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Authors

Kerr, Jacqueline

Anderson, Cheryl

Lippman, Scott M

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Physical activity, sedentary behaviour, diet, and cancer: an update and emerging new evidence

Jacqueline Kerr, PhD,
Moores Cancer Center; Department of Family Medicine and Public Health, University of California, La Jolla, San Diego, CA, USA

Cheryl Anderson, PhD,
Moores Cancer Center; Department of Family Medicine and Public Health, University of California, La Jolla, San Diego, CA, USA

Scott M Lippman, MD
Moores Cancer Center; Department of Medicine, University of California, La Jolla, San Diego, CA, USA

Abstract

The lifestyle factors of physical activity, sedentary behaviour, and diet are increasingly being studied for their associations with cancer. Physical activity is inversely associated with and sedentary behaviour is positively (and independently) associated with an increased risk of more than ten types of cancer, including colorectal cancer (and advanced adenomas), endometrial cancers, and breast cancer. The most consistent dietary risk factor for premalignant and invasive breast cancer is alcohol, whether consumed during early or late adult life, even at low levels. Epidemiological studies show that the inclusion of wholegrain, fibre, fruits, and vegetables within diets are associated with reduced cancer risk, with diet during early life (age <8 years) having the strongest apparent association with cancer incidence. However, randomised controlled trials of diet-related factors have not yet shown any conclusive associations between diet and cancer incidence. Obesity is a key contributory factor associated with cancer risk and mortality, including in dose–response associations in endometrial and post-menopausal breast cancer, and in degree and duration of fatty liver disease-related hepatocellular carcinoma. Obesity produces an inflammatory state, characterised by macrophages clustered around enlarged hypertrophied, dead, and dying adipocytes, forming crown-like structures. Increased concentrations of aromatase and interleukin 6 in inflamed breast tissue and an increased number of macrophages, compared with healthy tissue, are also observed in women with normal body mass index, suggesting a metabolic obesity state. Emerging randomised controlled trials of physical activity and dietary factors and mechanistic studies of immunity, inflammation, extracellular matrix mechanics, epigenetic

Correspondence to: Prof Scott M Lippman, Moores Cancer Center, 3855 Health Sciences Drive, University of California San Diego, La Jolla, CA 92093, USA, slippman@ucsd.edu.

Contributors

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Declaration of interests

We declare no competing interests.

or transcriptional regulation, protein translation, circadian disruption, and interactions of the multibiome with lifestyle factors will be crucial to advance this field.

Introduction

More than half of cancers occurring today are believed to be preventable by applying knowledge that we already have, highlighting the growing field of implementation science.[1] In particular, diet, nutrition, physical inactivity, and obesity are thought to be important contributors to the increasing cancer incidence worldwide. Cancer burden can be reduced by changes in individual and population behaviours, and by public health efforts in the presence of robust scientific knowledge and a social commitment to change. This Series paper includes emerging data for the effects of physical activity, sedentary behaviour, diet, and obesity as major determinants of cancer risk and mortality.

Physical activity, sedentary behaviour, and cancer risk

The first article[2] to suggest an association between exercise and cancer prevention was published in 1945. At the time, exercise was conceptualised as a single, planned bout of high-intensity, hard, sweaty work. Today, physical activity is defined as a behaviour that can occur anywhere, as part of our daily routine. Nonetheless, guidelines for cancer risk and mortality for patients with and survivors of cancer have continued to focus on moderate-to-vigorous exercise as having the greatest benefits to health.[3,4] Guidelines from 2008,[5] however, acknowledge that any physical activity is better than none for older adults (age >65 years), who are at the highest risk of cancer, and who are often cancer survivors. As research into physical activity has expanded to include different types of activity, such as active transportation, correlates of physical activity have also expanded to include built environment characteristics, such as walkable streets.[6] Another notable shift in the direction of research has occurred in the last decade, with the emergence of sedentary behaviour (eg, time spent seated on a daily basis) as an independent risk factor for cancer incidence and mortality,[7] such that many health organisations are emphasising the limitation of sitting time in addition to promoting physical activity.

A key limitation in this area of research has been the reliance on self-reports of activity and sedentary behaviour, which are affected by the limitations of high random error and systematic bias. For example, national surveys using self-reports suggested that up to 60% of US adults were meeting physical activity guidelines.[8] However, accelerometer data indicated that less than 10% were meeting these guidelines.[8] Therefore, the use of objective quantitative monitors (eg, accelerometers) to measure total activity, activity intensity, and sedentary behaviour represent a major methodological advance. Although these devices do not provide totally unbiased measures of activity (ie, estimates can be affected by wear time or processing methods), newer 24 h protocols and machine-learning methods to classify additional behaviours, such as cycling, are improving this emerging science.[9] Furthermore, in our searches, we found no randomised controlled trials (RCTs) studying the association between physical activity or sedentary behaviour and cancer incidence or mortality, which will be crucial for our future understanding of this topic.

Emerging evidence for physical activity and cancer

Cancer incidence

Our search of the published literature yielded 23 reviews of physical activity and cancer risk, of which 19 were meta-analyses. Five[10-14] included prospective studies only, whereas the others included case-control designs. The case-control studies provided larger risk estimates, reflecting bias in this type of design.[15] The largest review[11] was a pooled analysis of 12 prospective European and US cohorts that included 1·44 million participants and 186 932 cases of cancer with self-reported physical activity. This pooled analysis concluded that high levels of physical activity during leisure time (the 90th percentile compared with the 10th percentile) were associated with reduced risks of 13 types of cancer, ranging from a hazard ratio (HR) of 0·58 (95% CI 0·37–0·89) for oesophageal adenocarcinoma to 0·90 (0·87–0·93) for breast cancer, but increased risks of melanoma (1·27; 1·16–1·40) and prostate cancer (1·05; 1·03–1·08). A review[10] of 126 studies found a 10% reduction in risk across cancer types associated with physical activity, but a threshold effect meant that physical activity exceeding two times the current recommendations did not provide additional benefits. Two other reviews[13,16] concluded that the associations were not linear, whereas another[17] found a linear association. Five prospective studies[14,18-21] were identified, four of which[14,18,20,21] found a significant inverse association of physical activity with cancer of the digestive tract, pancreas, ovaries, and breasts, and one of which[19] found no association for prostate cancer.

Physical activity was inversely associated with risk of breast cancer in the Nurses' Health Study II,[22] with the strongest inverse associations between adolescent activity and premenopausal risk. In a 2017 case-control study,[23] there was an inverse correlation between physical activity during adolescence and risk of all pathological subtypes of breast cancer. Recreational physical activity has been associated with a reduced risk of aggressive triple-negative breast cancer.[24] Prospective data from the Black Women's Health Study[25] found that high levels of exercise were associated with reduced breast cancer incidence. Only one case-control study[26] used accelerometer-measured activity with 996 incident cases of breast cancer and 1164 controls, reporting a 61% reduced risk of cancer when comparing the highest versus the lowest quartile of moderate-to-vigorous activity. At least six large prospective cohort studies using accelerometers are ongoing, with well monitored disease outcomes including cancer. One such study is the Women's Health Initiative OPACH Study.[27]

Physical activity can reduce the overall risk of cancers of the digestive system, especially in men.[18] Physical activity reduces the risk of colon cancer by about 20–25% in both men and women in a dose–response manner.[20] Physical activity is also associated with a roughly 15% risk reduction of colonic adenomas, the precursors of colon cancer.[28] This association holds for both sexes and, importantly, is most notable for advanced adenomas (35% risk reduction; see also the later section about sedentary behaviour). Unlike the conventional adenoma findings, the effect of physical activity on serrated polyps remains unclear.

The World Cancer Research Fund's continuous update review[29] summarises evidence from recreational physical activity, occupational physical activity, and walking as a means of transport on cancer risk. The review concludes that most studies and nearly all cohorts

show an inverse association between increased physical activity and the risk of endometrial cancer—an association that is becoming increasingly clear with the publication of a more rigorous study.[30] Another 2017 cohort study[31] of more than 80 000 women from Norway added further evidence to this association: the study used repeated measures of physical activity and showed that the inverse association was independent of body-mass index (BMI). The authors concluded that 21·9% (95% CI 7·1–34·3) of endometrial cancers could be avoided if women with low levels of physical activity (≤4 in a self-reported scale of physical activity of 1–10) increased their physical activity levels to 5–10. In a 2017 case-control study,[32] physical activity was associated with a reduced risk of colorectal, endometrial, and post-menopausal breast cancer, with the greatest risk reduction in endometrial cancer, and no evidence of interaction with BMI.

Cancer mortality

Our search yielded nine reviews[33-42] of physical activity and cancer mortality, of which five were meta-analyses. Three reviews reported on all cancer-related mortality and six of these nine reviews focused on mortality from breast or colon cancer. Most studies reported on physical activity both before and after diagnosis. A large meta-analysis[43] of 71 studies found that individuals who were most physically active had an HR of 0·83 (95% CI 0·79–0·87) for all-cancer mortality in the general population before diagnosis, and an HR of 0·78 (0·74–0·84) among cancer survivors. In the general population before diagnosis, a minimum of 2·5 h per week of moderate-to-vigorous activity led to a significant 13% reduction in cancer mortality. Patients who completed 15 metabolic equivalents of task (MET) h per week of physical activity before diagnosis had a 27% lower risk of mortality from cancer than those who did not attain this level; one MET is defined as the energy it takes to sit still, moderate activity is classified as requiring between three and six METs, and vigorous activity is classified as requiring over six METs. The association between physical activity and mortality risk was even more notable in cancer survivors, in whom 15 MET h per week after diagnosis decreased risk of mortality from cancer by 35%. Overall, the meta-analytic reviews indicated that post-diagnosis physical activity has stronger associations with mortality risk reduction (typically associated with around a 14% greater reduction in risk) than pre-diagnosis activity.[44] However, this finding could also be due to short follow-up periods to recurrence or reverse causation. In our search, we identified two prospective observational cohort studies of physical activity and cancer mortality. In a cohort[45] of 830 men with stage II–IV incident prostate cancer, prostate cancer mortality was reduced by 44% in those performing recreational physical activity after diagnosis compared with those who did none. In a cohort[46] of 1327 women with breast cancer, physical activity after diagnosis was associated with a 54% reduced risk of mortality from breast cancer compared with those who did not do any physical activity. Physical activity before diagnosis was not significantly associated with mortality risk. Notably, neither of these studies used accelerometers to assess physical activity.

Emerging evidence for sedentary behaviour and cancer

Cancer incidence

We identified four meta-analyses[47-50] of sedentary behaviour and cancer incidence. In the largest review of 43 studies of time spent watching television and sitting,[47] higher levels of sedentary behaviour were associated with a 54% increased risk of colorectal cancer incidence and a 66% increased risk of endometrial cancer incidence. 11 observational studies[26,47-49,51-57] evaluated associations between sedentary behaviour and cancer. The most consistent finding across these studies was the association between sedentary behaviour and increased incidence of colorectal and endometrial cancer.[50,58] Sedentary behaviour was associated with a 54% increased risk of colon cancer for time spent watching television, 24% for occupational sitting, and 24% for total time spent sitting.[47] As with physical activity, a 2015 report[59] found that sedentary behaviour increased the risk of advanced colon adenomas, suggesting that sedentary behaviour is an early contributor to oncogenesis. Sedentary behaviour also increased adenoma recurrence in men[60] and raised the risk of colorectal cancer, independent of the amount of physical activity.[61] A large cross-sectional accelerometer study[62] of 1672 men found that, for each 1 h increase in sedentary behaviour, there was a 16% increased likelihood of having an increased prostate-specific antigen (PSA) concentration (odds ratio 1·16 [95% CI 1·06–1·27]). However, in this cross-sectional study, it is possible that the tumour (as indicated by the presence of elevated PSA) affected the patients' behaviour rather than the other way around. In a large, population-based prospective cohort study,[63] occupational sedentariness was an independent risk factor for increased premenopausal breast cancer. In the accelerometer-based case-control study[26] examining physical activity in women with breast cancer (which, being a case-control study, also has design limitations), the risk of breast cancer was increased by 81% in people with the longest amount of time spent sitting, after adjustment for moderate-to-vigorous physical activity. Sedentary behaviour was also associated with breast cancer risk in the Black Women's Health Study,[55] especially for risk of oestrogen receptor-negative tumours.

Cancer mortality

Our search found three reviews of sedentary behaviour and cancer mortality, two of which were meta-analyses. In the largest meta-analysis[64] of 13 studies, which included 1 005 791 adults, time spent sitting was associated with increased mortality from cancer, with hazard ratios between 12% and 22% for people in the least active quartile. Of 16 observational studies,[49,55,57,64-76] ten (60%) found at least one significant association between higher self-reported sedentary behaviour and increased mortality from cancer. Sedentary behaviour has been associated with an increased risk of all-cause mortality, colorectal cancer-specific mortality, and reduced quality of life in colorectal cancer survivors.[77-79]

Mechanisms of physical activity and effects of sedentary behaviour on cancer

Physical activity is believed to reduce the risk of developing cancers because of its role in helping to maintain a healthy weight, although activity has numerous other beneficial

effects on health and disease risk. The biological bases underlying the associations between physical activity and cancer risk are incompletely defined. However, a laboratory-based study of exercise[80] has suggested beneficial changes in circulating concentrations of insulin, insulin-related pathways, and inflammation. A review[81] of 18 exercise trials also concluded that physical activity can reduce oestradiol concentrations in women, exposure to high levels of which is a risk factor for breast cancer. The effects of physical activity or sedentary behaviour, or both, on the immune system, epigenetics, protein translation, and microbiome, including in relation to cancer development, are under active study.[82,83] For example, a small study[84] of young adults found that regular exercise was associated with increased immune response or surveillance, which is known to prevent cancer development. Physical activity upregulated cell cycle and DNA repair pathways in men with prostate cancer under active surveillance.[85] Although sedentary behaviour might be related to cancer biomarkers of low energy expenditure, postural effects could also be involved. The physiological mechanisms activated by standing (postural blood flow, energy expenditure, and muscle contraction) can lead to improved glucose regulation, mitochondrial function, and endothelial function.[86,87] Two studies[88,89] of cancer survivors showed that time spent sitting was associated with a increased risk of metabolic syndrome, increased insulin resistance, and higher levels of C-reactive protein. One laboratory-based study[90] showed the acute effects of prolonged sitting on glucose dysregulation. Physical activity and sedentary behaviour, and the physiological and mechanistic effects of these behaviours, are under active investigation.[91-93]

The association between increased physical activity and reduced risk of post-menopausal breast cancer is considered “probable” by the World Cancer Research Fund and the American Institute for Cancer Research.[94] Some evidence[95,96] suggests a protective role of physical activity against breast cancer in *BRCA1* mutation carriers, especially physical activity in adolescence or early adulthood. The molecular basis of this association might be related to direct effects on the wild-type *BRCA* allele, which could mitigate the deleterious effect of the inherited mutated allele. For example, a 2016 clinical study[97] found that prolonged or uninterrupted periods of sedentary behaviour were associated with decreased *BRCA1* mRNA expression, irrespective of overall physical activity level. Differences in the protective role of physical activity in patients with *BRCA1* mutations could also be due to delayed diagnosis and overall risk might remain unchanged if adjusting for this delay. Similar patterns of sedentary behaviour and physical activity affect telomere length, which is a major independent predictor of cancer and other severe chronic diseases.[98] Building on preclinical findings and early clinical physical activity results, emerging clinical work suggests that sedentary behaviour can have profound effects on the gut microbiota.[99]

Emerging evidence for dietary patterns and cancer

An association between cancer and specific nutrients in food has been reported in the scientific literature for several decades. However, the ability to consistently determine the association between dietary factors and cancer risk has been limited by several major factors, including heterogeneous pathophysiology, study durations, identification of aetiologically relevant time window, and measurement error in dietary assessment methods.[100] Nonetheless, vast epidemiological evidence has amassed suggesting that diet

affects cancer risk and mortality.[101-104] RCTs of individual nutrients, foods, or food groups, however, have generally been inconclusive or have shown some increased risk with certain dietary components, in contrast with observational studies. This apparent paradox has resulted in an increased focus on the study of overall dietary patterns as a risk factor for cancer, since individuals consume foods, not nutrients, and foods are generally consumed in a pattern that can be more easily described.

Dietary patterns are defined as the quantities, proportions, or combinations of different foods and beverages in diets and the frequency with which they are consumed.[105] Dietary patterns are usually characterised using three main approaches: the creation of an a priori index based on a set of dietary recommendations, reached by scientific consensus or by investigators with an evidence-based approach; data-driven methods that aim to identify which components of the diet occur together to explain variations in food or beverage intake across dietary patterns, which are independent of the study outcomes; or examination of individuals' intake preferences based on the foods and drinks that are included and excluded in their diets. This pattern is usually based on qualitative self-reported behaviours rather than detailed questionnaires (eg, vegetarianism).

In addition to the general search criteria used for this Series paper, this section focuses on the three most common malignancies: breast, colorectal, and prostate cancer. We include findings from selected observational studies of diet and cancer to highlight the overall shift over time in the approach used to study dietary factors and cancer and to illustrate key concepts in study design related to the conflicting findings regarding diet or nutrients and cancer obtained when using observational versus RCT designs.

Breast cancer

The most consistent dietary risk factor for breast cancer is alcohol.[106] Analyses show that alcohol consumption, both in early (twenties) and late adult life (age >60 years), was independently associated with increased cancer risk, even at low levels, in the Nurses' Health Study II.[107] Most studies examining the association between dietary patterns and breast cancer focus on post-menopausal breast cancer risk. Together, these studies suggest that dietary patterns rich in fruits, vegetables, wholegrains, and fibre, and low in animal products and refined carbohydrates, could reduce the risk of post-menopausal breast cancer.[108-113] Fewer studies have examined the association between dietary patterns and the risk of premenopausal breast cancer but the findings have been similar.[114-118] No convincing evidence suggests that changing dietary pattern after breast cancer diagnosis will improve the prognosis for most women with early-stage breast cancer. Dietary effects might be important in reducing the risk of breast cancer in specific subgroups of the population such as those with oestrogen receptor-negative breast cancer. Notably, adult intake of fruit and vegetables is associated with a decreased risk of oestrogen receptor-negative breast cancer, which is supported by an inverse association between carotenoids and oestrogen receptor-negative breast cancer.[114,115] A large pooled analysis[114] of eight cohort studies (comprising >80% of the world's published prospective data on this topic) found that circulating carotenoid concentration was inversely associated with breast cancer development, especially with oestrogen receptor-negative disease. Another large study

showed that, although fruit and vegetable intake had no effect on overall risk of breast cancer in the European Prospective Investigation into Cancer and Nutrition cohort[116] of about 330 000 women from ten European countries, a pooled analysis[117] of 993 466 women from 20 prospective cohort studies, who were followed up over 11–20 years, reported a significant inverse association between vegetable intake and risk of oestrogen receptor-negative breast cancer. The controversial difference in association between oestrogen receptor-positive or oestrogen receptor-negative breast cancer and dietary patterns has been confirmed and extended in two subsequent studies.[113,118]

By contrast with the large number of cohort studies, RCTs of diet and breast cancer are scarce. The Women's Health Initiative study[119] found that, in post-menopausal women, a low-fat dietary pattern did not result in a significant reduction in breast cancer risk during an 8-year follow-up period. However, non-significant trends in some subgroups (including in those patients with progesterone receptor-negative tumours) suggested reduced risk associated with a low-fat dietary pattern. A high dietary intake of saturated fat has been associated with an increased risk of oestrogen receptor-positive disease.[120] The PREDIMED trial[121] was the first RCT to provide data to suggest that a Mediterranean diet supplemented with extra-virgin olive oil was beneficial in the prevention of breast cancer.

Colorectal cancer

Studies have shown that diets rich in fruits, vegetables, fibre, legumes, wholegrains, lean meats or seafood, and low-fat dairy; moderate in alcohol intake; and low in red and processed meats, saturated fat, and sugar are associated with a reduced risk of colorectal cancer.[109,111,112,122-126] These studies vary in the approach used to assess dietary patterns across studies. For example, when patterns are defined by an index or score, protective effects on colorectal cancer have been recorded.[127] Factors such as sex, tumour location, physical activity, and microbiome can affect the association between dietary patterns and colorectal cancer risk. Dietary patterns seem to be particularly associated with tumour development in the distal colorectal regions.[109,111,112,122-124] By contrast with the epidemiological data for colorectal cancer (and adenoma), no effect on the recurrence of colorectal adenomas was reported in RCTs testing the effects of low-fat and high-fibre dietary patterns.[128] In the most robust of these RCTs,[128] a 50% increase in self-reported vegetable and fruit consumption translated into only a 14% increase in serum total carotenoids at 1 year and a modest 5% increase at 4 years.

These data should be interpreted with caution, and factors such as intervention fidelity should be considered—eg, the degree to which increases in serum carotenoids reflect adherence to an intervention and whether or not consumption reached the threshold fibre intake necessary to find an effect. Adding to the complexity, a mouse study[129] shows that gut commensal microflora and dietary fibre affect inflammation and tumorigenesis associated with colorectal cancer through microbe-produced butyrate and other short chain fatty acids. *Fusobacterium nucleatum* seems to have a role in colorectal carcinogenesis through the suppression of the hosts' immune response to tumours. Evidence also suggests that diet affects intestinal *F nucleatum*.[130] A large prospective cohort study[130] using data from the Nurses' Health Study and the Health Professionals Follow-up Study on a total of

121 700 women and 51 529 men investigated the potential link between diet, microbiota, and colorectal cancer. Diets rich in wholegrains and dietary fibre, versus those rich in red and processed meat, refined grains, and dessert foods, were associated with reduced *F nucleatum*-positive, but not *F nucleatum*-negative, colorectal cancer, supporting a potential role for the intestinal microbiota in mediating the association between diet and colorectal cancer. Future trials of high-fibre diets should control for gut microbiota composition. Furthermore, low-grade gut inflammation caused by the microbiota weakens epithelial tight junctions and could lead to obesity and type 2 diabetes.[129]

Prostate cancer

Only a few studies have investigated dietary patterns and prostate cancer, and these vary greatly in the design and in the methods used to assess diet and to ascertain prostate cancer diagnosis.[111,131-133] Most of the studies[131,134,135] did not report clear or consistent associations between dietary patterns and the risk of prostate cancer. Patients with prostate cancer with a high intake of vegetables, fruits, fish, and wholegrains had better survival than did men on diets that reflect the typical American intake.[136] Greater adherence to the Mediterranean diet was associated with lower mortality from prostate cancer,[132] especially in men who had undergone a PSA screen within the past 3 years versus those who had not. Preliminary evidence[137] suggests that patients with prostate cancer who increase their vegetable fat and decrease their animal fat intakes have improved prostate cancer outcomes.

The Men's Eating and Living Study[138] is the first and only national RCT testing the efficacy of a dietary intervention (increased vegetable intake) in the prevention of the clinical progression of early-stage prostate cancer in patients undergoing active surveillance. The primary outcome is clinical progression, defined by PSA measurement and prostate biopsy. 478 (103%) of a targeted 464 patients have been enrolled and randomised at 91 study sites across the USA. Reducing the number of patients undergoing active surveillance who are subsequently treated with surgery or radiotherapy would minimise treatment-associated morbidity, improve patient quality of life, and reduce health-care costs. However, interventions to prevent progression, such as dutasteride,[139] remain underused and understudied. Consequently, even as the prevalence of patients on active surveillance increases, the incidence of progression while on active surveillance has not changed appreciably over the past decade.

Interpreting the paradoxical findings from RCTs and observational studies

The complexity of interpreting large RCTs of specific nutrient effects on cancer incidence can be illustrated by the NCI Intergroup Selenium and Vitamin E Cancer Prevention Trial (SELECT),[140] which tested whether selenium (200 μg daily), vitamin E (400 IU daily), or both, could reduce prostate cancer risk in a placebo-controlled RCT of more than 35 000 men, showing no association between the interventions and prostate cancer incidence. However, the trial showed that vitamin E intake increased the risk of prostate cancer by 13% compared with placebo (p=0·06),[141] and this increased risk became significant with additional follow-up (17%; p=0·008).[142] A prevailing perspective of these types of micronutrient RCTs is that they do not mimic the epidemiological situation, in which nutrient-deficient populations have a higher cancer risk than nutrient-sufficient

populations. In fact, the basis for the selenium intervention in the SELECT trial came from secondary endpoint (prostate cancer) results of an RCT, suggesting that the benefit of supplementation was limited to men with low plasma selenium concentrations. Therefore, a subsequent analysis[143] of SELECT investigated whether selenium might benefit men with low baseline concentrations of selenium. Contrary to this hypothesis, the analysis showed that selenium supplementation had no overall effect on prostate cancer incidence in men with low baseline selenium concentrations and significantly increased the risk of high-grade cancer. The selenium concentration in the overall study population and in the low-baseline group, however, were much higher in the SELECT population than previous studies in low-selenium populations.

In addition to these and other micronutrient studies (eg, folic acid[144]), several dietary studies have reported conflicting results between epidemiological and RCT data regarding dietary patterns. In fact, data suggest that dietary methyl donor depletion (eg, of folic acid or methionine) can produce long-lasting protection against colorectal cancer, possibly by epigenetic reprogramming of stem cells.[145] As illustrated by SELECT, findings from observational epidemiological studies might not directly translate to findings in RCTs for several reasons. First, early RCTs tested the hypothesis that a single component of the diet (ie, an individual nutrient or food) was causally associated with cancer risk. However, when one component of the diet is modified, by necessity, other components are also changed. For example, a decrease in overall fat intake will result in an increase of carbohydrate or protein intake, and an increase in fruit and vegetable intake might accompany a decrease in overall fat or saturated fat intake. Second, findings from the observational epidemiological data vary depending on the type of vegetable or fruit studied. For example, green, leafy vegetables show inverse associations with some cancers but starchy vegetables do not. This finding might be a result of the different nutrient profiles of various types of fruits and vegetables and an incomplete understanding of the mechanisms by which these nutrients affect and interact with each other when estimating cancer risk. Third, a complex dose–response interaction (eg, non-linear, threshold effect) with vitamins, minerals, and other micronutrients from the diet appears to exist that depends on the baseline concentration, leading to concerns that doses of micronutrients were too high and fibre too low in RCTs to be able to draw definitive conclusions from the results.[129,143] Finally, findings for an overall study population can differ from that in subpopulations, as explained in examples discussed previously.

Effects of diet in early life

Diet in early life can affect markers of adolescent growth and development, such as age at first menarche, age at peak height growth velocity, and peak height growth velocity. This association has implications for chronic diseases such as breast cancer, which has some risk factors stemming from adolescent growth and development. In a prospective longitudinal study[146] of girls born in the 1930s and 1940s living in the USA, high consumption of animal protein and low consumption of plant protein at ages 3–5 years was associated with earlier age at first menarche; high dietary fat intake at ages 1–2 years and high protein intake at ages 6–8 years were associated with earlier peak growth in adolescence; and high consumption of calories and animal protein 2 years before peak growth were associated

with higher peak growth velocity, after controlling for body size. These findings have been replicated in a study[147] from the UK. The more contemporary Avon Longitudinal Study of Parents and Children[148] reported that in 3298 girls born in 1991 and 1992, intake of animal protein at ages 3–5 years was positively associated with earlier age at first menarche and vegetable protein intake was associated with later onset of menarche. This finding was supported by the German Dortmund Nutritional and Anthropometric Longitudinal Design Study.[149]

Additionally, diet during preadolescence is related to peak height growth velocity, which is positively associated with the risk of breast cancer.[150] Animal protein intake is related to faster growth and higher attained height.[146] Emerging evidence indicates that, during adolescence, a diet high in fruits, vegetables, carotenoids, and fibre is associated with a reduced risk of premalignant breast lesions and invasive breast cancer.[151-155] Groups with high consumption of alcoholic beverages during adolescence had greater risk of premalignant breast disease compared with groups with low consumption.[147] A population-based cohort analysis[156] of breast cancer and fruit and vegetable intake in 90 476 adolescent women and women in early adulthood showed a stronger association between these factors than in studies of post-menopausal women. A prospective cohort study[157] of more than 44 000 women in the ongoing Nurses' Health Study II, showed that groups with high fibre intake (up to 25·3 g/day) during adolescence and early adulthood had a lower risk of breast cancer, especially of premenopausal breast cancer, than those with an intake of less than 14·7 g/day. High consumption of fish, fruit, and vegetables during adolescence is associated with a reduced risk of colorectal adenomas.[158,159] This association is biologically plausible, since dietary fibre can modify the composition of gut microbiota to metabolise and reduce circulating oestrogen.[129,157,160,161]

The importance of the timing of exposure during adolescence is further emphasised by the adverse effect of alcohol intake. Sustained intake before first pregnancy is substantially associated with an increased risk of proliferative benign breast lesions and invasive breast cancer.[107] In view of the biological processes of mammary gland development and terminal differentiation of cells with first pregnancy, the potential for diet composition to modify risk is substantial, but so far this hypothesis is poorly studied and understood. Growth in childhood and adolescence seems to be modified by diet composition and energy balance, with attained height and growth velocity (and age at menarche) serving as markers of these exposures, but potentially each operates independently to summarise risk accumulation during these years. Continued research into early life exposures should provide new insights into the mechanisms of development and prevention of breast cancer.[162]

Biological mechanisms for the effects of dietary patterns on cancer

The effects of dietary whole grains and fibre on colorectal cancer vary by intestinal microbiota.[130] High-protein diets can reduce the concentrations of beneficial microbiota and metabolites and immune protection.[163] High-fat diets can induce intestinal progenitor cells to a more stem cell-like fate, increasing tumour incidence. These effects are caused by specific dietary fatty acids, and not as a result of obesity.[164] Caloric restriction has the opposite effect, reducing the incidence of tumour initiation. The relative role of obesity

versus high-fat diets in cancer development is an ongoing debate. Data from several mouse models[163,164] indicate that high-fat diets can promote growth of breast and other cancers in the absence of obesity, suggesting a complex interplay between dietary fat (quality and quantity), obesity, inflammation, genetic background, and oncogenesis.[165] Dietary changes in rural African and African–American people produced large changes in microbiota, metabolites, and cancer risk.[129] The intestinal microbiome might promote the development of oestrogen receptor-positive breast cancer.[166] Additionally, plasma carotenoids have been shown to be inversely associated with the incidence of high-grade prostate cancer, and this association might be affected by single-nucleotide polymorphisms in specific DNA repair genes.[167,168] Emerging data indicate that, although fructose and glucose have the same caloric value, the two sugars are metabolised differently, which explains why fructose is the greater contributor to obesity and metabolic syndrome.[169]

Emerging evidence for obesity as a cancer risk factor

Obesity is a global health problem that is expected to increase substantially in both severity and the number of people affected over the next few decades. Worldwide, about 640 million adults and 110 million children and adolescents were obese in 2013—a two-times increase since 1980.[170] In the USA, more than a third of adults (about 79 million) are obese. With the dramatic rise in prevalence of obesity in the USA and worldwide,[161,170,171] this factor is becoming a major contributor to cancer risk and mortality, and is also a cause of many comorbidities. A 2016 review[170] conducted by a working group of the International Agency for Research on Cancer (IARC) found that being overweight or obese increases the risk of incidence of at least 13 types of cancer. Before this report, five cancers were known to be associated with being overweight or obese: oesophageal adenocarcinoma; colorectal cancer; breast cancer in post-menopausal women; uterine cancer; and kidney cancer. The IARC report linked an additional eight cancers to being overweight: liver cancer, carcinoma of the gastric cardia, gallbladder cancer; pancreatic cancer, thyroid cancer, ovarian cancer, meningioma, and multiple myeloma. Together, these 13 cancers account for 42% of all new cancer diagnoses worldwide.[170] The most consistent evidence is for post-menopausal breast cancer, colorectal cancer, and endometrial cancer. For some cancers (eg, endometrial), the group found a clear dose response—ie, the higher the patient's BMI, the greater the risk.[172,173] Nearly 25% of the relative contribution to cancer has since been ascribed to being overweight and obese.[174] Evidence increasingly suggests that these factors are important after the diagnosis of cancer and affect the course of disease. In 2014, the American Society of Clinical Oncology joined the consensus report of the World Cancer Research Federation and the American Institute of Cancer Research, highlighting the global concern of obesity.[175] Important racial disparities exist in this context. For example, obesity shows stronger associations with increased prostate cancer risk in African-American men than non-Hispanic white men.[176]

A 2017 review[177] analysed five observational breast cancer studies and found no evidence of benefit of weight loss on survival in obese or overweight cancer survivors, consistent with data in formerly obese mice that suggested that weight normalisation alone might not be sufficient to reverse the effects of chronic obesity on epigenetic reprogramming and inflammatory signals in the mammary tumour microenvironment.[178] More recent data

identifying a hyperadipose inflammatory state in women with a healthy BMI adds to the complexity of this result. A 2016 systematic review[179] of eight small RCTs that tested weight loss interventions in obese or overweight survivors of breast and endometrial cancer has produced encouraging preliminary results regarding RCT feasibility and short-term weight loss and favourable biomarker effects. The review also identified some challenges of achieving substantial weight loss in particular subgroups, such as in African–American cancer survivors. Several ongoing RCTs and studies assessing long-term interventions will provide potentially definitive assessment of whether or not weight loss can improve cancer outcomes in overweight and obese people.

Breast cancer

More than two-thirds of US women are overweight or obese, which is associated with an increased risk of oestrogen receptor-positive post-menopausal breast cancer risk, including primary cancers of the breast (37% increase), endometrium (97%), and colon (89%). Women's Health Initiative studies found a clear linear dose–response association between BMI and duration of being overweight or obese with an increased risk of post-menopausal breast cancer.[172,173] Childhood and adolescent obesity have been associated with a reduced incidence of premenopausal breast cancer[146,150] and an increased risk of several other cancers, such as endometrial,[180] colorectal,[181] and pancreatic[182] cancers. Although the health risks of obesity far outweigh any potential benefit on risk of premenopausal breast cancer, this surprising association suggests potential adiposity effects in this crucial early life window, which are under active investigation. Hyperadipose inflammatory states have been unexpectedly shown in women with healthy BMIs.[183] Macroeconomic forces, such as urbanisation and rising incomes, are leading to reduced levels of physical activity[184] and increases in consumption of high-glycaemic index foods and calorie-dense foods, adding to the growing burden of obesity on cancer incidence.

Hepatocellular and pancreatic carcinoma

Hepatocellular carcinoma is the cancer with the fastest rising incidence in the USA and causes the second-highest number of cancer-related deaths worldwide. Established risk factors for liver cancer (eg, hepatitis B) are addressed through vaccines, and agricultural and food policy reforms in China in the mid-1980s resulted in a dramatic decrease in aflatoxin exposure, meaning that primary prevention measures have led to declining rates of hepatocellular carcinoma incidence and mortality.[185] However, rising obesity rates portend a rapidly increasing trajectory in the incidence of this disease related to obesity.[161,170,171] In high-income and middle-income countries, the increase in overweight individuals is causing a large increase in non-alcoholic fatty liver disease, the most common liver disease in the world (affecting almost 30% of Americans), of whom 80% are obese. Up to 25% of patients with non-alcoholic fatty liver disease develop a progressive inflammatory liver disease termed non-alcoholic steatohepatitis, which can progress to hepatocellular carcinoma. A major concern for the future is the role that obesity, diabetes, and fatty liver disease will have in the development of hepatocellular carcinoma.[186] The incidence of and several risk factors for hepatocellular carcinoma are substantially higher in Hispanic men than in men of other races or ethnicities.[187] The progression of non-alcoholic fatty liver disease to non-alcoholic steatohepatitis is especially associated with mitochondrial genetic background.[188] The risk

of hepatocellular carcinoma in patients with non-alcoholic fatty liver disease and cirrhosis is also linked to alcohol use, and alcohol and obesity are synergistic in increasing the risk of liver injury and incidence of hepatocellular carcinoma.[189]

Pancreatic cancer has the poorest prognosis of any major tumour type, with a 5-year survival rate of less than 8%. Obesity has also been consistently associated with an increased risk of pancreatic cancer (HR 1·43; 95% CI 1·11–1·85 for individuals with a BMI >30 kg/m^2 compared with those with a BMI of 21–23 kg/m^2).[190] However, weight loss programmes do not appear to decrease cancer risk.

Biological mechanisms underlying associations of obesity with breast and liver neoplasia

Obesity is associated with adipocyte hypertrophy, mitochondrial dysfunction, and oxidative and endoplasmic reticulum stress, which promote increased proinflammatory signalling, adipokine secretion, and cell death, creating a state of chronic low-grade inflammation. Adipocytes supply metabolic substrates, lipid-signalling agonists, and growth factors, and change intermediary metabolism, especially fatty acid oxidation. An altered metabolic microenvironment in obese patients can amplify reciprocal cellular interactions of tumour cells with local or stromal adipocytes, or both. Adipose tissue is an active metabolic organ, communicating and regulating a host of signalling molecules.[191,192] The adipokine leptin can stimulate inflammatory pathways in monocytes and macrophages to promote mammary tumour growth. By contrast, adiponectin is downregulated in obese people. Adipose-derived stem cells can become cancer-associated fibroblasts to promote oncogenesis. Leptin and adiponectin can modulate breast epithelial stem cell self-renewal to drive tumorigenesis.[193] A 2016 study[194] reported that modest (about 5%) weight loss improved human metabolic function and led to an improvement in adipose tissue biology and reduced inflammation.

Adipose tissue macrophages in crown-like structures induce the production of reactive oxygen and nitrogen species, upregulation of NF-κB, and activation and secretion of TNF α, interleukin 1β, interleukin 6, and prostaglandin E2.[191] Adipose tissue is responsible for synthesis of aromatase, the rate-limiting enzyme that converts androgens to oestrogens, and aromatase expression and enzymatic activity are increased in inflamed white adipose tissue within breast tissue. Women in the highest tertile of post-menopausal patients with breast cancer with regard to their oestrone:androstenedione ratios in their breast fat tissue (compared with those in the lowest tertile) were less likely to develop crown-like structures.[195] Notably, inflamed adipose tissue releases cell-free DNA capable of stimulating insulin resistance[196] and is a source for circulating exosomal microRNA, which can regulate glucose tolerance.[197] Direct crosstalk between adipose tissue and neoplastic cells has been identified for several cancer types, supported by observations of crown-like structures in adipose tissue from patients with endometrial, tongue, and liver neoplasia.[198] Adipocytes in the tumour microenvironment can promote tumour development and progression and affect immune clearance.[199] For example, in the breast, interleukin 6, T cells, mast cells, and other cells (eg, eosinophils) have been reported to be crucial factors for the modulation of neoplasia. Adipokines, dysbiosis, and immune system alterations could all help to explain the link between adipose tissue and several cancers.[200]

Future studies should go beyond BMI to assess breast tumorigenesis and investigate other key factors, such as distribution of adipose tissue compartments, since hyperadipose states (eg, with crown-like structures) have been reported in people with healthy BMIs.[183] Obesity-induced interstitial fibrosis promotes breast tumorigenesis by changing the function of the mammary extracellular matrix.[201] Circadian disruption is associated with an increased incidence of obesity, diabetes, and cancer in human beings. In mice, circadian dysfunction induces leptin resistance, a hallmark of obesity in human beings, suggesting a key mechanism of circadian dysfunction-induced obesity and metabolic syndromes.[202] The most evident epidemiological link between cancer and circadian dysfunction is for breast cancer. Data from a study[203] in mice showed that circadian dysfunction promotes non-alcoholic fatty liver disease-induced hepatocarcinogenesis by maintaining persistent genome-wide liver genetic dysregulation, metabolic disruption, and oncogene activation, closely mimicking that observed in obese human beings. The study found that circadian dysregulation of the bile acid receptor farnesoid X receptor and the xenobiotic receptor constitutive androstane receptor promotes non-alcoholic fatty liver disease-induced hepatocellular carcinoma. These findings are consistent with a chemopreventive benefit of improved liver histology in non-alcoholic steatohepatitis, as shown in an RCT of a farnesoid X receptor ligand.[204] New experimental and clinical models are beginning to address how these underlying changes subvert the biology of liver function, leading to cancer development, including the role of the immune system (eg, CD8 T cells, natural killer cells, interleukin 17 and M2 macrophage polarisation) and the microbiome.[205,206] Finally, gut microbiota-induced metabolites promote obesity-associated immune escape in hepatic tumorigenesis.[207]

Conclusion

This Series paper highlights the gaps, challenges, and prospects for further study into the associations between diet and activity levels and cancer incidence and mortality. Physical activity and sedentary behaviour are associated with major cancer-related outcomes, including quality of life.[208-210] A large prospective study[211] suggested that physical activity decreased in men and time spent sitting increased in women following a cancer diagnosis (compared with before diagnosis), especially in overweight and elderly patients. These results help to identify patient subgroups at the highest risk of these detrimental behaviours to appropriately target interventions. Accelerometers are becoming more wearable for continuous longitudinal monitoring of physical activity in both populations and individual patients. Furthermore, increasingly advanced computational techniques are available to investigate temporal and spatial patterns of daily variations in physical activity.[212,213] As a result, a precision medicine approach to physical activity interventions is expected to develop in the near future. Such a development, however, will require more transdisciplinary research and big data solutions. The National Cancer Institute, for example, is supporting this research shift through grant opportunities into associated research areas. This new investigation into big behavioural data (including the substantial microbiome changes observed in sedentary people[98]) is likely to enable discoveries in a similar way to genomic medicine, and will support more comprehensive studies into gene-environment interactions.

The existing epidemiological literature generally supports associations between diet and cancer risk, with emerging notable and consistent associations of a high intake of fruits and vegetables with a decreased risk of oestrogen receptor-negative breast cancer meriting definitive testing in RCTs. However, as noted, previous RCTs on individual nutrients and foods have generally been negative for several possible reasons. Future trials should instead focus on dietary patterns. Robust, large-scale RCTs are needed to definitively quantify the effects of health behaviours on cancer incidence, recurrence, and survival. Additionally, the increased role of obesity and non-alcoholic fatty liver disease or non-alcoholic steatohepatitis worldwide in cases of hepatocellular carcinoma is of future concern. There is also a dearth of research into early life exposures to cancer risk factors and minority populations.[162,214] New areas of research into cancers of the breast, liver, and other sites should include effects of circadian disruption and crown-like structures in individuals of a healthy bodyweight.[183,198,203,215] The interplay between genetics, diet, behaviours, environmental factors, inflammatory and metabolomic factors, microbiota (including viruses and protozoa), and immunity have important implications for the effects of lifestyle on cancer incidence and survival. Furthermore, this interplay suggests an increasing potential of microbiota as a crucial modifiable risk factor that should be controlled for in future studies of lifestyle factors.[129,200,216-218]

Finally, to reduce cancer incidence and mortality in the USA and worldwide, we need well designed studies into how best to implement and disseminate advice about cancer prevention, to determine how we can translate physical activity and dietary findings into clinical and community oncology practice. High BMI continues to have one of the highest rates of increase among the leading global health risks, accounting for 4 million deaths worldwide in 2015, 40% of which were in people who were not obese. The drivers of this global burden are likely related to the increased availability of energy-dense foods, reduced opportunities for physical activity that followed urbanisation, and other changes in the built environment.[219] Healthy lifestyle practices should be promoted throughout life, both at the individual and population level, as a means of achieving appropriate bodyweight and optimal metabolic health, and reducing the overall burden of cancer. Continued review of the evidence in global reports will support these efforts.

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References

1. Emmons KM, Colditz GA. Realizing the potential of cancer prevention—the role of implementation science. N Engl J Med 2017; 376: 986–90. [PubMed: 28273020]
2. Morris HP. Ample exercise and a minimum of food as measures for cancer prevention? Science 1945; 101: 457–59. [PubMed: 17798992]
3. Kushi LH, Doyle C, McCullough M, et al. , for the American Cancer Society 2010 Nutrition and Physical Activity Guidelines Advisory Committee. American Cancer Society Guidelines on nutrition and physical activity for cancer prevention: reducing the risk of cancer with healthy food choices and physical activity. CA Cancer J Clin 2012; 62: 30–67 [PubMed: 22237782]

4. World Cancer Research Fund, American Institute for Cancer Research. Food, nutrition, physical activity, and the prevention of cancer: a global perspective. Washington, DC, USA: American Institute for Cancer Research, 2007.
5. US Department of Health and Human Services. Physical activity guidelines for Americans. Bethesda, MD, USA: US Department of Health and Human Services, 2008.
6. Sallis JF, Cervero RB, Ascher W, Henderson KA, Kraft MK, Kerr J. An ecological approach to creating active living communities. Annu Rev Public Health 2006; 27: 297–322. [PubMed: 16533119]
7. Lynch BM, Dunstan DW, Vallance JK, Owen N. Don't take cancer sitting down: a new survivorship research agenda. Cancer 2013; 119: 1928–35. [PubMed: 23504979]
8. Troiano RP, Berrigan D, Dodd KW, Masse LC, Tilert T, McDowell M. Physical activity in the United States measured by accelerometer. Med Sci Sports Exerc 2008; 40: 181–88. [PubMed: 18091006]
9. Kerr J, Marinac CR, Ellis K, et al. Comparison of accelerometry methods for estimating physical activity. Med Sci Sports Exerc 2017; 49: 617–24. [PubMed: 27755355]
10. Liu L, Shi Y, Li T, et al. Leisure time physical activity and cancer risk: evaluation of the WHO's recommendation based on 126 high-quality epidemiological studies. Br J Sports Med 2016; 50: 372–78. [PubMed: 26500336]
11. 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 2016; 176: 816–25. [PubMed: 27183032]
12. Pizot C, Boniol M, Mullie P, et al. Physical activity, hormone replacement therapy and breast cancer risk: a meta-analysis of prospective studies. Eur J Cancer 2016; 52: 138–54. [PubMed: 26687833]
13. Kyu HH, Bachman VF, Alexander LT, et al. Physical activity and risk of breast cancer, colon cancer, diabetes, ischemic heart disease, and ischemic stroke events: systematic review and dose-response meta-analysis for the Global Burden of Disease Study 2013. BMJ 2016; 354: i3857 [PubMed: 27510511]
14. Hildebrand JS, Gapstur SM, Gaudet MM, Campbell PT, Patel AV. Moderate-to-vigorous physical activity and leisure-time sitting in relation to ovarian cancer risk in a large prospective US cohort. Cancer Causes Control 2015; 26: 1691–97 [PubMed: 26335264]
15. Farris MS, Mosli MH, McFadden AA, Friedenreich CM, Brenner DR. The association between leisure time physical activity and pancreatic cancer risk in adults: a systematic review and meta-analysis. Cancer Epidemiol Biomarkers Prev 2015; 24: 1462–73. [PubMed: 26174790]
16. Buffart LM, Singh AS, van Loon EC, Vermeulen HI, Brug J, Chinapaw MJ. Physical activity and the risk of developing lung cancer among smokers: a meta-analysis. J Sci Med Sport 2014; 17: 67–71. [PubMed: 23528254]
17. Shi Y, Li T, Wang Y, et al. Household physical activity and cancer risk: a systematic review and dose-response meta-analysis of epidemiological studies. Sci Rep 2015; 5: 14901. [PubMed: 26443426]
18. Keum N, Bao Y, Smith-Warner SA, et al. Association of physical activity by type and intensity with digestive system cancer risk. JAMA Oncol 2016; 2: 1146–53. [PubMed: 27196375]
19. Hrafnkelsdóttir SM, Torfadóttir JE, Aspelund T, et al. Physical activity from early adulthood and risk of prostate cancer: a 24-year follow-up study among Icelandic men. Cancer Prev Res 2015; 8: 905–11.
20. Boyle T, Keegel T, Bull F, Heyworth J, Fritschi L. Physical activity and risks of proximal and distal colon cancers: a systematic review and meta-analysis. J Natl Cancer Inst 2012; 104: 1548–61. [PubMed: 22914790]
21. Lakoski SG, Willis BL, Barlow CE, et al. Midlife cardiorespiratory fitness, incident cancer, and survival after cancer in men: the Cooper Center longitudinal study. JAMA Oncol 2015; 1: 231–37 [PubMed: 26181028]
22. Eliassen AH, Hankinson SE, Rosner B, Holmes MD, Willett WC. Physical activity and risk of breast cancer among postmenopausal women. Arch Intern Med 2010; 170: 1758–64. [PubMed: 20975025]

23. Lope V, Martin M, Castelló A, et al. , for GEICAM, the Spanish Breast Cancer Group. Physical activity and breast cancer risk by pathological subtype. Gynecol Oncol 2017; 144: 577–85. [PubMed: 28057355]
24. Ma H, Xu X, Clague J, et al. Recreational physical activity and risk of triple negative breast cancer in the California Teachers Study. Breast Cancer Res 2016; 18: 62. [PubMed: 27317095]
25. Rosenberg L, Palmer JR, Bethea TN, Ban Y, Kipping-Ruane K, Adams-Campbell LL. A prospective study of physical activity and breast cancer incidence in African-American women. Cancer Epidemiol Biomarkers Prev 2014; 23: 2522–31. [PubMed: 25103823]
26. Dallal CM, Brinton LA, Matthews CE, et al. Accelerometer-based measures of active and sedentary behavior in relation to breast cancer risk. Breast Cancer Res Treat 2012; 134: 1279–90. [PubMed: 22752209]
27. Lee IM, Shiroma EJ. Using accelerometers to measure physical activity in large-scale epidemiological studies: issues and challenges. Br J Sports Med 2014; 48: 197–201. [PubMed: 24297837]
28. Song JH, Kim YS, Yang SY, et al. Physical activity and other lifestyle factors in relation to the prevalence of colorectal adenoma: a colonoscopy-based study in asymptomatic Koreans. Cancer Causes Control 2013; 24: 1717–26. [PubMed: 23754755]
29. Aune D, Navarro Rosenblatt DA, Chan DS, et al. Anthropometric factors and endometrial cancer risk: a systematic review and dose-response meta-analysis of prospective studies. Ann Oncol 2015; 26: 1635–48. [PubMed: 25791635]
30. Beavis AL, Smith AJ, Fader AN. Lifestyle changes and the risk of developing endometrial and ovarian cancers: opportunities for prevention and management. Int J Womens Health 2016; 8: 151–67. [PubMed: 27284267]
31. Borch KB, Weiderpass E, Braaten T, Jareid M, Gavrilyuk OA, Licaj I. Physical activity and risk of endometrial cancer in the Norwegian Women and Cancer (NOWAC) study. Int J Cancer 2017; 140: 1809–18. [PubMed: 28108996]
32. Nunez C, Bauman A, Egger S, Sitas F, Nair-Shalliker V. Obesity, physical activity and cancer risks: results from the Cancer, Lifestyle and Evaluation of Risk study (CLEAR). Cancer Epidemiol 2017; 47: 56–63. [PubMed: 28126584]
33. Wu W, Guo F, Ye J, et al. Pre- and post-diagnosis physical activity is associated with survival benefits of colorectal cancer patients: a systematic review and meta-analysis. Oncotarget 2016; 7: 52095–103. [PubMed: 27437765]
34. Winzer BM, Whiteman DC, Reeves MM, Paratz JD. Physical activity and cancer prevention: a systematic review of clinical trials. Cancer Causes Control 2011; 22: 811–26. [PubMed: 21461921]
35. Friedenreich CM, Neilson HK, Farris MS, Courneya KS. Physical activity and cancer outcomes: a precision medicine approach. Clin Cancer Res 2016; 22: 4766–75. [PubMed: 27407093]
36. Li T, Wei S, Shi Y, et al. The dose-response effect of physical activity on cancer mortality: findings from 71 prospective cohort studies. Br J Sports Med 2016; 50: 339–45. [PubMed: 26385207]
37. Lahart IM, Metsios GS, Nevill AM, Carmichael AR. Physical activity, risk of death and recurrence in breast cancer survivors: a systematic review and meta-analysis of epidemiological studies. Acta Oncol 2015; 54: 635–54. [PubMed: 25752971]
38. Friedenreich CM, Wang Q, Neilson HK, Kopciuk KA, McGregor SE, Courneya KS. Physical activity and survival after prostate cancer. Eur Urol 2016; 70: 576–85. [PubMed: 26774959]
39. Borch KB, Braaten T, Lund E, Weiderpass E. Physical activity before and after breast cancer diagnosis and survival—the Norwegian women and cancer cohort study. BMC Cancer 2015; 15: 967 [PubMed: 26672980]
40. Schmid D, Leitzmann MF. Association between physical activity and mortality among breast cancer and colorectal cancer survivors: a systematic review and meta-analysis. Ann Oncol 2014; 25: 1293–311. [PubMed: 24644304]
41. Otto SJ, Korfage IJ, Polinder S, et al. Association of change in physical activity and body weight with quality of life and mortality in colorectal cancer: a systematic review and meta-analysis. Support Care Cancer 2015; 23: 1237–50. [PubMed: 25318696]

42. Des Guetz G, Uzzan B, Bouillet T, et al. Impact of physical activity on cancer-specific and overall survival of patients with colorectal cancer. Gastroenterol Res Pract 2013; 340851 [PubMed: 24222762]
43. Li T, Wei S, Shi Y, et al. The dose-response effect of physical activity on cancer mortality: findings from 71 prospective cohort studies. Br J Sports Med 2016; 50: 339–45. [PubMed: 26385207]
44. Schmid D, Leitzmann MF. Association between physical activity and mortality among breast cancer and colorectal cancer survivors: a systematic review and meta-analysis. Ann Oncol 2014; 25: 1293–311. [PubMed: 24644304]
45. Friedenreich CM, Wang Q, Neilson HK, Kopciuk KA, McGregor SE, Courneya KS. Physical activity and survival after prostate cancer. Eur Urol 2016; 70: 576–85. [PubMed: 26774959]
46. Borch KB, Braaten T, Lund E, Weiderpass E. Physical activity before and after breast cancer diagnosis and survival - the Norwegian women and cancer cohort study. BMC Cancer 2015; 15: 967 [PubMed: 26672980]
47. Schmid D, Leitzmann MF. Television viewing and time spent sedentary in relation to cancer risk: a meta-analysis. J Natl Cancer Inst 2014; 106: dju098. [PubMed: 24935969]
48. Cong YJ, Gan Y, Sun HL, et al. Association of sedentary behaviour with colon and rectal cancer: a meta-analysis of observational studies. Br J Cancer 2014; 110: 817–26. [PubMed: 24263062]
49. Biswas A, Oh PI, Faulkner GE, et al. Sedentary time and its association with risk for disease incidence, mortality, and hospitalization in adults: a systematic review and meta-analysis. Ann Intern Med 2015; 162: 123–32. [PubMed: 25599350]
50. Shen D, Mao W, Liu T, et al. Sedentary behavior and incident cancer: a meta-analysis of prospective studies. PLoS One 2014; 9: e105709. [PubMed: 25153314]
51. Boyle T, Fritschi L, Heyworth J, Bull F. Long-term sedentary work and the risk of subsite-specific colorectal cancer. Am J Epidemiol 2011; 173: 1183–91. [PubMed: 21421743]
52. Cohen SS, Matthews CE, Bradshaw PT, et al. Sedentary behavior, physical activity, and likelihood of breast cancer among Black and White women: a report from the Southern Community Cohort Study. Cancer Prev Res 2013; 6: 566–76.
53. Lynch BM, Courneya KS, Friedenreich CM. A case-control study of lifetime occupational sitting and likelihood of breast cancer. Cancer Causes Control 2013; 24: 1257–62. [PubMed: 23526070]
54. Cook MB, Matthews CE, Gunja MZ, Abid Z, Freedman ND, Abnet CC. Physical activity and sedentary behavior in relation to esophageal and gastric cancers in the NIH-AARP cohort. PLoS One 2013; 8: e84805. [PubMed: 24367697]
55. Nomura SJ, Dash C, Rosenberg L, Palmer J, Adams-Campbell LL. Sedentary time and breast cancer incidence in African American women. Cancer Causes Control 2016; 27: 1239–52. [PubMed: 27632430]
56. Simons CC, Hughes LA, van Engeland M, Goldbohm RA, van den Brandt PA, Weijenberg MP. Physical activity, occupational sitting time, and colorectal cancer risk in the Netherlands cohort study. Am J Epidemiol 2013; 177: 514–30. [PubMed: 23420352]
57. van Uffelen JG, Wong J, Chau JY, et al. Occupational sitting and health risks: a systematic review. Am J Prev Med 2010; 39: 379–88. [PubMed: 20837291]
58. Patel AV, Hildebrand JS, Campbell PT, et al. Leisure-time spent sitting and site-specific cancer incidence in a large U.S. cohort. Cancer Epidemiol Biomarkers Prev 2015; 24: 1350–59. [PubMed: 26126627]
59. Cao Y, Keum NN, Chan AT, Fuchs CS, Wu K, Giovannucci EL. Television watching and risk of colorectal adenoma. Br J Cancer 2015; 112: 934–42. [PubMed: 25590667]
60. Molmenti CL, Hibler EA, Ashbeck EL, et al. Sedentary behavior is associated with colorectal adenoma recurrence in men. Cancer Causes Control 2014; 25: 1387–95. [PubMed: 25060482]
61. Namasivayam V, Lim S. Recent advances in the link between physical activity, sedentary behavior, physical fitness, and colorectal cancer. F1000Res 2017; 6: 199. [PubMed: 28344777]
62. Loprinzi PD, Kohli M. Effect of physical activity and sedentary behavior on serum prostate-specific antigen concentrations: results from the National Health and Nutrition Examination Survey (NHANES), 2003–2006. Mayo Clin Proc 2013; 88: 11–21. [PubMed: 23274016]
63. Johnsson A, Broberg P, Johnsson A, Tornberg ÅB, Olsson H. Occupational sedentariness and breast cancer risk. Acta Oncol 2017; 56: 75–80. [PubMed: 27919198]

64. Ekelund U, Steene-Johannessen J, Brown WJ, et al. , for the Lancet Physical Activity Series 2 Executive Committee, Lancet Sedentary Behaviour Working Group. Does physical activity attenuate, or even eliminate, the detrimental association of sitting time with mortality? A harmonised meta-analysis of data from more than 1 million men and women. Lancet 2016; 388: 1302–10. [PubMed: 27475271]

65. Cao Y, Meyerhardt JA, Chan AT, Wu K, Fuchs CS, Giovannucci EL. Television watching and colorectal cancer survival in men. Cancer Causes Control 2015; 26: 1467–76. [PubMed: 26293240]

66. Dunstan DW, Barr EL, Healy GN, et al. Television viewing time and mortality: the Australian Diabetes, Obesity and Lifestyle Study (AusDiab). Circulation 2010; 121: 384–91. [PubMed: 20065160]

67. Katzmarzyk PT. Standing and mortality in a prospective cohort of Canadian adults. Med Sci Sports Exerc 2014; 46: 940–46. [PubMed: 24152707]

68. Keadle SK, Moore SC, Sampson JN, Xiao Q, Albanes D, Matthews CE. Causes of death associated with prolonged TV viewing: NIH-AARP Diet and Health study. Am J Prev Med 2015; 49: 811–21. [PubMed: 26215832]

69. Lynch BM, Friedenreich CM, Kopciuk KA, Hollenbeck AR, Moore SC, Matthews CE. Sedentary behavior and prostate cancer risk in the NIH-AARP Diet and Health study. Cancer Epidemiol Biomarkers Prev 2014; 23: 882–89. [PubMed: 24526287]

70. Matthews CE, Cohen SS, Fowke JH, et al. Physical activity, sedentary behavior, and cause-specific mortality in black and white adults in the Southern Community Cohort study. Am J Epidemiol 2014; 180: 394–405. [PubMed: 25086052]

71. Matthews CE, George SM, Moore SC, et al. Amount of time spent in sedentary behaviors and cause-specific mortality in US adults. Am J Clin Nutr 2012; 95: 437–45. [PubMed: 22218159]

72. Seguin R, Buchner DM, Liu J, et al. Sedentary behavior and mortality in older women: the Women's Health Initiative. Am J Prev Med 2014; 46: 122–35. [PubMed: 24439345]

73. Stamatakis E, Chau JY, Pedisic Z, et al. Are sitting occupations associated with increased all-cause, cancer, and cardiovascular disease mortality risk? A pooled analysis of seven British population cohorts. PLoS One 2013; 8: e73753. [PubMed: 24086292]

74. Ukawa S, Tamakoshi A, Wakai K, Kurozawa Y. Associations of daily walking and television viewing time with liver cancer mortality: findings from the Japan Collaborative Cohort study. Cancer Causes Control 2014; 25: 787–93. [PubMed: 24728669]

75. Kim Y, Wilkens LR, Park SY, Goodman MT, Monroe KR, Kolonel LN. Association between various sedentary behaviours and all-cause, cardiovascular disease and cancer mortality: the Multiethnic Cohort Study. Int J Epidemiol 2013; 42: 1040–56. [PubMed: 24062293]

76. Proper KI, Singh AS, van Mechelen W, Chinapaw MJ. Sedentary behaviors and health outcomes among adults: a systematic review of prospective studies. Am J Prev Med 2011; 40: 174–82. [PubMed: 21238866]

77. Arem H, Pfeiffer RM, Engels EA, et al. Pre- and postdiagnosis physical activity, television viewing, and mortality among patients with colorectal cancer in the National Institutes of Health-AARP Diet and Health Study. J Clin Oncol 2015; 33: 180–88. [PubMed: 25488967]

78. Campbell PT, Patel AV, Newton CC, Jacobs EJ, Gapstur SM. Associations of recreational physical activity and leisure time spent sitting with colorectal cancer survival. J Clin Oncol 2013; 31: 876–85. [PubMed: 23341510]

79. Lynch BM, Cerin E, Owen N, Hawkes AL, Aitken JF. Television viewing time of colorectal cancer survivors is associated prospectively with quality of life. Cancer Causes Control 2011; 22: 1111–20. [PubMed: 21656163]

80. Ballard-Barbash R, Friedenreich CM, Courneya KS, Siddiqi SM, McTiernan A, Alfano CM. Physical activity, biomarkers, and disease outcomes in cancer survivors: a systematic review. J Natl Cancer Inst 2012; 104: 815–910. [PubMed: 22570317]

81. Ennour-Idrissi K, Maunsell E, Diorio C. Effect of physical activity on sex hormones in women: a systematic review and meta-analysis of randomized controlled trials. Breast Cancer Res 2015; 17: 139. [PubMed: 26541144]

82. Epigenetics Hibler E. and colorectal neoplasia: the evidence for physical activity and sedentary behavior. Curr Colorectal Cancer Rep 2015; 11: 388–96. [PubMed: 27212896]
83. Robinson MM, Dasari S, Konopka AR, et al. Enhanced protein translation underlies improved metabolic and physical adaptations to different exercise training modes in young and old humans. Cell Metab 2017; 25: 581–92. [PubMed: 28273480]
84. Zheng Q, Cui G, Chen J, et al. Regular exercise enhances the immune response against microbial antigens through up-regulation of toll-like receptor signaling pathways. Cell Physiol Biochem 2015; 37: 735–46. [PubMed: 26356264]
85. Magbanua MJ, Richman EL, Sosa EV, et al. Physical activity and prostate gene expression in men with low-risk prostate cancer. Cancer Causes Control 2014; 25: 515–23. [PubMed: 24504435]
86. Olufsen MS, Ottesen JT, Tran HT, Ellwein LM, Lipsitz LA, Novak V. Blood pressure and blood flow variation during postural change from sitting to standing: model development and validation. J Appl Physiol (1985) 2005; 99: 1523–37 [PubMed: 15860687]
87. Thosar SS, Johnson BD, Johnston JD, Wallace JP. Sitting and endothelial dysfunction: the role of shear stress. Med Sci Monit 2012; 18: RA173–80. [PubMed: 23197245]
88. Wiseman AJ, Lynch BM, Cameron AJ, Dunstan DW. Associations of change in television viewing time with biomarkers of postmenopausal breast cancer risk: the Australian Diabetes, Obesity and Lifestyle Study. Cancer Causes Control 2014; 25: 1309–19. [PubMed: 25053405]
89. Lynch BM, Dunstan DW, Healy GN, Winkler E, Eakin E, Owen N. Objectively measured physical activity and sedentary time of breast cancer survivors, and associations with adiposity: findings from NHANES (2003–2006). Cancer Causes Control 2010; 21: 283–88. [PubMed: 19882359]
90. Saunders TJ, Larouche R, Colley RC, Tremblay MS. Acute sedentary behaviour and markers of cardiometabolic risk: a systematic review of intervention studies. J Nutr Metab 2012; 712435. [PubMed: 22754695]
91. Ashcraft KA, Peace RM, Betof AS, Dewhirst MW, Jones LW. Efficacy and mechanisms of aerobic exercise on cancer initiation, progression, and metastasis: a critical systematic review of in vivo preclinical data. Cancer Res 2016; 76: 4032–50. [PubMed: 27381680]
92. Brown JC, Kontos D, Schnall MD, Wu S, Schmitz KH. The dose-response effects of aerobic exercise on body composition and breast tissue among women at high risk for breast cancer: a randomized trial. Cancer Prev Res 2016; 9: 581–88.
93. Thyfault JP, Du M, Kraus WE, Levine JA, Booth FW. Physiology of sedentary behavior and its relationship to health outcomes. Med Sci Sports Exerc 2015; 47: 1301–05. [PubMed: 25222820]
94. World Cancer Research Fund, American Institute for Cancer Research. Continuous update project report. Food, nutrition, physical activity, and the prevention of breast cancer 2010. http://www.wcrf.org/sites/default/files/Breast-Cancer-2010-Report.pdf (accessed June 25, 2017).
95. Pettapiece-Phillips R, Narod SA, Kotsopoulos J. The role of body size and physical activity on the risk of breast cancer in BRCA mutation carriers. Cancer Causes Control 2015; 26: 333–44. [PubMed: 25579073]
96. Pijpe A, Manders P, Brohet RM, et al. Physical activity and the risk of breast cancer in BRCA1/2 mutation carriers. Breast Cancer Res Treat 2010; 120: 235–444. [PubMed: 19680614]
97. Pettapiece-Phillips R, Kotlyar M, Chehade R, et al. Uninterrupted sedentary behavior downregulates BRCA1 gene expression. Cancer Prev Res 2016; 9: 83–88.
98. Edwards MK, Loprinzi PD. Sedentary behavior, physical activity and cardiorespiratory fitness on leukocyte telomere length. Health Promot Perspect 2016; 7: 22–27. [PubMed: 28058238]
99. Bressa C, Bailén-Andrino M, Pérez-Santiago J, et al. Differences in gut microbiota profile between women with active lifestyle and sedentary women. PLoS One 2017; 12: e0171352. [PubMed: 28187199]
100. Kelemen LE. Food frequency questionnaires: not irrelevant yet. Cancer Epidemiol Biomarkers Prev 2006; 15: 1054.
101. Harmon BE, Boushey CJ, Shvetsov YB, et al. Associations of key diet-quality indexes with mortality in the Multiethnic Cohort: the Dietary Patterns Methods Project. Am J Clin Nutr 2015; 101: 587–97. [PubMed: 25733644]

102. Liese AD, Krebs-Smith SM, Subar AF, et al. The Dietary Patterns Methods Project: synthesis of findings across cohorts and relevance to dietary guidance. J Nutr 2015; 145: 393–402. [PubMed: 25733454]
103. George SM, Ballard-Barbash R, Manson JE, et al. Comparing indices of diet quality with chronic disease mortality risk in postmenopausal women in the Women's Health Initiative Observational Study: evidence to inform national dietary guidance. Am J Epidemiol 2014; 180: 616–25. [PubMed: 25035143]
104. Reedy J, Krebs-Smith SM, Miller PE, et al. Higher diet quality is associated with decreased risk of all-cause, cardiovascular disease, and cancer mortality among older adults. J Nutr 2014; 144: 881–89. [PubMed: 24572039]
105. US Department of Agriculture. Report from the Nutrition Evidence Library Technical Expert Collaborative. A series of systematic reviews on the relationship between dietary patterns and health outcomes. March 2014. https://www.cnpp.usda.gov/sites/default/files/usda_nutrition_evidence_flbrary/DietaryPatternsReport-FullFinal.pdf (accessed June 25, 2017).
106. Chen WY, Rosner B, Hankinson SE, Colditz GA, Willett WC. Moderate alcohol consumption during adult life, drinking patterns, and breast cancer risk. JAMA 2011; 306: 1884–90. [PubMed: 22045766]
107. Liu Y, Colditz GA, Rosner B, et al. Alcohol intake between menarche and first pregnancy: a prospective study of breast cancer risk. J Natl Cancer Inst 2013; 105: 1571–78. [PubMed: 23985142]
108. Buckland G, Travier N, Cottet V, et al. Adherence to the mediterranean diet and risk of breast cancer in the European prospective investigation into cancer and nutrition cohort study. Int J Cancer 2013; 132: 2918–27 [PubMed: 23180513]
109. Engeset D, Dyachenko A, Ciampi A, Lund E. Dietary patterns and risk of cancer of various sites in the Norwegian European Prospective Investigation into Cancer and Nutrition cohort: the Norwegian Women and Cancer study. Eur J Cancer Prev 2009; 18: 69–75. [PubMed: 19077568]
110. Fung TT, Hu FB, Hankinson SE, Willett WC, Holmes MD. Low-carbohydrate diets, dietary approaches to stop hypertension-style diets, and the risk of postmenopausal breast cancer. Am J Epidemiol 2011; 174: 652–60. [PubMed: 21832271]
111. Key TJ, Appleby PN, Spencer EA, Travis RC, Roddam AW, Allen NE. Cancer incidence in vegetarians: results from the European Prospective Investigation into Cancer and Nutrition (EPIC-Oxford). Am J Clin Nutr 2009; 89: 1620S–1626S. [PubMed: 19279082]
112. Mai V, Kant AK, Flood A, Lacey JV Jr, Schairer C, Schatzkin A. Diet quality and subsequent cancer incidence and mortality in a prospective cohort of women. Int J Epidemiol 2005; 34: 54–60. [PubMed: 15649959]
113. Potter J, Brown L, Williams RL, Byles J, Collins CE. Diet quality and cancer outcomes in adults: a systematic review of epidemiological studies. Int J Mol Sci 2016; 17: E1052.
114. Eliassen AH, Hendrickson SJ, Brinton LA, et al. Circulating carotenoids and risk of breast cancer: pooled analysis of eight prospective studies. J Natl Cancer Inst 2012; 104: 1905–16. [PubMed: 23221879]
115. Eliassen AH, Liao X, Rosner B, Tamimi RM, Tworoger SS, Hankinson SE. Plasma carotenoids and risk of breast cancer over 20 y of follow-up. Am J Clin Nutr 2015; 101: 1197–205. [PubMed: 25877493]
116. Emaus MJ, Peeters PH, Bakker MF, et al. Vegetable and fruit consumption and the risk of hormone receptor-defined breast cancer in the EPIC cohort. Am J Clin Nutr 2016; 103: 168–77. [PubMed: 26607934]
117. Jung S, Spiegelman D, Baglietto L, et al. Fruit and vegetable intake and risk of breast cancer by hormone receptor status. J Natl Cancer Inst 2013; 105: 219–36. [PubMed: 23349252]
118. Bakker MF, Peeters PH, Klaasen VM, et al. Plasma carotenoids, vitamin C, tocopherols, and retinol and the risk of breast cancer in the European Prospective Investigation into Cancer and Nutrition cohort. Am J Clin Nutr 2016; 103: 454–64. [PubMed: 26791185]
119. Prentice RL, Caan B, Chlebowski RT, et al. Low-fat dietary pattern and risk of invasive breast cancer: the Women's Health Initiative Randomized Controlled Dietary Modification trial. JAMA 2006; 295: 629–42. [PubMed: 16467232]

120. Sieri S, Chiodini P, Agnoli C, et al. Dietary fat intake and development of specific breast cancer subtypes. J Natl Cancer Inst 2014; 106: dju068. [PubMed: 24718872]

121. Toledo E, Salas-Salvadó J, Donat-Vargas C, et al. Mediterranean diet and invasive breast cancer risk among women at high cardiovascular risk in the PREDIMED trial: a randomized clinical trial. JAMA Intern Med 2015; 175: 1752–60. [PubMed: 26365989]

122. Bamia C, Lagiou P, Buckland G, et al. Mediterranean diet and colorectal cancer risk: results from a European cohort. Eur J Epidemiol 2013; 28: 317–28. [PubMed: 23579425]

123. Beresford SA, Johnson KC, Ritenbaugh C, et al. Low-fat dietary pattern and risk of colorectal cancer: the Women's Health Initiative Randomized Controlled Dietary Modification trial. JAMA 2006; 295: 643–54. [PubMed: 16467233]

124. Bradbury KE, Appleby PN, Key TJ. Fruit, vegetable, and fiber intake in relation to cancer risk: findings from the European Prospective Investigation into Cancer and Nutrition (EPIC). Am J Clin Nutr 2014; 100 (suppl 1): 394S–8S. [PubMed: 24920034]

125. Fung TT, Hu FB, Wu K, Chiuve SE, Fuchs CS, Giovannucci E. The Mediterranean and Dietary Approaches to Stop Hypertension (DASH) diets and colorectal cancer. Am J Clin Nutr 2010; 92: 1429–35. [PubMed: 21097651]

126. Wirfält E, Midthune D, Reedy J, et al. Associations between food patterns defined by cluster analysis and colorectal cancer incidence in the NIH-AARP diet and health study. Eur J Clin Nutr 2009; 63: 707–17. [PubMed: 18685556]

127. Park SY, Boushey CJ, Wilkens LR, Haiman CA, Le Marchand L. High-quality diets associate with reduced risk of colorectal cancer: analyses of diet quality indexes in the multiethnic cohort. Gastroenterology 2017; published online April 17. DOI:10.1053/j.gastro.2017.04.004.

128. Schatzkin A, Lanza E, Corle D, et al. Lack of effect of a low-fat, high-fiber diet on the recurrence of colorectal adenomas. Polyp Prevention Trial Study Group. N Engl J Med 2000; 342: 1149–55. [PubMed: 10770979]

129. O'Keefe SJ. Diet, microorganisms and their metabolites, and colon cancer. Nat Rev Gastroenterol Hepatol 2016; 13: 691–706. [PubMed: 27848961]

130. Mehta RS, Nishihara R, Cao Y, et al. Association of dietary patterns with risk of colorectal cancer subtypes classified by *Fusobacterium nucleatum* in tumor tissue. JAMA Oncol 2017; published online Jan 26. DOI:10.1001/jamaoncol.2016.6374.

131. Bosire C, Stampfer MJ, Subar AF, et al. Index-based dietary patterns and the risk of prostate cancer in the NIH-AARP diet and health study. Am J Epidemiol 2013; 177: 504–13. [PubMed: 23408548]

132. Kenfield SA, DuPre N, Richman EL, Stampfer MJ, Chan JM, Giovannucci EL. Mediterranean diet and prostate cancer risk and mortality in the Health Professionals Follow-up Study. Eur Urol 2014; 65: 887–94. [PubMed: 23962747]

133. Muller DC, Severi G, Baglietto L, et al. Dietary patterns and prostate cancer risk. Cancer Epidemiol Biomarkers Prev 2009; 18: 3126–29. [PubMed: 19861522]

134. World Cancer Research Fund International, American Institute for Cancer Research. Continuous Update Project Report. Diet, nutrition, physical activity, and prostate cancer 2014. http://www.wcrf.org/sites/default/files/Prostate-Cancer-2014-Report.pdf (accessed June 25, 2017).

135. Key TJ, Appleby PN, Travis RC, et al. Carotenoids, retinol, tocopherols, and prostate cancer risk: pooled analysis of 15 studies. Am J Clin Nutr 2015; 102: 1142–57 [PubMed: 26447150]

136. Yang M, Kenfield SA, Van Blarigan EL, et al. Dietary patterns after prostate cancer diagnosis in relation to disease-specific and total mortality. Cancer Prev Res 2015; 8: 545–51.

137. Richman EL, Kenfield SA, Chavarro JE, et al. Fat intake after diagnosis and risk of lethal prostate cancer and all-cause mortality. JAMA Intern Med 2013; 173: 1318–26. [PubMed: 23752662]

138. Parsons JK, Pierce JP, Mohler J, et al. The Men's Eating and Living (MEAL) Study (CALGB 70807 [Alliance]): recruitment feasibility and baseline demographics of a randomized trial of diet in men on active surveillance for prostate cancer. BJU Int 2017; published online April 24. DOI:10.1111/bju.13890.

139. Fleshner NE, Lucia MS, Egerdie B, et al. Dutasteride in localised prostate cancer management: the REDEEM randomised, double-blind, placebo-controlled trial. Lancet 2012; 379: 1103–11. [PubMed: 22277570]

140. Lippman SM, Goodman PJ, Klein EA, et al. Designing the Selenium and Vitamin E Cancer Prevention Trial (SELECT). J Natl Cancer Inst 2005; 97: 94–102. [PubMed: 15657339]
141. Lippman SM, Klein EA, Goodman PJ, et al. Effect of selenium and vitamin E on risk of prostate cancer and other cancers: the Selenium and Vitamin E Cancer Prevention Trial (SELECT). JAMA 2009; 301: 39–51. [PubMed: 19066370]
142. Klein EA, Thompson IM Jr, Tangen CM, et al. Vitamin E and the risk of prostate cancer: the Selenium and Vitamin E Cancer Prevention Trial (SELECT). JAMA 2011; 306: 1549–56. [PubMed: 21990298]
143. Kristal AR, Darke AK, Morris JS, et al. Baseline selenium status and effects of selenium and vitamin E supplementation on prostate cancer risk. J Natl Cancer Inst 2014; 106: djt456. [PubMed: 24563519]
144. Vollset SE, Clarke R, Lewington S, et al. Effects of folic acid supplementation on overall and site-specific cancer incidence during the randomised trials: meta-analyses of data on 50,000 individuals. Lancet 2013; 381: 1029–36. [PubMed: 23352552]
145. Hanley MP, Kadaveru K, Perret C, Giardina C, Rosenberg DW. Dietary methyl donor depletion suppresses intestinal adenoma development. Cancer Prev Res 2016; 9: 812–20.
146. Berkey CS, Gardner JD, Frazier AL, Colditz GA. Relation of childhood diet and body size to menarche and adolescent growth in girls. Am J Epidemiol 2000; 152: 446–52. [PubMed: 10981459]
147. Berkey CS, Willett WC, Frazier AL, et al. Prospective study of adolescent alcohol consumption and risk of benign breast disease in young women. Pediatrics 2010; 125: e1081–87. [PubMed: 20385629]
148. Rogers IS, Northstone K, Dunger DB, Cooper AR, Ness AR, Emmett PM. Diet throughout childhood and age at menarche in a contemporary cohort of British girls. Public Health Nutr 2010; 13: 2052–63. [PubMed: 20529402]
149. Günther AL, Karaolis-Danckert N, Kroke A, Remer T, Buyken AE. Dietary protein intake throughout childhood is associated with the timing of puberty. J Nutr 2010; 140: 565–71. [PubMed: 20042466]
150. Colditz GA, Bohlke K, Berkey CS. Breast cancer risk accumulation starts early: prevention must also. Breast Cancer Res Treat 2014; 145: 567–79. [PubMed: 24820413]
151. Boeke CE, Tamimi RM, Berkey CS, et al. Adolescent carotenoid intake and benign breast disease. Pediatrics 2014; 133: e1292–98. [PubMed: 24709924]
152. Cohen K, Liu Y, Luo J, Appleton CM, Colditz GA. Plasma carotenoids and the risk of premalignant breast disease in women aged 50 and younger: a nested case-control study. Breast Cancer Res Treat 2017; 162: 571–80. [PubMed: 28190250]
153. Frazier AL, Rosenberg SM. Preadolescent and adolescent risk factors for benign breast disease. J Adolesc Health 2013; 52 (5 suppl): S36–40.
154. Liu Y, Colditz GA, Cotterchio M, Boucher BA, Kreiger N. Adolescent dietary fiber, vegetable fat, vegetable protein, and nut intakes and breast cancer risk. Breast Cancer Res Treat 2014; 145: 461–70. [PubMed: 24737167]
155. Su X, Tamimi RM, Collins LC, et al. Intake of fiber and nuts during adolescence and incidence of proliferative benign breast disease. Cancer Causes Control 2010; 21: 1033–46. [PubMed: 20229245]
156. Farvid MS, Chen WY, Michels KB, Cho E, Willett WC, Eliassen AH. Fruit and vegetable consumption in adolescence and early adulthood and risk of breast cancer: population based cohort study. BMJ 2016; 353: i2343. [PubMed: 27170029]
157. Farvid MS, Eliassen AH, Cho E, Liao X, Chen WY, Willett WC. Dietary fiber intake in young adults and breast cancer risk. Pediatrics 2016; 137: e20151226. [PubMed: 26908709]
158. Nimptsch K, Bernstein AM, Giovannucci E, Fuchs CS, Willett WC, Wu K. Dietary intakes of red meat, poultry, and fish during high school and risk of colorectal adenomas in women. Am J Epidemiol 2013; 178: 172–83. [PubMed: 23785116]
159. Nimptsch K, Malik VS, Fung TT, et al. Dietary patterns during high school and risk of colorectal adenoma in a cohort of middle-aged women. Int J Cancer 2014; 134: 2458–67. [PubMed: 24493161]

160. Desai MS, Seekatz AM, Koropatkin NM, et al. A dietary fiber-deprived gut microbiota degrades the colonic mucus barrier and enhances pathogen susceptibility. Cell 2016; 167: 1339–53.e21. [PubMed: 27863247]

161. Ng M, Fleming T, Robinson M, et al. Global, regional, and national prevalence of overweight and obesity in children and adults during 1980–2013: a systematic analysis for the Global Burden of Disease Study 2013. Lancet 2014; 384: 766–81. [PubMed: 24880830]

162. Clarke MA, Joshu CE. Early life exposures and adult cancer risk. Epidemiol Rev 2017; 39: 11–27 [PubMed: 28407101]

163. Thaiss CA, Zmora N, Levy M, Elinav E. The microbiome and innate immunity. Nature 2016; 535: 65–74. [PubMed: 27383981]

164. Beyaz S, Mana MD, Roper J, et al. High-fat diet enhances stemness and tumorigenicity of intestinal progenitors. Nature 2016; 531: 53–58. [PubMed: 26935695]

165. Di Daniele N, Noce A, Vidiri MF, et al. Impact of Mediterranean diet on metabolic syndrome, cancer and longevity. Oncotarget 2017; 8: 8947–79. [PubMed: 27894098]

166. Kwa M, Plottel CS, Blaser MJ, Adams S. The intestinal microbiome and estrogen receptor-positive female breast cancer. J Natl Cancer Inst 2016; 108: djw029. [PubMed: 27107051]

167. Chan JM, Darke AK, Penney KL, et al. Selenium- or vitamin E-related gene variants, interaction with supplementation, and risk of high-grade prostate cancer in SELECT. Cancer Epidemiol Biomarkers Prev 2016; 25: 1050–58. [PubMed: 27197287]

168. Nordström T, Van Blarigan EL, Ngo V, et al. Associations between circulating carotenoids, genomic instability and the risk of high-grade prostate cancer. Prostate 2016; 76: 339–48. [PubMed: 26585352]

169. Lyssiotis CA, Cantley LC. Metabolic syndrome: F stands for fructose and fat. Nature 2013; 502: 181–82. [PubMed: 24108049]

170. Lauby-Secretan B, Scoccianti C, Loomis D, Grosse Y, Bianchini F, Straif K, for the International Agency for Research on Cancer Handbook Working Group. Body fatness and cancer—viewpoint of the IARC Working Group. N Engl J Med 2016; 375: 794–98. [PubMed: 27557308]

171. NCD Risk Factor Collaboration. Trends in adult body-mass index in 200 countries from 1975 to 2014: a pooled analysis of 1698 population-based measurement studies with 19·2 million participants. Lancet 2016; 387: 1377–96. [PubMed: 27115820]

172. Arnold M, Jiang L, Stefanick ML, et al. Duration of adulthood overweight, obesity, and cancer risk in the Women's Health Initiative: a longitudinal study from the United States. PLoS Med 2016; 13: e1002081. [PubMed: 27529652]

173. Neuhouser ML, Aragaki AK, Prentice RL, et al. Overweight, obesity, and postmenopausal invasive breast cancer risk: a secondary analysis of the women's health initiative randomized clinical trials. JAMA Oncol 2015; 1: 611–21. [PubMed: 26182172]

174. Nimptsch K, Pischon T. Obesity biomarkers, metabolism and risk of cancer: an epidemiological perspective. Recent Results Cancer Res 2016; 208: 199–217. [PubMed: 27909909]

175. Ligibel JA, Alfano CM, Courneya KS, et al. American Society of Clinical Oncology position statement on obesity and cancer. J Clin Oncol 2014; 32: 3568–74. [PubMed: 25273035]

176. Barrington WE, Schenk JM, Etzioni R, et al. Difference in association of obesity with prostate cancer risk between US African American and Non-Hispanic white men in the Selenium and Vitamin E Cancer Prevention Trial (SELECT). JAMA Oncol 2015; 1: 342–49. [PubMed: 26181184]

177. Jackson SE, Heinrich M, Beeken RJ, Wardle J. Weight loss and mortality in overweight and obese cancer survivors: a systematic review. PLoS One 2017; 12: e0169173. [PubMed: 28060948]

178. Rossi EL, de Angel RE, Bowers LW, et al. Obesity-associated alterations in inflammation, epigenetics, and mammary tumor growth persist in formerly obese mice. Cancer Prev Res 2016; 9: 339–48.

179. Chlebowski RT, Reeves MM. Weight loss randomized intervention trials in female cancer survivors. J Clin Oncol 2016; 34: 4238–48. [PubMed: 27903147]

180. Dougan MM, Hankinson SE, Vivo ID, Tworoger SS, Glynn RJ, Michels KB. Prospective study of body size throughout the life-course and the incidence of endometrial cancer among

premenopausal and postmenopausal women. Int J Cancer 2015; 137: 625–37. [PubMed: 25641700]

181. Kantor ED, Udumyan R, Signorello LB, Giovannucci EL, Montgomery S, Fall K. Adolescent body mass index and erythrocyte sedimentation rate in relation to colorectal cancer risk. Gut 2016; 65: 1289–95. [PubMed: 25986947]
182. Genkinger JM, Kitahara CM, Bernstein L, et al. Central adiposity, obesity during early adulthood, and pancreatic cancer mortality in a pooled analysis of cohort studies. Ann Oncol 2015; 26: 2257–66. [PubMed: 26347100]
183. Iyengar NM, Brown KA, Zhou XK, et al. Metabolic obesity, adipose inflammation and elevated breast aromatase in women with normal body mass index. Cancer Prev Res (Phila) 2017; 10: 235–43. [PubMed: 28270386]
184. Sallis JF, Cerin E, Conway TL, et al. Physical activity in relation to urban environments in 14 cities worldwide: a cross-sectional study. Lancet 2016; 387: 2207–17. [PubMed: 27045735]
185. Chen JG, Egner PA, Ng D, et al. Reduced aflatoxin exposure presages decline in liver cancer mortality in an endemic region of China. Cancer Prev Res 2013; 6: 1038–45.
186. Petrick JL, Kelly SP, Altekruse SF, McGlynn KA, Rosenberg PS. Future of hepatocellular carcinoma incidence in the United States forecast through 2030. J Clin Oncol 2016; 34: 1787–94. [PubMed: 27044939]
187. Haile RW, John EM, Levine AJ, et al. A review of cancer in U.S. Hispanic populations. Cancer Prev Res 2012; 5: 150–63.
188. Schröder T, Kucharczyk D, Bär F, et al. Mitochondrial gene polymorphisms alter hepatic cellular energy metabolism and aggravate diet-induced non-alcoholic steatohepatitis. Mol Metab 2016; 5: 283–95. [PubMed: 27069868]
189. Loomba R, Yang HI, Su J, et al. Synergism between obesity and alcohol in increasing the risk of hepatocellular carcinoma: a prospective cohort study. Am J Epidemiol 2013; 177: 333–42. [PubMed: 23355498]
190. Genkinger JM, Kitahara CM, Bernstein L, et al. Central adiposity, obesity during early adulthood, and pancreatic cancer mortality in a pooled analysis of cohort studies. Ann Oncol 2015; 26: 2257–66. [PubMed: 26347100]
191. Hotamisligil GS. Inflammation, metaflammation and immunometabolic disorders. Nature 2017; 542: 177–85. [PubMed: 28179656]
192. Kang YE, Kim JM, Joung KH, et al. The roles of adipokines, proinflammatory cytokines, and adipose tissue macrophages in obesity-associated insulin resistance in modest obesity and early metabolic dysfunction. PLoS One 2016; 11: e0154003. [PubMed: 27101398]
193. Esper RM, Dame M, McClintock S, et al. Leptin and adiponectin modulate the self-renewal of normal human breast epithelial stem cells. Cancer Prev Res 2015; 8: 1174–83.
194. Magkos F, Fraterrigo G, Yoshino J, et al. Effects of moderate and subsequent progressive weight loss on metabolic function and adipose tissue biology in humans with obesity. Cell Metab 2016; 23: 591–601. [PubMed: 26916363]
195. Mullooly M, Yang HP, Falk RT, et al. Relationship between crown-like structures and sex-steroid hormones in breast adipose tissue and serum among postmenopausal breast cancer patients. Breast Cancer Res 2017; 19: 8. [PubMed: 28103902]
196. Nishimoto S, Fukuda D, Higashikuni Y, et al. Obesity-induced DNA released from adipocytes stimulates chronic adipose tissue inflammation and insulin resistance. Sci Adv 2016; 2: e1501332. [PubMed: 27051864]
197. Thomou T, Mori MA, Dreyfuss JM, et al. Adipose-derived circulating miRNAs regulate gene expression in other tissues. Nature 2017; 542: 450–55. [PubMed: 28199304]
198. Itoh M, Kato H, Suganami T, et al. Hepatic crown-like structure: a unique histological feature in non-alcoholic steatohepatitis in mice and humans. PLoS One 2013; 8: e82163. [PubMed: 24349208]
199. Deng T, Lyon CJ, Bergin S, Caligiuri MA, Hsueh WA. Obesity, inflammation, and cancer. Annu Rev Pathol 2016; 11: 421–49. [PubMed: 27193454]
200. Tilg H, Cani PD, Mayer EA. Gut microbiome and liver diseases. Gut 2016; 65: 2035–44. [PubMed: 27802157]

201. Seo BR, Bhardwaj P, Choi S, et al. Obesity-dependent changes in interstitial ECM mechanics promote breast tumorigenesis. Sci Transl Med 2015; 7: 301ra130.
202. Kettner NM, Mayo SA, Hua J, Lee C, Moore DD, Fu L. Circadian dysfunction induces leptin resistance in mice. Cell Metab 2015; 22: 448–59. [PubMed: 26166747]
203. Kettner NM, Voicu H, Finegold MJ, et al. Circadian homeostasis of liver metabolism suppresses hepatocarcinogenesis. Cancer Cell 2016; 30: 909–24. [PubMed: 27889186]
204. Neuschwander-Tetri BA, Loomba R, Sanyal AJ, et al. Farnesoid X nuclear receptor ligand obeticholic acid for non-cirrhotic, non-alcoholic steatohepatitis (FLINT): a multicentre, randomised, placebo-controlled trial. Lancet 2015; 385: 956–65. [PubMed: 25468160]
205. Gomes AL, Teijeiro A, Burén S, et al. Metabolic inflammation-associated IL-17A causes non-alcoholic steatohepatitis and hepatocellular carcinoma. Cancer Cell 2016; 30: 161–75. [PubMed: 27411590]
206. Komaroff AL. The microbiome and risk for obesity and diabetes. JAMA 2017; 317: 355–56. [PubMed: 28006047]
207. Loo TM, Kamachi F, Watanabe Y, et al. Gut microbiota promotes obesity-associated liver cancer through PGE2-mediated suppression of antitumor immunity. Cancer Discov 2017; 7: 522–38. [PubMed: 28202625]
208. Gaskin CJ, Craike M, Mohebbi M, et al. Associations of objectively measured moderate-to-vigorous physical activity and sedentary behavior with quality of life and psychological well-being in prostate cancer survivors. Cancer Causes Control 2016; 27: 1093–103. [PubMed: 27469939]
209. Ehlers DK, Rogers LQ, Courneya KS, Robbs RS, McAuley E. Effects of BEAT Cancer randomized physical activity trial on subjective memory impairments in breast cancer survivors. Psychooncology 2017; published online April 16. DOI:10.1002/pon.4438.
210. van Roekel EH, Winkler EA, Bours MJ, et al. Associations of sedentary time and patterns of sedentary time accumulation with health-related quality of life in colorectal cancer survivors. Prev Med Rep 2016; 4: 262–69. [PubMed: 27419042]
211. Fassier P, Zelek L, Partula V, et al. Variations of physical activity and sedentary behavior between before and after cancer diagnosis: Results from the prospective population-based NutriNet-Sante cohort. Medicine 2016; 95: e4629. [PubMed: 27749527]
212. Jankowska MM, Schipperjin J, Kerr J, Altintas I. An applied cyberGIS in the age of complex spatial health data. Montreal, QC, Canada: GIScience, 2016: 147–52.
213. Bae S, Dey AK, Low CA. Using passively collected sedentary behavior to predict hospital readmission. Heidelberg, Germanyy: Ubicomp, 2016: 616–21.
214. Ford ME, Magwood G, Brown ET, et al. Disparities in obesity, physical activity rates, and breast cancer survival. Adv Cancer Res 2017; 133: 23–50. [PubMed: 28052820]
215. Touitou Y, Reinberg A, Touitou D. Association between light at night, melatonin secretion, sleep deprivation, and the internal clock: health impacts and mechanisms of circadian disruption. Life Sci 2017; 173: 94–106. [PubMed: 28214594]
216. Paulsen JA, Ptacek TS, Carter SJ, et al. Gut microbiota composition associated with alterations in cardiorespiratory fitness and psychosocial outcomes among breast cancer survivors. Support Care Cancer 2017; 25: 1563–70. [PubMed: 28064384]
217. Heymsfield SB, Wadden TA. Mechanisms, pathophysiology, and management of obesity. N Engl J Med 2017; 376: 254–66. [PubMed: 28099824]
218. Lynch SV, Pedersen O. The human intestinal microbiome in health and disease. N Engl J Med 2016; 375: 2369–79. [PubMed: 27974040]
219. The GBD 2015 Obesity Collaborators. Health effects of overweight and obesity in 195 countries over 25 years. N Engl J Med 2017; 377: 13–27 [PubMed: 28604169]

Search strategy and selection criteria

The evidence presented in this Series paper focuses on the most recent published scientific literature on this topic. The data were selected from studies published and available on PubMed between Jan 1, 2010, and Oct 20, 2016, and focused on studies enrolling adult human beings published in English. The earliest date in this range was chosen as 2010 to provide an update on emerging areas of evidence, including sedentary behaviour and rigorous accelerometer-based measures. Our search terms were “physical activity”, “exercise”, “sedentary behavior”, “sitting”, “television”, “lifestyle”, “dietary patterns”, “obesity”, “overweight”, and “cancer”. All types of cancer were included, and all study designs were considered, including meta-analyses, review articles, prospective cohorts, and randomised controlled trials.