Dose Finding in Physical Activity and Cancer Risk Reduction

Anne McTiernan, MD, PhD[1]

The 2018 US Physical Activity Guidelines Advisory Committee found strong grade evidence that physical activity is associated with reduced risk for bladder, breast, colon, endometrial, renal, and gastric cancers and esophageal adenocarcinoma.[1,2] Risk reductions ranged from approximately 10% to 20%. Reduction in risk of other cancers was also seen, but with lower grades of evidence. The US guidelines of 150 to 300 minutes per week of moderate aerobic exercise (or equivalent energy expenditure with vigorous activity) therefore included cancer risk reduction as a likely outcome of this dose of exercise.[3] Yet the committee recognized the difficulty in determining cancer risk reductions of specific types, amounts, frequencies, and intensities of exercise. It further noted that given the inconsistent methods of measuring and categorizing physical activity levels in epidemiologic studies, it was not possible to determine exact levels of physical activity that provide given levels of effect. The question remains: how much exercise provides how much benefit in reducing risk for specific cancers?

In the article that accompanies this editorial, Matthews and colleagues[4] go a long way toward answering this question. In a well-designed and conducted study, the authors pooled individual patient data from nine prospective cohort studies that had collected data on leisure-time physical activity and followed participants to determine incidence of specific cancers. They categorized exercise levels as metabolic equivalent task (MET) hours, where METs are used to specify intensity such as light intensity (1.6 to 2.9 METs), moderate intensity (3 to 5.9 METs), and vigorous intensity (more than 6.0 METs) activities.[5] Amounts of total physical activity were then calculated as MET-hours/week by multiplying individual exercise METs by hours per week engaged in that exercise and summing over all types of exercise. After harmonizing data across the studies, the authors determined associations between several levels of amount and intensity of exercise with cancer risk, specifically 7.5, 15, 22.5, and 30 MET-hours/week. With more than 50,000 incident cases of cancer accrued across a median 10 years of follow-up, the authors reported that engaging in the US guidelines recommended levels of exercise (7.5 to 15 MET-hours/week or approximately 150 to 300 minutes/week of moderate intensity exercise) was associated with reduced risks of seven cancers: colon (in men) and breast, endometrial, kidney, myeloma, liver, and non-Hodgkin lymphoma (in women).

With a series of illustrative graphs, the authors depict the shape of dose-response curves of physical activity level and specific cancers. For several cancers, there were clear linear dose-response trends of increasing risk reduction with increasing amount of activity: breast, colon (in men), endometrial, and head and neck cancers and esophageal adenocarcinoma. For these cancers, engaging in more physical activity than recommended by the US guidelines produced greater protection. For other cancers, including kidney, gastric, liver, and non-Hodgkin lymphoma in women, risk reduction plateaued at higher levels of activity.

In a subset of five cohorts, the authors then assessed the effects of moderate versus vigorous activity on the risk of specific cancers. They found that moderate-intensity activity was associated with reduced risks for breast and kidney cancer, and vigorous activity was associated with reduced risk for endometrial cancer. Risk for colon cancer was reduced with either intensity of activity. There was, however, some evidence of attenuation of benefit from vigorous activity on colon and endometrial cancer risks at the highest levels of vigorous activity.

The study also presents data separately for women and men, which is important because physical activity may have different effects on cancer biology depending on sex, and because women and men typically engage in different amounts and levels of exercise.[6] Although the effects were greater for men than women for colon cancer and were seen in women but not men for non-Hodgkin lymphoma, recommended levels of physical activity reduced cancer risk in both women and men. Furthermore, dose-response relationships were seen in both women and men.

There were some limitations to the study. All physical activity was self-reported; national data suggest that self-report may significantly overestimate levels of physical activity compared with objective measurement.[6] This reduces the ability to prescribe specific doses of exercise to produce given levels of risk reduction. However, it does not invalidate the findings that for reducing risk for most types of cancer, exercising for longer amounts of time at moderate intensity or greater produces larger effects.

ASSOCIATED CONTENT

See accompanying article on page 686

Author affiliations and support information (if applicable) appear at the end of this article.

Accepted on December 4, 2019 and published at ascopubs.org/journal/jco on January 17, 2020: DOI https://doi.org/10.1200/JCO.19.03172

Disclaimers: A.M. was a member of the 2008 and 2018 US Physical Activity Guidelines Advisory Committees. She also serves as an expert witness and consultant in litigation on use of talcum powder products and risk of ovarian cancer.

The cohorts were largely composed of white individuals, and no data were presented for specific race/ethnic groups. Future epidemiologic studies are needed that focus on people from black, Latin, Asian American, and Native American populations because their exercise levels may differ from those of whites and because the effects of exercise on cancer risk could be unique to individual race/ethnic populations.

Matthews et al[4] limited their investigation of dose-response to 15 cancers they previously found to be associated with leisure-time physical activity.[7] Furthermore, because all of the source studies were prospective cohorts, only the more common cancers accrued in sufficient numbers to have power to detect hypothesized associations. Therefore, data are missing on some of the rarer cancers. Case-control studies of these rare cancers could fill this gap, particularly with data pooled across multiple studies to increase power to detect risk reductions of 10% to 20%. Data also were not provided for lung cancer because of concerns about residual confounding effects of smoking. Nevertheless, the Matthews et al report included data for 15 cancers, which account for a large proportion of cancer cases in the United States.[8]

There are more than 100 types of cancer when it is classified according to tissue and cell of origin, but molecular subtyping has identified multiple classifications of cancers that can differ by etiology, prognosis, and treatment response. Few studies have had large enough sample sizes to address the effects of physical activity by molecular subtypes, although Matthews et al differentiated effects for some cancers by histology (eg, esophageal adenocarcinoma).

The source cohorts included in the article by Matthews et al[4] ascertained physical activity using a variety of questionnaire types with different classifications of exercise modality, and almost all questions focused on aerobic activities. Therefore, the harmonized, pooled data reports only on the aerobic activity part of the US Guidelines. Still missing from the body of knowledge is whether strength training is associated with cancer risk, and if so, what types, frequency, or duration provide optimal benefit.

In the absence of randomized controlled clinical trials to test the effects of different types and doses of physical activity on incidence for specific cancers,[9] epidemiologic data can provide important information. Identifying the biologic mechanisms linking exercise to cancer risk supports the observed associations. Several cancers are obesity-related (such as colon, endometrial, kidney, and postmenopausal breast cancer and esophageal adenocarcinoma).[10] The role of physical activity in reducing adiposity can therefore represent one mechanism.[11] Physical activity alone has modest effects on obesity, however, so obesity control is unlikely to be the sole mechanism linking exercise to cancer risk.[11] Randomized trials of mechanistic effects in humans have shown that exercise alters hormones, angiogenesis, oxidative stress, cell proliferation, and other cancer biomarkers that further support the link between exercise and cancer risk reduction.[12-16] Animal models provide additional evidence of exercise effects on reducing tumor initiation.[17] However, the literature on mechanistic studies of exercise and cancer risk is limited, and concerted efforts are needed to identify pathways through which exercise affects cancer risk. This will aid in establishing physical activity as a prevention treatment, as well as determining dose of physical activity needed to change intermediate markers or biomarkers of cancer risk.

Evaluation of any preventive agent requires assessment of risks and benefits. Some recreational physical activities and sports may increase some health risks, although overall benefits are thought to outweigh risks.[2] The culture or setting of some sports and physical activities may also increase exposure to cancer-causing agents. Examples include unprotected sun exposure,[7,18] talcum powder products,[19] air pollution,[20] smokeless tobacco,[21] muscle-building products,[22] synthetic turf materials,[23] and alcohol.[21] Individuals should avoid these potential carcinogens as much as possible; there are few data on whether physical activity can attenuate the effects of carcinogens on risk for specific cancers.

Although questions remain about the exact types, frequency, and intensity of physical activity that provide greatest risk reduction, Matthews et al provide strong evidence that the current US recommended levels of aerobic physical activity provide cancer protection in a dose-dependent manner. Clinicians can feel confident in advising patients to follow the guidelines, and aim to increase to the maximum levels recommended, as their health and life circumstances allow.

AFFILIATION

[1]Fred Hutchinson Cancer Research Center, Epidemiology Program, Division of Public Health Sciences, Seattle, WA

CORRESPONDING AUTHOR

Anne McTiernan, MD, PhD, Fred Hutchinson Cancer Research Center, Epidemiology Program, Division of Public Health Sciences, 1100 Fairview Ave N, Seattle, WA 98109; e-mail: amctiern@fhcrc.org.

AUTHOR'S DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST AND DATA AVAILABILITY STATEMENT

Disclosures provided by the author and data availability statement (if applicable) are available with this article at DOI https://doi.org/10.1200/JCO.19.03172.

ACKNOWLEDGMENT

Supported by Grants No. BCRF-19-107 from the Breast Cancer Research Foundation and CA20920 from the National Cancer Institute.

REFERENCES

1. McTiernan A, Friedenreich CM, Katzmarzyk PT, et al: Physical activity in cancer prevention and survival: A systematic review. Med Sci Sports Exerc 51: 1252-1261, 2019
2. Office of Disease Prevention and Health Promotion: 2018 Physical Activity Guidelines Advisory Committee Scientific Report. https://health.gov/paguidelines/second-edition/report/
3. Piercy KL, Troiano RP, Ballard RM, et al: The physical activity guidelines for Americans. JAMA 320:2020-2028, 2018
4. Matthews CE, Moore SC, Arem H, et al: Amount and intensity of leisure-time physical activity and lower cancer risk. J Clin Oncol 38:686-697, 2020
5. Ainsworth BE, Haskell WL, Herrmann SD, et al: 2011 compendium of physical activities: A second update of codes and MET values. Med Sci Sports Exerc 43: 1575-1581, 2011
6. Troiano RP, Berrigan D, Dodd KW, et al: Physical activity in the United States measured by accelerometer. Med Sci Sports Exerc 40:181-188, 2008
7. Moore SC, Lee IM, Weiderpass E, et al: Association of leisure-time physical activity with risk of 26 types of cancer in 1.44 million adults. JAMA Intern Med 176: 816-825, 2016
8. Siegel RL, Miller KD, Jemal A: Cancer statistics, 2019. CA Cancer J Clin 69:7-34, 2019
9. Ballard-Barbash R, Hunsberger S, Alciati MH, et al: Physical activity, weight control, and breast cancer risk and survival: Clinical trial rationale and design considerations. J Natl Cancer Inst 101:630-643, 2009
10. Renehan AG, Tyson M, Egger M, et al: Body-mass index and incidence of cancer: A systematic review and meta-analysis of prospective observational studies. Lancet 371:569-578, 2008
11. Jakicic JM, Powell KE, Campbell WW, et al: Physical activity and the prevention of weight gain in adults: A systematic review. Med Sci Sports Exerc 51: 1262-1269, 2019
12. de Roon M, May AM, McTiernan A, et al: Effect of exercise and/or reduced calorie dietary interventions on breast cancer-related endogenous sex hormones in healthy postmenopausal women. Breast Cancer Res 20:81, 2018
13. Duggan C, Tapsoba JD, Wang CY, et al: Dietary weight loss and exercise effects on serum biomarkers of angiogenesis in overweight postmenopausal women: A randomized controlled trial. Cancer Res 76:4226-4235, 2016
14. Campbell PT, Gross MD, Potter JD, et al: Effect of exercise on oxidative stress: A 12-month randomized, controlled trial. Med Sci Sports Exerc 42:1448-1453, 2010
15. Fedewa MV, Hathaway ED, Ward-Ritacco CL: Effect of exercise training on C reactive protein: A systematic review and meta-analysis of randomised and non-randomised controlled trials. Br J Sports Med 51:670-676, 2017
16. McTiernan A: Mechanisms linking physical activity with cancer. Nat Rev Cancer 8:205-211, 2008
17. Ashcraft KA, Peace RM, Betof AS, et al: Efficacy and mechanisms of aerobic exercise on cancer initiation, progression, and metastasis: A critical systematic review of in vivo preclinical data. Cancer Res 76:4032-4050, 2016
18. Grossman DC, Curry SJ, Owens DK, et al: Behavioral counseling to prevent skin cancer: US Preventive Services Task Force Recommendation Statement. JAMA 319:1134-1142, 2018
19. Ramsey ML: Athlete's foot: Clinical update. Phys Sportsmed 17:78-93, 1989
20. Tainio M, de Nazelle AJ, Götschi T, et al: Can air pollution negate the health benefits of cycling and walking? Prev Med 87:233-236, 2016
21. Diehl K, Thiel A, Zipfel S, et al: How healthy is the behavior of young athletes? A systematic literature review and meta-analyses. J Sports Sci Med 11:201-220, 2012
22. Li N, Hauser R, Holford T, et al: Muscle-building supplement use and increased risk of testicular germ cell cancer in men from Connecticut and Massachusetts. Br J Cancer 112:1247-1250, 2015
23. Perkins AN, Inayat-Hussain SH, Deziel NC, et al: Evaluation of potential carcinogenicity of organic chemicals in synthetic turf crumb rubber. Environ Res 169: 163-172, 2019

AUTHOR'S DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Dose Finding in Physical Activity and Cancer Risk Reduction

The following represents disclosure information provided by the author of this manuscript. All relationships are considered compensated unless otherwise noted. Relationships are self-held unless noted. I = Immediate Family Member, Inst = My Institution. Relationships may not relate to the subject matter of this manuscript. For more information about ASCO's conflict of interest policy, please refer to www.asco.org/rwc or ascopubs.org/journal/jco/site/ifc.

Open Payments is a public database containing information reported by companies about payments made to US-licensed physicians (Open Payments).

No potential conflicts of interest were reported.