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Physical Activity and Digestive System Cancer Risk
Still Chasing the Promise

Heather Greenlee, ND, PhD

The promise of health behaviors to prevent cancer was established in the landmark 1981 publication by Doll and Peto,[1] who estimated that 30% of cancer deaths were attributable to lifestyle and environmental factors. Though Doll and Peto did not address physical activity or exercise, shortly thereafter, in 1984, another landmark publication by Garabrant et al[2] established physical activity as a potential major factor related to colon cancer risk. In that study, the authors observed that men diagnosed with colon cancer were more likely than noncancer controls to have occupations requiring low levels of physical activity. Numerous subsequent observational studies and, more recently, randomized controlled trials have interrogated the role of physical activity and other lifestyle behaviors as risk factors related to a range of cancers.[3,4]

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The relationship between physical activity and digestive system cancers has been of particular interest because physical activity may affect the functioning of the whole gastrointestinal tract. These include local effects, such as diluting potentially carcinogenic bile acids and decreasing intestinal transit time, thereby limiting the time potential carcinogens are in contact with the gut.[5] Physical activity may also have systemic effects, such as increasing immune function and decreasing inflammation, insulin resistance, and circulating sex hormones,[5,6] which have been linked to carcinogenesis. But which of these mechanisms is the key factor to preventing digestive system cancers, or the combinations that are the most important, is not known.

In 2002, the American Cancer Society set guidelines on physical activity for cancer prevention,[7] as did the World Cancer Research Fund and the American Institute for Cancer Research in 2007.[3] These guidelines have been updated since,[4] and the current recommendations translate roughly into 10 metabolic equivalent task (MET)-hours per week, which is the equivalent to walking at an average pace for approximately 3.3 hours per week.

These recommendations have brought attention to the link between physical activity and cancer risk. However, the recommendations themselves are not finely detailed, and questions remain about the type, dose, duration, and intensity of physical activity needed to meaningfully affect risk of specific cancers. Studies suggest that colon, breast, and endometrial cancers may be the most affected by physical activity.[3] However, it has been difficult or impossible to compare the relative risks associated with physical activity for cancers at different anatomical sites because each study uses different populations and methods of ascertaining exposures and outcomes.

In this issue of *JAMA Oncology*, Keum et al[8] report on physical activity and digestive system cancer risk using data from more than 43 000 men who participated in the Health Professionals Study over a period of more than 26 years. They estimated the association between total physical activity as measured by self-reported leisure time activities and all cancers of the digestive system. The findings are provocative. For all digestive system cancers, they estimated a 26% reduction in risk (HR, 0.74; 95% CI, 0.59-0.93), comparing their high total physical activity group (≥63 MET-hours/wk or 21 hours/wk of walking at an average pace [average of 3 hours/d]) vs the reference group of 8.9 MET-hours/wk or less (≤126 min/wk of walking at an average pace [average of 18 min/d]).

In analyses stratified by location in the digestive system, the results were especially pronounced in the upper (mouth and pharynx to small intestine) and lower (colon and rectum) regions of the digestive tract, with no associations observed for cancers of the digestive accessory organs (pancreas, liver, gallbladder). The association between physical activity and upper digestive tract cancers was independent of body mass index (BMI) and history of diabetes, among a host of other confounders. The association with colorectal cancer, however, was not statistically significant after adjustment for BMI and diabetes. There was no added benefit of weight lifting (the only form of strength training exercise assessed) in addition to aerobic physical activity (eg, walking, jogging, running) on overall digestive system cancer risk.

The intensity of physical activity did not affect digestive system cancer risk, as long as a certain number of MET-hours were obtained. The benefits of physical activity on decreasing digestive system cancer risk plateaued at 30 MET-hours/wk, which is equivalent to walking at a normal pace approximately 10 hours per week or 90 minutes per day.

The study is notable for a few reasons. First, it is unique in that it reports the association between physical activity and multiple specific types of digestive system cancers, including digestive accessory organs, thus allowing for a comparison of risks across cancer sites. Extensive covariate data allowed controlling for confounders and comorbidities. Second, it examined physical activity by type and intensity, showing that aerobic exercise was more beneficial than weight training. And third, the units of analysis used to describe the amount of physical activity are readily translatable into public health messaging.

However, there are important limitations to note. Although this is an elegantly designed and executed cohort study, as a study of non–ethnically diverse health professionals, the results may not be generalizable outside of well-educated and affluent white men. Studies are needed to understand the role of physical activity in the disease processes of other populations with different genetic, behavioral, and environmental exposures. In addition, the physical activity measure only accounts for leisure-time physical activity and does not account for patterns of overall physical activity, most importantly occupational physical activity, which leads to the next point. There is a growing body of literature suggesting that sedentary behavior may be a driving factor related to digestive system cancer risk. Increased time spent engaging in sedentary behavior is associated with increased insulin resistance even among individuals meeting targeted physical activity guidelines.[9] Going forward, physical activity analyses need to either adjust for sedentary behavior or estimate the joint effect of physical activity and sedentary behavior.

These results point to specific questions that need to be answered in the physical activity and digestive system cancer literature. What are the mechanisms by which physical activity intensity affects digestive system cancer risk? Studies are needed to identify which, if any, biomarkers, such as vitamin D, insulinlike growth factor 1, adiponectin, and genes or genotypes,[10,11] may modify or interact with physical activity to affect digestive system cancer outcomes. What is it about aerobic exercise, as opposed to strengthening activities, that affects risk? If these results reflect causal relationships, how many digestive system cancers can be avoided by simply walking 90 minutes per day?

Currently, digestive system cancers account for 37% of cancer deaths worldwide.[12] Do the study results change how we should approach public health messaging and clinical guidelines concerning physical activity? The results from Keum et al[8] suggest that for the prevention of digestive system cancers, more aerobic exercise is needed than currently recommended by the American Cancer Society and the American Institute for Cancer Research. More importantly, we know that Americans, across all populations and age groups, are exercising at levels much lower than national recommendations.[13] Recent estimates suggest that adults spend up to 70% of their waking time in sedentary activity, with less than 5% spent in moderate to vigorous activity.[14] The important question now is how do we change behavior and get people to achieve and maintain recommended levels of physical activity. We know that publishing national guidelines is not enough to improve physical activity.

What might be learned from a multilevel view of physical activity promotion? Possible interventions range from those directed at the individual to larger-scale efforts to modify the workplace and the built environment. On the individual level, there is a huge rise in wearable devices to track and theoretically motivate physical activity, but it remains to be seen whether wearing these devices results in sustained increases in physical activity. Studies have shown that direct suggestions by physicians can increase physical activity.[15] Health insurers and employers are experimenting with innovative methods to increase physical activity, but the jury is out on whether they are effective in the long term—or effective enough to affect disease outcomes. It has been well established that features of the built environment correlate with the amount of physical activity, and we need to experiment with these approaches to understand how to build physical activity–promoting structures, communities, and cities.

The challenge with population-based cancer prevention research is that testing these interventions in a large population is costly and can take decades. A more efficient approach is to target populations at highest risk of cancer. Studies can focus on those at higher risk of digestive system cancers, based on family history, genetic testing, precancerous biomarkers (ie, colorectal adenomas), or history of digestive system cancers.

So where do we go from here? How might we achieve the promise of physical activity as an effective approach to digestive system cancer prevention? For now, the general message stays the same for general health promotion and disease prevention—exercise 30 to 45 minutes every day. What we have learned from Keum et al[8] is that for digestive system cancer prevention, more exercise is better; especially for prevention of gastrointestinal tract cancers, it is important to engage in aerobic exercise, and exercise intensity does not matter as long as the minimum number of MET-hours are achieved. What remains to be identified is the most effective achievable level of physical activity, because for the general US population, walking 90 minutes a day is still a challenge, even at the slowest pace.

ARTICLE INFORMATION

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The Preventability of Cancer
Stacking the Deck

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Over the past year, major attention has focused on whether cancer arises by chance or as a result of external factors that, if modifiable, could imply that cancer is preventable and not simply the result of random events. The underlying truth of this debate has major implications for everything from the Vice President's Moonshot[1]—are we preventing cancer or only aiming to treat it after it develops?—all the way to policies and practices that may determine cancer risk for future generations.

Although Vogelstein and colleagues[2] have previously advocated for prevention as the first line of attack in the war on cancer—holding treatment in reserve, as plan B, when prevention fails—members of that same research group have also recently contended that cancer is largely due to chance, a position that has received far more attention.[3] The basis for this later assertion is the underlying relation of increasing cancer risk with age,[4] or, as modeled recently by Tomasetti and Vogelstein,[3] the underlying relation of increasing cancer risk with number of stem cell divisions. This increasing risk with age or stem cell division can be explained in at least 2 non-mutually exclusive ways, the relative contributions of which are currently under intense debate. Tomasetti and Vogelstein, on the one hand, propose that random, accumulated mutations during cell division are largely responsible for this relation—essentially that "bad luck" drives the development of most cancers.[3] Wu and colleagues,[5] on the other hand, as well as several other investigators, posit an alternative hypothesis whereby external—or extrinsic or exogenous—factors that increase the rate of cell turnover or the chance of genomic damage during cell division are greater drivers of cancer risk. In classic epidemiology, we might refer to these external factors as environmental or lifestyle factors.

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Examples of environmental influences on cancer risk are abundant. If we go back in history, one of the first examples is the high incidence of scrotal cancer among young chimney sweeps in 16th- and 17th-century Britain, which declined with the banning of "chimney boys."[6] This epidemic of scrotal cancer was not due to chance but rather to exposure to a carcinogen, coal tar. Likewise, classic studies of migrants that compared individuals who migrated with those who remained in their home countries clearly show that cancer risk is responsive to the external environment of the adopted country, be it sunlight or diet or other external factors.[7] Finally, the dramatic increase in lung cancer mortality with the popularity of cigarette smoking in the 1900s and its subsequent decline by one-third over the past 25 years also speak to the strong influence of environmental factors on cancer risk.

Analysis of Preventable Cancer Risk Factors

To bring this issue to the fore, Song and Giovannucci[8] used data from the prospective Harvard cohorts, the Nurses' Health Study (NHS) and the Health Professionals Follow-up Study (HPFS), to reexamine the contribution of lifestyle factors to cancer occurrence. Using an approach used by numerous investigators before them, they calculated cancer incidence and mortality rates in participants with varying lifestyle factors to estimate the risk of cancer conferred by these factors, and by exten-