women relative risks [RR] estimates were provided separately), we performed fixed effect models to estimate

summary effects between categories, and included the latter in the meta-analysis. In addition, one systematic review (Behrens et al., 2015) presented multiple estimates based on timing in life measures for the same physical activity domain (e.g., distant past, recent, consistent over time) and we selected the consistent over time measure (same criteria used by the authors).

Stratified and subgroup analyses

We also performed stratified analyses combining estimates by study design (case-control and all study design – cohort and case-control), sex, and other physical activity domains (e.g., total physical activity, occupational physical activity) within and across studies. In addition, considering all study designs, we re-performed subgroup analysis conducted in the original meta-analyses.

Estimation of summary effect

We standardized the least active category as reference group across meta-analyses and then performed the meta-analysis of physical activity (i.e., high vs low category) and each cancer site according to cancer indicators. We estimated summary effect measures and its 95% confidence intervals using random effect models.

Heterogeneity between studies

Heterogeneity between studies was estimated using the I^2 measure of inconsistency (Hardy; Thompson, 1998; Ioannidis et al., 2007) and 95% prediction intervals. The 95% prediction interval accounts for heterogeneity between studies and represents the range in which a future study will lie (Riley et al., 2011).

Small study effect and excess significance biases

Bias in the body of evidence was assessed by small study effect and excess significance tests. The presence of small study effects bias was assessed for each meta-analysis based on the regression asymmetry test proposed by Egger and colleagues (Egger et al., 1997). We considered small study effect bias when the Egger's test P value < 0.10 and the magnitude of association in the largest study (smaller standard error) of a meta-analysis was more conservative than the meta-analysis random effects estimate (Sterne et al., 2011).

The excess significance test was used to evaluate whether the expected number of studies (E) differs from the actual observed number of studies (O) with statistically significant results ($P < 0.05$) included in each meta-analysis, regardless of the direction of the association (Ioannidis; Trikalinos, 2007). The difference between O and E is evaluated using a two-sided binomial test considering $P < 0.10$ for O greater than E (one-sided $P < 0.05$) as the statistical significance threshold (Ioannidis; Trikalinos, 2007).

All statistical analyses were performed using Stata version 13.0 (College Station, TX).

Grading the evidence

As proposed by previous umbrella reviews (Ioannidis et al., 2014; Tsilidis et al., 2015; Bellou et al., 2016; Markozannes et al., 2016; Kyrgiou et al., 2017), we classified the evidence from meta-analysis with nominally statistically significant results ($P < 0.05$) as strong, highly suggestive, suggestive, or weak, following the criteria described in Table 1.

Table 1 - Summary of evidence grading for meta-analyses of cohort studies associating physical activity and risk of developing or dying from cancer

Evidence	Criteria used	Decreased Risk	
		Any physical activity	Recreational physical activity
Strong	$P^* < 10^{-6}$; >1,000 cases; $P < 0.05$ of the largest study in a meta-analysis; $I^2 < 50\%$; no small study effect [¶] ; prediction interval excludes the null value; no excess significance bias [†]	None	Colon cancer, inc. or mort.
Highly suggestive	$P^* < 10^{-6}$; >1,000 cases; $P < 0.05$ of the largest study in a meta-analysis	Breast cancer, inc. and All cancer, mort.	None
Suggestive	$P^* < 10^{-3}$; >1,000 cases	Colon cancer, inc. or mort., Lung inc., and Endometrial, inc.	All cancer, mort., and Lung, inc.
Weak	$P^* < 0.05$	Meningioma, inc. or mort., Multiple cancer sites, inc, or mort., Pancreas, inc.	Esophageal, inc. and Meningioma, inc. or mort.

Abbreviations: inc., incidence; mort., mortality;

*P indicates the p-values of the meta-analysis random effects model.

[¶]Small study effect is based on the P-value from the Egger's regression asymmetry test ($P \leq 0.1$) where the random effects summary estimate was larger compared to the point estimate of the largest study (smallest standard error) in a meta-analysis.

[†]Based on the p-value ($P > 0.1$) of the excess significance test using the largest study (smallest standard error) in a meta-analysis as the plausible effect size.

Sensitivity analyses

We performed credibility ceilings sensitivity analyses for associations showing at least weak evidence ($P < 0.05$). Credibility ceilings evaluate potential spurious precision of the combined effect estimates (Salanti; Ioannidis, 2009). This tool re-estimates the meta-analysis pooled effect size using inflated variances for each study. The variance is inflated by considering the number of studies showing effects on the same direction and the probability of each study for its true effect size to be in different direction from the one suggested by its point estimate (Salanti; Ioannidis, 2009). We evaluated a series of values to examine what credibility ceiling would be necessary to make the associations non-significant at the 0.05 level (Salanti; Ioannidis, 2009). Lastly, we performed a sensitivity analyses excluding each criterion used for grading the evidence to analyze the impact in the results.

3.3. RESULTS

Description of meta-analyses

Of the 2,975 records retrieved from the search in databases, we finally selected a total of 19 systematic reviews of observational studies (Figure 1). Systematic reviews of randomized controlled trials were eligible, but were not found in the literature search. Eleven out of 19 reviews (58%) scored ≥ 6 points in the 11-items AMSTAR criteria, indicating a moderate to high methodological quality (Table S4). Limited statistical tests and sensitivity analyses were performed in original meta-analyses. Statistical significance was assessed in all reviews through the fixed/random effect 95% CI (i.e., none reported the exact P-value). None of the reviews performed excess significance, credibility ceiling, and 95% prediction intervals tests. I^2 heterogeneity estimates ($n=17$, 90%), small study effect test ($n=18$, 95%), and number of cases ($n=18$, 95%) were reported in the majority of the original meta-analyses (Table S1).

Figure 1 - Flow chart of systematic reviews and meta-analyses selection

Reviews included associations on 22 different cancer sites using 541 original studies, of which 297 (55%) were cohort and 244 (45%) case-control studies. Most of the original studies, 344 (64%), had cancer incidence as outcome, 35 (6%) mortality, and 162 (30%) incidence and mortality. A total of 725,074 cancer cases and 42,428 cancer deaths were included in these meta-analyses. All except for six comparisons (gastric mortality, esophageal mortality, meningioma risk, kidney mortality, Hodgkin lymphoma risk, pancreatic mortality) included more than 1,000 cases in the meta-analyses (Table S5-S6).

Results presented below are based on the primary analysis ('any physical activity' and recreational physical activity approaches), which included only cohort studies.

Summary effect size

Eight out of the 26 comparisons (31%) based on the any physical activity approach showed statistically significant associations ($P < 0.05$) in the random effect model. From those cancer sites, summary random effect size showed a 0.93 to 0.71 relative risk of cancer among those in the most active category as compared with the least active group. When the random effects $P < 10^{-6}$ was used as a threshold, only overall cancer mortality (RR 0.79; 95% CI 0.75-0.85), colon cancer (RR 0.81; 95% CI 0.75-0.88), and breast cancer incidence (RR 0.87; 95% CI 0.84-0.90) remained statistically significant (Figure 2 and Table S7).

Figure 2 - Robustness of evidence grading for meta-analyses of cohort studies associating any physical activity and risk of developing or dying from cancer

*Figure 2 Footnote: I, incidence; M, mortality; I+M, incidence and mortality; NS, association not statistically significant ($P > 0.05$); +, yes; -, no; Number of studies refers to number of studies included in the random effect model; Random effect P refers to P-value of the summary random effects estimate; Number of cases refers to number of cancer cases or deaths included in the analysis; Largest study with $P < 0.05$ refers to P-value of the largest study (smallest SE) in each meta-analysis; Small study bias is based on the P-value from the Egger's regression asymmetry test ($P < 0.1$) where the random effects summary estimate was larger compared to the point estimate of the largest study in a meta-analysis; Excess significance bias is based on the p-value ($P < 0.1$) of the excess significance test using the largest study (smallest standard error) in a meta-analysis as the plausible effect size; Evidence grading refers to robustness evidence grading criteria;

For recreational physical activity, five (25%) out of 20 comparisons showed statistically significant associations based on the $P < 0.05$ threshold. Among those, only colon cancer (RR 0.79; 95% CI 0.71-0.86) remained statistically significant at $P < 10^{-6}$ threshold (Figure 3 and Table S8).

Figure 3 - Robustness of evidence grading for meta-analyses of cohort studies associating recreational physical activity and risk of developing or dying from cancer

*Figure 3 Footnote: I, incidence; M, mortality; I+M, incidence and mortality; NS, association not statistically significant ($P > 0.05$); +, yes; -, no; Number of studies refers to number of studies included in the random effect model; Random effect P refers to P-value of the summary random effects estimate; Number of cases refers to number of cancer cases or deaths included in the analysis; Largest study with $P < 0.05$ refers to P-value of the largest study (smallest SE) in each meta-analysis; Small study bias is based on the P-value from the Egger's regression asymmetry test ($P < 0.1$) where the random effects summary estimate was larger compared to the point estimate of the largest study in a meta-analysis; Excess significance bias is based on the p-value ($P < 0.1$) of the excess significance test using the largest study (smallest standard error) in a meta-analysis as the plausible effect size; Evidence grading refers to robustness evidence grading criteria.

Heterogeneity between studies - I^2 and 95% prediction intervals

Half (n=13) of the meta-analyses of the ‘any physical activity’ approach had I^2 smaller than 25%, whereas seven (27%) (all cancer mortality, colon, lung, gastric, bladder, multiple myeloma, and ovary) showed moderate to high heterogeneity ($I^2 \geq 50\%$). Only all cancer mortality and breast cancer presented a definite direction for the effect size (i.e., the intervals did not include the null value) when 95% prediction intervals were considered (Figure 2 and Table S7).

Regarding recreational physical activity, seven out of 20 meta-analyses (35%) had $I^2 > 50\%$, and 18 (90%) included null value when 95% prediction intervals presented a definite direction for the effect size (Figure 3 and Table S8).

Small study effects and excess significance biases

Out of the 26 studies, four (15%) (breast, all cancer mortality, colon, and pancreas) had a $P < 0.1$ on the Egger asymmetry test and the effect estimate of the largest study was more conservative compared to the summary random effects estimate, indicating potential small-study effect bias. Regarding the excess of significance bias, four (15%) cancer sites (all cancer mortality, colon, lung, gastric) had observed number of studies showing statistically significant results higher beyond chance than the expected (Figure 2 and Table S7).

For recreational physical activity, only multiple myeloma meta-analysis showed small-study effect bias, whereas only lung cancer presented evidence of excess significance bias (Figure 3 and Table S8).

Robustness of evidence

None of the associations were supported by strong evidence in the ‘any physical activity’ analyses. The associations between physical activity and breast cancer incidence and all cancer mortality were supported by highly suggestive evidence. Colon cancer, endometrial, and lung cancers were judged as suggestive evidence. Two other cancer sites (meningioma, pancreas, and multiple cancer sites) were supported by weak evidence (Table 1, Figure 2 and Table S7).

There was strong evidence for an association between recreational physical activity and colon cancer (RR 0.79; 95% CI 0.71-0.86). Lung cancer (RR 0.79; 95% CI 0.70-0.90) and all cancer mortality (RR 0.81; 95% CI 0.74-0.90) were supported by a

suggestive evidence. Esophageal cancer presented only weak evidence (Table 1, Figure 3 and Table S8).

Stratified and subgroup analyses

The stratified analyses results are presented in the appendix (Tables S9-S17). Most of the associations found in the analysis stratified by sex (Table S9-S12) and physical activity domains (total, occupation, and ‘other physical activity’ domains) (Table S13-S15) were graded as weak evidence or were not statistically significant, but data were generally more limited and many studies had not provided separate effects for men and women. Considering case-control studies, the association between any physical activity and colon and breast cancers were supported by highly suggestive evidence (Table S16). For recreational physical activity, only breast cancer was supported by highly suggestive evidence in case-control studies (Table S17).

The majority of the subgroup analyses conducted for each cancer were also supported by weak evidence or were not statistically significant. We found strong evidence for the associations between physical activity and distal colon cancer, breast cancer among women that never used hormone replacement therapy (for estimates based on physical activity measured in hours/week and METs-h/week, adjusted by adiposity), endometrial cancer (e.g., for studies with number of cases higher than 3,500 and with occupational physical activity measures), and non-cardia gastric cancer (Table S18-S39).

Sensitivity analyses

Of the eight meta-analyses showing random effects $P < 0.05$ in the ‘any physical activity’ approach, 4 (breast, colon, endometrial, and all cancer mortality) would remain statistically significant even with a 10% credibility ceiling, and two (breast cancer and all cancer mortality) even with a 20% credibility ceiling (Table S7 and Figure S1). Two (colon cancer and all cancer mortality) out of five meta-analyses of recreational physical activity showing random effects $P < 0.05$ remained statistically significant when 10% credibility was used (Table S8 and Figure S2), but none of those survived to 20% credibility ceiling.

When we performed sensitivity analyses excluding sequentially each criterion used in the grading of evidence, the association between any physical activity and breast

cancer, stemming from cohort studies, was supported by strong evidence after excluding the small study effects criterion (Table S40).

3.3. DISCUSSION

Principal findings and possible explanations

In this umbrella review summarizing the evidence of associations between physical activity and different cancer sites, we synthesized data from 22 different cancer sites, 725,074 cancer cases and 42,428 cancer deaths, and evaluated the credibility of the epidemiological evidence. In our primary analysis, stemming from cohort studies, physical activity showed a negative and statistically significant association ($P < 0.05$) with seven cancer sites (colon, breast, endometrial, lung, esophageal, pancreas, and meningioma). However, we found that only the associations with colon cancer and breast cancer were supported by strong evidence and highly suggestive evidence, respectively.

The association between physical activity and incidence of breast and colon cancers was recognized long ago (IARC, 2002; WCRF, 2018), whereas associations with other cancer sites has emerged in the last decade (Behrens; Leitzmann, 2013; Behrens et al., 2014; 2015; Keimling et al., 2014; Zhong et al., 2014; Niedermaier et al., 2015; Schmid et al., 2015; Brenner et al., 2016; Psaltopoulou et al., 2016). However, it is also plausible these associations may be flawed due to biases in the literature, overestimating the potential effect of physical activity on the incidence and mortality of cancer. In fact, this phenomenon has been as detected by previous umbrella reviews on other subjects (Ioannidis et al., 2014; Tsilidis et al., 2015; Bellou et al., 2016; Markozannes et al., 2016, Kyrgiou et al., 2017).

Through an array of statistical analyses, we found substantial uncertainty in the literature of physical activity and cancer. When stringent P-value was considered ($P < 10^{-6}$), only colon cancer, breast cancer, and all cancer mortality associations remained statistically significant. Moderate to high heterogeneity ($I^2 \geq 50\%$) was found in a third of the meta-analyses. When such heterogeneity was considered in the 95% prediction intervals, only colon cancer, breast cancer, and all-cancer mortality presented a definite direction for the effect size. We identified few additional hints of bias in the

literature though the small study effect and excess significance tests.

Comparison with other studies

Criteria for evaluating the evidence have been proposed by different researchers (Hill, 1965; Guyatt et al., 2008; Ioannidis, 2016; Lawlor et al., 2017) and organizations (USDHEW, 1964; IARC, 2002; WCRF, 2018). The umbrella review approach evaluates the credibility of evidence using an array of statistical tests and sensitivity analyses to obtain hints of uncertainty and bias in the body of literature. Although it is not possible to estimate the exact extent or source of bias that affects the evidence on physical activity and cancer, the criteria that we use aim to capture indirectly the potential effect of biases. The IARC and the WCRF have their own group of experts and criteria to judge the evidence of potential carcinogens to humans, which do not include detailed evaluation of bias in the body of literature. On the other hand, both organizations consider the biological mechanisms evidence, which is beyond the scope of this umbrella review.

Both IARC and WCRF found convincing evidence to support the association between physical activity and colon cancer, in agreement with the conclusions of our umbrella review for recreational physical activity. In the subgroup analysis, we found that only the association with distal colon cancer was supported by strong evidence, whereas proximal colon cancer evidence was judged as suggestive. Colon cancer had suggestive evidence for association with any physical activity with hints of heterogeneity and bias. There are plausible biological mechanisms supporting the association between physical activity and colon cancer, such as reducing body fatness, inflammation, insulin levels and insulin resistance (WCRF, 2018).

The IARC and WCRF classified the association between physical activity and breast cancer as sufficient (highest grade) and probable (second highest grade), respectively. We found highly suggestive evidence that physical activity decreases the risk of breast cancer, albeit we also observed small-study effect bias for this association. Small-study effect may either be related to bias or random error or heterogeneity (Sterne et al., 2011). Regarding the heterogeneity, the WCRF, but not the IARC, provides separate grading of evidence for menopausal status, suggesting limited evidence for the association between moderate to vigorous physical activity and premenopausal breast cancer and convincing evidence for postmenopausal breast cancer. Similarly, we found

that premenopausal and postmenopausal breast cancers were supported by weak and highly suggestive evidence, respectively. Hormone replacement therapy (HRT) is associated with increased risk of breast cancer and may be an important confounder in postmenopausal breast cancer studies (WCRF, 2010). We found strong evidence supporting a negative association between physical activity and breast cancer among never HRT users (i.e., analysis less prone to confounding). Additional biological evidence supporting the association between physical activity and breast cancer includes postulated effects on body fatness, certain hormone metabolisms (e.g., fasting insulin, estrogens and androgens) and strengthening of the immune system (WCRF, 2010).

Our findings are in agreement with IARC and WCRF, except for endometrial cancer, for which the association with physical activity is considered as probable evidence (second highest grade) by the WCRF. We found only suggestive evidence to support the association between any physical activity and endometrial cancer, because the most stringent P threshold ($P < 10^{-6}$) and 95% prediction interval criteria were not satisfied. The P-value criteria might be due to small number of cohort studies on endometrial cancer ($n=18$) as compared to breast ($n=38$) and colon cancer ($n=28$) literature. In fact, when we considered both cohort and case-control designs, and therefore increased the statistical power, the association between physical activity and endometrial cancer was supported by highly suggestive evidence. However, case-control studies presented higher effect size estimates than cohort studies, probably reflecting more bias. The source of heterogeneity (i.e., reflected in the 95% prediction intervals) in our results on endometrial cancer might be due to obesity status. Endometrial cancer is an obesity-related cancer (Kyrgiou et al., 2017) and BMI may mediate the association between physical activity and endometrial cancer (Moore et al., 2016). For instance, Moore et al. (2016) found that leisure-time physical activity (LTPA) was associated with endometrial cancer only among individuals with high BMI. Other mechanisms suggested for this association are hormone-related, such as reducing insulin level and insulin resistance, decreasing estradiol and regulating estrogen metabolism (WCRF, 2013).

Other cancer sites (esophageal, meningioma, lung, pancreas) showed less consistent results with substantial uncertainty in the literature. None of these cancer sites supported more stringent P thresholds used to avoid spurious precision results derived from meta-analyses of observational studies. Three (esophageal, meningioma,

pancreas) out of four did not have more than 1000 cases to state conclusion. Heterogeneity (I^2 and 95% prediction intervals) and/or bias (small-study effect and excess significant biases) were present in all these meta-analyses. Finally, other cancer sites (bladder, chronic/small lymphocytic lymphoma, diffuse large B-cell lymphoma, follicular lymphoma, gastric, glioma, Hodgkin and non-Hodgkin lymphoma, kidney, leukemia, multiple myeloma, ovary, rectum, thyroid) did not showed statistically significant associations at $P < 0.05$ threshold. IARC and WCRF also have also considered these associations between physical activity and these cancer sites with limited evidence. However, a recent pooled data from 12 cohorts examined the association between leisure-time physical activity (LTPA) and 26 types of cancer and 187 thousand cancer cases. LTPA was inversely associated (at $P < 0.05$) with 13 cancer sites (colon, breast, endometrial, esophageal adenocarcinoma, liver, kidney, gastric cardia, myeloid leukemia, myeloma, head and neck, rectal, and bladder), and positively associated with melanoma and prostate cancer (Moore et al., 2016). Although this paper was not included in our umbrella review, as did not meet the eligibility criteria (i.e., was not a systematic review of literature), we recognize its importance to the physical activity and cancer literature. Thus, we applied our grading evidence criteria to their findings. We found that only the association between LTPA and breast, kidney, melanoma, and lung cancers were supported by strong evidence (Table S41). Therefore, despite the uncertainty or bias that was found for many malignancies, these associations could be confirmed as genuine in the future.

Physical activity is associated with obesity and diabetes, and these phenotypes have also been associated to cancer at several sites (Giovannucci et al., 2010; Tsilidis et al., 2015; Lauby-Secretan et al., 2016). Deciphering the exact causal contribution of each of these factors is not easy. Both low within-population variability of and measurement error for physical activity are also important concerns. Future prospective cohort studies with objective measures (e.g., through accelerometers) of physical activity trajectories may reduce misclassification and, therefore, reduce current uncertain evidence for some cancer sites. In parallel, randomized controlled trials of physical activity may help address directly the causal effects. Given the very long follow-up required to study cancer outcomes, these studies are difficult to conduct. However, given its potential major importance, physical activity interventions may need to be studied with large randomized trials, much like other interventions (e.g., drugs)

have been studied (Naci; Ioannidis, 2013; Dal-Re et al., 2015).

Limitations

Umbrella reviews rely on methodological quality and report transparency of meta-analysis. Despite the fact that the systematic reviews included in our umbrella were of moderate to high methodological quality and were published on average in 2014 (2005 to 2017), some studies may have not been included either because systematic reviews did not identify them or they were too recent to be included (Moore et al., 2016). We re-performed most of the analysis reported in systematic reviews, however substantial data were missing from some subgroup analyses (Table S42-S46). We encourage future systematic reviews to report each individual-study estimate included in its primary and main subgroup (sex, cancer location, histology) meta-analyses.

Our analyses are based on the comparison between most active and least active groups. A limitation of this approach is that measurement and classification of physical activity across studies are heterogeneous and might not be comparable. Finally, tests used to obtain hints of bias in the body of evidence (small-study effect and excess significance tests) have low power if the meta-analyses include less than ten studies, and they may not identify the exact source of bias (Lau et al., 2006; Sterne et al., 2011).

Conclusions

Despite the fact that physical activity has been associated with a lower risk of several cancers in the literature, the associations for only colon and breast were supported by strong or highly suggestive evidence, respectively. Evidence from other cancer sites was less consistent, presenting hints of uncertainty and/or bias, but could be confirmed as genuine in the future.

What is already known:

- Physical activity has been traditionally linked with lower risks of breast and colon cancer
- Recently, multiple meta-analyses have showed that physical activity might be additionally associated with lower risk of several other cancer sites.
- If these associations are causal, a substantial burden of cancer could be avoided worldwide, but it is also plausible that some associations may be flawed due to biases in the literature.

What are the new findings:

- This umbrella review synthesizes and evaluates the robustness of evidence and appraises uncertainty and bias in the body of literature of the association between physical activity and the risk of developing or dying from cancer.
- Of the 22 major anatomical cancer sites included in our primary analysis, only colon cancer and breast cancer were supported by strong or highly suggestive evidence.
- Evidence from other cancer sites was less consistent, presenting hints of uncertainty and bias in the literature.

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4. ATIVIDADE FÍSICA DURANTE A ADOLESCÊNCIA E RISCO DE ADENOMA COLORRETAL NA FASE ADULTA

Este capítulo apresenta o artigo “*Physical activity during adolescence and risk of colorectal adenoma in women*” de autoria de Leandro Fórnias Machado de Rezende, Dong Hoon Lee, NaNa Keum, Katharina Nimptsch, Mingyang Song, I-Min Lee, José Eluf-Neto, Shuji Ogino, Charles Fuchs, Jeffrey Meyerhardt, Andrew T Chan, Walter Willett, Edward Giovannucci, Kana Wu. O artigo foi submetido para publicação na revista British Journal of Cancer.

Esse manuscrito foi elaborado durante o estágio de pesquisa no exterior na Harvard T.H. Chan School of Public Health. Donghoon Lee e eu trabalhamos em parceria nesse manuscrito e contribuímos igualmente na elaboração do mesmo, de modo que compartilhamos a primeira autoria.

Para citação: Rezende LFM, Lee DH, Keum N, Nimptsch K, Song M, Lee IM, Eluf-Neto J, Ogino S, Fuchs C, Meyerhardt, Chan AT, Willett W, Giovannucci E, Wu K. Physical activity during adolescence and risk of colorectal adenoma in women. In preparation.

Physical activity during adolescence and risk of colorectal adenoma in women: results from the Nurses' Health Study II

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ABSTRACT

Background: Physical activity during adulthood has been consistently associated with lower risk of colorectal adenomas and cancer (particularly colon), but whether physical activity during adolescence may also play a role in colorectal carcinogenesis is unclear.

Methods: We used data from 28,250 women in the Nurses' Health Study II who provided data on physical activity during adolescence (12-22 years) in 1997, a validated high-school food frequency questionnaire in 1998 and underwent at least one lower bowel endoscopy from 1998 to 2011. We used logistic regression models for clustered data to examine the association between physical activity during adolescence and risk of adenomas later in life. We also evaluated the joint associations of physical activity during adolescence and adulthood with regard to risk of colorectal adenoma.

Results: Physical activity during adolescence was inversely associated with risk of colorectal adenomas (2373 cases), independent of physical activity during adulthood. The multivariable-adjusted odds ratio (OR) of all adenomas was 0.89 (95% CI 0.77 to 1.02; $P_{\text{trend}} = 0.03$) comparing women with ≥ 72 metabolic equivalent of tasks-hours/week (MET-h/week) to < 21 MET-h/week. Women with high physical activity during both adolescence (≥ 53.3 MET-h/week) and adulthood (≥ 23.1 MET-h/week) had the lowest risk of adenoma later in life (all adenoma: OR 0.71; 95% CI 0.58 to 0.87; advanced adenoma: 0.61; 95% CI 0.45 to 0.82).

Conclusions: Our findings suggest that physical activity during adolescence may lower risk of colorectal adenoma; those who maintained higher levels of physical activity both early and later in life had the lowest risk of adenoma.

4.1. INTRODUCTION

Most of the evidence on risk factors for colorectal cancer is based on epidemiological studies including mid-to late life populations (WCRF, 2018). Considering the long process of colorectal carcinogenesis, it is biologically plausible that early-life exposures (e.g., those affecting insulin-IGF pathways) may contribute to colorectal cancer risk (Vogelstein et al., 1988; Leslie et al., 2002). However, studies examining a role of early-life exposures (other than body fatness) on colorectal carcinogenesis are limited (Nimptsch et al., 2011; 2013; 2014; Clarke; Joshi, 2017).

Physical activity during adulthood is one of the most consistent factors associated with reduced risk of colorectal cancer (IARC, 2002; WCRF, 2018; Rezende et al., 2018). Evidence suggests that physical activity may potentially act during the early stages of colorectal carcinogenesis as it is associated with lower risk of adenoma, especially advanced adenoma (Wolin et al., 2011), an established precursor of colorectal cancer (Vogelstein et al., 1988; Leslie et al., 2002; Strum, 2016). Notwithstanding, there is limited evidence regarding early-life physical activity and risk of colorectal adenomas and cancer (Lee et al., 1991; Levi et al., 1999; Tavani et al., 1999). We hypothesize that higher physical activity during adolescence is associated to lower risk of colorectal adenomas later in life, which may have important public health implications for adolescents in terms of cancer prevention. To test this hypothesis, we utilized data from a large cohort study of US women, the Nurses' Health Study II (NHSII).

4.2. METHODS

Study population

The NHSII enrolled 116,608 female nurses residing in the US aged 25-42 years old in 1989, when participants completed a baseline self-administered questionnaire about lifestyle risk factors and diagnosed conditions. Since then, biennial questionnaires were sent to update this information, with response rates over 93%. More details about the NHS II are described elsewhere (Bao et al., 2016; 2018). This study was approved by the Institutional Review Boards of the Brigham and Women's Hospital and the Harvard T.H. Chan School of Public Health.

Assessment of physical activity

The 1997 questionnaire inquired about physical activity during adolescence and early adulthood. Participants reported average hours a week (none, 1, 2-5, 6-10, 11-20, 21-40, 41-60, 61-90, 90+ h/week) of walking to and from school or work, moderate recreational activities (e.g., hiking, walking for exercise, casual cycling, yard work), and strenuous recreational activities (e.g., running, aerobics, lap swimming) during grades 7-8 (12-13 years), grades 9-12 (14-17 years), ages 18-22, ages 23-29, and ages 30-34. We assigned average metabolic equivalent of task (MET) for each of these activities to classify intensities (i.e., walking 3 MET, moderate 4.5 MET, and strenuous 7 MET) based on the compendium of physical activities (Ainsworth et al., 1993; 2011). We summed MET-h/week in each of these activities to obtain total physical activity. In this study, we calculated average of total physical activity from ages 12 to 22 to estimate the engagement in physical activities during adolescence.

Adult recreational physical activity (32-64 years of age) was assessed in 1989, 1991, 1997, 2001, 2005, and 2009 (Wolf et al., 1994). Participants reported average time spent per week on a variety of recreational activities. We assigned MET values for each of these activities (Ainsworth et al., 1993; 2011) to obtain average total physical activity (in MET-h/week) in each questionnaire cycle where physical activity was assessed. More details regarding reproducibility and validity of the physical activity questionnaires are described in the Supplemental Material as well as in previous publications (Jacobs et al., 1993; Ainsworth et al., 1993; Wolf et al., 1994; Hunter et al., 1994, Chasan-Taber et al., 1996, Baer et al., 2005, Maruti et al., 2008). Cumulative average adult physical activity was calculated using all available data up to and including the questionnaire 2-years prior to the follow-up cycle at which the most recent endoscopy was reported. Total physical activity during adolescence (12 to 22 years) and cumulative average adult physical activity were weakly correlated (Spearman $r = 0.19$; $P < 0.001$).

Assessment of dietary factors and other covariates

In 1991 and every 4 years thereafter, diet was assessed through a validated semi-quantitative food frequency questionnaire (FFQ) (Yuan et al. 2017; 2018). In addition, in 1998, 47,355 participants (55% of the cohort), at that time 34-51 years old, completed a validated FFQ inquiring about diet during high school. Previous analyses

showed that the risk factor profiles of this subsample were similar to those who did not respond to the high school FFQ (Nimptsch et al., 2013).

Height and current weight were obtained on the 1989 baseline questionnaire which also included a 9-level figure on body shape representing body fatness (the higher the values, the higher body fatness) at age 5, 10 and 20 years. Weight and other relevant covariates such as lifestyle factors (e.g., aspirin use, smoking status, alcohol intake, family history of colorectal cancer) were updated every 2 years (Nimptsch et al., 2011).

Outcome ascertainment

Polyps are often asymptomatic and detected during a lower bowel endoscopy (i.e., either sigmoidoscopy or colonoscopy). Between 1998 and 2011, participants were asked on their biannual follow-up questionnaire whether they underwent a lower bowel endoscopy, the reasons for endoscopy (symptoms or screening) and whether colorectal polyps were diagnosed. Participants who reported a diagnosis of colorectal polyps were mailed a form requesting permission to obtain and review medical records. Study investigators who were blinded to exposure status (e.g., physical activity) reviewed medical records and recorded anatomical location (proximal, distal, and rectum), subtype (adenoma only, serrated lesions only, both adenoma and serrated lesions) (East et al., 2015), and histology and size (advanced: defined as size ≥ 1 cm or any mention of villous histology or high-grade dysplasia; non-advanced: < 1 cm and tubular adenomas) of colorectal polyps.

Statistical analysis

For this analysis, we included 28,250 women who responded to a) the 1997 questionnaire, which included information about physical activity during adolescence and adulthood, b) the 1998 FFQ high school questionnaire, and c) underwent at least one lower bowel endoscopy during our follow-up period, i.e., 1998 to 2011. To consider individuals who underwent multiple endoscopies between 1998 and 2011 and reduce potential bias due to time-varying exposure, we used an Anderson-Gill data set structure with a new record for each 2-year follow-up during which participants underwent an endoscopy. Therefore, participants who underwent multiple endoscopies during follow-up could have multiple observations in the dataset. Exposure and covariates were set at

one cycle (2 years) prior the endoscopy. Once polyps were diagnosed, participants were censored for later follow-up cycles.

We used multivariable logistic regression (PROC GENMOD) for clustered data (i.e., each participant was defined as a cluster, therefore accounting for multiple endoscopies) to estimate odds ratios (OR) and 95% confidence intervals for the association between total physical activity during adolescence (<21, 21 to 35.9, 36 to 47.9, 48 to 71.9, ≥ 72 MET-h/week) and risk of adenoma. Categories of physical activity were derived based on its distribution and informative cutoffs (Maruti et al., 2008). We also estimated associations per 21 MET-h/week (i.e., equivalent to 1 hour of moderate intensity physical activity every day, which is the recommended physical activity level for children and adolescents (WHO, 2010) and tested for trend via a Wald test by including the median of physical activity in each category as a single continuous exposure variable into the models.

We ran different multivariable models adjusting for several adolescent and adult covariates selected based on the literature on risk factors for colorectal adenomas or cancer (Nimptsch et al., 2011; 2013; 2014; Clarke; Joshi, 2017; WCRF, 2018). The first model (age-adjusted) included age at baseline, time period of endoscopy, number of reported endoscopies, time in years since most recent endoscopy and reason for current endoscopy. The second multivariable model was additionally adjusted for height (continuous), body fatness (1, 2, 3, 4, 5, ≥ 6) at 5 years (i.e., body shape at age 5 was the strongest predictor of adenoma (Nimptsch et al., 2011), total calories (quintiles), unprocessed red meat and processed meat (quintiles), total dairy (quintiles), and total fiber (quintiles) during adolescence and current (adult) aspirin use (yes/no), alcohol intake (<4.9, 5-9.9, 10-14.9, ≥ 15 g/d), pack-years of smoking (never, 0-10, >10-20, >20-40, >40 pack-years), and family history of colorectal cancer (yes/no). We also ran additional analyses including cumulative average adult physical activity (quintiles), adult body mass index (BMI, <25, 25 to 29.9, ≥ 30 kg/m²), and television viewing during adolescence (<3.5, 3.5 to 6.9, 7 to 10.4, 10.5 to 13.9, ≥ 14 h/week) to examine whether the associations were independent of these exposures. Finally, we tested the influence of other potential confounders during adolescence (i.e., total folate intake, total calcium intake and western dietary pattern during high school, pack-years of smoking before age 20, and BMI at age 18) and adulthood (postmenopausal hormone use, total fiber, red and processed meat intake) by including these variables separately

(i.e., one by one) to the multivariable model. These covariates did not alter the magnitude of associations found in the multivariable model, therefore, we excluded them from the final model. We used missing indicator for participants with missing information on covariates.

To explore whether the association between physical activity during adolescence and adenomas differ by potential effect modifiers, we performed subgroup analyses by family history of colorectal cancer, age at adenoma diagnosis (<50 years and $\geq$ 50 years), BMI at 18 years (<23 kg/m² and $\geq$ 23 kg/m²), and smoking status (never and ever). Tests for interaction were performed by including the multiplicative term (cross-product term) of the exposure and each of the stratified variables in the model. We also evaluated joint associations of physical activity during adolescence and adulthood with regard to risk of adenoma. Distribution of physical activity level differed between adolescence (median 40.1 MET-week; interquartile range from 23.8 to 70.4) and adulthood (median 26.4 MET-week; interquartile range from 8.7 to 28.6). Therefore, we classified participants into four groups according to physical activity and stage of life defining high physical activity a priori as highest tertile ($\geq$ 53.3 MET-h/week for adolescence and $\geq$ 23.1 MET-h/week for adulthood) and low physical activity as the bottom two tertiles. We used SAS 9.4 for all analyses (SAS institute Inc., Cary, NC, USA). A P-value of <0.05 was considered statistically significant.

4.3. RESULTS

Among 28,250 women included in the study, 2373 adenoma cases were diagnosed between 1998 and 2011 (proximal colon: 1171, distal colon: 1029, rectum: 398). Characteristics of the participants by level of physical activity during adolescence are shown in Table 1. Participants with higher levels of physical activity during adolescence were more likely to have lower body fatness at 5-20 years and lower BMI at 18 years. On the other hand, they were more likely current smokers and to have higher total energy and unprocessed red meat intake during both adolescence and adulthood (Table 1).

Table 1 - Baseline characteristics of participants by total physical activity during adolescence, Nurses' Health Study II, 1997

Characteristic*	Total physical activity during adolescence (in MET-h/week)				
	<21 (n=5,689)	21 to <36 (n=6,589)	36 to <48 (n=4,568)	48 to <72 (n=6,019)	72+ (n=5,385)
Age at 1997 questionnaire return, yrs.†	51.4 (4.8)	51.0 (4.9)	50.8 (5.0)	50.7 (5.1)	50.5 (5.1)
Number of endoscopies during the study period (n)	1.6 (0.8)	1.6 (0.8)	1.5 (0.8)	1.5 (0.8)	1.6 (0.8)
Height (baseline) (inches)	64.8 (2.5)	64.8 (2.6)	65.0 (2.6)	65.0 (2.6)	65.1 (2.7)
BMI at age 18 years (kg/m ²)	21.4 (3.5)	21.2 (3.2)	21.1 (3.1)	21.0 (3.0)	20.8 (2.8)
Current BMI (kg/m ²)	25.7 (5.6)	25.6 (5.4)	25.7 (5.7)	25.7 (5.4)	26.0 (5.5)
Waist (inches)	30.9 (5.1)	30.8 (5.1)	30.7 (5.0)	30.5 (4.8)	30.7 (5.0)
Hip (inches)	39.4 (4.4)	39.4 (4.4)	39.3 (4.3)	39.2 (4.3)	39.3 (4.3)
Waist/hip ratio	0.78(0.08)	0.78(0.08)	0.78(0.08)	0.78(0.08)	0.78(0.08)
Body shape [§] (% of ≥5)					
At 5 years of age	8.6	7.1	6.3	6.6	5.0
At 10 years of age	16.5	13.2	11.6	10.9	8.4
At 20 years of age	14.3	10.8	9.6	8.4	6.8
Smoking					
Before 20 years of age (%)	24.4	22.7	22.9	21.7	23.5
Current smokers (%)	5.9	6.7	7.3	8.3	10.0
Current alcohol intake (g/d),	3.9 (6.3)	4.2 (6.5)	4.2 (6.4)	4.1 (6.3)	4.2 (6.5)
Current physical activity (MET/week)	17.2 (17.9)	19.0 (18.1)	20.6 (20.5)	22.2 (20.4)	26.0 (24.0)
Time spent watching television					
During adolescence (hours/week)	7.6 (6.3)	7.5 (6.0)	7.5 (5.8)	7.7 (6.0)	8.1(6.2)
Current (hours/week)	8.9 (6.9)	8.8 (6.4)	8.8 (6.4)	9.1 (6.6)	9.3 (6.8)
Premenopausal (%)	52.5	52.9	52.2	52.5	52.1
Family history of colorectal cancer (%)	27.7	27.4	25.6	26.3	27.9
Current Aspirin use (≥2 twice a week)	8.8	8.7	9.8	9.2	9.4
<i>Dietary intake during adolescence</i>					
Total energy intake (kcal/day)	2609 (778)	2692 (756)	2739 (767)	2797 (775)	2934 (799)
Unprocessed red meat (g/day)	105.3 (49.2)	107.7 (52.2)	107.1 (51.2)	108.3 (51.7)	111.5 (52.7)
Processed meat (g/day)	23.5 (20.1)	22.6 (18.3)	22.7 (17.9)	22.5 (18.1)	23.9 (19.8)
Total dairy (servings/day)	2.6 (1.5)	2.8 (1.4)	2.8 (1.5)	3.0 (1.5)	3.1 (1.6)
Total fiber (g/day)	19.8 (4.9)	20.5 (5.2)	20.8 (5.1)	21.2 (5.3)	21.5 (5.5)
Total calcium (mg/day)	1057 (358)	1078 (344)	1088 (343)	1097 (340)	1091 (342)
Total folate (µg/day)	304 (88)	317 (91)	318 (90)	326 (98)	328 (96)
<i>Adult dietary intake (baseline**)</i>					
Total energy intake (kcal/day)	1707 (474)	1766 (470)	1793 (479)	1817 (489)	1886 (508)
Unprocessed red meat (g/day)	51.8 (40.6)	54.0 (39.3)	55.3 (41.6)	56.1 (42.5)	61.0 (44.7)
Processed meat during (g/day)	6.3 (10.0)	6.2 (8.8)	6.6 (9.7)	6.5 (8.6)	7.4 (10.1)
Total fiber (g/day)	18.8 (5.4)	19.2 (5.5)	19.2 (5.3)	19.4 (5.3)	19.2 (5.2)
Total calcium (mg/day)	1072 (433)	1074 (415)	1072 (423)	1064 (420)	1041 (404)
Total folate (µg/day)	473 (236)	480 (230)	478 (228)	482 (235)	474 (224)

Physical activity during adolescence was inversely associated with risk of adenoma, independent of physical activity during adulthood (Table 2). The magnitude of association was modest, with multivariable-adjusted OR of 0.89 (95% CI 0.77 to 1.02) comparing ≥ 72 MET-h/week to < 21 MET-h/week (reference group). The OR of adenoma per 21 MET-h/week was 0.96 (95% CI 0.93 to 0.99; $P_{\text{trend}} = 0.02$). Results were similar after further adjustment for physical activity and BMI during adulthood and television watching during adolescence (Table S1).

Table 2 - Odds ratio of colorectal adenoma associated with total physical activity during adolescence by colorectal location. Nurses' Health Study II, 1997-2011

	Total physical activity during adolescence (in MET-h/week)					Per 21 MET-h/week	P _{trend}
	<21	21 to <36	36 to <48	48 to <72	72+		
All adenomas							
N Cases	503	579	416	466	409		
Age-adjusted*	1	1.01(0.90-1.15)	1.06(0.93-1.22)	0.90(0.79-1.03)	0.88(0.77-1.01)	0.96(0.93-0.99)	0.01
Multivariable†	1	1.02(0.90-1.16)	1.07(0.94-1.23)	0.91(0.80-1.04)	0.89(0.77-1.02)	0.96(0.93-0.99)	0.02
Multivariable† plus adult physical activity	1	1.02(0.90-1.16)	1.08(0.94-1.23)	0.92(0.80-1.05)	0.90(0.78-1.03)	0.96(0.93-1.00)	0.03
Location							
<i>Proximal adenomas</i>							
N Cases	252	290	205	227	197		
Age-adjusted*	1	1.02(0.85-1.21)	1.05(0.87-1.27)	0.88(0.73-1.06)	0.85(0.70-1.03)	0.95(0.91-0.99)	0.03
Multivariable†	1	1.02(0.85-1.21)	1.06(0.87-1.28)	0.89(0.73-1.07)	0.86(0.70-1.04)	0.95(0.91-1.00)	0.04
Multivariable† plus adult physical activity	1	1.02(0.86-1.22)	1.06(0.88-1.29)	0.90(0.74-1.08)	0.87(0.72-1.07)	0.96(0.91-1.00)	0.07
<i>Distal adenomas</i>							
N Cases	219	255	174	193	188		
Age-adjusted*	1	1.03(0.85-1.23)	1.02(0.83-1.25)	0.86(0.71-1.05)	0.93(0.76-1.14)	0.97(0.92-1.02)	0.21
Multivariable†	1	1.04(0.87-1.26)	1.04(0.85-1.28)	0.88(0.72-1.07)	0.94(0.76-1.15)	0.97(0.92-1.02)	0.22
Multivariable† plus adult physical activity	1	1.04(0.86-1.26)	1.04(0.85-1.28)	0.88(0.72-1.08)	0.94(0.77-1.16)	0.97(0.92-1.02)	0.26
<i>Rectal adenomas</i>							
N Cases	84	86	73	81	74		
Age-adjusted*	1	0.90(0.66-1.21)	1.11(0.80-1.52)	0.93(0.68-1.27)	0.94(0.69-1.30)	0.99(0.92-1.07)	0.80
Multivariable†	1	0.91(0.67-1.24)	1.13(0.82-1.55)	0.94(0.69-1.29)	0.94(0.68-1.30)	0.99(0.91-1.07)	0.76
Multivariable† plus adult physical activity	1	0.92(0.68-1.25)	1.15(0.84-1.58)	0.96(0.70-1.32)	0.97(0.69-1.35)	0.99(0.92-1.08)	0.90

*Adjusted for age, time period of endoscopy, number of reported endoscopies, time in years since most recent endoscopy and reason for current endoscopy.

†Additionally adjusted for height (*inches*), body shape at 5 years (1, 2, 3, 4, 5, ≥6), total calories during adolescence (*quintiles*), unprocessed red meat and processed meat during high school (*quintiles*), total dairy during adolescence (*quintiles*), total fiber during adolescence (*quintiles*), current (adult) aspirin use (*yes/no*), current (adult) alcohol intake (<4.9, 5-9.9, 10-14.9, 15+ g/d), current (adult) pack-years of smoking (*never, 0-10, >10-20, >20-40, 40+ pack-years*), and family history of colorectal cancer (*yes/no*).

When we analyzed data separately by location, physical activity during adolescence was associated with lower risk of proximal adenomas, but not rectal and distal adenomas (Table 2). Furthermore, we observed inverse associations for adenoma only, but not for serrated lesions only (Table 3). The inverse associations also appeared to be stronger among women with no family history of colorectal cancer and age at adenoma diagnosis ≥ 50 years, although the interaction was only statistically significant for the later ($P < 0.01$) (Table S2).

We assessed joint associations of physical activity during adolescence and adulthood with regard to risk of adenomas. We observed non-significant lower risk of adenoma among women with high physical activity during adolescence only (OR 0.93; 95% CI 0.83 to 1.04) and during adulthood only (OR 0.91; 95% CI 0.82 to 1.02) compared to women with low physical activity in both stages of life. The strongest inverse association was found for women with high physical activity during both adolescence and adulthood (OR 0.76; 95% CI 0.66 to 0.88) (Figure 1). Inverse associations were more pronounced for advanced adenoma than for non-advanced adenoma. Participants with high physical activity during both adolescence and adulthood had a 39% lower risk of advanced adenomas (0.61; 95% CI 0.45 to 0.82) compared to women with low physical activity during both stages of life.

Table 3 - Odds ratio of colorectal adenoma associated with total physical activity during adolescence by stage and subtype of colorectal polyp. Nurses' Health Study II, 1997-2011

	Total physical activity during adolescence (in MET-h/week)					Per 21 MET-h/week	P-trend
	<21	21 to <36	36 to <48	48 to <72	72+		
Colorectal adenomas							
By Stage							
<i>Advanced</i>							
N Cases	105	156	110	106	89		
Age-adjusted*	1	1.31(1.02-1.69)	1.34(1.02-1.76)	0.98(0.75-1.29)	0.92(0.69-1.23)	0.94(0.88-1.00)	0.07
Multivariable†	1	1.34(1.04-1.73)	1.36(1.03-1.78)	1.00(0.76-1.32)	0.91(0.68-1.23)	0.94(0.88-1.00)	0.06
Multivariable† plus adult physical activity	1	1.35(1.05-1.74)	1.38(1.05-1.81)	1.02(0.77-1.35)	0.94(0.70-1.27)	0.95(0.88-1.01)	0.11
<i>Non-advanced</i>							
N Cases	294	318	225	257	247		
Age-adjusted*	1	0.95(0.81-1.12)	0.98(0.82-1.17)	0.85(0.71-1.01)	0.90(0.76-1.07)	0.97(0.93-1.01)	0.16
Multivariable†	1	0.96(0.81-1.13)	0.99(0.83-1.19)	0.86(0.72-1.02)	0.91(0.76-1.09)	0.97(0.93-1.02)	0.21
Multivariable† plus adult physical activity	1	0.96(0.81-1.13)	0.99(0.83-1.19)	0.86(0.72-1.03)	0.92(0.77-1.10)	0.97(0.93-1.02)	0.24
By Subtype							
<i>Adenoma only</i>							
N Cases	406	490	341	363	331		
Age-adjusted*	1	1.06(0.93-1.22)	1.08(0.93-1.26)	0.87(0.75-1.01)	0.88(0.76-1.03)	0.95(0.92-0.99)	0.01
Multivariable†	1	1.07(0.94-1.23)	1.10(0.95-1.28)	0.88(0.76-1.02)	0.90(0.77-1.05)	0.95(0.92-0.99)	0.01
Multivariable† plus adult physical activity	1	1.07(0.94-1.23)	1.10(0.95-1.28)	0.89(0.76-1.03)	0.90(0.77-1.06)	0.96(0.92-0.99)	0.02
<i>Serrated lesions only</i>							
N Cases	339	378	272	347	309		
Age-adjusted*	1	0.98(0.84-1.14)	1.02(0.87-1.21)	0.99(0.85-1.16)	0.98(0.83-1.15)	1.00(0.96-1.04)	0.85
Multivariable†	1	0.99(0.85-1.16)	1.04(0.88-1.23)	1.01(0.86-1.18)	0.97(0.82-1.14)	0.99(0.95-1.03)	0.69
Multivariable† plus adult physical activity	1	0.99(0.85-1.15)	1.04(0.88-1.23)	1.01(0.86-1.18)	0.97(0.83-1.15)	0.99(0.96-1.03)	0.77
<i>Both adenoma and serrated lesions</i>							
N Cases	97	89	75	103	78		
Age-adjusted*	1	0.81(0.61-1.09)	1.01(0.74-1.36)	1.04(0.79-1.38)	0.89(0.65-1.20)	1.00(0.93-1.07)	0.91
Multivariable†	1	0.81(0.61-1.09)	0.99(0.72-1.35)	1.03(0.77-1.37)	0.84(0.61-1.14)	0.98(0.91-1.06)	0.60
Multivariable† plus adult physical activity	1	0.82(0.61-1.10)	1.00(0.73-1.36)	1.05(0.79-1.40)	0.86(0.63-1.17)	0.99(0.92-1.06)	0.74

*Adjusted for age, time period of endoscopy, number of reported endoscopies, time in years since most recent endoscopy and reason for current endoscopy.

†Additionally adjusted for height (*inches*), body shape at 5 years (1, 2, 3, 4, 5, ≥6), total calories during adolescence (*quintiles*), unprocessed red meat and processed meat during adolescence (*quintiles*), total dairy during adolescence (*quintiles*), total fiber during adolescence (*quintiles*), current (adult) aspirin use (*yes/no*), current (adult) alcohol intake (<4.9, 5-9.9, 10-14.9, 15+ g/d), current (adult) pack-years of smoking (*never, 0-10, >10-20, >20-40, 40+ pack-years*), and time spent watching television during adolescence (0.5, 0.5-1, 1-1.5, 1.5-2, 2+ h/day)

Figure 1 - Joint association of total physical activity during adolescence and adulthood with regard to risk of colorectal adenoma - Nurses' Health Study II, 1997-2011

Footnote: High physical activity (PA) at adolescence was defined as the highest tertile (≥ 53.3 MET-h/week); low was defined as the two bottom tertiles (< 53.5 MET-h/week). High PA at adulthood was defined as highest tertile (≥ 23.1 MET-h/week); low was defined as two bottom tertiles (< 23.1 MET-h/week).

Number of all adenomas: *Low PA adolescence- Low PA adulthood* (n=1192); *Low PA adolescence- High PA adulthood* (n=453); *High PA adolescence- Low PA adulthood* (n=463); *High PA adolescence- High PA adulthood* (n=265);

Number of non-advanced adenomas: *Low PA adolescence- Low PA adulthood* (n=659); *Low-high* (n=258); *High-low* (n=261); *High-high* (n=163);

Number of advanced adenomas: *Low PA adolescence- Low PA adulthood* (n=305); *Low PA adolescence- High PA adulthood* (n=105); *High PA adolescence- Low PA adulthood* (n=103); *High PA adolescence- High PA adulthood* (n=53)

4.4. DISCUSSION

In this large study, physical activity during adolescence was inversely associated with risk of colorectal adenomas, independent of physical activity during adulthood. We also found that women who were physically active during both adolescence and adulthood had the lowest risk of colorectal adenoma later in life.

Physical activity may potentially affect carcinogenesis by decreasing body fatness, inflammation, and insulin levels (Friedenreich; Orenstein, 2002; McTiernan, 2008; Giovannucci, 2018). High levels of insulin and insulin resistance, which can stimulate proliferation and apoptosis (Giovannucci, 2001), are associated with higher risk of adenoma in adults (Yoon et al., 2015). Physical activity throughout life, including during adolescence, may decrease insulin resistance and increase glucose uptake by skeletal muscle (McTiernan, 2008; Giovannucci, 2018), especially by improving body composition (i.e., reducing visceral adipose tissue (Verheggen et al., 2016). In addition, recent data suggest that physical activity may affect composition and diversity of gut microbiota resulting in more favorable metabolic and inflammatory profiles (Clarke et al., 2014; O'Sullivan et al., 2015; Blottière, 2017). However, more human studies on that topic are needed, especially accounting for possible confounding by diet.

In adults, physical activity is considered an established risk factor for colon but not rectal cancer (IARC, 2002; Rezende et al., 2018; WCRF, 2018). The association between physical activity during adulthood and colorectal adenomas supports a potential protective effect of physical activity on earlier stages of carcinogenesis. A meta-analysis including 20 case-control and cohort studies found a 16% (RR 0.84; 95% CI 0.77 to 0.90) lower risk of colon adenomas among most active individuals during adulthood as compared to the least active group. Observed inverse associations were stronger for large or advanced adenomas, a subtype more likely to progress to colorectal cancer than small or non-advanced adenomas (Wolin et al., 2011). Nonetheless, studies examining the association between early-life physical activity and cancer risk, including colorectal adenomas and colorectal cancer, are sparse (Clarke; Joshu, 2017). To the best of our knowledge, only two case-control studies investigated the association between early-life physical activity and colorectal cancer later in life. A hospital-based case-control study conducted in Italy, including 1225 cases and 4154 controls, found that

high levels of occupational physical activity, but not leisure activities, at 15 to 19 years was associated with lower risk of colon cancer when compared least active group (Tavani et al., 1999). Similarly, another hospital-based case-control study conducted between 1992 and 1997 in the Swiss canton of Vaud also observed an inverse association between occupational physical activity, but not leisure activity at age 15 to 19 with regard to colorectal cancer (Levi et al., 1999).

To our knowledge, our study is the first to show an inverse association between physical activity during both adolescence and adulthood on risk of colorectal adenoma. These associations were also stronger for advanced adenomas. Similarly, in the Harvard Alumni Health Study, a cohort study including 17,148 adults, physical activity was assessed in 1962/1966, when participants were 30-79 years of age, and again 1977 (45 to 94 years) (Lee et al., 1991). In that study, only high levels of physical activity during both periods, but not in either one, was associated with lower risk of colon cancer. Despite differences in age group, results from Harvard Alumni study are in accordance with our findings about a possible role of physical activity throughout life on colon carcinogenesis.

Some limitations should be considered while interpreting our results. Physical activity during both adolescence and adulthood was self-reported and some misclassification of exposure is inevitable. However, both adolescent and adult physical activity questionnaires showed reasonable reproducibility, and the adult questionnaire was also validated (Jacobs et al., 1993; Wolf et al., 1994; Chasan-Taber et al., 1996; Baer et al., 2005). Additionally, physical activity during adolescence and adulthood were only weakly correlated ($r=0.19$). Misclassification of physical activity is likely to be non-differential because information was collected prior to diagnosis of colorectal adenomas, and therefore would bias associations towards the null. Although our analyses considered a large number of potential lifestyle and dietary confounders during both adolescence and adulthood, residual confounding due to imperfect adjustment or unmeasured confounders cannot be ruled out.

In conclusion, we found an inverse association between physical activity during adolescence and risk of colorectal adenomas in women, independent of physical activity during adulthood. Associations were slightly stronger for advanced adenomas. Participants with high levels of physical activity during both adolescence and adulthood had the lowest risk of colorectal adenomas relative to groups least active in both or

either periods. Our findings suggest that physical activity during adolescence may play a role in early stages of colorectal carcinogenesis, which have important implications for cancer prevention.

Conflict of Interest: none.

Funding: The Nurses' Health Study II was funded by the National Cancer Institute, National Institutes of Health (UM1 CA176726 and R01 CA67262).

Leandro F3rnias Machado de Rezende receives a doctoral fellowship from Sao Paulo Research Foundation (FAPESP), grant #2016/21390-0 and #2014/25614-4.

NIH/NCI grant R03 CA197879 and by an investigator-initiated grant from the American Institute for Cancer Research (AICR) to Kana Wu.

Acknowledgments: The authors would like to thank the Channing Division of Network Medicine, Department of Medicine, Brigham and Women's Hospital and Harvard Medical School.

The authors would like to thank the participants and staff of the Nurses' Health Study II for their valuable contributions as well as the following state cancer registries for their help: AL, AZ, AR, CA, CO, CT, DE, FL, GA, ID, IL, IN, IA, KY, LA, ME, MD, MA, MI, NE, NH, NJ, NY, NC, ND, OH, OK, OR, PA, RI, SC, TN, TX, VA, WA and WY. The authors assume full responsibility for analyses and interpretation of these data.

Key Message

Physical activity during adolescence was associated with lower risk of colorectal adenomas, independent of physical activity during adulthood. Women who were physically active during both adolescence and adulthood had the lowest risk of colorectal adenoma later in life. Our findings suggest that physical activity during adolescence may play a role in early stages of colorectal carcinogenesis, which have important implications for cancer prevention.

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SUPPLEMENTARY FILE

Reproducibility and validity of physical activity questionnaires

In 2000, a sample of 160 participants that completed the 1997 questionnaire on physical activity was asked about again their average of physical activity during adolescence and early adulthood for sake of examine reproducibility. On average, the correlations between the 1997 and the 2000 assessment was 0.64 for total physical activity, 0.76 for strenuous, 0.70 for strenuous plus moderate. By age group, spearman rho correlation for hours/week in strenuous activity was 0.63 in grade 7 to 8, 0.71 in grades 9 to 12, and 0.69 at ages 18 to 22. Walking activity presented similar reproducibility results, whereas moderate physical activity was lower across all periods (0.37 for grades 7 and 8, 0.36 for grades 9 to 12, and 0.52 for ages 18 to 22).[1]

In adults, physical activity questionnaire showed good validity when comparing physical activity in the previous year to both recall of physical activity in the previous week ($r = 0.79$) and activity in diaries ($r = 0.62$). Similar physical activity questions has also showed a have a moderate correlation with maximal oxygen consumption ($r = 0.54$)[2] and lower resting pulse ($r = 0.45$).[3]

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Table S1 - Odds ratio of colorectal adenoma associated with total physical activity during adolescence by location, stage and subtype of colorectal polyps. Nurses' Health Study II, 1997-2011

	Total physical activity during adolescence (in MET-h/week)					Per 21 MET-h/week	P _{trend}
	<21	21 - <36	36 - <48	48 - <72	72+		
All adenomas							
Multivariable† plus adult PA and BMI, and television watching during adolescence	1	1.03(0.91-1.17)	1.07(0.94-1.23)	0.91(0.80-1.05)	0.88(0.77-1.02)	0.96(0.93-0.99)	0.01
Multivariable† plus adult BMI	1	1.02(0.90-1.16)	1.07(0.93-1.22)	0.90(0.79-1.03)	0.88(0.76-1.01)	0.96(0.92-0.99)	0.01
Multivariable† plus adult PA and BMI	1	1.02(0.90-1.16)	1.07(0.93-1.23)	0.91(0.79-1.04)	0.88(0.77-1.01)	0.96(0.93-0.99)	0.01
By Location							
<i>Proximal adenomas</i>							
Multivariable† plus adult PA and BMI, and television watching during adolescence	1	1.02(0.86-1.22)	1.06(0.87-1.28)	0.89(0.74-1.08)	0.86(0.70-1.05)	0.95(0.90-1.00)	0.04
Multivariable† plus adult BMI	1	1.01(0.85-1.21)	1.05(0.87-1.27)	0.88(0.73-1.06)	0.85(0.69-1.03)	0.95(0.90-0.99)	0.03
Multivariable† plus adult PA and BMI	1	1.02(0.85-1.21)	1.05(0.87-1.28)	0.89(0.73-1.07)	0.86(0.70-1.05)	0.95(0.90-1.00)	0.04
<i>Distal adenomas</i>							
Multivariable† plus adult PA and BMI, and television watching during adolescence	1	1.05(0.87-1.27)	1.03(0.84-1.27)	0.88(0.71-1.07)	0.92(0.74-1.13)	0.96(0.91-1.01)	0.14
Multivariable† plus adult BMI	1	1.04(0.86-1.25)	1.04(0.84-1.27)	0.87(0.71-1.06)	0.92(0.75-1.13)	0.97(0.92-1.02)	0.17
Multivariable† plus adult PA and BMI	1	1.04(0.86-1.25)	1.03(0.84-1.27)	0.87(0.71-1.06)	0.92(0.75-1.13)	0.97(0.92-1.02)	0.18
<i>Rectal adenomas</i>							
Multivariable† plus adult PA and BMI, and television watching during adolescence	1	0.93(0.68-1.27)	1.19(0.86-1.64)	0.98(0.71-1.35)	0.97(0.69-1.36)	0.99(0.92-1.08)	0.89
Multivariable† plus adult BMI	1	0.91(0.67-1.24)	1.13(0.82-1.55)	0.94(0.69-1.29)	0.94(0.67-1.30)	0.99(0.91-1.07)	0.74
Multivariable† plus adult PA and BMI	1	0.92(0.68-1.25)	1.15(0.83-1.58)	0.96(0.70-1.32)	0.96(0.69-1.35)	0.99(0.92-1.08)	0.88
By Stage							
<i>Advanced</i>							
Multivariable† plus adult PA and BMI, and television watching during adolescence	1	1.36(1.05-1.75)	1.37(1.04-1.81)	1.02(0.78-1.35)	0.94(0.70-1.26)	0.94(0.88-1.01)	0.09
Multivariable† plus adult BMI	1	1.34(1.04-1.72)	1.35(1.03-1.78)	0.99(0.76-1.31)	0.90(0.67-1.21)	0.94(0.88-1.00)	0.05
Multivariable† plus adult PA and BMI	1	1.35(1.05-1.74)	1.37(1.04-1.80)	1.01(0.77-1.34)	0.93(0.69-1.25)	0.94(0.88-1.01)	0.08
<i>Non-advanced</i>							
Multivariable† plus adult PA and BMI, and television watching during adolescence	1	0.96(0.81-1.13)	0.99(0.82-1.19)	0.86(0.72-1.02)	0.90(0.75-1.08)	0.97(0.92-1.01)	0.16
Multivariable† plus adult BMI	1	0.95(0.81-1.12)	0.99(0.82-1.18)	0.85(0.71-1.02)	0.90(0.75-1.08)	0.97(0.93-1.01)	0.17
Multivariable† plus adult PA and BMI	1	0.95(0.81-1.12)	0.99(0.82-1.18)	0.85(0.71-1.02)	0.90(0.75-1.08)	0.97(0.93-1.01)	0.18
By subtype							
<i>Adenoma only</i>							
Multivariable† plus adult PA and BMI, and television watching during adolescence	1	1.08(0.94-1.24)	1.10(0.95-1.29)	0.89(0.76-1.03)	0.90(0.77-1.05)	0.95(0.92-0.99)	0.01
Multivariable† plus adult BMI	1	1.07(0.93-1.23)	1.10(0.95-1.28)	0.88(0.76-1.02)	0.89(0.76-1.04)	0.95(0.92-0.99)	0.01
Multivariable† plus adult PA and BMI	1	1.07(0.93-1.23)	1.10(0.95-1.28)	0.88(0.76-1.02)	0.90(0.77-1.05)	0.95(0.92-0.99)	0.02
<i>Serrated lesions only</i>							
Multivariable† plus adult PA and BMI, and television watching during adolescence	1	0.98(0.84-1.14)	1.03(0.88-1.22)	0.99(0.85-1.16)	0.94(0.79-1.11)	0.98(0.95-1.02)	0.44
Multivariable† plus adult BMI	1	0.99(0.85-1.15)	1.03(0.88-1.22)	0.99(0.85-1.16)	0.95(0.80-1.11)	0.99(0.95-1.03)	0.49
Multivariable† plus adult PA and BMI	1	0.98(0.84-1.14)	1.03(0.87-1.21)	0.99(0.84-1.15)	0.94(0.80-1.11)	0.98(0.95-1.02)	0.44
<i>Both adenoma and Serrated lesions</i>							
Multivariable† plus adult PA and BMI, and television watching during adolescence	1	0.81(0.60-1.09)	0.98(0.71-1.34)	1.03(0.77-1.38)	0.81(0.59-1.12)	0.97(0.90-1.05)	0.50
Multivariable† plus adult BMI	1	0.81(0.60-1.08)	0.97(0.71-1.32)	1.01(0.76-1.35)	0.81(0.59-1.10)	0.97(0.90-1.05)	0.45
Multivariable† plus adult PA and BMI	1	0.81(0.60-1.09)	0.98(0.72-1.33)	1.02(0.76-1.35)	0.81(0.59-1.11)	0.97(0.90-1.05)	0.48

*Adjusted for age, time period of endoscopy, number of reported endoscopies, time in years since most recent endoscopy and reason for current endoscopy.

†Additionally adjusted for height (*inches*), body shape at 5 years (1, 2, 3, 4, 5, ≥6), total calories during adolescence (*quintiles*), unprocessed red meat and processed meat during adolescence (*quintiles*), total dairy during adolescence (*quintiles*), total fiber during adolescence (*quintiles*), current (adult) aspirin use (*yes/no*), current (adult) alcohol intake (<4.9, 5-9.9, 10-14.9, 15+ g/d), current (adult) pack-years of smoking (*never, 0-10, >10-20, >20-40, 40+ pack-years*), time spent watching television during adolescence (0.5, 0.5-1, 1-1.5, 1.5-2, 2+ h/day)

Table S2 - Stratified analysis: Association between total physical activity during adolescence and risk of colorectal adenoma. Nurses' Health Study II, 1997-2011

	Total physical activity during adolescence (Per 21 MET-h/week)		
	Odds ratio	95% Confidence interval	P _{interaction}
All adenomas			
Family history of colorectal cancer			0.14
No (N cases = 1807)	0.95	(0.91 to 0.98)	
Yes (N cases = 564)	1.01	(0.94 to 1.08)	
Age at diagnosis			<0.01
<50 years (N cases = 538)	1.01	(0.94 to 1.08)	
≥50 years (N cases = 1833)	0.94	(0.90 to 0.98)	
BMI at 18 years			0.65
<23 kg/m ² (N cases = 1855)	0.98	(0.94 to 1.01)	
≥23 kg/m ² (N cases = 499)	0.91	(0.84 to 0.98)	
Smoking			0.79
Never (N cases = 1492)	0.97	(0.93 to 1.01)	
Ever (N cases = 877)	0.95	(0.90 to 1.00)	

†Adjusted for age, time period of endoscopy, number of reported endoscopies, time in years since most recent endoscopy and reason for current endoscopy, height (*inches*), body shape at 5 years (1, 2, 3, 4, 5, ≥6), total calories during adolescence (*quintiles*), unprocessed red meat and processed meat during high school adolescence (*quintiles*), total dairy during adolescence (*quintiles*), total fiber during adolescence (*quintiles*), current (adult) aspirin use (*yes/no*), current (adult) alcohol intake (<4.9, 5-9.9, 10-14.9, 15+ g/d), current (adult) pack-years of smoking (*never, 0-10, >10-20, >20-40, 40+ pack-years*).

5. ASSOCIAÇÃO ENTRE TIPO E INTENSIDADE DA ATIVIDADE FÍSICA E BIOMARCADORES DE INFLAMAÇÃO E RESPOSTA À INSULINA RELACIONADOS AO RISCO DE CÂNCER

Este capítulo apresenta o artigo “*Association of type and intensity of physical activity with plasma biomarkers of inflammation and insulin response*” de autoria de Dong Hoon Lee*, Leandro Fórnias Machado de Rezende*, José Eluf-Neto, Kana Wu, Fred K. Tabung, Edward L. Giovannucci. O artigo foi submetido para publicação na revista *International Journal of Cancer*.

Esse manuscrito foi elaborado durante o estágio de pesquisa no exterior na Harvard T.H. Chan School of Public Health. Donghoon Lee e eu trabalhamos em parceria nesse manuscrito, e contribuímos igualmente na elaboração do mesmo, de modo que compartilhamos a primeira autoria.

Para citação: Lee DH, Rezende LFM, Eluf-Neto J, Wu K, Tabung FK, Giovannucci E. Association of type and intensity of physical activity with plasma biomarkers of inflammation and insulin response. In preparation.

Association of type and intensity of physical activity with plasma biomarkers of inflammation and insulin response

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ABSTRACT

Background: Several biological mechanisms linking physical activity with cancer have been proposed. However, the influence of specific components of physical activity (i.e., volume, type and intensity), as well as interaction with adiposity and diet, on inflammatory and insulin levels remain unclear. *Methods:* We used cross-sectional data from 7,219 men who provided plasma samples in the Health Professionals Follow-up Study, 1992-1994. Details on physical activity were assessed using questionnaires. C-reactive protein (CRP), interleukin 6 (IL6), tumor necrosis factor α receptor 2 (TNF α R2), adiponectin, C-peptide and triglycerides/high density lipoprotein cholesterol ratio (TG/HDL) were assessed. *Results:* Total physical activity was favorably associated with all biomarkers. Comparing the highest (63+ MET-h/week) to the lowest (0 to 9 MET-h/week) physical activity groups, the multivariable-adjusted percent relative difference in concentration of biomarkers was -32% for CRP, -22% for IL6, -7% for TNF α R2, +9% for adiponectin, -22% for C-peptide, and -20% for TG/HDL. These differences were modestly attenuated after adjustment for body mass index (BMI). For the same volume of physical activity, the association was stronger for men engaging in both aerobic and resistance exercises compared to those engaging in aerobic only. However, for the same volume of physical activity, we did not find additional benefit of engaging in vigorous activities ($\geq 20\%$ of the total volume) as compared to those who did smaller amount of vigorous activities. Physical activity showed similar benefits for these biomarkers regardless of BMI and dietary pattern. *Conclusion:* High physical activity, preferably aerobic plus resistance training, was associated with favorable cancer-related biomarker profiles.

5.1. INTRODUCTION

Deciphering the role of physical activity on cancer prevention is of high interest (Giovannucci, 2018). Currently, convincing evidence from epidemiological studies supports the association between physical activity and cancers of the colon and breast, and possibly endometrium (IARC, 2002; WCRF, 2018; Rezende et al., 2018). Recently, findings from a pooled data from 12 prospective cohort studies including 1.44 million participants suggested a protective effect of physical activity on 13 types of cancers (Moore et al. 2016). Most of these cancers (esophageal adenocarcinoma, gallbladder, liver, kidney, small intestine, gastric cardia, endometrial, myeloid leukemia, myeloma, colon, rectum, breast, and non-hodgkin lymphoma) are established related to body fatness (WCRF, 2018; Lauby-Secretan et al., 2016), which is the major candidate for mediating physical activity and cancer risk (McTiernan et al., 2008; Giovannucci, 2018a; 2018b). To explore the biological mechanisms of these associations is important to support or to refute putative effects of physical activity on cancer risk (McTiernan et al., 2008).

Several biological mechanisms linking physical activity and cancer have been proposed. High physical activity is associated with long-term weight management and control (Donnelly et al., 2009) and lower visceral adiposity (Verheggen et al., 2016), which may reduce levels of several metabolic and endocrine biomarkers involved in carcinogenesis (Iyengar et al., 2016; Olson et al., 2017; Giovannucci, 2018a; 2018b; WCRF, 2018). For instance, adiposity is associated with insulin resistance and elevated fasting insulin, which stimulate cell proliferation and inhibit apoptosis (Iyengar et al., 2016; O'Flanagan et al., 2017; Olson et al., 2017; WCRF, 2018). Obesity-associated inflammation may also promote tumorigenesis and disease progression (Iyengar et al., 2016; O'Flanagan et al., 2017; Olson et al., 2017; WCRF, 2018). Of note, fasting biomarkers of inflammation (e.g., C-reactive protein (CRP), interleukin-6 (IL6), adiponectin, tumor necrosis factor alpha receptor 2 (TNF α R2)) and insulin response (e.g., C-peptide, triglycerides/high-density lipoprotein-cholesterol ratio (TG/HDL)) have been associated with higher risk of cancers in prospective studies (Giovannucci, 2001; Roddam et al., 2008; Al-Lamki et al., 2010; Waldner et al., 2012; Bao et al., 2013; Chen et al., 2013; Wang et al., 2015).

Some studies suggest that physical activity may also have direct effects on biomarkers of inflammation and insulin response, regardless of reductions in body weight and adiposity (Cronin et al., 2017; Fedewa et al., 2017; Kang et al., 2017; Giovannucci et al., 2018b). However, the importance of different components of physical activity on cancer biomarkers remains unclear (McTiernan, 2008). It is particularly important to determine the amount of total physical activity associated with a healthy biomarker profile, both mediated through and independent of body weight. Moreover, evaluating the associations of different types (aerobic vs resistance) and intensities of physical activity (moderate vs vigorous) with biomarkers, as well as interactions with other lifestyle risk factors, is also important to provide evidence for implementing physical activity interventions at the individual and population level.

In this study, we investigated the associations of different types and intensities of physical activity with biomarkers of inflammatory and insulin response. We also investigated whether potential benefits of physical activity on biomarkers of inflammatory and insulin response differed according to adiposity and dietary pattern.

5.2. METHODS

Study population

The Health Professionals Follow-up Study (HPFS) is an ongoing prospective U.S. cohort which was initiated in 1986 with the enrollment of 51,529 middle-aged (40 to 75 years) male health professionals. Details of the cohort are described elsewhere (Rimm et al., 1991). Briefly, participants completed questionnaires on demographic, medical, lifestyle, and other health-related information at enrollment and updated every two years. Diet was assessed using validated food frequency questionnaires at enrollment and updated every four years. The follow-up rate for the cohort exceeded over 90%.

Between 1993 and 1994, blood samples were collected from 18,225 men who were free of major diseases including cardiovascular disease, cancer, and diabetes. A blood kit was sent to each volunteered cohort member and the samples were returned to the lab in EDTA tubes via overnight courier. Details of the procedures for blood collection, handling, and storage have been previously described (Wei et al., 2005). In

the current study, we included participants who were previously selected for nested case-control studies within the HPFS that measured plasma biomarkers of CRP, IL6, TNF α R2, adiponectin, C-peptide, TG, and HDL. A total of 7,219 participants who provided valid physical activity data and blood samples were included in the final analysis.

This study was approved by the Institutional Review Board of the Brigham and Women's Hospital and the Human Subjects Committee Review Board of the Harvard T.H. Chan School of Public Health.

Assessment of physical activity

Physical activity was assessed by questionnaires in 1986 and every 2 years. In each cycle, participants reported their average time spent per week in walking, jogging, running, bicycling, swimming, tennis, squash/racket ball, calisthenics/rowing, and outdoor work. In 1990 and every 2 years, participants were asked to report their average weekly amount of weight lifting/weight machine. Each activity was assigned a metabolic equivalent task (MET) which represent metabolic rates for specific activity divided by metabolic rates at rest (Ainsworth et al., 1993). All activities were summed to derive total physical activity in units of MET-hours per week. By intensity of physical activity, vigorous activities, defined as MET ≥ 6 , were calculated by summing MET hours of activities including jogging, running, bicycling, swimming, tennis, squash/racquetball, and calisthenics/rowing. Moderate activities, defined as MET < 6 , included walking, heavy outdoor work, and weight lifting/weight machine. By type of physical activity, aerobic activities were calculated by including walking, stair climbing, jogging, running, bicycling, swimming, tennis, squash/racquetball, calisthenics/rowing, and heavy outdoor work. Resistance training included weight lifting/weight machine. The validity and reproducibility of the physical activity questionnaire with four 1-week activity diaries across different seasons has been previously described (Chasa-Taber et al., 1996).

Biomarker assessment

We assessed CRP, IL6, TNF α R2, and adiponectin as markers of inflammation. Moreover, C-peptide and TG/HDL were assessed as markers of hyperinsulinemia and insulin resistance, respectively. The laboratory procedures were described in detail

previously (Pai et al., 2004; Song et al., 2013). Briefly, CRP was measured by a high sensitivity immunoturbidimetric assay (Denka Seiken Co, Tokyo, Japan). IL6 and TNF α R2 were measured by enzyme-linked immunosorbent assays (R&D systems, Minneapolis, MN). Adiponectin was measured with the use of a competitive radioimmunoassay (Linco Research, St. Charles, MO). C-peptide was measured using ELISA (Diagnostic Systems Laboratories/Beckman Coulter). TG and HDL were measured using standard methods with the use of reagents from Roche Diagnostics (Indianapolis, IN) and Genzyme (Cambridge, MA). The mean intra-assay coefficient of variation for most assays was <10%.

Assessment of covariates

Self-reported questionnaires were used to collect medical and lifestyle information in 1986 and every 2 years. We calculated BMI using self-reported height (m) and weight (kg). Smoking status and regular aspirin/NSAID use (≥ 2 standard tablets of aspirin (325 mg) or NSAID per week) were reported. Chronic disease comorbidity score was calculated by summing the number of prevalent diseases and conditions including hypercholesterolemia, high blood pressure, diabetes, heart disease, cancer, rheumatoid/other arthritis. For this analysis, we used 1992 and 1994 questionnaires for these variables (data collected closest to blood draw). Diet was assessed using a validated semiquantitative food frequency questionnaire (FFQs) in 1986 and every 4 years. Participants reported their dietary intake (>130 food items) in the previous year. Using the 1994 FFQ, we calculated three dietary pattern scores which were developed to capture the inflammatory or insulin potential of the diet: empirical dietary inflammatory pattern (EDIP), empirical dietary index for hyperinsulinemia (EDIH), and empirical dietary index for insulin resistance (EDIR). The development and validation of these dietary patterns have been previously described (Tabung et al., 2016a; 2016b). Distinct from the biennial questionnaires, participants were asked to report their waist circumference using a provided tape following the same instruction in 1987 and 1996. Lastly, we calculated predicted fat mass and percent fat using previously developed anthropometric prediction equations based on age, race, height, weight, and waist circumference. These equations were previously validated using dual-energy x-ray absorptiometry (DXA) and obesity-related biomarkers in an independent dataset (Lee et al., 2017).

Statistical analyses

The distribution of biomarkers was tested for normality and then natural log transformed. Descriptive statistics for continuous variable were presented as means and standard deviations, and categorical variables were presented as proportions according to total physical activity categories.

Generalized linear models were used to examine the association between physical activity and biomarker concentrations. We recalibrated all biomarkers using the method previously described by Rosner et al. (2008) to account for variation in sample handling and laboratory drift between batches. To reduce measurement errors in physical activity, we used average of physical activity questionnaires collected in 1992 and 1994. Total physical activity was categorized into 5 groups (i.e., 0 to 8.9, 9 to 20.9, 21 to 41.9, 42 to 62.9, and 63+ MET-hour/week). The cut-offs were based on multiples of 3 MET-hour/week which corresponds to 1 hour per week of normal walking for easier interpretation (Keum et al., 2016). All multivariable models adjusted for the potential confounders including age at blood draw (continuous, years), race (white or non-white), case-control status, smoking status (never, former or current), regular aspirin/NSAID use (yes or no), chronic diseases/conditions (0, 1, 2 or 3+) and dietary pattern (quintiles). Of note, we adjusted for EDIP score for biomarkers of inflammation (i.e., CRP, IL6, TNF α R2, adiponectin), EDIH score for a biomarker of hyperinsulinemia (i.e., C-peptide), and EDIR score for a biomarker of insulin resistance (i.e., TG/HDL). Since adiposity is likely a potential mediator between physical activity and biomarkers, we additionally ran a model further adjusting for BMI (18.5-24.9, 25-29.9 or ≥ 30 kg/m²). For a sensitivity analysis, we adjusted for predicted fat mass and percent fat, instead of BMI, to better adjust for adiposity. To explore whether the associations between physical activity and biomarkers vary by diet quality and/or adiposity, we conducted stratified analyses by dietary pattern (below or above median) and/or BMI (below or above median; 25.4 kg/m²). We tested for interaction by including the cross-terms of physical activity (continuous) and stratification variables (binary).

For the same volume of physical activity, the association between physical activity and biomarkers may be different by type and intensity of activities. Thus, we examined the joint association of total physical activity and type (aerobic only vs. aerobic plus resistance training) and intensity (moderate plus little vigorous activities

(<20% of total volume; median of 0.2 MET-h/week) vs. moderate plus moderate vigorous activity ($\geq$ 20% of the total volume; median of 17.4 MET-h/week) of activities in relation to plasma biomarkers. To examine the independent association of type (aerobic vs. resistance training) and intensity (moderate vs. vigorous activity) of physical activity, we further conducted analyses mutually adjusting for each other.

All tests were two-sided and $P < 0.05$ was considered to be statistically significant. All data analyses were performed using SAS software, version 9.4 for UNIX (SAS Institute, Inc).

5.3. RESULTS

The characteristics of study population according to total physical activity are presented in Table 1. Participants with higher physical activity had lower BMI and diets with lower inflammatory and insulinemic potential. The lowest EDIP, EDIH, and EDIR were found in the second highest physical activity group (42-62.9 MET-h/week). The proportions of current smokers and participants with 3 or more chronic disease/condition were lower with higher physical activity.

Table 1 - Characteristics of the study population by categories of total physical activity, Health Professionals Follow-up Study, 1992-1994

Characteristic	Total physical activity (MET-h/week)				
	0 to <9	9 to <21	21 to <42	42 to <63	63+
Participants, N	1178	1603	2132	1101	1205
Age at 1994 questionnaire return, yrs	62.0 (8.8)	61.4 (8.7)	62.2 (8.8)	61.8 (8.5)	63.0 (8.5)
Plasma biomarkers					
C-reactive protein (mg/L)	1.2 (4.5)	0.9 (3.0)	0.9 (3.0)	0.7 (2.7)	0.7 (3.0)
Interleukin-6 (pg/L)	1.6 (2.2)	1.5 (2.2)	1.3 (2.0)	1.2 (5.5)	1.2 (2.0)
Tumor necrosis factor alpha receptor 2 (ng/mL)	2.7 (1.3)	2.7 (1.3)	2.7 (1.3)	2.7 (1.3)	2.7 (1.2)
Adiponectin (μ/mL)	6.0 (1.6)	6.0 (1.6)	6.0 (1.6)	6.7 (1.6)	6.7 (1.6)
C-peptide (ng/mL)	2.7 (1.8)	2.2 (1.8)	2.2 (1.8)	2.0 (1.8)	2.0 (1.8)
Triglyceride/High-density lipoproteins ratio	3.3 (2.2)	3.0 (2.0)	2.7 (2.0)	2.5 (2.0)	2.5 (2.2)
Lifestyle risk factors					
Body mass index (kg/m ²)	26.9 (4.1)	26.2 (3.4)	25.7 (3.2)	25.4 (2.9)	25.2 (2.9)
Empirical dietary Inflammatory pattern (% above median)	23.9	20.5	18.9	17.7	19.8
Empirical dietary index for hyperinsulinemia (% above median)	23.0	20.6	19.0	17.8	20.3
Empirical dietary index for insulin resistance (% above median)	20.4	20.0	20.0	19.4	20.3
Smoking status (%)					
Never	39.3	45.0	47.0	48.3	47.5
Former	49.8	49.0	48.3	47.4	48.3
Current	11.0	6.0	4.7	4.3	4.2
Regular aspirin/NSAID user (%)	14.0	14.9	13.0	13.9	14.8
Chronic diseases/conditions comorbidity score					
No chronic diseases/conditions	36.3	38.5	42.5	45.1	44.2
1 chronic diseases/conditions	31.5	33.3	31.6	31.3	31.5
2 chronic diseases/conditions	19.3	18.0	16.4	15.9	16.6
≥3 chronic diseases/conditions	13.0	10.2	9.5	7.7	7.7

Values are presented as mean (SD) for continuous variables and percentage for categorical variables.

There was a decreasing trend of CRP, IL6, TNF α R2, C-peptide and TG/HDL (all $P_{trend} < 0.001$) and an increasing trend of adiponectin with higher total physical activity level ($P_{trend} = 0.002$) (Table 2). The concentrations of biomarkers were favorable in the highest (63+ MET-h/week) compared to lowest (0 to 9 MET-h/week) physical activity groups, though these differences were modestly attenuated after adjustment for BMI. The multivariable-adjusted percent relative difference (RD) in concentration of biomarkers unadjusted and adjusted for BMI, respectively were -32% and -24% for CRP, -22% and -18% for IL6, -7% and -7% for TNF α R2, +9% and +6% for adiponectin, -22% and -16% for C-peptide, and -20% and -14% for TG/HDL (Figure 1). Adjusting for adiposity using predicted fat mass or percent fat, instead of BMI, showed similar but slightly larger attenuations of the associations for all biomarkers (data not shown).

Table 2 - Association between total physical activity and plasma biomarkers of inflammation and insulin response, HPFS 1992-1994

	Total physical activity (MET-h/week)					P _{trend} ‡
	0 to <9	9 to <21	21 to <42	42 to <63	63+	
C-reactive protein (mg/L)						
Number of participants	802	1033	1319	673	742	
Multivariable†	1.12(1.04, 1.21)	0.95(0.88, 1.01)*	0.91(0.86, 0.97)*	0.75(0.69, 0.82)*	0.77(0.71, 0.83)*	<0.001
Interleukin-6 (pg/L)						
Number of participants	462	597	796	407	441	
Multivariable†	1.61(1.48, 1.75)	1.46(1.36, 1.57)*	1.31(1.23, 1.40)*	1.20(1.10, 1.31)*	1.25(1.14, 1.36)*	<0.001
Tumor necrosis factor alpha receptor 2 (ng/mL)						
Number of participants	647	808	1065	521	561	
Multivariable†	2.78(2.73, 2.84)	2.68(2.63, 2.73)*	2.71(2.66, 2.75)	2.64(2.58, 2.70)*	2.57(2.52, 2.63)*	<0.001
Adiponectin (μ/mL)						
Number of participants	705	882	1098	555	607	
Multivariable†	5.91(5.71, 6.13)	6.17(5.98, 6.36)*	6.26(6.09, 6.44)*	6.43(6.18, 6.68)*	6.46(6.22, 6.71)*	0.002
C-peptide (ng/mL)						
Number of participants	540	745	1052	564	602	
Multivariable†	2.58(2.46, 2.71)	2.32(2.22, 2.42)*	2.16(2.08, 2.24)*	2.10(2.00, 2.20)*	2.02(1.93, 2.12)*	<0.001
Triglyceride/High-density lipoproteins ratio						
Number of participants	572	723	916	471	484	
Multivariable†	3.04(2.86, 3.22)	2.84(2.69, 2.99)*	2.67(2.54, 2.79)*	2.44(2.29, 2.61)*	2.44(2.28, 2.60)*	<0.001

† Values are multivariable-adjusted absolute biomarker concentrations adjusted for: age at blood draw (continuous), smoking (never, past or current smokers), race (White or non-White), chronic diseases/conditions (0, 1, 2 or 3+), case/control status, dietary pattern (empirical dietary inflammatory pattern for c-reactive protein, interleukin-6 and tumor necrosis factor alpha receptor 2; empirical dietary index for hyperinsulinemia for C-peptide; empirical dietary index for insulin resistance for triglyceride/High-density lipoproteins ratio).

‡ P value for linear trend test was obtained using physical activity as a continuous variable.

* P<0.05 (significant difference in plasma biomarker against the reference group (lowest total physical activity)).

Joint associations of total physical activity and type of activity (aerobic only vs. aerobic plus resistance training) with plasma biomarkers of inflammation and insulin response are shown in Tables 3 and S1 and Figure 1. The concentrations of biomarkers were favorable in the highest (63+ MET-h/week) compared to lowest (0 to 9 MET-h/week) physical activity groups. For the same volume of physical activity, these associations were stronger for men engaging in both aerobic plus resistance training compared to those engaging in aerobic only. The multivariable-adjusted percent RD in concentration of biomarkers associated with aerobic only and aerobic plus resistance training, respectively were -29% and -36% for CRP, -20% and -29% for IL6, -8% and -8% for TNF α R2, +7% and +11% for adiponectin, -18% and -30% for C-peptide, and -19% and -19% for TG/HDL. Higher aerobic activity was associated with decreasing trends of CRP, IL6, TNF α R2, C-peptide, TG/HDL (all $P_{trend}<0.001$) and an increasing trend of adiponectin ($P_{trend}=0.006$), independent of resistance training. On the other hand, higher resistance training did not show a significant trend with those plasma biomarkers, independent of aerobic activity (Table S2).

Table 3 - Joint association of total physical activity and type of activity with plasma biomarkers of inflammation and insulin response, HPFS 1992-1994

	Total physical activity (MET-h/week)				
	0 to <9	9 to <21	21 to <42	42 to <63	63+
C-reactive protein (mg/L)					
Aerobic only	1.13 (1.05, 1.23)	0.96 (0.89, 1.04)*	0.93 (0.87, 1.00)*	0.81 (0.73, 0.89)*	0.80 (0.72, 0.88)*
Aerobic plus resistance training	0.95 (0.68, 1.34)*	0.86 (0.73, 1.02)*	0.86 (0.76, 0.97)*	0.65 (0.55, 0.75)*	0.72 (0.63, 0.82)*
Interleukin-6 (pg/L)					
Aerobic only	1.63 (1.50, 1.78)	1.48 (1.37, 1.60)	1.32 (1.23, 1.43)*	1.20 (1.08, 1.34)*	1.30 (1.17, 1.45)*
Aerobic plus resistance training	1.21 (0.82, 1.79)	1.37 (1.14, 1.64)	1.28 (1.13, 1.45)*	1.20 (1.02, 1.41)*	1.16 (1.00, 1.33)*
Tumor necrosis factor alpha receptor 2 (ng/mL)					
Aerobic only	2.79 (2.74, 2.85)	2.69 (2.64, 2.74)	2.72 (2.67, 2.77)	2.66 (2.59, 2.73)*	2.58 (2.52, 2.65)*
Aerobic plus resistance training	2.64 (2.43, 2.87)	2.64 (2.53, 2.76)	2.67 (2.59, 2.75)	2.58 (2.48, 2.69)*	2.56 (2.47, 2.65)*
Adiponectin (μ/mL)					
Aerobic only	5.95 (5.73, 6.17)	6.13 (5.92, 6.34)	6.29 (6.09, 6.50)	6.52 (6.21, 6.83)	6.39 (6.09, 6.70)
Aerobic plus resistance training	5.40 (4.65, 6.26)	6.36 (5.89, 6.86)	6.16 (5.83, 6.51)	6.23 (5.80, 6.69)	6.60 (6.19, 7.03)*
C-peptide (ng/mL)					
Aerobic only	2.60 (2.47, 2.73)	2.34 (2.24, 2.45)*	2.18 (2.09, 2.27)*	2.18 (2.05, 2.31)*	2.14 (2.02, 2.27)*
Aerobic plus resistance training	2.39 (1.95, 2.91)*	2.20 (1.98, 2.44)*	2.11 (1.97, 2.25)*	1.96 (1.81, 2.13)*	1.82 (1.68, 1.97)*
Triglyceride/High-density lipoproteins ratio					
Aerobic only	3.01 (2.83, 3.21)	2.90 (2.73, 3.07)	2.64 (2.50, 2.79)*	2.33 (2.16, 2.53)*	2.43 (2.24, 2.64)*
Aerobic plus resistance training	3.38 (2.64, 4.31)	2.60 (2.29, 2.94)	2.73 (2.48, 3.00)	2.70 (2.40, 3.04)	2.44 (2.19, 2.72)*

† Values are multivariable-adjusted absolute biomarker concentrations adjusted for: age at blood draw (continuous), smoking (never, past or current smokers), race (White or non-White), chronic diseases/conditions (0, 1, 2 or 3+), case/control status, dietary pattern (empirical dietary inflammatory pattern for c-reactive protein, interleukin-6 and tumor necrosis factor alpha receptor 2; empirical dietary index for hyperinsulinemia for C-peptide; empirical dietary index for insulin resistance for triglyceride/High-density lipoproteins ratio).

* P<0.05 (significant difference in plasma biomarker against the reference group (lowest total physical activity group with aerobic only)).

Figure 1 - Multivariable-adjusted percent relative difference in biomarker concentrations comparing the highest (63+ MET-h/week) with the lowest (0 to <9 MET-h/week) physical activity groups

Legend: A) with additional adjustment for BMI (B) by type of physical activity and (C) by intensity of physical activity; HPFS 1992-1994. Abbreviation: CRP, C-reactive protein; IL6, interleukin 6; TNFαR2, tumor necrosis factor α receptor 2; TG/HDL, triglycerides/high density lipoprotein cholesterol ratio.

Joint associations of total physical activity and intensity of activity (mostly moderate activities vs. moderate plus vigorous activities ($\geq 20\%$ of the total volume)) with plasma biomarkers of inflammation and insulin response are shown in Tables 4 and S3 and Figure 1. Comparing the highest (mostly moderate activities) to lowest (mostly moderate activities) physical activity groups, the multivariable-adjusted percent RD in concentration of biomarkers was -42% for CRP, -43% for IL6, -8% for TNF α R2, +10% for adiponectin, -18% for C-peptide, and -26% for TG/HDL. For the same volume of physical activity, we did not find additional benefit of engaging in vigorous intensity as compared to those who did smaller amount of vigorous activities. Higher moderate activity was associated with decreasing trends of all biomarkers (all $P_{\text{trend}} < 0.001$) and an increasing trend of adiponectin ($P_{\text{trend}} = 0.006$), independent of vigorous activity. Moreover, higher vigorous activity was associated with decreasing trend of CRP, TNF α R2, C-peptide, and TG/HDL, independent of moderate activity (Table S4).

Table 4 - Joint association of total physical activity and intensity with plasma biomarkers of inflammation and insulin response, HPFS 1992-1994

	Total physical activity (MET-h/week)				
	0 to <9	9 to <21	21 to <42	42 to <63	63+
C-reactive protein (mg/L)					
<20% vigorous	1.20 (1.08, 1.33)	0.94 (0.84, 1.07)*	0.87 (0.75, 1.00)*	0.89 (0.72, 1.10)	0.70 (0.56, 0.88)*
≥20% vigorous	1.04 (0.92, 1.16)	0.95 (0.87, 1.03)*	0.92 (0.86, 0.99)*	0.73 (0.67, 0.80)*	0.78 (0.71, 0.85)*
Interleukin-6 (pg/L)					
<20% vigorous	1.64 (1.47, 1.84)	1.39 (1.21, 1.60)	1.33 (1.15, 1.54)	0.85 (0.68, 1.06)*	0.93 (0.72, 1.20)*
≥20% vigorous	1.56 (1.38, 1.77)	1.49 (1.37, 1.62)	1.31 (1.22, 1.40)*	1.29 (1.17, 1.42)*	1.29 (1.18, 1.42)*
Tumor necrosis factor alpha receptor 2 (ng/mL)					
<20% vigorous	2.78 (2.71, 2.85)	2.67 (2.58, 2.75)	2.66 (2.57, 2.75)	2.62 (2.49, 2.77)	2.56 (2.41, 2.72)
≥20% vigorous	2.78 (2.70, 2.87)	2.69 (2.63, 2.75)	2.72 (2.67, 2.76)	2.64 (2.58, 2.71)*	2.58 (2.52, 2.64)*
Adiponectin (μ/mL)					
<20% vigorous	5.82 (5.55, 6.10)	6.15 (5.82, 6.49)	6.33 (5.93, 6.74)	6.38 (5.77, 7.05)	6.40 (5.76, 7.11)
≥20% vigorous	6.03 (5.73, 6.36)	6.18 (5.94, 6.42)	6.24 (6.05, 6.44)	6.43 (6.16, 6.72)*	6.47 (6.21, 6.74)*
C-peptide (ng/mL)					
<20% vigorous	2.61 (2.43, 2.80)	2.33 (2.16, 2.52)	2.24 (2.08, 2.42)*	1.90 (1.68, 2.15)*	2.15 (1.87, 2.47)
≥20% vigorous	2.55 (2.38, 2.74)	2.31 (2.20, 2.43)*	2.14 (2.05, 2.22)*	2.13 (2.03, 2.25)*	2.01 (1.91, 2.11)*
Triglyceride/High-density lipoproteins ratio					
<20% vigorous	2.98 (2.75, 3.23)	2.90 (2.64, 3.18)	2.63 (2.35, 2.94)	2.51 (2.11, 2.98)	2.22 (1.84, 2.68)*
≥20% vigorous	3.10 (2.84, 3.40)	2.81 (2.64, 3.00)	2.67 (2.54, 2.82)	2.43 (2.26, 2.61)*	2.47 (2.30, 2.65)*

† Values are multivariable-adjusted absolute biomarker concentrations adjusted for: age at blood draw (continuous), smoking (never, past or current smokers), race (White or non-White), chronic diseases/conditions (0, 1, 2 or 3+), case/control status, dietary pattern (empirical dietary inflammatory pattern for c-reactive protein, interleukin-6 and tumor necrosis factor alpha receptor 2; empirical dietary index for hyperinsulinemia for C-peptide; empirical dietary index for insulin resistance for triglyceride/High-density lipoproteins ratio).

* P<0.05 (significant difference in plasma biomarker against the reference group (lowest total physical activity group with <20% vigorous activity)).

We further examined the association between total physical activity and the aforementioned plasma biomarkers stratified by diet and BMI (Figure 2). Participants with poor diet or high BMI had higher inflammation and insulin profiles than those with good diet or low BMI, respectively. We generally observed greater differences in plasma biomarkers when stratified by BMI than diet. Physical activity showed similar benefits for these biomarkers across diet and BMI groups, except for C-peptide which showed slightly higher reduction among those with poor diet ($P_{\text{interaction}}=0.01$). Similar patterns were shown when stratified by both diet and BMI (Figure S1).

Figure 2 - Joint association of total physical activity, diet and body mass index with plasma markers of inflammation and insulin response, HPFS 1992-1994.

Abbreviation: CRP, C-reactive protein; IL6, interleukin 6; TNFαR2, tumor necrosis factor α receptor 2; TG/HDL, triglycerides/high density lipoprotein cholesterol ratio.

5.4. DISCUSSION

In this large cross-sectional study, we found that high volume of physical activity was associated with favorable cancer-related biomarker profiles. Given the same volume of physical activity, engaging in moderate intensity exercises or aerobic plus resistance exercises may offer additional beneficial changes in the circulating levels of biomarkers of inflammation and insulin compared to engaging in higher vigorous intensity exercises or aerobic exercises alone, respectively. Moreover, the combined influence of physical activity, good diet and low adiposity may provide substantial improvement in circulating biomarkers related to cancer risk.

Comparison with previous studies

Consistent with our findings, a number of intervention studies have shown the effect of physical activity on improving biomarkers of inflammation and insulin (BIRD; Hawley, 2017; Fedewa et al., 2017; Kang et al., 2017). However, the influence of specific components of physical activity (e.g., volume, intensity, and type) on these biomarkers remains unclear. Moreover, majority of previous studies were done among unhealthy populations with diseases. In the current study of generally healthy 7,219 men at blood draw, we found that increase in total physical activity was associated with lower levels of circulating biomarkers of inflammation and insulin response. We observed the benefit of engaging in physical activity even for the low volume of PA (after 9 MET-h/week). The biomarkers of inflammation and insulin response gradually decreased with higher physical activity until 63 MET-h/week, showing a linear trend. Over 63 MET-h/week of physical activity, we found a relatively small benefit for TNF α R2, C-peptide, and adiponectin, no change in CRP and TG/HDL, and even slightly increased IL6. This finding suggests that higher volume of physical activity is associated with linearly decreasing trend of inflammatory and insulin related biomarkers. There was no harmful influence of engaging in high volume of physical activity, although we found slightly increased IL6 in the most active group (63+ MET-h/week) compared to the second most active group (42-62.9 MET-h/week). Because IL6 is a sensitive cytokine that increases substantially but acutely in response to exercise (Astrom et al., 2010), the most active group with very high volume of physical activity may have reflected this acute change in our analysis.

When we adjusted for BMI, the associations between physical activity and the biomarkers of inflammation and insulin were modestly attenuated but remained statistically significant. Given that BMI is an imperfect measure of adiposity, we conducted additional analysis by adjusting for predicted fat mass and percent fat to better control adiposity but we found similar moderate attenuation of the estimates. Growing evidence suggests that high adiposity increases cancer risk through several mechanisms including upregulation of inflammation and insulin response (Giovannucci, 2001; Kitahara et al., 2014; Iyengar et al., 2016). Physical activity may act on inflammation and insulin pathways by reduction of adiposity which is likely a mediator in the relationship between physical activity and the biomarkers of inflammation and insulin response (McTiernan, 2008). Thus, adjustment of adiposity could be an over adjustment in the aforementioned relationship to some extent. In our study, we found evidence that high physical activity has both direct (independent) and indirect (mediated through adiposity) influence on improving the biomarkers of inflammation and insulin response.

Type and intensity are important aspects of physical activity which may allow us to provide detailed and effective physical activity guideline for the general population. Regarding the types of physical activity, a recent review of the literature on physical activity and insulin sensitivity in humans suggested that combination of aerobic and resistance training may be more effective to improve insulin resistance than either modality alone (Bird; Hawley, 2017). In our study, for the same amount of MET-hours per week, aerobic plus resistance training was associated with a lower levels of CRP, IL6, and C-peptide, and higher levels of adiponectin, than aerobic training only. On the other hand, we did not find evidence of additional benefits of vigorous intensity physical activity over moderate intensity in regards to the biomarker levels. Similarly, a recent systematic review found that high-intensity interval training suggested similar benefits to moderate-intensity continuous training for body fat reduction (Keating et al., 2017).

Physical activity, adiposity, and diet have complex interrelationships (Giovannucci, 2018b). Physical activity and diet may influence adiposity but they also have direct influence on the circulating cancer-related biomarkers. Moreover, physical activity may interact with adiposity and dietary pattern. Therefore, it is crucial to understand how these 'triad' of physical activity, diet, and adiposity influence the

biomarkers of inflammation and insulin response. As expected, participants with high adiposity or poor dietary pattern had higher levels of inflammation and insulin response compared to those with low adiposity or good dietary pattern, respectively. In addition, the combined influence of physical activity, dietary pattern, and adiposity was substantial. Lean people with high physical activity and good dietary pattern had approximately 2 to 3 folds lower CRP, IL6, C-peptide, and TG/HDL than overweight/obese people with low physical activity and poor dietary pattern. Interestingly, we found the decrease in inflammatory and metabolic markers per unit increment of physical activity was broadly similar across adiposity level or dietary pattern. Thus, physical activity improves biomarkers on all groups stratified by diet and adiposity.

Biological mechanisms

The biological mechanisms linking physical activity and cancer risk are not fully elucidated, and may differ for inflammatory and insulin related pathways. Inflammation is strongly associated with adiposity level. While the results for physical activity were only attenuated moderately by controlling for BMI, it is possible that physical activity may lower biomarkers largely through reductions in visceral adiposity, and measures of BMI may be too crude to distinguish this. For example, relatively short-term (months, one year) physical activity interventions can cause substantial reductions in visceral adiposity which correlates with biomarkers but have little effect on overall BMI (Verheggen et al., 2016). It is important to consider the role of adiposity while interpreting the association between physical activity and cancer biomarkers (Giovannucci, 2018a; 2018b). Similarly, physical activity may influence insulin biomarkers through changes in visceral adiposity and fatty liver, but also acutely through immediate (e.g., one day) improvements in muscle insulin sensitivity (Hawley; Lessard, 2008; Pedersen; Febbraio, 2012).

The effects of higher physical activity on inflammatory and insulin markers are likely to strongly affect cardiometabolic diseases such as cardiovascular diseases and diabetes directly, but may also decrease the risk of several types of cancer (Giovannucci, 2001; 2010). Chronic inflammatory state induced by obesity, both at the systemic and the tissue level (white adipose tissue), may increase susceptibility to tumor development and growth via angiogenesis, enhanced hormone signaling and metabolic

disorders (Iyengar et al., 2016; O’Flanagan et al., 2017; Olson et al., 2017; WCRF, 2018). Insulin can stimulate resisting cell deaths, sustaining proliferative signaling and evading growth suppressors (Iyengar et al., 2016; O’Flanagan et al., 2017; Olson et al., 2017; WCRF, 2018).

Strengths and limitations

Our study has several strengths. First, a large sample provided sufficient power to examine the independent and joint associations of physical activity (type and intensity) and also interaction with diet and adiposity in relation to various biomarkers of inflammation and insulin response. Second, we collected detailed information on lifestyle factors and medical history which allowed us to finely control for potential confounding. Third, average of two repeated measures of physical activity with detailed information on volume, type, and intensity of activities reduced within-person measurement errors and allowed us to study the important aspects of physical activity in relation to the biomarkers.

There are several limitations to our study. Our study included predominantly white male health professionals which may limit the generalizability. However, it strengthens the internal validity and the characteristics of participants were similar to the large multi-ethnic cohorts in the U.S. Moreover, measurement errors from two questionnaires based physical activity and a single measure of biomarkers are inevitable but such measurement errors are likely to be non-differential which may have attenuated the associations. The advantage of relying on highly medically educated health professionals is that they manifest a wide range of physical activity and in general report fairly accurately. In Women’s Lifestyle validation study, objective measures of physical activity showed consistent but slightly stronger associations with cardiometabolic and endocrine biomarkers compared to questionnaire-based physical activity, though the use of two questionnaires in our study may have improved assessment of physical activity (Alessa et al., 2017).

Public health implications

Our results require confirmation but have several important implications. First, for these cancer-related biomarkers, the effect of physical activity was fairly linear, up to a level of 63 MET-hours per week. Thus, while improvement is seen at any level, a

high level is required for optimization. Second, while aerobic activity constitutes the vast majority of the activity and benefits, incorporating some resistance training may have additional benefits for the same level of total MET-hours. Third, benefits are similar for the same accumulated MET-hours for vigorous and non-vigorous activity. Importantly, this allows some flexibility in the amount of time spent and intensity of work-out if one wants to attain a certain MET-hours. For example, if a goal is to attain 50 MET-hours per week, this can be done with 11 hours of brisk walking (moderate activity), 7 hours of running, or 8 hours of moderate and 2 hours of vigorous activity. Lastly, our results indicate that physical activity has relatively similar benefits for these biomarkers across different strata of BMI and diet, and optimal results are achieved by maximizing all three.

Funding: This work was supported by the National Institutes of Health (UM1 CA167552 and R01 HL35464).

Conflict of interest disclosures: The authors declared no conflicts of interest.

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World Cancer Research Fund/American Institute for Cancer Research. Continuous Update Project Expert Report 2018. *Body fatness and weight gain and the risk of cancer.* Available from: dietandcancerreport.org

SUPPLEMENTARY FILE

Table S1 - Joint association of total physical activity and type of activity with plasma biomarkers of inflammation and insulin response, HPFS 1992-1994

	Total physical activity (MET-h/week)				
	0 to <9	9 to <21	21 to <42	42 to 63	63+
C-reactive protein (mg/L)					
Multivariable†					
Aerobic only	1.13 (1.05, 1.23)	0.96 (0.89, 1.04)*	0.93 (0.87, 1.00)*	0.81 (0.73, 0.89)*	0.80 (0.72, 0.88)*
Aerobic plus resistance training	0.95 (0.68, 1.34)*	0.86 (0.73, 1.02)*	0.86 (0.76, 0.97)*	0.65 (0.55, 0.75)*	0.72 (0.63, 0.82)*
Multivariable† plus adult BMI					
Aerobic only	1.21 (1.12, 1.31)	1.08 (1.00, 1.17)	1.07 (1.00, 1.15)	0.93 (0.84, 1.03)*	0.93 (0.84, 1.02)*
Aerobic plus resistance training	1.12 (0.80, 1.55)	1.02 (0.86, 1.20)	1.01 (0.90, 1.14)	0.78 (0.67, 0.91)*	0.90 (0.79, 1.03)*
Interleukin-6 (pg/L)					
Multivariable†					
Aerobic only	1.63 (1.50, 1.78)	1.48 (1.37, 1.60)	1.32 (1.23, 1.43)*	1.2 (1.08, 1.34)*	1.30 (1.17, 1.45)*
Aerobic plus resistance training	1.21 (0.82, 1.79)	1.37 (1.14, 1.64)	1.28 (1.13, 1.45)*	1.2 (1.02, 1.41)*	1.16 (1.00, 1.33)*
Multivariable† plus adult BMI					
Aerobic only	1.70 (1.56, 1.86)	1.59 (1.46, 1.73)	1.43 (1.33, 1.55)*	1.31 (1.17, 1.46)*	1.42 (1.27, 1.58)
Aerobic plus resistance training	1.34 (0.91, 1.98)	1.51 (1.26, 1.82)	1.40 (1.24, 1.59)	1.32 (1.12, 1.56)	1.30 (1.12, 1.50)*
Tumor necrosis factor alpha receptor 2 (ng/mL)					
Multivariable†					
Aerobic only	2.79 (2.74, 2.85)	2.69 (2.64, 2.74)	2.72 (2.67, 2.77)	2.66 (2.59, 2.73)*	2.58 (2.52, 2.65)*
Aerobic plus resistance training	2.64 (2.43, 2.87)	2.64 (2.53, 2.76)	2.67 (2.59, 2.75)	2.58 (2.48, 2.69)*	2.56 (2.47, 2.65)*
Multivariable† plus adult BMI					
Aerobic only	2.81 (2.75, 2.87)	2.72 (2.67, 2.77)	2.75 (2.70, 2.80)	2.7 (2.63, 2.77)	2.62 (2.55, 2.69)*
Aerobic plus resistance training	2.68 (2.47, 2.92)	2.68 (2.57, 2.80)	2.71 (2.63, 2.79)	2.63 (2.53, 2.74)*	2.61 (2.51, 2.71)*
Adiponectin (μ/mL)					
Multivariable†					
Aerobic only	5.95 (5.73, 6.17)	6.13 (5.92, 6.34)	6.29 (6.09, 6.50)	6.52 (6.21, 6.83)	6.39 (6.09, 6.70)
Aerobic plus resistance training	5.40 (4.65, 6.26)	6.36 (5.89, 6.86)	6.16 (5.83, 6.51)	6.23 (5.80, 6.69)	6.60 (6.19, 7.03)*
Multivariable† plus adult BMI					
Aerobic only	5.87 (5.66, 6.09)	5.97 (5.76, 6.18)	6.08 (5.88, 6.29)	6.28 (5.99, 6.59)	6.15 (5.86, 6.45)
Aerobic plus resistance training	5.22 (4.51, 6.05)	6.08 (5.64, 6.56)	5.93 (5.62, 6.27)	5.93 (5.52, 6.36)	6.20 (5.82, 6.61)
C-peptide (ng/mL)					
Multivariable†					
Aerobic only	2.60 (2.47, 2.73)	2.34 (2.24, 2.45)*	2.18 (2.09, 2.27)*	2.18 (2.05, 2.31)*	2.14 (2.02, 2.27)*
Aerobic plus resistance training	2.39 (1.95, 2.91)*	2.20 (1.98, 2.44)*	2.11 (1.97, 2.25)*	1.96 (1.81, 2.13)*	1.82 (1.68, 1.97)*
Multivariable† plus adult BMI					
Aerobic only	2.71 (2.57, 2.85)	2.51 (2.39, 2.63)	2.38 (2.28, 2.49)*	2.39 (2.25, 2.54)*	2.37 (2.23, 2.51)*
Aerobic plus resistance training	2.68 (2.21, 3.26)	2.47 (2.23, 2.74)	2.33 (2.18, 2.49)*	2.19 (2.02, 2.37)*	2.06 (1.90, 2.23)*
Triglyceride/High-density lipoproteins ratio					
Multivariable†					
Aerobic only	3.01 (2.83, 3.21)	2.90 (2.73, 3.07)	2.64 (2.50, 2.79)*	2.33 (2.16, 2.53)*	2.43 (2.24, 2.64)*
Aerobic plus resistance training	3.38 (2.64, 4.31)	2.60 (2.29, 2.94)	2.73 (2.48, 3.00)	2.70 (2.40, 3.04)	2.44 (2.19, 2.72)*
Multivariable† plus adult BMI					
Aerobic only	3.10 (2.92, 3.30)	3.06 (2.88, 3.24)	2.85 (2.70, 3.01)	2.56 (2.37, 2.77)*	2.65 (2.45, 2.87)*
Aerobic plus resistance training	3.68 (2.91, 4.66)	2.70 (2.40, 3.05)	2.99 (2.73, 3.28)	3.05 (2.71, 3.42)	2.76 (2.48, 3.07)

† Multivariable model including age at blood draw (continuous), smoking (never, past or current smokers), race (White or non-White), chronic diseases/conditions (0, 1, 2 or 3+), case/control status, dietary pattern (empirical dietary inflammatory pattern for c-reactive protein, interleukin-6 and tumor necrosis factor alpha receptor 2; empirical dietary index for hyperinsulinemia for C-peptide; empirical dietary index for insulin resistance for triglyceride/High-density lipoproteins ratio).

* P<0.05 (significant difference in plasma biomarker against the reference group (lowest total physical activity group with aerobic only)).

Table S2 - Association of resistance training and aerobic physical activity with plasma biomarkers of inflammation and insulin response, HPFS 1992-1994

	Physical activity (MET-h/week)								
	0	>1 to <4.5	4.5 to <9	9 to <13.5	13.5 to <21	21 to <42	42 to 63	63+	P _{trend} [‡]
C-reactive protein (mg/L)									
Multivariable†									
Resistance training	0.97 (0.91, 1.04)	0.86 (0.77, 0.96)	0.86 (0.73, 1.01)	0.87 (0.71, 1.06)	0.71 (0.53, 0.97)				0.06
Aerobic	0.94 (0.60, 1.47)	1.14 (0.99, 1.32)	0.88 (0.77, 1.00)	0.86 (0.76, 0.99)	0.84 (0.75, 0.95)	0.80 (0.73, 0.88)	0.72 (0.65, 0.81)	0.69 (0.62, 0.77)	<0.001
Multivariable† plus adult BMI									
Resistance training	1.09 (1.02, 1.17)	1.01 (0.91, 1.13)	1.01 (0.86, 1.20)	1.06 (0.87, 1.29)	0.85 (0.64, 1.15)				0.34
Aerobic	1.13 (0.73, 1.75)	1.26 (1.09, 1.44)	1.00 (0.87, 1.14)	1.02 (0.90, 1.17)	0.99 (0.88, 1.11)	0.96 (0.87, 1.06)	0.87 (0.78, 0.97)	0.85 (0.76, 0.95)	<0.001
Interleukin-6 (pg/L)									
Multivariable†									
Resistance training	1.46 (1.35, 1.57)	1.32 (1.17, 1.49)	1.32 (1.10, 1.58)	1.36 (1.10, 1.68)	1.40 (1.05, 1.87)				0.51
Aerobic	1.58 (0.93, 2.69)	1.68 (1.44, 1.95)	1.40 (1.21, 1.61)	1.32 (1.15, 1.52)	1.45 (1.29, 1.64)	1.26 (1.15, 1.39)	1.14 (1.02, 1.29)	1.19 (1.07, 1.34)	<0.001
Multivariable† plus adult BMI									
Resistance training	1.56 (1.44, 1.69)	1.45 (1.28, 1.64)	1.45 (1.20, 1.74)	1.51 (1.22, 1.87)	1.53 (1.14, 2.04)				0.80
Aerobic	1.75 (1.04, 2.97)	1.77 (1.52, 2.06)	1.50 (1.30, 1.74)	1.46 (1.27, 1.68)	1.58 (1.40, 1.79)	1.39 (1.26, 1.54)	1.26 (1.12, 1.42)	1.33 (1.18, 1.49)	0.004
Tumor necrosis factor alpha receptor 2 (ng/mL)									
Multivariable†									
Resistance training	2.71 (2.66, 2.75)	2.63 (2.56, 2.71)	2.64 (2.53, 2.76)	2.70 (2.56, 2.84)	2.60 (2.43, 2.79)				0.50
Aerobic	2.70 (2.41, 3.02)	2.73 (2.64, 2.83)	2.74 (2.65, 2.83)	2.64 (2.55, 2.72)	2.65 (2.58, 2.73)	2.67 (2.61, 2.73)	2.60 (2.53, 2.67)	2.53 (2.46, 2.60)	<0.001
Multivariable† plus adult BMI									
Resistance training	2.74 (2.70, 2.79)	2.67 (2.60, 2.75)	2.68 (2.56, 2.80)	2.75 (2.61, 2.90)	2.65 (2.47, 2.84)				0.72
Aerobic	2.75 (2.46, 3.08)	2.76 (2.66, 2.86)	2.77 (2.68, 2.87)	2.68 (2.59, 2.77)	2.69 (2.61, 2.77)	2.71 (2.65, 2.78)	2.65 (2.57, 2.72)	2.58 (2.51, 2.65)	<0.001
Adiponectin (μ/mL)									
Multivariable†									
Resistance training	6.22 (6.04, 6.40)	6.11 (5.81, 6.43)	6.30 (5.83, 6.80)	6.20 (5.66, 6.80)	6.94 (6.06, 7.95)				0.44
Aerobic	6.64 (5.43, 8.12)	5.75 (5.39, 6.13)	6.30 (5.93, 6.70)	6.23 (5.87, 6.62)	6.33 (6.00, 6.67)	6.44 (6.16, 6.72)	6.54 (6.21, 6.88)	6.60 (6.28, 6.93)	0.006
Multivariable† plus adult BMI									
Resistance training	6.05 (5.87, 6.24)	5.86 (5.57, 6.17)	6.02 (5.58, 6.50)	5.91 (5.40, 6.47)	6.67 (5.84, 7.63)				0.60
Aerobic	6.29 (5.16, 7.67)	5.65 (5.30, 6.01)	6.11 (5.75, 6.49)	6.01 (5.66, 6.38)	6.09 (5.78, 6.42)	6.16 (5.89, 6.43)	6.24 (5.93, 6.57)	6.25 (5.95, 6.58)	0.04
C-peptide (ng/mL)									
Multivariable†									
Resistance training	2.36 (2.26, 2.47)	2.13 (1.99, 2.27)*	2.21 (2.00, 2.44)	2.21 (1.96, 2.49)	1.98 (1.69, 2.33)				0.12
Aerobic	2.36 (1.75, 3.19)	2.33 (2.13, 2.55)	2.44 (2.26, 2.65)	2.23 (2.06, 2.42)	2.10 (1.97, 2.25)	2.03 (1.92, 2.14)	2.02 (1.90, 2.16)	1.92 (1.81, 2.04)	<0.001
Multivariable† plus adult BMI									
Resistance training	2.53 (2.42, 2.64)	2.34 (2.19, 2.50)*	2.45 (2.23, 2.71)	2.45 (2.18, 2.76)	2.13 (1.82, 2.49)				0.19
Aerobic	2.53 (1.89, 3.39)	2.46 (2.26, 2.69)	2.63 (2.43, 2.85)	2.45 (2.27, 2.66)	2.30 (2.15, 2.46)	2.26 (2.14, 2.38)	2.25 (2.11, 2.40)	2.16 (2.03, 2.30)	0.003
Triglyceride/High-density lipoproteins ratio									
Multivariable†									
Resistance training	2.71 (2.59, 2.84)	2.79 (2.57, 3.03)	2.89 (2.53, 3.30)	2.49 (2.11, 2.94)	2.34 (1.81, 3.02)				0.20
Aerobic	2.38 (1.73, 3.27)	3.15 (2.82, 3.53)	2.78 (2.50, 3.09)	2.90 (2.61, 3.23)	2.66 (2.43, 2.92)	2.57 (2.37, 2.78)	2.41 (2.20, 2.64)	2.35 (2.15, 2.56)	<0.001
Multivariable† plus adult BMI									
Resistance training	2.88 (2.75, 3.02)	3.04 (2.81, 3.30)	3.11 (2.74, 3.54)	2.73 (2.32, 3.20)	2.52 (1.97, 3.23)				0.48
Aerobic	2.67 (1.97, 3.63)	3.27 (2.93, 3.64)	2.92 (2.63, 3.24)	3.06 (2.76, 3.40)	2.85 (2.60, 3.11)	2.81 (2.60, 3.04)	2.67 (2.44, 2.92)	2.61 (2.39, 2.85)	<0.001

† Multivariable model including age at blood draw (continuous), smoking (never, past or current smokers), race (White or non-White), chronic diseases/conditions (0, 1, 2 or 3+), case/control status, dietary pattern (empirical dietary inflammatory pattern for c-reactive protein, interleukin-6 and tumor necrosis factor alpha receptor 2; empirical dietary index for hyperinsulinemia for C-peptide; empirical dietary index for insulin resistance for triglyceride/High-density lipoproteins ratio) and mutually adjusted for aerobic and resistance trainings.‡ P value for linear trend test was obtained using physical activity as a continuous variable. * P<0.05 (significant difference in plasma biomarker against the reference group (lowest aerobic or resistance training group)).

Table S3 - Joint association of total physical activity and intensity with plasma biomarkers of inflammation and insulin response, HPFS 1992-1994

	Total physical activity (MET-h/week)				
	0 to <9	9 to <21	21 to <42	42 to 63	63+
C-reactive protein (mg/L)					
Multivariable†					
<20% vigorous	1.20 (1.08, 1.33)	0.94 (0.84, 1.07)*	0.87 (0.75, 1.00)*	0.89 (0.72, 1.10)	0.70 (0.56, 0.88)*
≥20% vigorous	1.04 (0.92, 1.16)	0.95 (0.87, 1.03)*	0.92 (0.86, 0.99)*	0.73 (0.67, 0.80)*	0.78 (0.71, 0.85)*
Multivariable† plus adult BMI					
<20% vigorous	1.29 (1.17, 1.43)	1.06 (0.94, 1.20)	1.01 (0.88, 1.16)*	1.03 (0.84, 1.27)	0.83 (0.67, 1.05)*
≥20% vigorous	1.11 (0.99, 1.24)	1.07 (0.99, 1.17)*	1.07 (1.00, 1.14)*	0.86 (0.78, 0.94)*	0.93 (0.85, 1.01)*
Interleukin-6 (pg/L)					
Multivariable†					
<20% vigorous	1.64 (1.47, 1.84)	1.39 (1.21, 1.60)	1.33 (1.15, 1.54)	0.85 (0.68, 1.06)*	0.93 (0.72, 1.20)*
≥20% vigorous	1.56 (1.38, 1.77)	1.49 (1.37, 1.62)	1.31 (1.22, 1.40)*	1.29 (1.17, 1.42)*	1.29 (1.18, 1.42)*
Multivariable† plus adult BMI					
<20% vigorous	1.71 (1.53, 1.92)	1.50 (1.30, 1.72)	1.44 (1.24, 1.67)	0.94 (0.75, 1.17)*	1.03 (0.80, 1.32)*
≥20% vigorous	1.64 (1.44, 1.86)	1.61 (1.47, 1.76)	1.42 (1.32, 1.53)*	1.40 (1.27, 1.55)	1.43 (1.30, 1.57)
Tumor necrosis factor alpha receptor 2 (ng/mL)					
Multivariable†					
<20% vigorous	2.78 (2.71, 2.85)	2.67 (2.58, 2.75)	2.66 (2.57, 2.75)	2.62 (2.49, 2.77)	2.56 (2.41, 2.72)
≥20% vigorous	2.78 (2.70, 2.87)	2.69 (2.63, 2.75)	2.72 (2.67, 2.76)	2.64 (2.58, 2.71)*	2.58 (2.52, 2.64)*
Multivariable† plus adult BMI					
<20% vigorous	2.80 (2.73, 2.88)	2.70 (2.61, 2.79)	2.69 (2.60, 2.79)	2.67 (2.53, 2.81)	2.61 (2.46, 2.77)
≥20% vigorous	2.80 (2.72, 2.89)	2.72 (2.66, 2.78)	2.75 (2.71, 2.80)	2.68 (2.62, 2.75)	2.62 (2.56, 2.68)*
Adiponectin (μ/mL)					
Multivariable†					
<20% vigorous	5.82 (5.55, 6.10)	6.15 (5.82, 6.49)	6.33 (5.93, 6.74)	6.38 (5.77, 7.05)	6.40 (5.76, 7.11)
≥20% vigorous	6.03 (5.73, 6.36)	6.18 (5.94, 6.42)	6.24 (6.05, 6.44)	6.43 (6.16, 6.72)*	6.47 (6.21, 6.74)*
Multivariable† plus adult BMI					
<20% vigorous	5.73 (5.47, 6.01)	6.00 (5.68, 6.34)	6.09 (5.71, 6.49)	6.14 (5.57, 6.78)	6.12 (5.52, 6.79)
≥20% vigorous	5.96 (5.66, 6.28)	5.99 (5.76, 6.22)	6.04 (5.84, 6.23)	6.18 (5.92, 6.45)	6.18 (5.93, 6.44)
C-peptide (ng/mL)					
Multivariable†					
<20% vigorous	2.61 (2.43, 2.80)	2.33 (2.16, 2.52)	2.24 (2.08, 2.42)*	1.90 (1.68, 2.15)*	2.15 (1.87, 2.47)
≥20% vigorous	2.55 (2.38, 2.74)	2.31 (2.2, 2.43)*	2.14 (2.05, 2.22)*	2.13 (2.03, 2.25)*	2.01 (1.91, 2.11)*
Multivariable† plus adult BMI					
<20% vigorous	2.72 (2.54, 2.91)	2.51 (2.33, 2.72)	2.47 (2.30, 2.67)	2.14 (1.9, 2.42)*	2.41 (2.11, 2.75)
≥20% vigorous	2.69 (2.51, 2.89)	2.50 (2.37, 2.63)	2.34 (2.24, 2.44)*	2.35 (2.22, 2.48)*	2.24 (2.12, 2.35)*
Triglyceride/High-density lipoproteins ratio					
Multivariable†					
<20% vigorous	2.98 (2.75, 3.23)	2.90 (2.64, 3.18)	2.63 (2.35, 2.94)	2.51 (2.11, 2.98)	2.22 (1.84, 2.68)*
≥20% vigorous	3.10 (2.84, 3.40)	2.81 (2.64, 3.00)	2.67 (2.54, 2.82)	2.43 (2.26, 2.61)*	2.47 (2.30, 2.65)*
Multivariable† plus adult BMI					
<20% vigorous	3.08 (2.85, 3.33)	3.04 (2.77, 3.34)	2.88 (2.58, 3.21)	2.71 (2.29, 3.20)	2.45 (2.04, 2.94)
≥20% vigorous	3.20 (2.93, 3.49)	2.96 (2.78, 3.15)	2.88 (2.73, 3.04)	2.69 (2.51, 2.89)	2.72 (2.53, 2.91)

† Multivariable model including age at blood draw (continuous), smoking (never, past or current smokers), race (White or non-White), chronic diseases/conditions (0, 1, 2 or 3+), case/control status, dietary pattern (empirical dietary inflammatory pattern for c-reactive protein, interleukin-6 and tumor necrosis factor alpha receptor 2; empirical dietary index for hyperinsulinemia for C-peptide; empirical dietary index for insulin resistance for triglyceride/High-density lipoproteins ratio).

* P<0.05 (significant difference in plasma biomarker against the reference group (lowest total physical activity group with <20% vigorous activity)).

Table S4 - Association of moderate and vigorous physical activities with plasma biomarkers of inflammation and insulin response, HPFS 1992-1994

	Total physical activity (MET-h/week)					
	0 to <9	9 to <21	21 to <42	42 to 63	63+	P _{trend} ‡
C-reactive protein (mg/L)						
Multivariable†						
Moderate	0.92 (0.87, 0.98)	0.82 (0.77, 0.88)*	0.79 (0.73, 0.86)*	0.77 (0.67, 0.88)	0.66 (0.53, 0.82)*	<0.001
Vigorous	0.91 (0.85, 0.97)	0.85 (0.79, 0.93)	0.72 (0.66, 0.79)*	0.73 (0.64, 0.84)*	0.75 (0.66, 0.85)*	0.002
Multivariable† plus adult BMI						
Moderate	1.04 (0.98, 1.11)	0.96 (0.90, 1.02)	0.94 (0.86, 1.01)	0.93 (0.81, 1.06)	0.80 (0.65, 0.99)	<0.001
Vigorous	1.04 (0.97, 1.11)	1.01 (0.93, 1.09)	0.85 (0.78, 0.94)*	0.86 (0.76, 0.98)*	0.90 (0.79, 1.02)	0.02
Interleukin-6 (pg/L)						
Multivariable†						
Moderate	1.45 (1.36, 1.55)	1.34 (1.25, 1.44)	1.25 (1.15, 1.36)*	1.03 (0.88, 1.20)*	1.16 (0.92, 1.47)	<0.001
Vigorous	1.30 (1.20, 1.40)	1.24 (1.14, 1.36)	1.19 (1.08, 1.32)	1.25 (1.1, 1.44)	1.21 (1.05, 1.38)	0.40
Multivariable† plus adult BMI						
Moderate	1.56 (1.46, 1.67)	1.45 (1.35, 1.57)	1.38 (1.26, 1.5)*	1.14 (0.98, 1.33)*	1.30 (1.03, 1.64)	<0.001
Vigorous	1.40 (1.30, 1.52)	1.36 (1.24, 1.50)	1.32 (1.19, 1.46)	1.37 (1.19, 1.57)	1.33 (1.16, 1.53)	0.55
Tumor necrosis factor alpha receptor 2 (ng/mL)						
Multivariable†						
Moderate	2.72 (2.68, 2.77)	2.66 (2.61, 2.70)	2.60 (2.55, 2.65)*	2.53 (2.44, 2.63)*	2.57 (2.44, 2.71)	<0.001
Vigorous	2.65 (2.60, 2.69)	2.66 (2.60, 2.72)	2.61 (2.55, 2.68)	2.60 (2.51, 2.68)	2.57 (2.48, 2.66)	0.02
Multivariable† plus adult BMI						
Moderate	2.75 (2.71, 2.80)	2.69 (2.65, 2.74)	2.64 (2.58, 2.69)*	2.58 (2.49, 2.67)*	2.61 (2.48, 2.76)	<0.001
Vigorous	2.68 (2.63, 2.73)	2.70 (2.64, 2.76)	2.65 (2.59, 2.72)	2.63 (2.55, 2.72)	2.61 (2.52, 2.70)	0.03
Adiponectin (μ/mL)						
Multivariable†						
Moderate	6.16 (5.99, 6.34)	6.36 (6.17, 6.56)	6.40 (6.17, 6.63)	6.46 (6.06, 6.89)	6.99 (6.34, 7.72)	0.006
Vigorous	6.30 (6.10, 6.50)	6.45 (6.21, 6.70)	6.56 (6.28, 6.85)	6.55 (6.16, 6.96)	6.49 (6.11, 6.90)	0.18
Multivariable† plus adult BMI						
Moderate	5.98 (5.81, 6.16)	6.13 (5.94, 6.33)	6.12 (5.89, 6.35)	6.15 (5.76, 6.56)	6.68 (6.06, 7.36)	0.06
Vigorous	6.10 (5.91, 6.31)	6.20 (5.96, 6.44)	6.26 (5.99, 6.54)	6.30 (5.93, 6.69)	6.18 (5.82, 6.57)	0.28
C-peptide (ng/mL)						
Multivariable†						
Moderate	2.26 (2.18, 2.34)	2.08 (2.01, 2.16)*	2.08 (1.99, 2.17)*	1.90 (1.75, 2.07)*	2.24 (1.99, 2.53)	0.001
Vigorous	2.31 (2.22, 2.41)	2.12 (2.02, 2.22)*	2.09 (1.98, 2.20)*	1.97 (1.83, 2.13)*	2.07 (1.92, 2.23)*	0.007
Multivariable† plus adult BMI						
Moderate	2.44 (2.35, 2.54)	2.28 (2.19, 2.37)*	2.32 (2.22, 2.44)	2.14 (1.97, 2.32)*	2.54 (2.26, 2.85)	0.07
Vigorous	2.53 (2.43, 2.64)	2.36 (2.24, 2.48)*	2.33 (2.20, 2.45)*	2.19 (2.03, 2.36)*	2.31 (2.15, 2.50)	0.01
Triglyceride/High-density lipoproteins ratio						
Multivariable†						
Moderate	2.76 (2.63, 2.89)	2.59 (2.46, 2.73)	2.44 (2.30, 2.60)*	2.26 (2.03, 2.52)*	2.37 (2.00, 2.82)	<0.001
Vigorous	2.68 (2.54, 2.83)	2.49 (2.33, 2.65)	2.46 (2.29, 2.64)	2.34 (2.10, 2.60)	2.45 (2.21, 2.71)	0.01
Multivariable† plus adult BMI						
Moderate	2.92 (2.79, 3.07)	2.82 (2.68, 2.97)	2.68 (2.51, 2.85)	2.50 (2.24, 2.78)*	2.64 (2.23, 3.12)	0.001
Vigorous	2.86 (2.70, 3.02)	2.70 (2.53, 2.88)	2.72 (2.54, 2.92)	2.57 (2.32, 2.86)	2.70 (2.44, 2.98)	0.06

† Multivariable model including age at blood draw (continuous), smoking (never, past or current smokers), race (White or non-White), chronic diseases/conditions (0, 1, 2 or 3+), case/control status, dietary pattern (empirical dietary inflammatory pattern for c-reactive protein, interleukin-6 and tumor necrosis factor alpha receptor 2; empirical dietary index for hyperinsulinemia for C-peptide; empirical dietary index for insulin resistance for triglyceride/High-density lipoproteins ratio) and mutually adjusted for moderate and vigorous activities.

‡ P value for linear trend test was obtained using physical activity as a continuous variable

* P<0.05 (significant difference in plasma biomarker against the reference group (lowest moderate or vigorous activity group)).

Figure S1 - Joint associations of total physical activity, diet and body mass index with plasma markers of inflammation and insulin response, HPFS 1992-1994

Abbreviation: CRP, C-reactive protein; IL6, interleukin 6; TNFαR2, tumor necrosis factor α receptor 2; TG/HDL, triglycerides/high density lipoprotein cholesterol ratio.

6. PREVENTABILIDADE DE CÂNCER MEDIANTE AUMENTO DA ATIVIDADE FÍSICA NO BRASIL

Este capítulo apresenta o artigo “*Preventable fractions of colon and breast cancers by increasing physical activity in Brazil: perspectives from plausible counterfactual scenarios*” de autoria de Leandro Fórnias Machado de Rezende, Leandro Martim Totaro Garcia, Grégore Iven Mielke, Dong Hoon Lee, Kana Wu, Edward Giovannucci e José Eluf-Neto. O artigo foi originalmente publicado na revista *Cancer Epidemiology* e pode ser acessado gratuitamente no link: <https://www.sciencedirect.com/science/article/pii/S1877782118303436>.

Essa publicação apresenta material suplementar extenso, disponível apenas no link da revista.

Para citação: Rezende LFM, Garcia LMT, Mielke GI, Lee DH, Wu K, Giovannucci E, Eluf-Neto J. Preventable fractions of colon and breast cancers by increasing physical activity in Brazil: perspectives from plausible counterfactual scenarios. *Cancer Epidemiol.* 2018;56:38-45.

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

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Word count

Abstract: 250

The total manuscript: 2986

Highlights: 80

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 ($\geq 8,000$ 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 $\geq 8,000$ MET-min/week. Plausible counterfactual scenarios suggested the following impact on cancer prevention: reaching physical activity recommendation: 1.3% (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 sizable impact on breast and colon cancer prevention in Brazil.

6.1. INTRODUCTION

Convincing evidence supports the association between physical activity and lower risk of colon and breast cancers (IARC, 2002; WCRF, 2018, Rezende et al., 2018). Potential protective effect of physical activity for other cancer sites has been recently suggested (Liu et al., 2011, Behrens; Leitzmann, 2013; Behrens et al., 2013; 2014; Zhong et al., 2014; Farris et al., 2015; Niedermaier et al., 2015; Schmid et al., 2015; Brenner et al., 2016; Moore et al., 2016, Psaltopoulou et al., 2016), but the evidence is less consistent and dose-response shape unknown (Rezende et al., 2018). Physical activity may exert major influences on cancer risk mainly through weight management and adiposity level (Donnelly et al., 2009; Giovannucci, 2018), and additionally via direct effects on hormones and inflammatory markers (McTiernan, 2008; Koelwyn et al., 2017; Giovannucci, 2018). 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 to 6 MET) or 75 min/week in vigorous activities (>6 MET) (WHO, 2010). However, higher levels of total physical activity (i.e., $\geq 8,000$ MET-min/week) have been recently suggested to provide optimum risk reduction returns in non-communicable diseases (NCDs), especially for breast and colon cancers (Kyu et al., 2016).

Globally, lack physical activity accounts for, on average, 12% of breast cancer and 18% of colon cancer (Whiteman; Wilson, 2016). 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 (Murray et al., 2003, Rezende; Eluf-Neto, 2016). Frequently, studies have obtained RR from meta-analyses comparing the most and the least active groups, which is heterogeneously defined across primary studies. Therefore, 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) (Murray et al., 2003, Rezende; Eluf-Neto, 2016). 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 25x25) targeted a 10% reduction in the prevalence of insufficient physical activity for 2025 (WHO, 2014). Reducing gender inequality in physical activity is also important (Althoff et al., 2017; Mielke et al., 2017). Globally, the prevalence of insufficient physical inactivity is, on average, 20% lower in women than in men (Mielke et al., 2017). 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 (Mielke et al., 2015). Reducing disparities in physical activity between gender and geographic areas may have a positive impact in 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 ($\geq 8,000$ MET-min/week), (ii) reaching the WHO recommendation for physical activity (≥ 600 MET-min/week) (World Health Organization (WHO, 2010) (iii) a 10% reduction in prevalence of insufficient physical activity (WHO, 2014), (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.

6.2. METHODS

Physical activity data: current distribution and counterfactual scenarios

We used data from the National Health Survey (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 (IBGE, 2013; Szwarcwald et al., 2014). 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) (Ainsworth et al., 2011). To obtain total volume of physical activity, we summed-up MET-min/week across domain 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 to 3,999, 4,000 to 7,999, and $\geq 8,000$ MET-min/week) according to cut-offs used in the RR estimates.

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

- Theoretical minimum risk exposure level: everyone reaches $\geq 8,000$ MET-min/week (Kyu et al., 2016);
- WHO recommendation for physical activity: everyone achieves ≥ 600 MET-min/week (WHO, 2010);
- WHO 25x25: a 10% reduction in the prevalence of insufficient physical activity (<600 MET-min/week) (WHO, 2014);
- 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);
- 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.

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

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 (IARC, 2002; WCRF, 2018; Rezende et al., 2018). 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) (GBD Risk Factor Collaborators, 2016; Kyu et al., 2016) synthesizing the associations of total physical activity (<600, 600 to 3,999, 4000 to 7,999, and $\geq 8,000$ 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 (Ferlay et al., 2013). Estimated cancer cases for each federative unit in 2012 by sex was obtained from Brazilian National Cancer Institute (IBGE, 2011). Both sources have been used to inform cancer prevention strategies in Brazil. Details about these estimated cancer incidence data have been published elsewhere (INCA, 2011; Ferlay et al., 2013). 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 (Forman et al., 2013). Breast cancer (postmenopausal) was defined as cases in women aged ≥ 45 years as reported in the GLOBOCAN 2012 (Ferlay et al., 2013) (Table S3).

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 (Murray et al., 2003, Rezende; Eluf-Neto, 2016):

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

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 to 7,999, and $\geq 8,000$ 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 (Murray et al., 2003, Rezende; Eluf-Neto, 2016).

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) 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 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 (Ferlay et al., 2013). Projections of cancer incidence were calculated by multiplying age-specific cancer incidence in 2012 by the population structure expected for 2025 (Ferlay et al., 2013).

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

6.3. RESULTS

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 $\geq 8,000$ MET-min/week, the reference group used in our study to represent the theoretical minimum risk exposure level. The prevalence of $\geq 8,000$ MET-min/week in men was almost 4 times as high as the prevalence in women (Figure 1). Counterfactual scenarios of physical activity by sex are presented in the Figure 1.

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 $\geq 8,000$ 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 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) (Figure 2, Table S5-S7).

Table 1 - Theoretical minimum risk exposure level ($\geq 8,000$ 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									
<i>Total</i>	54,598	12.29	6,712	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									
<i>Total</i>	NA	NA	NA	9,189	18.47	1,697	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									
<i>Total</i>	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

Figure 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 $\geq 8,000$ 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)

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 25x25 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).

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

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).

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 min/week)	MET-	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.

6.4. 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 $\geq 8,000$ 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 (Friedenreich et al., 2010; Parkin et al., 2011; Inoue et al., 2012; Lee et al., 2012; Wang et al., 2012; Hayes et al., 2013; Brenner, 2014; Park et al., 2014; Rezende et al., 2015; Olsen et al., 2015; Van Gemert et al., 2015; Azevedo e Silva et al., 2016; Whiteman; Wilson, 2016; Brenner et al., 2017; Charafeddine et al., 2017; Islami et al., 2017; Naing et al., 2017). 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 (Levin, 1953) has been most frequently used. Friedenreich and colleagues' study was the only study that estimated potential impact of different counterfactual scenarios of physical activity (i.e., $\geq 3,000$ MET-min/week and ≥ 600 MET-min/week) on cancer prevention (FRIEDENREICH et al., 2010). 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 $\geq 8,000$ 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 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 (WCRF, 2018). The last statement from the International Agency for Research on Cancer support the association for colon and breast cancers only (IARC, 2002). Recently, a pooled analysis from 12 cohort studies (Moore et al., 2016) and several systematic reviews suggested that physical activity is associated with lower risk of bladder, breast, colon, endometrial, oesophageal, gastric, glioma, kidney, lung, ovarian, pancreas, prostate (Woling et al., 2009; Liu et al., 2011; Boyle et al., 2012; Behrens, Leitzmann, 2013; Zhong et al., 2014; Keimling et al., 2014; Behrens et al., 2014; Schmid et al., 2015; Niedermaier et al., 2015; Farris et al., 2015; Kyu et al., 2016; Pizot et al., 2016; Psaltopoulou et al., 2016; Brenner et al., 2016; Neilson et al., 2017). Although physical activity could be confirmed with convincing protective effect for these cancers in the future, it's also likely presence of bias in the literature favoring positive results (Boffetta et al., et al., 2008). 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. Consequently, only associations between physical activity and colon and breast cancers were supported by strong and highly suggestive evidence, respectively. 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 (Rezende et al., 2018).

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 (Lawlor et al., 2016; Munafò; Davey Smith, 2018). Further results on type, intensity, and volume of physical activity from The Physical Activity Collaboration of the National Cancer Institute's Cohort Consortium (Moore et al., 2016); 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 (Rothman, 1976). 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 (Lauby-Secretan et al., 2016; WCRF, 2018).

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 (Moreira et al., 2017). 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 (Ainsworth et al., 2011). Questionnaires assessing physical activity level in the typical week tend to overestimate total energy expenditure compared to objective-measures (e.g., doubly labelled water) (Dowd et al., 2018). 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 (Mielke et al., 2014). 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 sizable impact on breast and colon cancer prevention in Brazil.

Acknowledgment: none.

Funding: Leandro F3rnias 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.

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7. PREVENTABILIDADE DE CÂNCER E ESTILO DE VIDA NO BRASIL

Este capítulo apresenta o artigo “*Proportion of cancer cases and deaths attributable to lifestyle risk factors in Brazil*” de autoria de Leandro Fórnias Machado de Rezende, Dong Hoon Lee, Maria Laura da Costa Louzada, Mingyang Song, Edward Giovannucci, José Eluf-Neto. O artigo foi submetido para publicação na revista *Cancer Epidemiology*.

Para citação: Rezende LFM, Lee DH, Louzada MLC, Song M, Giovannucci E, Eluf-Neto J. Proportion of cancer cases and deaths attributable to lifestyle risk factors in Brazil. In preparation.

Proportion of cancer cases and deaths attributable to lifestyle risk factors in Brazil

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Word count

Abstract: 220

The total manuscript: 4027

Novelty & Impact Statements

Lifestyle risk factors (tobacco smoking, alcohol consumption, overweight and obesity, unhealthy diet, and lack of physical activity) has been consistently associated with increased risk of at least 20 types of cancer. This study showed that, in Brazil, about 26.5% of all cancer cases and 33.6% of all cancer deaths were attributable to lifestyle risk factors and could be potentially avoided. These findings are useful to inform strategies for cancer prevention and control in Brazil.

ABSTRACT

Lifestyle risk factors (tobacco smoking, alcohol consumption, overweight and obesity, unhealthy diet, and lack of physical activity) have been associated with increased risk of at least 20 types of cancer. We estimated the proportion of cancer cases and deaths that could be potentially avoided by eliminating or reducing lifestyle risk factors in Brazil. We obtained the distribution of lifestyle risk factors by sex and age from recent representative health surveys in Brazil; relative risks from pooled analyses of prospective studies and meta-analyses; and cancer cases and deaths in 2012 from GLOBOCAN. We found that 26.5% (114,497 cases) of all cancer cases and 33.6% (63,371 deaths) of all cancer deaths could be potentially avoided by eliminating lifestyle risk factors in Brazil. Plausible reductions in these exposures based on policy targets and cancer prevention recommendations could have potentially avoided 4.5% (19,731 cases) and 6.1% (11,480 deaths) of all cancer cases and deaths, respectively. Tobacco smoking accounted for most of the preventable cancer cases and deaths, followed by high body mass index and alcohol consumption. Larynx, lung, oral cavity/pharynx, esophagus and colorectum cancer cases and deaths could be at least halved by eliminating these lifestyle risk factors. Findings from this study may be useful to inform strategies for cancer prevention and control across Brazil.

7.1. INTRODUCTION

Cancer is the second leading cause of death in Brazil (Brasil 2018). In 2012, 224,000 cancer deaths occurred and 437,000 new cancer cases were diagnosed (Ferlay et al., 2013). By 2025, the burden of cancer is projected to increase by 50% due to population growth and aging (Ferlay et al., 2013). Besides changes in the population structure, the increasing prevalence of lifestyle risk factors may pose additional challenges to cancer control. (NCD Risk Factor Collaborators, 2013; Martins et al., et al. 2013; Mielke et al., 2014; Rezende et al., 2018) Lifestyle risk factors (tobacco smoking, alcohol consumption, overweight and obesity, unhealthy diet, and lack of physical activity) have been associated with increased risk of at least 20 types of cancer (IARC, 2002; 2018 Bagnardi et al., 2015; Bouvard et al., 2015; Carter et al., 2015; Lauby-Secretan et al., 2016; Rezende et al., 2018a; WCRF, 2018a; 2018b; 2018c; 2018d; 2018e). Therefore, cancer prevention through lifestyle modification is one of the most attractive and realistic approaches for cancer control in Brazil.

Quantitative estimation of preventable cancer cases and deaths is useful to inform cancer prevention strategies (Colditz; Wei, 2012). The preventability of cancer can be estimated by contrasting cancer rates between low- and high-risk populations, although deciphering the contribution of each risk factor might be difficult using this method (Colditz; Wei, 2012). Thus, the classical population attributable fraction (PAF) approach has been extensively used to estimate the proportion of cancer that could be potentially avoided by eliminating or reducing modifiable risk factors (Whiteman; Webb et al., 2015; Azevedo e Silva et al., 2016; Rezende; Eluf-Neto, 2016; Islami; 2017; 2018; Brown et al., 2018).

In Brazil, previous studies on preventability of cancer have focused on single risk factors (Thuler et al., 2016; Rezende et al., 2018b), cancer outcome (either incidence or mortality) (Thuler et al., 2016; Rezende et al., 2018b), historical exposure profile (Azevedo e Silva et al., 2016), or single exposure estimate for all age groups (Azevedo e Silva et al., 2016, Thuler et al., 2016). In addition, despite the large land mass of Brazil and massive regional disparities in cancer mortality, preventability of cancer has been estimated for the country as a whole (Azevedo e Silva et al., 2016, Thuler et al., 2016).

Herein, we estimated the proportion and number of cancer cases and deaths attributable to lifestyle risk factors in Brazil in 2012. We provided estimates of preventability of cancer due to lifestyle risk factors, individually and in combination, by sex and cancer site, sex in Brazil. We also considered two counterfactual (alternative) exposure scenarios for the lifestyle risk factors at the population level.

7.2. METHODS

Lifestyle exposure data: current distribution and counterfactual scenarios

We included in our study lifestyle risk factors with convincing evidence for causing cancer in humans according to the International Agency for Research on Cancer (IARC), the World Cancer Research Fund (WCRF), results from recent meta-analyses, and for which exposure data were available (Table 1) IARC, 2002; 2018; Taylor et al., 2007; Bagnardi et al., 2015; Bouvard et al., 2015; Carter et al., 2015; Lauby-Secretan et al., 2016; Rezende et al., 2018a; WCRF, 2018a; 2018b; 2018c; 2018d). Data on the distribution of lifestyle risk factors were calculated from the most recent nationally representative surveys conducted in Brazil. The distribution of lifestyle risk factors was estimated by sex and age groups (20-44, 45-54, 55-64, 65-74, and ≥ 75 years), while accounting for the complex sample design.

Table 1 - Lifestyle risk factors associated with cancer incidence and mortality considered in this study

Exposure	Distribution and theoretical minimum risk exposure level (in bold and italic)	Cancer sites-related (ICD-10)
Alcohol consumption (%) ⁸	<i>Abstainer (0 g/day)</i> Light (1 to 12.5 g/day) Moderate (12.6 to 49.9 g/day) Heavy (≥50 g/day)	Lip, oral cavity, pharynx (C00-C14); Esophagus (C15; squamous cell carcinoma only); Colorectum (C18-C20); Liver (C22); Gallbladder (C23); Pancreas (C25); Larynx (C32); female Breast (C50)
High body mass index (in kg/m ²) ^{9, 10}	Mean and standard deviation (22kg/m² and 1 sd)	Esophagus (C15; adenocarcinoma only); Stomach (C16.0; cardia only); Colorectum (C18-C20); Liver (C22); Gallbladder (C23); Pancreas (C25); female Breast (C50; postmenopausal cancers only); Corpus uteri (C54-C55); Ovary (C56); Kidney, renal pelvis (C64-C66); Thyroid (C73); Multiple myeloma (C90), Prostate (C61; advanced only)
Low dietary calcium consumption (%) ¹²	≥1000 mg/day 800-999 mg/day 600-799 mg/day 400-599 mg/day 200-399 mg/day 0-199 mg/day	Colorectum (C18-C20)
Low dietary fiber consumption (%) ¹³	≥30 g/day 20-29 g/day 10-19 g/day 0-9 g/day	Colorectum (C18-C20)
Low fruits and vegetables consumption (%) ¹³	≥400 g/day 300-399 g/day 200-299 g/day 100-199 g/day 0-99 g/day	Oral cavity, pharynx (C00-C14); Larynx (C32)
Low fruit consumption only (%) ¹³	≥250 g/day 200-249 g/day 150-199 g/day 100-149 g/day 50-99 g/day 0-49 g/day	Lung, bronchus, trachea (C33-C34)
Red meat consumption (%) ^{11, 12}	0-99 g/day 100-199 g/day 200-299 g/day 300-399 g/day ≥400 g/day	Colorectum (C18-C20)
Processed meat consumption (%) ^{11, 12}	0-49 g/day 50-99 g/day 100-149 g/day 150-199 g/day 200-249 g/day ≥250 g/day	Colorectum (C18-C20); Stomach (C16; non-cardia only)
Lack of physical activity (%) ¹⁵⁻¹⁷	≥8000 MET-min/week 4000-7999 MET-min/week 600-3999 MET-min/week <600 MET-min/week	Colon (C18); female Breast (C50; post-menopausal cancers only)
Passive smoking (%) ²⁶	No Yes	Lung, bronchus, trachea (C33-C34)
Smoking (%) ⁷	Never Former Current	Oral cavity, pharynx (C00-C14); Esophagus (C15); Stomach (C16); Colorectum (C18-C20); Liver (C22); Pancreas (C25); Nasal cavity/paranasal sinus (C30-C31); Larynx (C32); Lung, bronchus, trachea (C33-C34); Cervix (C53); Kidney, renal pelvis, ureter (C64-C66); Urinary bladder (C67); Myeloid leukemia (C92)

The National Health Survey (Pesquisa Nacional de Saúde - PNS) enrolled 57,962 adults aged ≥ 20 years in 2013, when participants completed a questionnaire about alcohol consumption, body mass index (BMI), fruits and vegetables consumption, physical activity, tobacco smoking, and passive smoking in Brazil (Szwarcwald et al., 2014). Alcohol consumption was calculated based on average frequency consumption (days/week) and number of drinks a day. One drink (dose) or 12.5 grams (g) of pure alcohol was considered equivalent to one can of beer, one glass of wine or one shot of any distilled spirit. Consumption of fruits and vegetables (raw and grilled salad, vegetables or legumes in g/day) was estimated based on average frequency (days/week) and number of servings per day (i.e., each serving defined as 80g). Anthropometric measurements for BMI (weight and height) were objectively obtained from a trained researcher using portable electronic scales and stadiometers. Total physical activity (in metabolic equivalent of tasks-minutes/week (MET-min/week)) was assessed using self-reported data (days/week and duration) on recreational, occupational, household, and commuting activities (walking or cycling to and/or from work; walking or cycling to and/or from other daily activities). The compendium of physical activities was used to assign MET to each domain of physical activity (Ainsworth et al., 2011). Prevalence of smoking (never, former, and current) was calculated based on reports of current and prior use of any product derived from tobacco (i.e., cigar, pipe, clove or Bali cigarettes and narghile). Smokeless products such as snuff and chewing tobacco were not considered. Passive smoking among never smokers (yes, no) was defined based on either daily, weekly or monthly exposure at home and work environments.

We used data from the National Household Budget Survey (Pesquisa de Orçamentos Familiares – POF) conducted in 2008–2009 to obtain an estimated consumption of dietary consumption of fiber, calcium, red and processed meat. POF collected two 24-hour real-time food records from 26,390 individuals aged ≥ 20 years (IBGE, 2011a). Reported food amounts were converted into grams or milligrams (mg) based on a food portion table (IBGE, 2011b) Total fiber and calcium intakes (expressed in g/day and mg/day, respectively) were estimated based on the Brazilian food composition table (IBGE, 2011c). Red meat consumption (g/day) was estimated based on the intake of beef, pork and lamb, whereas processed meat (g/day) on the intake of

meat preserved by smoking, curing, salting, addition of chemical preservatives (e.g., ham, bacon, pastrami, sausages and hot dogs).

We calculated the preventability of cancer by comparing the burden of cancer due to the observed distribution of lifestyle risk factors (Tables S1-S2) with two counterfactual (alternative) exposure scenarios:

- Theoretical minimum risk exposure level: lifestyle risk factors eliminated in the whole population as defined in Table 1.
- Plausible reduction in exposure level: This alternative exposure scenario was based on policy targets and cancer prevention recommendations, whenever available (WCRF, 2018; WHO, 2014). It included a 10% relative reduction in heavy alcohol consumption (≥ 50.0 g/day) (WHO, 2014); 1 kg/m² reduction of BMI mean at the population level; dietary calcium consumption of at least 200-399 mg/day; dietary fiber consumption of at least 10-19g/day; fruits and vegetables consumption of at least 100-199g/day (for fruit only: at least 50-99g/day); red meat consumption < 300 g/day (WCRF, 2018); processed meat consumption < 100 g/day (WCRF, 2018); reaching the physical activity recommendation for adults of at least 600 MET-min/week (WHO, 2010); a 30% relative reduction in prevalence of current tobacco use (i.e., then considered former smoker) and consequently in passive smoking among never smokers (WHO, 2014).

Cancer data: Relative Risk and Estimated Cancer Incidence and Deaths

We retrieved relative risks (RR) of exposure-cancer pairs from meta-analyses and large pooled analyses of cohort studies conducted worldwide due to lack of prospective studies to study cancer etiology in Brazil. We retrieved the maximally-adjusted RR (adjusted for the greatest number of potential confounders) by sex (Table S3).

Estimated number of new cancer cases diagnosed in Brazil in 2012 by sex and age-group were retrieved from the GLOBOCAN project (Ferlay et al., 2013). To obtain separate estimates for cancers of the colon and rectum, cardia and non-cardia stomach, and esophagus adenocarcinoma and squamous cell carcinoma, we used the corresponding proportion of these subtypes in Brazil by sex (Table S4) (Forman et al., 2013; Arnold et al., 2015; Colquhoun et al., 2015). We considered advanced prostate

cancer cases with stage 3-4 and postmenopausal breast cancer cases older than 45 years, as performed in other study (Rezende et al., 2018). Cancer deaths in Brazil in 2012 by sex and age-group were obtained from the Brazilian Mortality Information System (Brasil, 2018).

Statistical analysis

Preventability of cancer cases and death by sex and age-group was estimated using the following equation for potential impact fraction (PIF) (Murray et al., 2003):

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

where P_i is the proportion of the population at the level i of exposure, P'_i is the proportion of the population at the level i of exposure in the counterfactual scenario, and RR_i is the relative risk of cancer at the level i of exposure. Level i for each exposure is presented in Table 1.

For BMI, we calculated preventability of cancer using equation for continuous exposures (Murray et al., 2003):

$$PIF = \frac{\int RR(x)P(x)dx - \int RR(x)P^*(x)dx}{\int RR(x)P(x)dx}$$

where $P(x)$ is the population distribution of BMI (mean and standard deviation), $P^*(x)$ distribution of BMI in the counterfactual scenario (Table 1), $RR(x)$ is the relative risk of cancer per one increment unit in BMI, and dx indicates that the integration was done with respect to the BMI level. We used a log-logit function to represent each RR value across BMI units (REZENDE et al., 2018).

Preventability of each cancer site attributable to combined lifestyle risk factors were estimated using the joint PIF equation (MURRAY et al., 2003):

$$Joint\ PIF = 1 - \prod_{i=1}^n (1 - PIF_i)$$

Where PIF_i is each individual lifestyle risk factor PIF.

Number of cancer cases and deaths attributable to lifestyle risk factors were obtained by applying PIF estimates to cancer cases and cancers deaths in the corresponding cancer site or subsite, as defined in the Table 1. Then, we divided the number of attributable cases and deaths by total number of cancers in the corresponding cancer site. We summed-up the number of cancer cases and deaths attributable to combined lifestyle risk factors across cancer sites to obtain the number of all cancer cases and deaths that could be potentially avoided. Proportion of all cancer attributable to exposures was obtained by dividing the total number of attributable cases and deaths by total number of cancer cases (excluding non-melanoma skin cancer) and deaths, respectively.

All data analysis was performed in Stata version 15.0. Data input, scripts, and spreadsheet with all results are available at the Open Science Framework (OSF) webpage <https://osf.io/y5ar8/>.

7.3. RESULTS

Cancer Incidence

Lifestyle risk factors combined

Lifestyle risk factors accounted for 26.5% of all cancer cases (114,497 of 431,557 cases) in adults in Brazil (Figure 1). Tobacco smoking was the single most important risk factor in both men (20.8%; 45,654 cases) and women (10.1%; 21,357 cases). Alcohol consumption had the second highest PAF (5.9%) in men, although combined dietary factors (low consumption of fruits and vegetables, fiber, calcium, and consumption of red and processed meat) accounted for similar cancer burden (6.2%). High BMI had the second highest PAF in women (6.6%), followed by lack of physical activity (4.1%) and combined dietary factors (4.0%). The preventable cases accounted by combination of high BMI, alcohol consumption, lack of physical activity, and dietary factors was higher than cases accounted by smoking in women (15.2% vs 10.1%), but not in men (14.2% vs 20.8%).

Figure 1 - Proportion and number of all cancer cases attributable to lifestyle risk factors in Brazil in 2012, by exposure

The proportion of cancer cases accounted by all lifestyle risk factors combined ranged from 1.6% for prostate cancer to 86.6% for larynx cancer (Figure 2). From the 18 cancer sites considered in the cancer incidence analysis, five cancer sites (larynx, lung, oral cavity, esophagus and colorectum) had PAF >50%. Lung (17,944 cases) and breast cancers (14,350 cases) had the highest number of cases attributable to lifestyle risk factors in men and women, respectively.

Figure 2 - Proportion and number of cancer cases and deaths attributable to lifestyle risk factors in Brazil in 2012, by cancer site

Considering the plausible reduction in lifestyle risk factors, 4.6% of all cancer cases (19,850 of 431,557 cases) could be potentially avoided. Smoking had the highest PAF (2.1%), followed by high BMI (0.8%), and lack of physical activity (0.5%). Cancer sites with highest PAF were larynx (21.1%), oral cavity (16.4%), and lung (14.8%) in men, and larynx (16.3%), lung (12.7%), and colorectum (11.4%) in women (Supplementary file online).

Tobacco smoking and passive smoking

Lung cancer had the highest PAF (82.3%) and number of attributable cases (28,214) of smoking-related cancers, followed by cancers of the larynx (77.1%; 5,496 cases), oral cavity (49.1%; 8,132 cases) and esophagus (49.1%; 6,334 cases). Passive smoking accounted for 1.9% (375 cases) and 1.8% (255 cases) of lung cancer cases in men and women, respectively (Table 2).

Table 2 - Proportion and number of cancer cases attributable to lifestyle risk factors in Brazil in 2012, by exposure, sex, and cancer site

Exposure/ cancer site	Men			Women			Both		
	Number of cases	PAF (%)	Attributable cases	Number of cases	PAF (%)	Attributable cases	Number of cases	PAF (%)	Attributable cases
Smoking									
Lung	20,229	86.5	17,490	14,041	76.4	10,724	34,270	82.3	28,214
Larynx	6,281	78.5	4,934	850	66.2	563	7,131	77.1	5,496
Oral cavity/pharynx	11,901	53.1	6,313	4,653	39.1	1,819	16,554	49.1	8,132
Esophagus	9,713	52.6	5,106	3,191	38.5	1,228	12,904	49.1	6,334
Bladder	7,033	50.7	3,566	2,869	34.3	983	9,902	45.9	4,550
Liver	5,726	29.5	1,691	3,870	9.0	349	9,596	21.3	2,040
Stomach	12,606	25.8	3,251	7,078	8.2	578	19,684	19.5	3,829
Kidney	3,611	24.2	873	2,307	5.7	131	5,918	17.0	1,004
Cervix	-	-	-	18,503	15.7	2,907	18,503	15.7	2,907
Pancreas	4,640	9.6	444	5,222	11.2	586	9,862	10.4	1,030
Colorectum	16,359	12.1	1,986	17,579	8.5	1,489	33,938	10.2	3,475
High Body mass index									
Corpus uteri	-	-	-	6,366	36.5	2,326	6,366	36.5	2,326
Kidney	3,611	19.9	718	2,307	22.9	529	5,918	21.1	1,247
Gallbladder	1,456	15.9	231	2,593	20.9	542	4,049	19.1	773
Liver	5,726	15.0	858	3,870	17.9	692	9,596	16.2	1,550
Breast*	-	-	-	67,307	9.9	6,660	67,307	9.9	6,660
Colorectum	16,359	12.2	2,002	17,579	7.6	1,334	33,938	9.8	3,336
Pancreas	4,640	9.6	446	5,222	9.1	475	9,862	9.3	921
Multiple myeloma	1,866	8.4	156	1,642	6.6	109	3,508	7.6	265
Esophagus	9,713	6.4	626	3,191	7.7	247	12,904	6.8	873
Thyroid	2,576	12.3	316	11,210	4.5	502	13,786	5.9	818
Ovary	-	-	-	5,745	5.7	325	5,745	5.7	325
Stomach*	12,606	5.3	667	7,078	3.7	259	19,684	4.7	925
Prostate*	72,536	1.6	1,162	-	-	-	72,536	1.6	1,162
Alcohol consumption									
Oral cavity/pharynx	11,901	46.8	5,572	4,653	11.5	536	16,554	36.9	6,108
Esophagus*	9,713	34.3	3,328	3,191	12.0	383	12,904	28.8	3,711
Larynx	6,281	26.0	1,632	850	3.0	26	7,131	23.3	1,658

Gallbladder	1,456	20.6	300	2,593	4.0	105	4,049	10.0	405
Liver	5,726	9.6	552	3,870	6.9	268	9,596	8.5	820
Colorectum	16,359	9.1	1,483	17,579	0.8	137	33,938	4.8	1,620
Breast	-	-	-	67,307	3.1	2,116	67,307	3.1	2,116
Pancreas	4,640	3.1	146	5,222	0.5	25	9,862	1.7	171
Lack of Physical activity									
Colorectum*	16,359	11.1	1,811	17,579	11.8	2,067	33,938	11.4	3,878
Breast*	-	-	-	67,307	10.0	6,712	67,307	10.0	6,712
Low Fruits and vegetables consumption									
Larynx	6,281	26.3	1,652	850	23.9	203	7,131	26.0	1,855
Oral cavity/pharynx	11,901	26.5	3,152	4,653	24.0	1,117	16,554	25.8	4,269
Lung	20,229	15.3	3,089	14,041	14.2	1,995	34,270	14.8	5,084
Low dietary calcium consumption									
Colorectum	16,359	11.6	1,902	17,579	10.8	1,893	33,938	11.2	3,795
Low dietary fiber consumption									
Colorectum	16,359	11.8	1,923	17,579	9.3	1,626	33,938	10.5	3,550
Processed meat consumption									
Stomach*	12,606	5.0	626	7,078	5.6	393	19,684	5.2	1,019
Colorectum	16,359	5.4	883	17,579	4.7	833	33,938	5.1	1,716
Red meat consumption									
Colorectum	16,359	6.5	1,069	17,579	4.8	842	33,938	5.6	1,911
Passive smoking									
Lung	20,229	1.9	375	14,041	1.8	255	34,270	1.8	630

High body mass index

Corpus uteri (36.5%) had the highest PAF of BMI-related cancers, followed by kidney (21.1%), gallbladder (19.1%), and liver (16.2%). Most of the cancer cases attributable to BMI (58.2%) were from breast (6,660 cases), colorectum (3,336 cases), and corpus uteri (2,326 cases) (Table 2).

Alcohol consumption

Oral cavity had both the highest PAF (36.9%) and number of cases (6,108) due to alcohol. By sex, cancer sites with highest number of cases attributable to alcohol consumption were oral cavity (5,572 cases) and esophagus (3,328 cases) in men, and breast (2,116 cases) and oral cavity (536 cases) in women (Table 2).

Dietary factors

Low consumption of fruits and vegetables accounted for 26.0% (1,855 cases) of larynx, 25.8% (4,269 cases) of oral cavity/pharynx and 14.8% (5,084 cases) of lung cancer cases (Table 2). Low consumption of calcium and fiber, and high consumption of red and processed meat, accounted for 28.7% (9,755 cases) of colorectal cancer cases.

Lack of Physical activity

In women, colorectum cancer (11.8%; 2,067 cases) had the highest PAF, whereas breast cancer (10.0%; 6,712 cases) had the highest number of attributable cases. In men, 11.1% (1,811 cases) of colorectal cancers were due to lack of physical activity (Table 2).

Cancer Mortality

Lifestyle risk factors accounted for 33.7% of all cancer deaths (63,417 of 188,379 deaths) in Brazil (Figure 3). Ranking of lifestyle risk factors was similar to those observed for cancer incidence. Tobacco smoking accounted for the greatest proportion and number of cancer deaths in both men (28.4%; 28,404 deaths) and women (13.5%; 11,907 deaths). High BMI had the second highest PAF (6.9%; 13,011 deaths), with differences between men (6.5%; 6,543 deaths) and women (7.3%; 6,468 deaths) less pronounced than those observed in the incidence estimates. Dietary factors

and alcohol consumption accounted for 6.7% (12,692 deaths) and 4.5% (8,547 deaths) of all cancer deaths, respectively. Proportion and number of deaths of cancer sites attributable to each lifestyle risk factor are shown in Table 3.

Figure 3 - Proportion and number of total cancer deaths attributable to lifestyle risk factors in Brazil in 2012, by exposure and sex

In 13 out of the 20 cancer sites included in the cancer mortality analysis, the proportion of deaths that could be potentially avoided was higher than 20% (Figure 2). By cancer site, proportion of cancer deaths attributable to lifestyle risk factors ranged from 5.4% for prostate to 86.1% for larynx cancer. Lung cancer (19,956 deaths), colorectum cancer (8,872 deaths), and esophageal cancer (6,034 deaths) had the highest number of deaths due to lifestyle risk factors (Table 3).

Table 3 - Proportion and number of cancer deaths attributable to lifestyle risk factors in Brazil in 2012, by exposure, sex, and cancer site

Exposure/cancer site	Men			Women			Both		
	Cancer deaths	PAF (%)	Attributable deaths	Cancer deaths	PAF (%)	Attributable deaths	Cancer deaths	PAF (%)	Attributable deaths
Smoking									
Lung	14,246	86.3	12,295	9,208	75.9	6,991	23,454	82.2	19,286
Larynx	3,780	78.4	2,962	552	64.9	358	4,332	76.6	3,320
Oral cavity/pharynx	5,510	53.1	2,924	1,512	39.4	596	7,022	50.1	3,520
Esophagus	5,983	52.9	3,164	1,760	38.3	674	7,743	49.6	3,838
Nasal cavity/paranasal sinus	115	51.4	59	71	39.3	28	186	46.8	87
Bladder	2,231	50.5	1,127	1,061	32.4	344	3,292	44.7	1,471
Liver	4,986	29.5	1,469	3,761	8.8	331	8,747	20.6	1,801
Stomach	8,708	25.7	2,235	4,984	7.8	390	13,692	19.2	2,625
Kidney	1,694	24.8	421	1,028	5.6	58	2,722	17.6	479
Cervix	-	-	-	5,258	16.2	850	5,258	16.2	850
Myeloid leukemia	1,333	22.3	298	1,277	2.8	35	2,610	12.8	333
Colorectum	8,533	12.6	1,076	9,112	8.7	793	17,645	10.6	1,869
Pancreas	4,014	9.3	374	4,201	10.9	459	8,215	10.1	833
High body mass index									
Corpus uteri	-	-	-	3,416	36.1	1,233	3,416	36.1	1,233
Esophagus*	5,983	33.9	2,028	1,760	35.1	617	7,743	34.2	2,645
Kidney	1,694	19.7	333	1,028	22.8	234	2,722	20.8	567
Gallbladder	233	15.8	37	784	20.8	163	1,017	19.7	200
Stomach*	8,708	15.8	1,380	4,984	19.1	950	13,692	17.0	2,330
Liver	4,986	14.9	741	3,761	17.8	670	8,747	16.1	1,411
Breast	-	-	-	13,587	10.3	1,400	13,587	10.3	1,400
Pancreas	4,014	9.5	382	4,201	9.0	380	8,215	9.3	762
Colorectum*	8,533	9.4	806	9,112	6.0	547	17,645	7.7	1,352
Multiple myeloma	1,212	8.1	99	1,190	6.6	78	2,402	7.4	177
Thyroid	176	11.9	21	423	4.6	20	599	6.8	41
Ovary	-	-	-	3,106	5.7	177	3,106	5.7	177
Prostate*	13,344	5.4	716	-	-	-	13,344	5.4	716
Alcohol consumption									
Oral cavity/pharynx	5,510	45.8	2,522	1,512	11.1	168	7,022	38.3	2,690

Esophagus*	5,983	41.5	2,483	1,760	15.3	270	7,743	35.6	2,753
Larynx	3,780	25.4	958	552	2.8	16	4,332	22.5	974
Liver	4,986	9.4	467	3,761	6.5	245	8,747	8.1	712
Gallbladder	233	20.1	47	784	3.8	30	1,017	7.6	77
Colorectum	8,533	8.9	759	9,112	0.7	67	17,645	4.7	826
Breast	-	-	-	13,587	2.8	377	13,587	2.8	377
Pancreas	4,014	3.0	121	4,201	0.4	19	8,215	1.7	139
Lack of physical activity									
Breast*	-	-	-	13,587	10.6	1,444	13,587	10.6	1,444
Colorectum*	8,533	9.6	820	9,112	10.6	963	17,645	10.1	1,782
Low fruits and vegetables consumption									
Larynx	3,780	26.3	992	552	23.8	132	4,332	25.9	1,124
Oral cavity/pharynx	5,510	26.4	1,453	1512	24.0	362	7,022	25.9	1,815
Lung	14,246	15.2	2,172	9,208	14.2	1,305	23,454	14.8	3,477
Low dietary calcium consumption									
Colorectum	8,533	12.1	1,031	9,112	11.7	1,068	17,645	11.9	2,099
Low dietary fiber consumption									
Colorectum	8,533	12.1	1,032	9,112	9.9	906	17,645	11.0	1,938
Processed meat consumption									
Stomach*	8,708	7.3	639	4,984	6.9	343	13,692	7.2	982
Colorectum	8,533	5.4	464	9,112	5.1	465	17,645	5.3	928
Red meat consumption									
Colorectum	8,533	6.6	560	9,112	5.1	469	17,645	5.8	1,029
Passive smoking									
Lung	14,246	1.9	264	9,208	1.8	167	23,454	1.8	431

Considering the plausible reduction in the lifestyle risk factors, 6.1% of all cancer deaths (11,561 of 188,379 deaths) could be potentially avoided, with a higher proportion in men (7.3%; 7,289 deaths) than in women (4.8%; 4,272 deaths). The combination of high BMI, alcohol consumption, lack of physical activity and dietary factors accounted for more cancer deaths (3.3%; 6,230 deaths) than smoking (2.9%; 5,426 deaths) (Supplementary file online).

7.4. DISCUSSION

Main results and comparison with previous studies

In this study we found that 27% (114,497 cases) of all cancer cases and 34% (63,371 deaths) of all cancer deaths were attributable to lifestyle risk factors in Brazil in 2012. Tobacco smoking was the single major cause of cancer, accounting for more than half of all preventable cancer cases and deaths estimated. High BMI and alcohol consumption were the second most important lifestyle factors for women and men, respectively. Larynx, lung, oral cavity/pharynx, esophagus and colorectum cancer cases and deaths could be at least halved by eliminating lifestyle risk factors included in our analysis.

Preventability of cancer may vary by the method used to estimate it (Colditz; Wei, 2012). The classical PAF approach relies on information about (i) risk factors with convincing evidence for causing cancer, (2) exposure profile, (3) RR of cancer associated with exposure, and (4) number of cases/deaths. Variation in any of these parameters over time and populations may explain PAF differences between study's findings. Nonetheless, our results for PAF for all cancers due to lifestyle risk factors are comparable to recent studies, using similar methods, conducted in the Australia, China, United Kingdom (UK), and United States (US) (Whiteman et al., 2015; Islami et al., 2017; 2018; Brown et al. 2018). For instance, tobacco smoking was the leading factor contributing to cancer cases in all countries: 19.4% in US, 15.5% in Brazil (our study), 15.1% in UK, 14.8% in China, and 13.4% in Australia (Whiteman et al., 2015; Islami et al., 2017; 2018; Brown et al. 2018). Smoking-related cancer cases were higher in men than women, ranging from 43% in UK to 20-fold in China (Whiteman et al., 2015; Islami et al., 2017; 2018; Brown et al. 2018). High BMI had the second highest PAF among lifestyle factors in US (7.8%), UK (6.3%) and Brazil (4.9%), and the third

highest PAF in China (3.5%) and Australia (3.4%) (Whiteman et al., 2015; Islami et al., 2017; 2018; Brown et al. 2018). Alcohol consumption had the second highest PAF in Australia (2.8%), the third in UK (3.1%), US (5.6%) and Brazil (5.6%), and the fourth in China (3.1%) (Whiteman et al., 2015; Islami et al., 2017; 2018; Brown et al. 2018).

Our findings slightly differ from previous studies quantifying the preventability of cancer due to lifestyle risk factors in Brazil (Azevedo e Silva et al., 2016; Thuler et al., 2016; Rezende et al., 2018). For example, compared to our study, Azevedo e Silva and colleagues (2016) reported lower proportion of cancer cases due to smoking in both men (14.4% vs 20.8% in our study) and women (7.2% vs 10.1%). Tobacco smoking is constantly declining in Brazil (Monteiro et al., 2007) and our study used the most recent prevalence data, which would lead to lower estimates. However, our study also considered RR of cancers among former smokers, relative to never smokers, which were not considered by Azevedo e Silva and colleagues (2016). RR of lung cancer among heavy former smokers may remain at least threefold higher than never smokers after 25 years since quitting (Tindler et al., 2018). Azevedo e Silva and colleagues (2016) also reported lower PAF for all cancer cases due to high BMI (2.1% men; 3.3% women) compared to ours (3.3% men; 6.6% women). These differences could be relate to our use of continuous rather than categorical to estimates PAF, but mainly due to cancer sites considered with convincing evidence to be associated with high BMI (6 vs 13 cancer sites in our study) (Lauby-Secretan et al., 2016; WCRF, 2018). In addition, BMI has constantly increased over the last years in Brazil (Rezende et al., 2018), and anthropometrics measurements were considered five years apart (2008 vs 2013).

Implications for cancer prevention and control

Our estimates of preventability of cancer used recent exposure profile in Brazil. These estimates reflect the expected impact on cancer cases and deaths by eliminating/reducing current prevalence of lifestyle risk factors, but it does not account for cancers that have already been prevented by avoidance of ever being exposed. For instance, in Brazil, the broad framework of laws to control tobacco introduced in the late 1980s (e.g., advertising tobacco products is prohibited; alerts about health risks of smoking are placed on cigarette packets; several tobacco control bills were approved; smoking in places of collective use, public or private indoor, is prohibited) was responsible for halving the prevalence of tobacco smoking between 1989 (30%) and

2013 (15%) (Monteiro et al., 2007). Thus, current preventability of cancer due to smoking is lower than it was in the 1980s, but it does not mean cancer prevention strategies should be less vigilant about tobacco control. In fact, a full range of interventions and tools have been proposed to address the challenges of tobacco control in the 21st century (Glynn et al., 2010). For instance, regulation of flavored and candy-like tobacco products, among other youth-specific marketing strategies, is important to prevent tobacco addiction in the future generations (Glynn et al., 2010).

High BMI, alcohol consumption, unhealthy diet and lack physical activity are important targets for cancer prevention. We found that these lifestyle factors accounted for the highest proportion of cancer cases and deaths in women, but not in men. These lifestyle risk factor may increase cancer risk through several inflammatory and hormonal pathways, some of which are likely causal for cancer in women only (e.g., estrogen and breast and endometrial cancer) (WCRF, 2018). As opposed to smoking, the prevalence of these lifestyle risk factors is constantly increasing in Brazil (NCD Risk Factor Collaborators, 2013; Martins et al., 2013; Mielke et al., 2014). For instance, the caloric share of ultra-processed food and products increased from 20.8% in 2002/2003 to 25.4% in 2008/2009 (Martins et al., 2013). In the same period, consumption of vegetables, red and processed meat remained stable, dairy products decreased, and fruit intake slightly increased. High consumption of ultra-processed products is associated with an overall unhealthy dietary profile characterized by high consumption of free sugars and fat and low dietary fiber consumption (Louzada et al., 2017). Moreover, ultra-processed food intake has been recently linked with higher BMI, waist circumference and cancer risk (Fiolet et al., 2018; Silva et al., 2018). Public health actions aiming to reduce the intake of these products (e.g., taxation, food labeling) are necessary for obesity and cancer prevention. Further regulations in regard to alcohol sales and marketing (i.e., in Brazil, it is prohibited advertisements for alcoholic beverages on the radio and television between 6:00 AM to 9:00 PM; sell alcohol for people under 18 years of age; to drink and drive) would also be highly beneficial for cancer prevention in Brazil, especially for men. Rising prices of alcohol have shown to be an effective measure to reduce drinking (Wagenaar et al., 2009). Finally, despite modest increase in leisure-time physical activity over the past few years, commuting activities have steeply declined, and the prevalence of physical inactivity remains high in Brazil (Mielke et al., 2014). Expansion of physical activity programs in the Brazilian

primary health care system and improvement of built environment of public spaces (e.g., schools, cycle lanes, parks, sidewalks) towards active modes of living are key to increase population levels of physical activity in a sustainable manner (Gomes et al., 2014).

Limitations

Our study has some limitations that should be considered while interpreting the results. We used RR from meta-analyses and large pooled data from cohort studies conducted worldwide (Table S3). The RR might not be applicable to the Brazilian population if the (1) exposure, (2) latency of the disease, or (3) prevalence of effect modifiers are different between populations (Rezende; Eluf-Neto, 2016). For instance, the effect of high BMI on cancer risk may differ by smoking status due to residual confounding and reverse causation. Lean non-smokers tend to be different than lean smokers in terms of visceral adiposity and metabolic profiles. In addition, lean smokers also tend to have more preclinical malignancies and other chronic illnesses than lean non-smokers (Song; Giovannucci, 2016). Therefore, differences in the prevalence of current smokers between populations where RR were estimated and the Brazilian population may have biased our results. Future prospective studies to study etiologic factors of cancer in Brazil are desired.

Furthermore, we opted to estimate the preventability of cancer using the most recent exposure data in Brazil, which may not have properly accounted for the latency between exposures and cancer. This approach has been used in the literature due to uncertainty and variation in regard to latency of lifestyle exposures to cancer occurrence and deaths (Islami et al., 2018). We used data from POF 2008/09 and PNS 2013 in order to estimate the prevalence of lifestyle risk factors, although cancer cases and deaths were estimated for 2012. Depending on trends of cancer incidence and risk factors over time, this may have underestimated or overestimated the preventability of cancer.

We limited our estimates to associations supported by convincing evidence according to the IARC and the WCRF, and results from recent meta-analyses (IARC, 2002; 2018 Bagnardi et al., 2015; Bouvard et al., 2015; Carter et al., 2015; Lauby-Secretan et al., 2016; Rezende et al., 2018a; WCRF, 2018a; 2018b; 2018c; 2018d; 2018e) Our PAF estimates might be underestimated, especially for lifestyle exposures

with recent promising findings in regard to cancer prevention. For instance, a recent pooled analysis found that leisure-time physical activity was associated with lower risk of 13 types of cancer (Moore et al., 2016). If these associations turn out to be confirmed causal, our estimates on proportion of cancer cases and deaths due to lack of physical activity are underestimated. Regarding the dietary factors, calcium was the only nutrient considered in our analysis. The WCRF report assessed the association between consumption of dairy products (e.g., total dairy, milk, cheese) as well as calcium supplements as probable protective against colorectal cancer (WCRF, 2018). One potential interpretation is that both results on dairy products and calcium supplements support calcium as the key protective component. In fact, a meta-analysis of prospective studies found that calcium supplements and non-dairy products fortified with calcium may play a role in colorectal cancer prevention (Keum et al., 2014). In our study, we considered exposure as total dietary calcium consumption only.

PAF estimates did not either account for interaction between lifestyle risk factors nor exposures at earlier stages of life, which may also have underestimated the actual preventability of cancer in Brazil. Finally, this study focused on lifestyle risk factors, but reductions in other modifiable risk factors (e.g., infections) may certainly play an important role in cancer prevention. These modifiable risk factors were considered in a previous study in Brazil (Azevedo e Silva et al., 2016), but since then its prevalences have not been updated.

Conclusions

Lifestyle risk factors accounted for nearly 27% of cancer cases and one-third of cancer deaths in Brazil in 2012. Preventive actions focusing on tobacco control and prevention of overweight and obesity are likely to have the greatest impact on cancer prevention. Findings from this study may be useful to inform strategies for cancer prevention and control in Brazil.

Acknowledgment: none.

Funding: Leandro F3rnias Machado de Rezende receives a doctoral scholarship from Sao Paulo Research Foundation (FAPESP), grants 2014/25614-4 and 2016/21390-0.

Conflict of Interest: none.

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SUPPLEMENTARY MATERIAL

Table S1 - Distribution of lifestyle risk factors included in analysis by sex, adults ≥ 20 years

	Men	Women
Alcohol consumption (%)		
Abstainer	63.2	87.2
Light (<12.5 g/day)	2.2	2.3
Moderate (12.6 to 49.9 g/day)	9.7	4.9
Heavy (≥ 50 g/day)	24.9	5.6
High body mass index (in Kg/m²)		
Mean (standard deviation)	26.2 (4.5)	27.0 (5.5)
Low dietary calcium consumption (%)		
≥ 1000 mg/day	7.7	11.8
800-999 mg/day	29.6	32.8
600-799 mg/day	26.4	26.2
400-599 mg/day	15.8	13.8
200-399 mg/day	8.5	6.7
0-199 mg/day	12.0	8.7
Low dietary fiber consumption (%)		
≥ 30 g/day	7.4	13.7
20-29 g/day	37.5	52.4
10-19 g/day	31.0	23.3
0-9 g/day	24.1	10.6
Low fruits and vegetables consumption (%)		
≥ 400 g/day	4.5	7.7
300-399 g/day	8.5	11.7
200-299 g/day	18.8	22.6
100-199 g/day	38.3	36.9
0-99 g/day	29.9	21.1
Low Fruits consumption only (%)		
≥ 250 g/day	3.6	6.2
200-249 g/day	0.3	0.4
150-199 g/day	9.1	14.5
100-149 g/day	5.2	4.9
50-99 g/day	24.6	29.1
0-49 g/day	57.1	44.9
Passive smoking (%)		
No	84.3	85.8
Yes	15.7	14.2
Lack of physical activity (%)		
≥ 8000 MET-h/week	9.8	2.5
4000-7999 MET-h/week	9.3	5.3
600-3999 MET-h/week	36.8	41.5
<600 MET-h/week	44.2	50.7
Processed meat consumption (%)		
0-49 g/day	84.3	89.1
50-99 g/day	6.9	5.2
100-149 g/day	2.5	1.1
150-199 g/day	0.8	0.4
200-249 g/day	0.8	0.4
≥ 250 g/day	4.7	3.7
Red meat consumption (%)		
0-99 g/day	59.4	71.4
100-199 g/day	25.8	20.5
200-299 g/day	7.7	3.9
300-399 g/day	2.2	0.6
≥ 400 g/day	5.0	3.6
Smoking (%)		
Never	58.5	74.1
Former	22.1	14.6
Current	19.4	11.3

Table S2 - Distribution of lifestyle risk factors included in analysis by age-group and sex

	Men					Women				
	20-44 years	45-54 years	55-64 years	65-74 years	≥75 years	20-44 years	45-54 years	55-64 years	65-74 years	≥75 years
Alcohol consumption (in g/day)										
Abstainer	59.1	62.6	66.3	77.2	84.4	83.8	87.5	91.0	95.0	97.4
Light (<12.5 g/day)	1.6	2.0	3.6	4.6	2.9	2.4	2.3	2.5	2.0	0.8
Moderate (12.6 to 49.9 g/day)	10.9	9.6	8.7	6.0	3.8	6.2	4.8	3.6	1.3	1.1
Heavy (≥50 g/day)	28.4	25.8	21.4	12.2	8.9	7.5	5.4	2.9	1.8	0.6
High body mass index (in Kg/m²)										
Mean (standard deviation)	25.8 (4.5)	26.8 (4.5)	26.9 (4.6)	26.5 (4.5)	25.0 (4.2)	26.2 (5.5)	27.9 (5.4)	28.1 (5.3)	27.6 (5.5)	26.5 (4.8)
Low dietary calcium consumption (in mg/day)										
≥1000	6.9	8.2	9.0	10.3	9.5	11.6	12.2	12.4	14.5	7.6
800-999	28.5	32.3	32.7	27.1	31.2	33.6	32.8	31.5	31.8	29.1
600-799	26.8	24.8	26.6	25.1	29.8	26.5	26.9	25.0	23.2	26.8
400-599	16.1	16.0	14.3	17.7	10.3	13.4	14.2	14.9	13.3	14.9
200-399	9.4	7.3	5.4	9.0	8.1	6.3	6.1	7.5	7.2	10.3
0-199	12.4	11.4	12.0	10.8	11.1	8.6	7.8	8.7	10.0	11.3
Low dietary fiber consumption (in g/day)										
≥30	6.6	7.2	8.5	9.8	12.9	12.8	15.1	13.3	16.0	15.7
20-29	37.1	36.4	37.5	39.2	46.5	53.1	53.5	48.1	53.8	49.4
10-19	30.8	31.9	32.5	29.8	28.0	23.0	21.4	27.1	21.5	26.2
0-9	25.6	24.4	21.5	21.1	12.6	11.1	9.9	11.4	8.7	8.8
Low fruits and vegetables consumption (in g/day)										
≥400	3.5	4.7	5.7	7.2	8.3	6.3	7.4	11.0	11.0	9.2
300-399	7.3	9.3	10.4	10.6	9.4	10.7	12.5	13.5	13.2	10.5
200-299	17.4	19.2	22.9	20.6	19.4	20.1	24.4	24.6	28.5	27.6
100-199	38.6	39.0	37.1	37.7	36.5	37.8	37.3	35.4	32.6	36.3
0-99	33.2	27.8	24.1	23.8	26.4	25.0	18.4	15.6	14.6	16.4
Low fruits consumption only (in g/day)										
≥250	3.1	3.3	4.3	5.3	6.3	5.3	6.4	8.4	7.4	6.9
200-249	0.3	0.3	0.6	0.3	0.2	0.3	0.4	0.6	0.4	0.4
150-199	7.3	8.5	12.4	14.5	15.8	11.8	15.5	18.7	19.1	19.6

100-149	4.9	5.8	6.3	4.4	4.4	5.1	4.4	4.7	5.9	3.0
50-99	22.3	27.3	27.0	27.6	28.4	26.9	29.6	30.1	35.7	37.0
0-49	62.1	54.8	49.4	47.9	44.9	50.6	43.6	37.6	31.4	33.1
Passive smoking										
No	82.4	83.5	87.3	91.7	89.6	84.7	85.9	85.8	90.2	89.5
Yes	17.6	16.5	12.7	8.3	10.4	15.3	14.1	14.2	9.8	10.5
Lack of physical activity (in MET-h/week)										
≥8000	12.0	10.6	6.7	2.5	0.8	3.1	3.0	1.9	0.5	0.2
4000-7999	10.3	10.0	9.0	4.9	1.8	6.4	6.2	3.9	1.7	1.0
600-3999	40.4	34.2	33.5	31.3	21.6	45.4	43.4	39.5	31.3	16.2
<600	37.3	45.1	50.8	61.3	75.8	45.1	47.4	54.7	66.5	82.7
Processed meat consumption (in g/day)										
0-49	83.2	83.7	88.6	84.9	90.6	88.3	91.4	88.8	87.9	91.6
50-99	7.9	6.6	4.0	5.2	3.5	5.9	4.1	5.3	4.4	2.1
100-149	2.3	3.0	2.3	3.8	1.9	1.2	1.2	0.9	0.9	1.1
150-199	0.9	0.8	0.3	1.3	1.2	0.5	0.3	0.2	0.8	0.3
200-249	0.8	0.6	1.1	0.3	0.6	0.3	0.5	0.5	0.9	0.4
≥250	4.8	5.4	3.7	4.5	2.1	3.7	2.7	4.3	5.1	4.5
Red meat consumption (in g/day)										
0-99	57.5	58.5	63.0	62.4	76.0	69.8	73.0	73.1	75.2	74.5
100-199	26.1	27.4	25.8	23.2	16.5	21.4	20.5	18.6	17.4	19.4
200-299	8.6	6.8	5.3	8.3	4.5	4.4	3.5	4.4	2.4	1.2
300-399	2.5	1.7	2.2	1.5	0.7	0.7	0.4	0.5	0.5	0.5
≥400	5.2	5.5	3.7	4.6	2.3	3.7	2.7	3.4	4.4	4.4
Smoking										
Never	68.6	53.1	41.4	38.2	44.3	82.3	61.6	61.3	68.9	77.5
Former	13.1	23.5	35.7	46.1	44.9	9.0	19.9	23.1	22.3	18.2
Current	18.3	23.4	22.9	15.7	10.8	8.7	18.5	15.6	8.8	4.3

Table S3 - Relative risks for the associations between lifestyle risk factors and cancer sites

Cancer sites			
Exposure/cancer site (ICD-10)	Categories of exposure	Relative risk (95% CI)	
		Men	Women
Alcohol consumption			
Lip, oral cavity, pharynx (C00-C14)[1]	abstainer	1	1
	light	1.10	1.00
	moderate	2.01	1.67
	heavy	5.33	5.70
Esophagus (C15; squamous cell carcinoma only)[1]	abstainer	1	1
	light	1.20	1.07
	moderate	2.25	2.18
	heavy	4.69	8.32
Colorectum (C18-C20)[1]	abstainer	1	1
	light	1.03	1.00
	moderate	1.21	1.07
	heavy	1.53	1.24
Liver (C22)[1]	abstainer	1	1
	light	1.03	1.00
	moderate	1.08	1.24
	heavy	1.59	3.89
Gallbladder (C23)[1]	abstainer	1	1
	light	1.12	1.12
	moderate	1.00	1.00
	heavy	2.64	2.64
Pancreas (C25)[1]	abstainer	1	1
	light	1.00	1.00
	moderate	1.08	1.04
	heavy	1.16	1.17
Larynx (C32)[1]	abstainer	1	1
	light	1.00	1.00
	moderate	1.50	1.59
	heavy	2.77	1.55
Breast (C50)[1]	abstainer	-	1
	light	-	1.02
	moderate	-	1.23
	heavy	-	1.61
Smoking			
Lung, bronchus, trachea (C33-C34)[2]	never	1	1
	former	6.80	6.80
	current	25.30	22.90
Oral cavity, pharynx (C00-C14)[2]	never	1	1
	former	1.70	2.20
	current	5.70	5.60
Larynx (C32)[2]	never	1	1
	former	2.78	2.78
	current	17.40	17.40
Esophagus (C15)[2]	never	1	1
	former	2.60	2.20
	current	3.90	5.10
Stomach (C16)[2]	never	1	1
	former	1.50	1.10

	current	1.90	1.70
Colorectum (C18-C20)[2]	never	1	1
	former	1.20	1.20
	current	1.40	1.60
Pancreas (C25)[2]	never	1	1
	former	1.00	1.20
	current	1.60	1.90
Liver (C22)[2]	never	1	1
	former	1.50	1.10
	current	2.30	1.80
Kidney, renal pelvis, ureter (C64-C66)[2]	never	1	1
	former	1.50	1.20
	current	1.80	1.20
Urinary bladder (C67)[2]	never	1	1
	former	2.40	2.30
	current	3.90	3.90
Myeloid leukemia (C92)[2]	never	1	1
	former	1.40	1.10
	current	1.90	1.10
Cervix (C53)[3]	never	-	1
	former	-	1.50
	current	-	1.90
Nasal cavity/paranasal sinus (C30-C31)[2]	never	1	1
	former	1.70	2.20
	current	5.70	5.60
Passive smoking			
Lung, bronchus, trachea (C33-C34)[4]	no	1	1
	yes	1.27	1.27
Low consumption of fruits			
Lung, bronchus, trachea (C33-C34)[5, 6]	≥250g	1	1
	200-249g	1.04	1.04
	150-199g	1.09	1.09
	100-149	1.13	1.13
	50-99g	1.18	1.18
	0-49g	1.23	1.23
Low consumption of fruits and vegetables			
Oral cavity, pharynx (C00-C14)[7, 8]	≥400g	1	1
	300-399g	1.12	1.12
	200-299g	1.25	1.25
	100-199g	1.40	1.40
	0-99g	1.56	1.56
Larynx (C32)[7, 8]	≥400g	1	1
	300-399g	1.12	1.12
	200-299g	1.25	1.25
	100-199g	1.40	1.40
	0-99g	1.56	1.56
Consumption of red meat			
Colorectum (C18-C20)[8, 9]	0-99g	1	1
	100-199g	1.12	1.12
	200-299g	1.25	1.25
	300-399g	1.40	1.40
	≥400g	1.57	1.57
Consumption of processed meat			

Stomach (C16; non-cardia only)[8, 10]	0-49g	1	1
	50-99g	1.18	1.18
	100-149	1.39	1.39
	150-199g	1.64	1.64
	200-249g	1.94	1.94
	≥250g	2.29	2.29
Colorectum (C18-C20)[8, 9]	0-49g	1	1
	50-99g	1.14	1.14
	100-149	1.30	1.30
	150-199g	1.48	1.48
	200-249g	1.69	1.69
	≥250g	1.93	1.93
Low dietary consumption of fiber			
Colorectum (C18-C20)[8, 9]	≥30g	1	1
	20-29g	1.08	1.08
	10-19g	1.17	1.17
	0-9g	1.27	1.27
Low dietary consumption of calcium			
Colorectum (C18-C20)[8, 9]	≥1000mg	1	1
	800-999mg	1.06	1.06
	600-799mg	1.12	1.12
	400-599mg	1.19	1.19
	200-399mg	1.26	1.26
	0-199mg	1.34	1.34
Lack of physical activity			
Colon (C18)[11]	≥8000	1	1
	4000-7999	1.07	1.07
	600-3999	1.17	1.17
	<600	1.29	1.29
Breast (C50; post-menopausal cancers only)[11]	≥8000	-	1.00
	4000-7999	-	1.09
	600-3999	-	1.12
	<600	-	1.16
High Body Mass Index			
Breast (C50; post-menopausal cancers only)[12]	Per 1Kg/m ²	–	1.02
Colon (C18)[9]	Per 1Kg/m ²	1.04	1.02
Corpus uteri (C54-C55)[13]	Per 1Kg/m ²	–	1.08
Gallbladder (C23)[14]	Per 1Kg/m ²	1.04	1.05
Kidney, renal pelvis (C64-C66)[14]	Per 1Kg/m ²	1.05	1.05
Liver (C22)[15]	Per 1Kg/m ²	1.04	1.04
Multiple myeloma (C90)[16]	Per 1Kg/m ²	1.04	1.04
Esophagus (C15; adenocarcinoma only)[14]	Per 1Kg/m ²	1.09	1.08
Ovary (C56)[17]	Per 1Kg/m ²	–	1.01
Pancreas (C25)[18]	Per 1Kg/m ²	1.02	1.02
Prostate (C61; advanced only)[19]	Per 1Kg/m ²	1.02	–
Rectum (C20)[9]	Per 1Kg/m ²	1.02	1.01
Stomach (C16; cardia only)[10]	Per 1Kg/m ²	1.04	1.04
Thyroid (C73)[16]	Per 1Kg/m ²	1.03	1.01

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Table S4 - Proportions cancer subtypes in Brazil, by sex

Cancer site	Source	Fraction (%) of cancer site	
		Men	Women
Breast (postmenopausal)	GLOBOCAN 2012[1]	–	81
Colon	Cancer in Five Continents Volume X[2]	60	60
Rectum	Cancer in Five Continents Volume X[2]	40	40
Esophageal adenocarcinoma	Cancer in Five Continents Volume X[2, 3]	19	22
Esophagus Squamous Cell Carcinoma	Cancer in Five Continents Volume X[2, 3]	81	78
Prostate (advanced stage)	Hospital Cancer Registry of the State of São Paulo[4]	27	–
Stomach cardia	Cancer in Five Continents Volume X[2, 5]	33	19
Stomach non-cardia	Cancer in Five Continents Volume X[2, 5]	67	81

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Table S5 - Proportion and number of cancer cases attributable to plausible reduction in lifestyle risk factors in Brazil in 2012, by exposure, sex, and cancer site

Exposure/ cancer site	Men			Women			Both		
	Number of cases	PIF (%)	Attributable cases	Number of cases	PIF (%)	Attributable cases	Number of cases	PIF (%)	Attributable cases
Smoking									
Larynx	6,281	17.2	1,083	850	14.5	123	7,131	16.9	1,206
Lung	20,229	12.6	2,545	14,041	10.9	1,524	34,270	11.9	4,069
Oral cavity/pharynx	11,901	10.7	1,275	4,653	5.6	260	16,554	9.3	1,535
Esophagus	9,713	3.5	337	3,191	5.0	160	12,904	3.9	497
Bladder	7,033	3.6	251	2,869	2.9	83	9,902	3.4	334
Liver	5,726	3.0	174	3,870	1.9	73	9,596	2.6	247
Pancreas	4,640	2.9	133	5,222	1.8	93	9,862	2.3	226
Stomach	12,606	1.6	196	7,078	1.6	116	19,684	1.6	312
Cervix	-	-	-	18,503	1.2	213	18,503	1.2	213
Colorectum	16,359	0.9	145	17,579	1.0	181	33,938	1.0	326
Kidney	3,611	1.3	46	2,307	0.0	0	5,918	0.8	46
High Body mass index									
Corpus uteri	-	-	-	6,366	5.9	375	6,366	5.9	375
Kidney	3,611	3.8	138	2,307	3.6	83	5,918	3.7	221
Gallbladder	1,456	3.1	45	2,593	3.3	85	4,049	3.2	130
Liver	5,726	2.9	163	3,870	2.8	109	9,596	2.8	272
Colorectum*	16,359	2.3	383	17,579	1.2	206	33,938	1.7	589
Pancreas	4,640	1.8	85	5,222	1.4	74	9,862	1.6	158
Breast	-	-	-	67,307	1.5	994	67,307	1.5	994
Multiple myeloma	1,866	1.6	29	1,642	1.0	16	3,508	1.3	46
Esophagus	9,713	1.3	122	3,191	1.3	40	12,904	1.3	162
Thyroid	2,576	2.3	60	11,210	0.7	78	13,786	1.0	138
Stomach	12,606	1.0	128	7,078	0.6	41	19,684	0.9	169
Ovary	-	-	-	5,745	0.9	49	5,745	0.9	49
Prostate	72,536	0.3	223	-	-	-	72,536	0.3	223
Alcohol consumption									
Oral cavity/pharynx	11,901	3.3	389	4,653	0.9	40	16,554	2.6	429
Esophagus*	9,713	2.0	191	3,191	0.9	27	12,904	1.7	218
Larynx	6,281	1.7	105	850	0.0	0	7,131	1.5	105

Gallbladder	1,456	2.0	30	2,593	0.4	10	4,049	1.0	39
Liver	5,726	0.8	45	3,870	0.6	23	9,596	0.7	67
Colorectum	16,359	0.5	76	17,579	0.0	8	33,938	0.2	84
Breast	-	-	-	67,307	0.1	96	67,307	0.1	96
Pancreas	4,640	0.1	6	5,222	0.0	2	9,862	0.1	8
Lack of Physical activity									
Colorectum*	16,359	3.4	559	17,579	3.7	655	33,938	3.6	1,214
Breast*	-	-	-	67,307	1.7	1,113	67,307	1.7	1,113
Low Fruits and vegetables consumption									
Larynx	6,281	3.1	195	850	2.1	18	7,131	3.0	213
Oral cavity/pharynx	11,901	3.2	379	4653	2.1	99	16,554	2.9	478
Lung	20,229	2.1	417	14,041	1.6	219	34,270	1.9	635
Low dietary calcium consumption									
Colorectum	16,359	0.7	119	17,579	0.6	106	33,938	0.7	225
Low dietary fiber consumption									
Colorectum	16,359	1.6	267	17,579	0.8	139	33,938	1.2	405
Processed meat consumption									
Stomach	12,606	3.5	445	7,078	4.2	295	19,684	3.8	740
Colorectum	16,359	3.7	613	17,579	3.5	611	33,938	3.6	1224
Red meat consumption									
Colorectum	16,359	1.4	221	17,579	1.2	204	33,938	1.3	425
Passive smoking									
Lung	20,229	1.9	375	14,041	1.8	255	34,270	1.8	630

Oral cavity/pharynx	5,510	3.2	176	1,512	0.8	13	7,022	2.7	188
Esophagus*	5,983	2.4	142	1,760	1.1	19	7,743	2.1	162
Larynx	3,780	1.6	62	552	0.0	0	4,332	1.4	61
Gallbladder	233	2.0	5	784	0.4	3	1,017	0.7	7
Liver	4,986	0.8	38	3,761	0.5	21	8,747	0.7	58
Colorectum	8,533	0.5	39	9,112	0.0	4	17,645	0.2	43
Breast	-	-	-	13,587	0.1	17	13,587	0.1	17
Pancreas	4,014	0.1	5	4,201	0.0	1	8,215	0.1	6
Lack of physical activity									
Colorectum	8,533	3.0	258	9,112	3.4	314	17,645	3.2	571
Breast	-	-	-	13,587	1.8	247	13,587	1.8	247
Low fruits and vegetables consumption									
Larynx	3,780	3.1	117	552	2.1	11	4,332	3.0	128
Oral cavity/pharynx	5,510	3.1	173	1512	2.1	32	7,022	2.9	205
Lung	14,246	2.1	292	9,208	1.5	142	23,454	1.9	434
Low dietary calcium consumption									
Colorectum	8,533	0.8	65	9,112	0.7	60	17,645	0.7	125
Low dietary fiber consumption									
Colorectum	8,533	1.6	139	9,112	0.8	76	17,645	1.2	216
Processed meat consumption									
Stomach*	8,708	5.2	453	4,984	5.2	259	13,692	5.2	712
Colorectum	8,533	3.8	321	9,112	3.8	344	17,645	3.8	665
Red meat consumption									
Colorectum	8,533	1.3	115	9,112	1.3	116	17,645	1.3	230
Passive smoking									
Lung	14,246	0.5	67	9,208	0.5	49	23,454	0.5	116

Figure S1 - Proportion and number of all cancer cases attributable to reduction in lifestyle risk factors in Brazil in 2012, by exposure

Figure S2 - Proportion and number of cancer cases and deaths attributable to reduction in lifestyle risk factors in Brazil in 2012, by cancer site

Figure S3 - Proportion and number of total cancer deaths attributable to reduction in lifestyle risk factors in Brazil in 2012, by exposure and sex

8. CONSIDERAÇÕES FINAIS

All scientific work is incomplete - whether it be observational or experimental. All scientific work is liable to be upset or modified by advancing knowledge. That does not confer upon us a freedom to ignore the knowledge we already have, or to postpone the action that it appears to demand at a given time. (Hill, 1965: p. 300).

8.1. EVIDÊNCIAS EPIDEMIOLÓGICAS SOBRE ATIVIDADE FÍSICA E CÂNCER

A investigação do efeito putativo da atividade física na redução do risco do câncer se iniciou, ao que tudo indica, nos idos de 1920. Desde então, cada linha de evidência (Munafò; Davey Smith, 2018) tem oferecido indícios, por vezes, favoráveis à hipótese de causalidade, outras, no entanto, sugerindo efeito nulo ou associações espúrias oriundas de artefatos metodológicos e analíticos que resultaram em viés nos resultados. É a partir desse corpo de evidência, cinza, incompleto, passível de erro e mudança com o avanço do conhecimento que deduzimos causalidade, com maior ou menor confiança, mas nunca como prova definitiva. O desafio da inferência causal está, portanto, em “*to capture some objective truths about the material world in which we live, and any theory of inference should ideally be evaluated by how well it leads us to these truths*” (Rothman et al., 2008, p.22). Diante do exposto, apresento minha avaliação do corpo da evidência sobre atividade física e câncer à luz dos estudos conduzidos nessa pesquisa.

O conjunto de artigos apresentados nessa tese reforça a hipótese de que a atividade física praticada de maneira regular ao longo da vida pode reduzir o risco de alguns tipos de câncer na população. No Capítulo 3, avaliamos a associação entre atividade física e 22 tipos de câncer utilizando resultados de 541 estudos que, em conjunto, analisaram mais de 700 mil casos e mortes por câncer. Para examinar o resultado desses estudos, utilizamos uma miríade de análises e critérios estatísticos aplicados à síntese da evidência e avaliação de incerteza e viés na literatura. Evidências epidemiológicas convincentes de estudos realizados com adultos de meia idade e idosos que sugerem associação causal entre atividade física e redução do risco de câncer de

cólon e de mama pós-menopausa. Esses resultados são semelhantes às conclusões da IARC e da WCRF, que, por sua vez, utilizam critérios próprios para avaliação da evidência (IARC, 2002; WCRF, 2018).

Ainda não é claro, no entanto, se atividade física no início da vida (infância e adolescência) produz semelhante efeito protetor nesses tipos de câncer (cólon e mama). Estudos epidemiológicos que avaliaram essas associações são escassos na literatura. Nossos resultados, no entanto, oferecem algumas perspectivas iniciais relativamente ao câncer de cólon (Capítulo 4). Encontramos menor risco de adenoma colorretal, especialmente adenomas avançados, que apresentam maior probabilidade de progredir para câncer, em mulheres que praticaram ≥ 72 MET-h/semana do que aquelas que praticavam < 21 MET-h/semana. Outro resultado sugestivo foi a associação encontrada entre atividade física ao longo da vida (da adolescência à fase adulta) e o risco de adenomas. Mulheres que se mantiveram fisicamente ativas durante a adolescência e a fase adulta apresentam menor risco de adenomas em comparação àquelas que foram menos fisicamente ativas em um dos, ou em ambos os, períodos.

No tocante ao câncer de mama, resultados de um estudo anterior (também com dados do *Nurses' Health Study II*) sugeriu efeito protetor da atividade realizada em estágios iniciais da vida (Maruti et al., 2008). Mulheres com maior nível de atividade física (≥ 72 MET-h/semana) dos 12 aos 22 anos apresentaram menor risco de câncer de mama pré-menopausa relativamente às mulheres com menor nível de atividade física (< 21 MET-h/semana) no mesmo período. Também se observou menor risco de câncer de mama em mulheres que praticaram mais atividade física (≥ 39 MET-h/semana) dos 12 aos 55 anos em comparação àquelas que praticaram menos atividade física (< 21 MET-h/semana) no mesmo período (Maruti et al., 2008).

Em conjunto, esses resultados sugerem que atividade física no início da vida também pode reduzir o risco de câncer de cólon e mama, atuando, possivelmente, em estágios iniciais da carcinogênese. Esses achados, se confirmados causais, podem fornecer informações úteis sobre a importância de estímulos à prática de atividade física no início da vida para redução do risco de câncer na população.

O efeito protetor da atividade física em outros tipos de câncer (bexiga, endométrio, esôfago, estômago, fígado, glioma, leucemia, linfomas, meningioma, mieloma múltiplo, ovário, pâncreas, próstata, pulmão, reto, rim, tireoide, vesícula biliar) também é possível de ser genuíno. Não obstante, os resultados disponíveis na literatura

epidemiológica são menos consistentes, com possibilidade de resultados falso positivos e indícios de heterogeneidade e viés (Capítulo 3). Estudos de coorte que avaliaram associação entre atividade física e esses tipos de câncer, comparativamente aos cânceres de cólon e mama, são menos frequentes na literatura, além de menores em relação ao tamanho da amostra e número de casos estudados, resultando em menor precisão nas estimativas. Por exemplo, quando adotamos valores mais rígidos de significância estatística ($P < 10^{-3}$) de modo a reduzir a probabilidade de resultados falso positivos e considerar, de alguma maneira, a “precisão espúria” de meta-análises de estudos observacionais (Egger et al., 1998), mantiveram-se apenas as associações entre atividade física e os cânceres de cólon, mama pós-menopausa, endométrio e pulmão.

Avaliar a totalidade da evidência sobre determinada pergunta de pesquisa é essencial para inferência causal. No entanto, encontramos indícios de viés na literatura epidemiológica de alguns tipos de câncer (pulmão, estômago e pâncreas). Evidência de efeito de estudos pequenos e excesso de significância pode ser reflexo de viés na literatura, erro aleatório e/ou heterogeneidade entre os estudos (Sterne et al., 2011). A ocorrência de viés na literatura pode ter diversas causas. Uma explicação possível seria o favorecimento à disseminação e publicação de resultados que sugerem um efeito causal da atividade física na redução do risco do câncer. Diferentes atores envolvidos no processo de produção de conhecimento científico, como pesquisadores, revisores e editores, poderiam influenciar a ocorrência de viés de publicação (Dickersin, 1990).

Consistência nos achados de estudos realizados em diferentes populações e delineamentos metodológicos é desejável para inferir causalidade (Hill, 1965). Entretanto, encontramos evidência de heterogeneidade entre estudos ($I^2 > 50\%$ e intervalos de predição incluindo a nulidade) para a associação entre atividade física e alguns tipos de câncer (pulmão, estômago, bexiga, mieloma múltiplo e ovário). Esses resultados devem ser interpretados com cautela. Evidência estatística de heterogeneidade entre os resultados dos estudos pode ser de ordem clínica/biológica e/ou metodológica (Thompson, 1994; Higgins et al., 2003). Por exemplo, heterogeneidade entre estudos pode ser resultante de uma variação real no efeito da atividade física em câncer, como também de diferentes graus de confundimento, vieses (de informação e seleção), intensidade e variabilidade da exposição, prevalência de modificadores de efeito, ou mesmo ao acaso (Szklo; Nieto, 2014).

8.2. UMA VISÃO INTEGRATIVA SOBRE O ATIVIDADE FÍSICA, ADIPOSIDADE E O RISCO DE CÂNCER

O fato dos estudos epidemiológicos sobre atividade física e diversos tipos de câncer apresentarem resultados pouco consistentes na literatura perpassa, além dos fatores descritos anteriormente, pela complexa interdependência da atividade física, adiposidade e o risco desses cânceres na população. Nesse contexto, a visão integrativa da literatura epidemiológica e dos mecanismos biológicos da doença, proposta por Giovannucci (2018), pode auxiliar no entendimento dessas relações e indicar elementos complementares para interpretação e avaliação da evidência.

Primeiramente, é importante considerar a relação entre atividade física e adiposidade. Essa relação pode ser compreendida considerando, pelo menos, três abordagens metodológicas:

Comparação ecológica da distribuição da atividade física e do IMC entre populações ao longo da experiência humana: Em populações modernas (definidas relativamente aos modos de viver e das atividades cotidianas), o nível de atividade física é baixo e as atividades são realizadas majoritariamente no (pouco) tempo de lazer; as atividades sedentárias e uso de tecnologias são ubíquas; o IMC é uma boa medida populacional de adiposidade e apresenta altos níveis e variabilidade na população. Contrariamente, populações tradicionais apresentam altos níveis de atividade física, realizada majoritariamente nas atividades ocupacionais, de transporte e domésticas; uso de tecnologias e atividades sedentárias estão menos presentes no cotidiano; o IMC é baixo e tem pouca variabilidade. Essas comparações ecológicas sugerem uma relação entre atividade física e IMC na população (Giovannucci, 2018).

Efeito da atividade física na adiposidade entre indivíduos em uma mesma população: Ensaios clínicos randomizados de 6 a 12 meses de duração sugerem que atividade física pode auxiliar na manutenção do peso corporal (Donnelly et al., 2009). Intervenções de longa duração são difíceis de conduzir, mas é plausível que grupos de indivíduos com altos níveis de atividade física ao longo dos anos/décadas ganhem menos peso comparados àqueles com menor nível de atividade física (Giovannucci, 2018).

Efeito da atividade física na redução da gordura visceral: não há evidência consistente sobre o efeito da atividade física na redução do peso corporal (Donnelly et al., 2009). No entanto, a atividade física pode reduzir a gordura visceral, um forte preditor de biomarcadores relacionados ao risco de câncer, outras doenças crônicas não transmissíveis e mortalidade, a despeito da ausência de perda de peso (Verheggen et al., 2016; Giovannucci, 2018).

Diante desses resultados e observações teóricas, é biologicamente plausível inferir que a atividade física poderia reduzir o risco dos tipos de câncer relacionados com adiposidade. Atualmente, IARC e WCRF concluem que há evidências convincentes de que adiposidade está associada com o aumento no risco de pelo menos 13 tipos de câncer: estômago, pâncreas, vesícula biliar, fígado, colorretal, mama após menopausa, ovário, endométrio, próstata (estádio avançado), rim, tireoide, mieloma múltiplo e adenocarcinoma de esôfago (Lauby-Secretan et al., 2016; WCRF, 2018).

A aparente inconsistência de resultados de estudos epidemiológicos sobre atividade física e esses 13 tipos de câncer (exceto cólon e mama pós-menopausa) deve estar relacionada com a distribuição da atividade física e da adiposidade na população. Estudos epidemiológicos sobre atividade física e câncer incluem predominantemente populações modernas. Nesse contexto em que a grande parte da população passa a maior parte do tempo em atividades sedentárias, a atividade física aparenta ser um fator irrelevante, enquanto outros fatores se sobressaem, para explicar a variabilidade do IMC na população. Consequentemente, espera-se que os 13 tipos de câncer estejam mais fortemente associados com o IMC do que com a atividade física. Em populações tradicionais, por outro lado, esses tipos de câncer estariam mais fortemente associados com a atividade física do que com o IMC - devido ao baixo nível e variabilidade do IMC (Giovannucci, 2018).

De fato, essas observações convergem com o conceito de “força de associação de um fator de risco causal” descrito por Rothman (1976) em seu modelo de causas componentes e causas suficientes:

A component cause which requires, to complete the sufficient cause, other components with low prevalence is thereby a “weak” (component) cause. The presence of such a component cause modifies the probability of the outcome only slightly, from zero to an average value just slightly greater than zero, reflecting the rarity of the complementary component cause. On the other hand, a component cause which requires, to complete the sufficient cause, other components which are nearly ubiquitous is a “strong” (component) cause. In epidemiologic terms, a weak cause confers only a small increment in disease risk, whereas a strong cause will increase disease risk substantially (Rothman, 1976, p. 589-590).

Se essas observações estiverem corretas, espera-se que estudos com tamanho de amostra suficientemente grande para capturar alta variabilidade da atividade física entre os indivíduos da população consigam identificar associações com os 13 tipos de câncer. Com efeito, o maior estudo epidemiológico sobre atividade física e câncer conduzido até o momento reuniu 1,44 milhão de participantes e 187 mil casos de câncer de 12 coortes realizadas nos EUA e Europa. Nesse estudo, a atividade física esteve associada com 17 tipos de câncer, dentre os quais, os 13 tipos associados à adiposidade (Moore et al., 2016). As associações entre atividade física e os demais tipos de câncer (pulmão, esôfago, bexiga e cabeça e pescoço) sugeridas nesse estudo, possivelmente, devem-se a confundimento residual por tabagismo, uma vez que a análise restrita a pessoas que nunca fumaram mostrou associação nula (Moore et al., 2016). Apesar dos resultados desse estudo não oferecerem respostas definitivas, o forte padrão encontrado nas associações entre atividade física, IMC e os 13 tipos de câncer reforçam a hipótese de causalidade (Giovannucci, 2018).

Conhecimento sobre mecanismos biológicos que operam nas associações entre atividade física, adiposidade e câncer também pode fornecer informações úteis para essa triangulação de evidências (Lawlor et al., 2016; Munafò; Davey Smith, 2018; Giovannucci, 2018). No capítulo 5, evidenciamos que atividade física está associada com menor concentração de biomarcadores inflamatórios (proteína C-reativa, IL-6, TNF- α R2) e de resposta à insulina (peptídeo C e razão triglicerídeos/lipoproteína de alta densidade) relacionados ao risco de câncer. Comparando grupos extremos de atividade física (≥ 63 MET-h/semana v.s. 0 a 9 MET-h/semana), houve uma diferença relativa de 7% a 32% na concentração desses biomarcadores favorável ao grupo com maior nível de atividade física. Considerando o mesmo volume de atividade física (MET-h/semana),

encontramos uma otimização na diferença relativa da concentração desses biomarcadores em participantes que realizaram atividade física aeróbica e de força combinadas comparativamente aos que realizaram apenas atividade física aeróbica. Não houve benefícios adicionais na concentração desses biomarcadores em participantes que realizaram atividades de intensidade moderada e vigorosa comparativamente àqueles que realizaram apenas atividades moderadas.

Esses resultados corroboram com a hipótese de que a atividade física poderia reduzir os 13 tipos de câncer associados à adiposidade. A concentração desses biomarcadores está fortemente associada à adiposidade, sugerindo, portanto, que ambos - atividade física e obesidade - operam por mecanismos carcinogênicos semelhantes. Em populações modernas, espera-se que esses biomarcadores estejam mais fortemente associados com a adiposidade do que com a atividade física, padrão semelhante ao observado em relação ao risco dos 13 tipos de câncer (Giovannucci, 2018). De fato, encontramos maior diferença nesses biomarcadores quando comparamos grupos com diferentes níveis de IMC (do que atividade física). No entanto, vale ressaltar que as associações entre atividade física e os biomarcadores se mantiveram após ajuste por IMC, sugerindo existência de efeitos (indiretos) independentes da mudança no IMC (ex: gordura visceral).

A integração da evidência de estudos (i) epidemiológicos sobre atividade física, adiposidade e câncer; (ii) sobre padrões epidemiológicos da distribuição da atividade física e da adiposidade ao longo da experiência humana (populações tradicionais v.s. populações modernas); (iii) sobre o efeito da atividade física na adiposidade em indivíduos de uma mesma população; (iv) e sobre mecanismos biológicos envolvidos nas associações entre atividade física, adiposidade e câncer, sugerem que atividade física poderia reduzir o risco de até 13 tipos de câncer na população (Giovannucci, 2018).

8.3. PERSPECTIVAS PARA PREVENÇÃO DO CÂNCER NO BRASIL

Por mais que evidências fortes e convincentes sobre causalidade sejam desejáveis antes de decidirmos influenciar a vida das pessoas e da coletividade, isso não significa, necessariamente, que precisamos “cruzar todos os t’s e responder a todas as

críticas antes de agirmos” (Hill, 1965). Decisões clínicas e em saúde pública precisam ser tomadas.

Com efeito, a epidemiologia tem a missão de informar e auxiliar na tomada de decisão de políticas públicas e intervenções voltadas à melhoria da saúde da população (Galea, 2014). Foi com esse intuito que procuramos traduzir os conhecimentos descritos na literatura sobre o efeito da atividade física na redução do risco de câncer em informações potencialmente úteis para planejamento de intervenções e políticas públicas voltadas à prevenção de câncer no Brasil. Para tal, no capítulo 6, estimamos a preventabilidade de câncer mediante o aumento da atividade física. Consideramos nessas análises que atividade física poderia reduzir apenas o risco do câncer de cólon e de mama pós-menopausa, dado que os resultados para esses tipos de câncer são mais consistentes na literatura e o formato da curva dose-resposta conhecido. A partir dessas informações, e de dados da distribuição da atividade física na população, foi possível estimar a proporção e o número de casos de câncer de mama pós-menopausa e cólon que poderiam ser evitados mediante o aumento do nível de atividade física no Brasil.

Mostramos que o aumento da atividade física pode reduzir até 10 mil casos de câncer por ano (2,4% do total de casos de câncer, excluindo pele não melanoma; 12.3% do câncer de mama pós-menopausa; 6% do câncer de cólon) mediante aumento contrafactual de ≥ 8000 MET-minutos/semana (aproximadamente 5 horas de atividade física de intensidade moderada por dia!). É evidente que em populações modernas esse nível de atividade física é demasiado alto e, portanto, improvável de ser atingido pela maioria da população. De fato, dados da Pesquisa Nacional de Saúde mostram que apenas 6% da população brasileira atinge esse nível de atividade física. Nesse sentido, as análises considerando outros cenários contrafactuais foram úteis para estimar o impacto de aumentos plausíveis no nível de atividade física na prevenção dos casos de câncer. Por exemplo, se toda a população atingisse a recomendação de 150 minutos de atividade física por semana, poderíamos prevenir aproximadamente 2250 casos de câncer por ano. Esses casos correspondem a 1,7% do câncer de mama pós-menopausa e 6% do câncer de cólon. Em geral, outros cenários contrafactuais indicaram um potencial modesto de prevenção da doença, sugerindo, portanto, que altos níveis de atividade física são necessários para obter um impacto maior nos casos de câncer de mama e cólon - possivelmente refletindo a interrelação entre atividade física, adiposidade e risco

de câncer descrita anteriormente (Giovannucci, 2018). Por fim, os resultados apresentados por sexo e unidades federativas permitiu evidenciar populações que potencialmente se beneficiaram mais com o aumento da atividade física. O número de casos de câncer preveníveis em mulheres, por exemplo, foi aproximadamente 5 vezes maior do que em homens. Também encontramos maior preventabilidade de câncer em São Paulo, Rio de Janeiro e Distrito Federal, comparado às demais unidades federativas. É importante ressaltar que estas estimativas consideraram apenas a redução no risco do câncer de cólon e de mama pós-menopausa associada à prática de atividade física em adultos. Portanto, esses resultados podem estar subestimados caso a associação entre atividade física durante a adolescência e a redução no risco de câncer de cólon (Capítulo 4), e a relação entre atividade física e outros tipos de câncer, se confirmarem causais.

Comparada a outros fatores de risco relacionados ao estilo de vida (tabagismo, consumo de álcool, alimentação não saudável, excesso de peso/obesidade), a atividade física apresenta um menor preventabilidade de câncer. A eliminação do tabagismo (15% da população brasileira é fumante atualmente), por exemplo, poderia evitar 67 mil casos por ano no Brasil (15% do total de casos de câncer diagnosticados, excluindo pele não melanoma), equivalente a 6 vezes o número de casos que poderiam ser evitados mediante o aumento da atividade física (≥ 8000 MET-minutos/semana). Outros fatores como alimentação não saudável, IMC alto e consumo de álcool também se mostraram mais importantes para prevenção de câncer. Esses resultados são importantes na medida em que recursos direcionados ao controle do câncer são finitos, e prioridades precisam ser estabelecidas.

Não obstante, parece-me que a maneira mais realista e efetiva de controle do câncer no nosso país perpassa, inevitavelmente, pela priorização e incentivo da prevenção primária, de modo que a redução de todos fatores listados acima, indica ser o caminho mais próspero. No capítulo 7, estimamos que, aproximadamente, 27% dos casos de câncer e um terço das mortes por câncer poderiam ser evitados por ano mediante a eliminação desses fatores de risco no Brasil. Esses resultados são expressivos dado que outras formas de prevenção/ detecção precoce do câncer, como algumas estratégias de rastreamento, apresentam efeito limitado (Gøtzsche, 2015). É improvável, no entanto, que consigamos prevenir um número significativo de casos e mortes por câncer com estratégias de prevenção primária voltadas exclusivamente aos indivíduos, ao invés de populações. O enfrentamento dos determinantes sociais da saúde

- condições sociais em que indivíduos nascem, crescem, trabalham e envelhecem - é imperativo nesse sentido (Vineis; Wild, 2014). No tocante à atividade física, por exemplo, mudanças no ambiente construído de cidades (calçadas, ciclovias e parques), escolas, e locais de trabalho podem aumentar as oportunidades de realização de atividades físicas no cotidiano de maneira sustentável, segura, conveniente e prazerosa (Rezende; Rey-López, 2015).

8.4. UMA VISÃO OTIMISTA PARA O DESAFIO DO CONTROLE DO CÂNCER

Parafraseando Richard Doll (1994): “*Death (from cancer) in old age is inevitable, but before old age is not*”. É evitável, pois décadas de pesquisas propiciaram conhecer as causas do câncer na população – ao que tudo indica, a falta de atividade física parece ser uma delas. Nesse contexto, sem dúvida alguma, a epidemiologia exerceu um papel de protagonismo. Há certamente outras causas, ainda não identificadas, e quantificações de efeitos causais incorretas, que precisam ser corrigidas. O mundo continuará se transformando, as sociedades mudarão seus modos de viver, e novas ameaças colocarão em risco a saúde da população. Por essas razões, a epidemiologia continuará sendo necessária. No entanto, temos a possibilidade de utilizar as informações obtidas até o momento para tomar decisões baseadas em evidência e propor ações que reduzam o risco de câncer na população. O Estado, instituições acadêmicas e a sociedade civil, indústria, mídia, cientistas, profissionais de saúde e diversos outros atores devem fazer parte da solução. O desafio é enorme, mas nunca estivemos tão preparados.

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APÊNDICE A

Fração atribuível populacional: planejamento de ações de prevenção de doenças no Brasil

Comentário publicado na Revista de Saúde Pública em 2016, volume 50, páginas 1-6. Acesso disponível em <http://www.ncbi.nlm.nih.gov/pubmed/27305404>.

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RESUMO

Epidemiologia é o estudo da ocorrência, distribuição e determinantes de eventos relacionados à saúde da população, incluindo a aplicação desse conhecimento para a prevenção e o controle dos problemas de saúde. Entretanto, estudos epidemiológicos, na maioria das vezes, têm limitado suas perguntas de pesquisa aos fatores determinantes de desfechos em saúde. Pesquisas relacionadas à aplicação do conhecimento para ações de prevenção e controle de doenças têm sido negligenciadas. Nesse comentário, apresentamos uma descrição de como as estimativas de fração atribuível populacional podem fornecer importantes elementos para planejamento de ações de prevenção e controle de doenças no Brasil.

Palavras-chave: Epidemiologia. Prevenção & Controle. Risco Atribuível. Medidas de Associação, Exposição, Risco ou Desfecho. Avaliação de Resultado de Ações Preventivas.

INTRODUÇÃO

Epidemiologia é o estudo da ocorrência e distribuição de eventos relacionados à saúde da população, incluindo seus determinantes, e a aplicação desse conhecimento para a prevenção e o controle dos problemas de saúde (Porta, 2008). Em outras palavras, a epidemiologia tem 2 ações centrais: 1) identificar as causas dos eventos relacionados à saúde; 2) promover, proteger e restaurar a saúde da população (Galea, 2013). Um dos mais claros exemplos dessa dupla ação da epidemiologia ficara evidente no combate à cólera em Londres. Em 1849, John Snow, ao mapear os casos de cólera em Londres, identificou que a incidência da doença estava relacionada com a distribuição de água, contrariando a teoria dos miasmas, então predominante na época. Em um segundo momento, John Snow esteve envolvido diretamente nas ações de prevenção e controle da cólera, inclusive na remoção da *Broad Street pump* (Galea, 2013; Snow, 1986). Recentemente, essa transferência do conhecimento oriundo de estudos epidemiológicos para o planejamento de políticas e ações de prevenção populacional de doenças tem recebido o nome de “epidemiologia translacional” (Khoury et al., 2010).

Depois de Snow, muitos outros exemplos ao longo da história conseguiram preencher a lacuna entre o saber e o fazer (Galea, 2013). Entretanto, na história recente, a segunda ação da epidemiologia tem sido negligenciada. Desde o início da chamada “Epidemiologia Moderna”, epidemiologistas têm focado suas ações, quase que de forma obsessiva, em encontrar relações causais, utilizando para isso os métodos epidemiológicos (Galea, 2013). É compreensível que o campo tenha tomado tal caminho no passado, pois pouco se conhecia sobre os fatores determinantes das doenças na população, e obviamente, não se pode combater o que não se conhece. Entretanto, mesmo após a identificação desses determinantes, não se tem percebido o mesmo engajamento com a segunda ação relacionada à epidemiologia – aplicação do conhecimento para ações de prevenção e controle de doenças (Fine, 2013).

A dupla ação da epidemiologia está presente nas medidas de associação utilizadas em estudos populacionais. As medidas de associação utilizadas para estimar o real efeito da exposição na ocorrência da doença (teórico) (Rothman et al., 2008) são de dois tipos: 1) diferença relativa ou razão da incidência da doença entre expostos e não

expostos ao fator; 2) diferença absoluta da incidência da doença entre expostos e não expostos ao fator. As medidas de associação baseadas em diferenças relativas ou razões dão uma ideia de força de associação, e estão predominantemente presentes em estudos etiológicos, em que o objetivo principal é investigar as causas de desfechos relacionados à saúde. Já as medidas de associação baseadas em diferenças absolutas trazem uma perspectiva de estratégias de prevenção populacional ou impacto em saúde pública, uma vez que informam o excesso do risco da doença associado à exposição. Para uma maior compreensão das medidas de associação utilizadas em estudos epidemiológicos, uma vasta e detalhada literatura encontra-se disponível em livros texto de epidemiologia (Rothman et al., 2008; Gordis, 2014; Szklo; Nieto, 2014).

Para ilustrar a predominância de estudos etiológicos em epidemiologia, realizamos uma busca no Medline no dia 15/06/2015, sem limite de data, utilizando como descritores as medidas de associação baseadas em diferenças relativas e absolutas (material suplementar 1). No mundo, encontramos 268.750 registros de artigos baseados em diferenças relativas e somente 4.784 registros de artigos sobre diferenças absolutas. No Brasil, encontramos 4.352 registros de artigos sobre diferenças relativas e apenas 82 sobre diferenças absolutas. Vale ressaltar que, possivelmente, parte dos documentos (artigos, relatórios, livros e outras produções) que utilizam medidas de associação baseadas em diferenças absolutas esteja na literatura cinza. Entretanto, é improvável que a grande predominância encontrada em prol das medidas de associação de diferenças relativas seja muito menor quando considerada a literatura cinza.

Nesse contexto, apresentamos nesse comentário uma breve descrição de como as estimativas de fração atribuível populacional (FAP) podem ser calculadas a fim de fornecer importantes elementos para planejamento de ações de prevenção e controle de doenças no Brasil, possibilitando aproximar epidemiologistas do serviço de saúde e, consequentemente, de uma epidemiologia translacional.

ESTIMATIVAS DE FRAÇÃO ATRIBUÍVEL POPULACIONAL

A FAP, baseada em diferenças absolutas, estima a proporção da doença ou evento relacionado à saúde que seria prevenido na população caso o fator de risco fosse eliminado. Para tanto, a FAP fornece uma perspectiva de ações de prevenção da doença

considerando o risco da doença em indivíduos expostos e a prevalência da exposição na população. Nesse sentido, uma alta magnitude do risco da doença em indivíduos expostos, medida baseada em diferença relativa ou razão, pode ter um baixo impacto populacional se os fatores de risco a ela associados forem raros, ao passo que baixos riscos poderão refletir em um grande impacto em saúde pública quando as exposições forem frequentes. Esse conceito remete à celebre frase de Geoffrey Rose: “*A large number of people at small risk may give rise to more cases of disease than a small number of people at high risk*” (Rose, 1985). Nesse sentido, assim como as demais medidas de associação baseadas em diferenças absolutas, a FAP fornece importantes informações sobre o potencial impacto de programas de prevenção e intervenções em saúde pública, sendo extremamente útil para políticos, gestores e tomadores de decisão (Rockhill et al., 1998; Steenland; Armstrong, 2006; Darrow, 2014).

A FAP, em geral, é estimada em estudos de coorte, em que indivíduos expostos e não expostos ao fator de risco são acompanhados ao longo do tempo, permitindo medir a incidência do desfecho em ambos os grupos. A FAP pode ser estimada a partir da equação (Levin, 1953; 1978):

$$FAP = \frac{(I_{pop} - I_o)}{I_{pop}} \quad (1)$$

Em que I_{pop} é a incidência da doença em toda população, e I_o é a incidência da doença no grupo não exposto.

Entretanto, no Brasil, ainda são incipientes/inexistentes os estudos de coorte que permitem a mensuração da FAP, mas existem algumas equações que permitem estimá-la por meio de dados secundários disponíveis.

Em 1953, Morton Levin, mostrou que a equação 1 é uma função do risco relativo e da frequência do fator de risco na população. Portanto, a FAP também poderia ser estimada por meio da seguinte equação (Levin, 1953; 1978):

$$FAP = \frac{P_e(RR - 1)}{1 + P_e(RR - 1)} \quad (2)$$

Em que P_e é a prevalência da exposição na população e RR é o risco relativo.

Assim, seria possível estimar a FAP através de dados epidemiológicos sobre a prevalência da exposição no Brasil, e o risco relativo da doença para a exposição de interesse. Diversos inquéritos representativos da população do Brasil disponibilizam informações de prevalência de fatores de risco e proteção, permitindo inclusive a estratificação pelas cinco grandes regiões do país, unidades da federação, capitais e não capitais. São exemplos de inquéritos nacionais: Pesquisa de Orçamento Familiar (IBGE, 2010), Sistema de Vigilância de Fatores de Risco e Proteção para Doenças Crônicas por Inquérito Telefônico (Brasil, 2014), Pesquisa Nacional de Saúde do Escolar (BRASIL, 2013) e Pesquisa Nacional de Saúde (Szwarcwald, 2014).

Em relação ao risco relativo, idealmente, esses deveriam ser obtidos de estudos longitudinais com baixo risco de erros sistemáticos e confundimento. Além disso, estimativas de *odds ratio* de estudos caso-controle também têm sido utilizadas para estimar FAP (Levin, 1953; 1978). Essas medidas de associação deveriam ser oriundas de estudos que tivessem a mesma população alvo para a qual as estimativas de FAP seriam calculadas. Entretanto, com frequência, esses estudos não estão presentes em países de baixa e média renda, incluindo o Brasil. Portanto, na prática, utilizam-se estimativas disponíveis em revisões sistemáticas com meta-análise, além de estudos de coorte internacionais bem conduzidos. Essa “portabilidade” do RR oriundo de outra população alvo assume alguns pressupostos (Steenland; Armstrong, 2006): 1) exposição medida nas coortes e 2) latência da doença são similares à da população onde a FAP será estimada; 3) ausência de modificação de efeito.

A limitação inerente à equação 2 é a necessidade da utilização do RR bruto. Entretanto, na maioria das vezes, associações medidas em estudos epidemiológicos são acometidas por confundimento, e estratégias para ajuste são incorporadas. Quando estimativas de RR ajustadas são utilizadas na equação 2, ocorre um viés na medida de FAP. Na presença de confundimento positivo (RR bruto $>$ RR ajustado) a FAP será subestimada, ao passo que para confundimento negativo (RR bruto $<$ RR ajustado) a FAP será superestimada. O viés da FAP dependerá então da magnitude do confundimento (quanto maior a magnitude, maior o viés), da prevalência da variável de confusão (menor prevalência, maior o viés) e da força de associação entre exposição e desfecho (quanto menor a magnitude de associação, maior o viés) (Darrow; Steenland, 2011).

Na presença de confundimento, recomenda-se a utilização da seguinte equação:¹⁹

$$FAP = \frac{P_c (RR_{adj} - 1)}{(RR_{adj})} \quad (3)$$

Em que P_c é a prevalência da exposição entre os casos da doença e o RR_{adj} é o risco relativo ajustado por variáveis de confusão.

Sendo assim, para obter a P_c faz-se necessário medir a prevalência do fator de risco em subgrupos populacionais, ou pelo menos considerar a variação possível da exposição nesse subgrupo. Uma forma de obtê-la é medir a razão da prevalência da exposição entre a população de casos e a população geral, reportada nos estudos de coorte. Conhecendo a diferença relativa da prevalência da exposição entre casos da doença e a população geral, poder-se-á aplicar esse fator de correção sobre a prevalência da exposição na população geral, a fim de se obter a prevalência da exposição entre os casos da doença. Por exemplo, a exposição à inatividade física entre casos de câncer de cólon é 1,22 vezes a da população geral (Lee et al., 2012). Dessa forma, se a prevalência de inatividade física no Brasil é de aproximadamente 20%, estima-se que a prevalência de inatividade física entre os casos de câncer de cólon no Brasil seja de 24,4%.

Quando os dados de exposição estão disponíveis de forma contínua (ex: grama/dia) e os valores de risco relativo por unidade de aumento na exposição (RR_{dose}), utiliza-se a seguinte fórmula para obter a FAP:

$$FAP = \frac{R - 1}{R} \quad (4)$$

Em que $R = \exp[\ln(RR_{dose}) \times \bar{x}]$

RR_{dose} = risco relativo da doença por unidade de aumento da exposição.

$\bar{x}$ = media da exposição na população alvo.

Essa equação assume uma relação log-linear entre exposição e desfecho (Boffetta et al., 2009).

Essas medidas de impacto em saúde pública têm sido utilizadas por diversas organizações ao redor do mundo a fim de priorizar intervenções, determinar metas e iniciar políticas públicas. São exemplos disso: a Organização Mundial da Saúde, que por meio do *Global Burden of Disease study*, fornece informações dos principais fatores de risco modificáveis para doenças e agravos, utilizadas, inclusive, para determinação das metas de redução de doenças crônicas não transmissíveis para 2025 (WHO, 2014). Na América, desde 2009, a Organização Pan-americana de Saúde, a partir da publicação das estimativas de mortes atribuíveis ao consumo de sódio (PAHO, 2013), apoia um Grupo Consultivo Técnico que visa mobilizar políticas e intervenções para redução do consumo de sal. Nos Estados Unidos, o *Centers for Disease Control and Prevention* (CDC) fornece informações de anos de vida perdidos, anos de vida perdidos ajustado por incapacidade, e custos econômicos atribuíveis a alguns fatores de risco (por exemplo, o tabagismo) (CDC, 2005).

Para exemplificar a utilização das estimativas no Brasil, calculamos a FAP de mortalidade por doença cardiovascular associada à baixa ingestão de hortaliças. Segundo dados da Pesquisa de Orçamento Familiar realizada em 2008, a disponibilidade média de hortaliças nos domicílios brasileiros foi de 74,2 gramas per capita por dia (IBGE, 2010). A recomendação mínima de ingestão de frutas e hortaliças é de 400g/dia, que podem ser distribuídos em 240g de hortaliças e 160g de frutas. Uma recente meta-análise encontrou uma associação inversa entre o consumo de hortaliças e mortalidade por doenças cardiovasculares (HR 0,96 para cada porção de hortaliças/dia, equivalente a 77g/dia) (Wang et al., 2014). Utilizando a equação 4, estimamos que aproximadamente 9,6% dos casos de mortes por doenças cardiovasculares seriam evitados se a recomendação mínima diária de hortaliças fosse atingida no Brasil.

Para uma maior compreensão sobre estimativas de FAP, uma vasta literatura pode ser consultada a fim de obter maiores detalhes sobre as diferentes equações, limitações, pontos fortes e perspectivas do método (Greenland; Robins, 1988; Rockhill, 1998; Benichou, 2001; Steenland; Armstrong, 2006; Darrow; Steenland, 2011; Darrow, 2014). A partir disso, é possível compreender algumas medidas de impacto em saúde pública derivadas da FAP como: anos de vida perdidos, anos de vida perdidos por incapacidade e anos de vida ajustado por incapacidade (Steenland; Armstrong, 2006).

Também é possível obter subsídios para estimar intervalos de confiança da FAP, por meio do cálculo da variância da FAP ou mesmo por simulações de Monte Carlo (Steenland; Armstrong, 2006).

CONCLUSÃO

O objetivo desse comentário foi debater as possibilidades de utilização das estimativas de FAP por epidemiologistas no Brasil, e a sua importância para o planejamento de políticas e ações de prevenção de doenças. Entendemos que epidemiologistas têm um papel fundamental nessas ações, muitas vezes negligenciadas, e que através da utilização de dados secundários disponíveis, as estimativas de FAP configuram-se como uma importante via de aproximação e trabalho entre epidemiologistas e os serviços de saúde.

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