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Research Strategies for Nutritional and Physical Activity Epidemiology and Cancer Prevention

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Abstract

Very large international and ethnic differences in cancer rates exist, are minimally explained by genetic factors, and show the huge potential for cancer prevention. A substantial portion of the differences in cancer rates can be explained by modifiable factors and many important relationships have been documented between diet, physical activity, and obesity, and incidence of

important cancers. Other related factors such as the microbiome and the metabolome are emerging as important intermediary components in cancer prevention. It is possible with the incorporation of newer technologies and studies including long follow-up and evaluation of effects across the life cycle, additional convincing results will be produced. However, several challenges exist for cancer researchers, for example, measurement of diet and physical activity, and lack of standardization of samples for microbiome collection, and validation of metabolomic studies. The United States (US) National Cancer Institute convened the *Research Strategies for Nutritional and Physical Activity Epidemiology and Cancer Prevention Workshop* on 28-29 June, 2016 in Rockville, Maryland during which experts addressed the state of the science and areas of emphasis. The current paper of the authors reflects the state of the science and priorities for future research.

Keywords

Nutrition; Physical activity; Obesity; Microbiome; Technologies

BACKGROUND

Overall, current scientific thinking regarding the associations among nutrition, physical activity (PA), and obesity and human cancers have been derived mostly from prospective cohort studies and a few randomized controlled trials with cancer endpoints. Nutritional epidemiologic studies have largely assessed diet through food frequency questionnaires (FFQs) and, although with known limitations, promoted hypothesis testing and have influenced dietary guidance and policy (e.g. the United States Dietary Guidelines for Americans). Evidence on adiposity and cancer risk likewise comes from prospective studies that largely rely on self-reported weight and height and to a lesser degree, measured height and weight and validated measures such as pictograms of body shape. The relations of weight loss with cancer risk are poorly defined because of a lack of sustained weight loss in cohorts followed over the past half century. The current evidence between PA and cancer in humans has also relied on self-reported questionnaire data, and these data have informed national guidelines, for example, the Physical Activity Guidelines for Americans. To refine current concepts researchers have started incorporating emerging technologies for measuring diet and PA in human populations.

Although much has been learned during the last several decades of epidemiologic research on the role of nutrition and physical activity (PA) in cancer etiology, numerous questions remain regarding reported associations and concerning the best methods to use to assess associations. Recently other related factors including obesity, the microbiome and metabolome have been recognized as important in cancer prevention. The lack of clarity on some associations can be attributed in part to the long latencies between exposures and outcomes, study design, exposure assessment, and the complexity of the underlying biologic mechanisms. Overall, however, it seems evident that population changes in nutrition and PA have the potential to reverse the obesity epidemic and reduce the risk of major cancers and other chronic diseases.

To assess the state of the science and areas of emphasis, the United States (US) National Cancer Institute (NCI) convened the *Research Strategies for Nutritional and Physical Activity Epidemiology and Cancer Prevention Workshop* on 28-29 June, 2016 in Rockville, Maryland. This was followed by continued discussion among the authors, leading to the present paper highlighting the state of the science and priorities for future research (Table 1) in the following areas: nutrition and cancer epidemiology, physical activity and cancer epidemiology, obesity and cancer epidemiology, gut microbiome, metabolomics and biomarkers of dietary exposures, emerging technologies for measuring physical activity and sedentary behavior, dietary intake, hormones, gene-environment interactions, epigenetics and implementation of what is already known.

Nutrition and Cancer Epidemiology

State of the science—For nutritional epidemiology and cancer, researchers were initially inspired from ecological studies conducted in the 1970s, including Carroll and colleagues' (1) investigation of animal fat and breast cancer mortality across several countries. Strong associations were seen between total animal fat intake and many cancer types, but did not account for many confounding factors, motivating the need for more detailed studies. These initial studies, in addition to findings from dietary trials in laboratory animals, prompted dietary recommendations for reducing percentage of energy from fat in the diet. Results from later case-control studies mainly showed a positive association between fat intake and breast cancer. However, subsequently conducted prospective cohort studies were largely null, and did not confirm the results from case-control studies. Data from a pooling project of dietary fat and cancer using prospective data comprising 7,329 breast cancer cases showed null associations (2). This report that total fat intake in midlife is not a major cause of cancer was so impactful, it has changed dietary guidelines.

Randomized trials are thought to be the gold standard for research, but are limited for long-term prevention studies (3). In two large randomized trials that focused on reduction of total dietary fat, no clear effect was seen on incidence of breast or other cancers (4–6), although follow-up continues in the Women's Health Initiative trial. Some of the major micronutrient cancer prevention trials on various cancer endpoints showed some evidence of benefit including risk reduction of prostate cancer, gastric cancer and even all cancers, incidence or mortality, in some trials (7–9). However, other trials reported null findings (10, 11), mixed findings in participants (men vs. women) (12), or findings of an increased risk (13, 14). Large randomized trials of diet and cancer are expensive and logistically challenging, and may fail to give clear answers because of poor intervention adherence, limited trial duration, population-specific effects, and interventions done too late in the time course of disease development.

In summary, total fat intake in midlife may not be a major cause of cancer. Alcohol, even at low doses, is a risk factor for breast cancer, but has distinct associations with different cancer types. Processed meats increase risk for colorectal cancer. Overall fruit and vegetable consumption may not strongly relate to risk of cancer in general, but some of these foods may be related to specific types, or subtypes, of cancer (e.g., vegetables and reduced risk of ER negative breast cancer). Greater growth/stature and height, all associated with nutrition

are linked to common cancers such breast, ovary, endometrium, kidney. Trans fat intake is an important risk factor for cardiovascular disease, diabetes, and other endpoints; with further follow-up, the reduction in diabetes from trans fat avoidance is likely to lead to lower risks of some cancer. The benefits of micronutrient supplements are likely to be seen primarily in populations with low baseline intakes.

Research priorities—Key research priorities include investigating dietary intakes across the life course. Many studies have examined diet during mid-life and later, but much evidence exists that exposures during earlier life are particularly important for some cancers (15). Identifying the optimal time in life for dietary exposures in preventing (or promoting) various cancers is vital. Furthermore, it is important to investigate the long latencies between exposure and diagnosis of cancer and few studies have examined diet and cancer with this latency. For almost all dietary exposures, additional detail is needed in understanding dose-response relationships. Further details are also needed on the definitions of exposures; until recently, fruits and vegetables have been combined into very broad groups, despite the large variation in their composition and the variable effects on cancer risk. Understanding the molecular effects of consuming various dietary patterns is also warranted. Studies are needed that have large numbers of cases to investigate these details adequately. The molecular heterogeneity of cancer also needs to be considered which will require tissue analysis and large numbers of endpoints. Integration of genomics, metabolomics, epigenetics and molecular characterization of tumors is likely to be useful in establishing causality. Additional use of biomarkers of exposure can be helpful, but often the necessary samples, such as multiple 24-hour urine samples, are not available for prospective analyses. Short-term feeding studies assessing biomarkers with application of findings to cohort studies (ideally replicated cohort studies in combination with short term trials with intermediate biomarkers) will be needed. Given the cost of intervention trials with chronic disease outcomes having uncertain latencies, a future research strategy may emphasize cohort studies with repeated measures of intake and objective measures, including biomarkers when possible, in combination with intervention trials with premalignant lesions as endpoints.

A major concern is still the problem of measurement errors. Metabolomics is emerging as an important objective tool for the identification of dietary biomarkers and also for identifying biomarkers of dietary patterns (16), but limited research exists. A future research direction will be to strengthen dietary assessment that involves developing and applying intake biomarkers from body fluids, particularly urine and blood. There are a few established urine-based intake biomarkers, including a doubly-labeled water (DLW) biomarker of total energy intake, a urinary nitrogen biomarker of protein intake, and 24-hour excretion based biomarkers of sodium and potassium. Blood-based biomarkers of several micronutrients have also shown promise in human feeding study evaluation (17). Once established, the objective intake measures can be used to correct self-report assessments for measurement error.

New data analysis techniques should also be assessed. For example, a multivariate adaptation of regression calibration and the method of triads (18, 19) has been described (20) that requires the FFQ, a biomarker, and a second biological variable that is correlated

with the true dietary intake but has errors that are unlikely to be correlated with those of the biomarker. A disadvantage of this approach is that the resulting effect estimates (relating "true" diet to disease, for instance) are in standard deviation units (of the latent true intake), but advantages are that usual hypothesis testing is preserved, and that with care in choosing the variables all assumptions will seem reasonable (which is a challenge with regression calibration).

Understanding the effects of diet, nutrition and PA in cancer prognosis is also important, and research programs should be designed to examine these effects over the life course. Some of the cancer-related outcomes can be studied in integrated health care settings where, for example, some may have infrastructural research resources. Expansion of linkage with ongoing cohort studies should be supported. New research studies should also be conducted outside the industrialized world and the "demographic transition" changes that are occurring worldwide need to be examined.

Physical Activity (PA) and Cancer Epidemiology

State of the science—A framework for research in PA and cancer control (21, 22) delineated clear time points in the cancer experience from prevention to death during which PA could be used to reduce cancer risk, improve coping and rehabilitation during and after treatment, and improve survival after cancer. There is now consistent evidence that PA reduces the risk of several cancer sites from over 400 observational epidemiologic studies that have been conducted worldwide. The evidence, from both case-control and prospective studies, is particularly strong for breast, colon and endometrial cancers with some evidence for lung, and pancreatic cancers (23). Numerous meta-analyses on PA and cancer risk have attempted to quantify the associations for several different cancer sites. Heterogeneity exists in how PA was originally defined and measured, what type of comparisons were made, the types of study designs and how confounding and effect modification were addressed. For example, BMI is an important factor to adjust appropriately in PA and breast cancer because body fatness reduces the risk of premenopausal breast cancer but increases it for post-menopausal women. To address this issue, Neilson and colleagues (24) published a recent meta-analysis of moderate-vigorous recreational PA and breast cancer risk that stratified the results by menopausal status and BMI. They found that PA was inversely associated with breast cancer risk in pre-menopausal women who had a normal BMI <25 but not ≥25 (overweight/obese). For postmenopausal women, they noted an inverse effect amongst all categories of BMI.

Recently, Moore et al. (25) published results from the NCI cohort consortium pooling project of 1.44 million people (43% men and 57% women) of leisure-time PA and risk of 26 types of cancers and reported that 13 cancer sites have lower risks with higher activity levels. In subgroup analyses, the investigators found that the inverse association with lung cancer was limited to current and former smokers and that the inverse association with myeloma was limited to never smokers. For BMI, they noted an inverse PA association with lung cancer only with normal BMI (<25) and the inverse PA association with endometrial cancer only for BMI >25. When developing guidelines for cancer prevention, there is limited evidence on the exact dose of activity required for cancer risk reduction. Neilson et al. (24)

found a non-linear dose-response effect with an inflection point around 25 MET-hrs/week suggesting less breast cancer benefit beyond 4 hours per week of vigorous intensity PA. A threshold effect was not found in the pooled analysis by Moore et al. (25).

Research priorities—Important research priorities include more observational research studies of PA for several cancer sites that have insufficient evidence. Assessing effect modification by various factors will help identify if high-risk groups exist that could be targeted for more personalized prevention recommendations. There is also a need to understand associations by different time periods in life when PA may be particularly relevant. Another focus should be improved objective measurement of all parameters of PA and sedentary behaviors (i.e., type, intensity, dose, and timing in life), to move beyond what questionnaires alone can provide. Whenever possible, future research studies should examine associations by tumor subtype to generate hypotheses about the underlying biologic mechanisms that mediate the effect of PA on cancer risk. For example, hormone receptor status, tumor histology and grade may all be important factors that have not yet been fully investigated. In addition, future research priorities should be joint assessment of PA and sedentary behavior within the same study population to differentiate the effects of each type of behavior on cancer risk. Finally, more exercise intervention trials are needed that examine different types and doses of activity biomarkers associated with cancer risk.

Obesity and Cancer Epidemiology

State of the science—For obesity and cancer, the first major review of evidence emerged from the 2002 International Agency for Cancer Research (IARC) report (26) which stated that there is “sufficient evidence in humans for cancer preventive effect of avoidance of weight gain for cancers of the colon, esophagus (adenocarcinoma), kidney (renal cell), breast (postmenopausal), and corpus uteri”. There was moderate level of evidence for association with colon cancer (RRs1.35-1.99); large evidence for association with breast, uterus, and kidney cancers (RR 2.0-4.9); and very large evidence for association with cancer of the esophagus (adenocarcinoma) (RR 5.0+) (26). In the following year, Calle et al. 2003 (27), published a landmark study showing that obesity in women and men was associated with substantial increased mortality of several cancers in the American Cancer Society prospective cohort study (28). Since 2002, the body of evidence of the association between obesity and cancer has continued to grow. Based on cause-and-effect inference from epidemiologic studies, animal models and studies of biological mechanisms, a recent International IARC working group concluded that the absence of excess body fatness significantly lowers the risk of cancer at thirteen organ sites - esophagus (adenocarcinoma), gastric cardia, colon and rectum, liver, gallbladder, pancreas, postmenopausal breast cancer, corpus uteri, kidney (renal cell), meningioma, thyroid and multiple myeloma (29). There is now consistent evidence from more than 30 prospective cohort studies showing an association between obesity and colon and rectal cancers, and the association is stronger for men compared to women (30, 31).

Research priorities—Key research priorities include understanding the timing of weight gain and risk, the impact of adolescent and early adult adiposity, and the benefits of weight loss as well as whether the obesity paradox (better survival with greater adiposity after

diagnosis) seen for colorectal, kidney cancer and NHL is real or due to methodological limitations. Whether obesity is positively related to post-diagnosis outcomes (cancer recurrence or survival) depends strongly on the other risk factor pathways that also lead to a cancer diagnosis, and on the comparative properties of the cancers that develop via obesity-related versus other pathways. There is need to improve approaches to modeling weight gain across life course and cancer risk. An important methodologic issue is the need to confirm whether adiposity is measured correctly and whether adiposity varies by age, race/ethnicity, regions of the world, and whether more precise technology for adipose and subcutaneous fat and body fat distribution can improve beyond simple BMI and waist and hip circumferences. Another issue is whether metabolic health by obesity phenotypes is important. There is also the need to understand the impact of obesity on second primary cancers and cancer recurrence (32). Since childhood adiposity is associated with some cancers, there is a need to understand what the trans-generational impact on cancer risk is, and how childhood adiposity and timing is in relation to cancer. Other important questions include how to decrease cancer burden in the approximately 720 million adults worldwide who are obese and need to consider the mechanistic approach to identify targets and strategies to break the obesity-cancer links. The mechanistic targets and intervention strategies for offsetting the enhancing effects of obesity on cancer metastases need to be examined. Another important question is whether intentional weight loss following chronic obesity reverses the pro-cancer effects of obesity. Evidence exists that some dietary patterns, such as Mediterranean diet, can be beneficial for weight control, and that healthy diet plus PA can be beneficial. Thus, effective ways to translate this knowledge into practice at the individual, organizational, local, and national levels are needed.

Gut Microbiome

State of the science—Humans are a superorganism made up of microbial and human cells. While considerable understanding exists regarding the association between human ‘pathogens’ and health, there is little information about the ‘normal’ microbial flora in relation to health. To address this gap in knowledge, the NIH Common Fund program launched the Human Microbiome Project (HMP) in 2007 (33) and in 2008 the European Commission launched the Metagenomics of the Human Intestinal Tract project (34). In 2016, the White House announced the National Microbiome Initiative.

Diet shapes the initial colonization and maintenance of our gut microbiome (35). In turn, the gut microbiome influences the metabolism and bioavailability of carbohydrates, proteins, fats, and many other bioactive compounds (36). In some cases, the bacterial activity can produce harmful carcinogens; for example, nitrate-reducing bacteria in the gastrointestinal tract act on certain foods such as red meat and produce potentially harmful cancer inducing *N*-nitroso compounds (37, 38). Specific dietary patterns have also been reported to influence the gut microbiome. For example, an American type diet compared to an African diet is associated with notable differences attributable to bacterial metabolism including higher secondary bile acids, lower short chain fatty acids, and higher proliferative biomarkers (39, 40). Certain microbes can also produce butyrate from dietary fiber and decrease colonic inflammation (40).

Gut microbiota may be important in common health disorders such as, obesity (41–45) and colorectal cancer risk (46). There is emerging evidence that human obesity is associated with low abundance of intestinal *Bacteroidetes* and an abundance of *Firmicutes* (44, 47, 48) and is associated with reduced bacterial diversity in studies of obese twins (42). Based on the impact of diet and obesity on the gut microbiome, potential mechanisms by which the bacterial microbiome modulates carcinogenesis include inflammation, genotoxicity, and metabolism (49).

Research priorities—US-funded microbiome research in recent years has resulted in major advances, particularly in three primary areas: *a)* basic biology of microbiomes; *b)* applied studies (including intervention studies for disease prevention or treatment; and *c)* development of tools and resources. However, numerous methodological challenges and gaps in knowledge remain. Few epidemiological studies have evaluated the role of the microbiome in population health, especially in prospective study designs. In developing epidemiologic studies various points need to be considered: *1)* Collection methods must preserve the microbial signature or "biomarker" in the field over days in suboptimal storage conditions; *2)* Collection methods must be optimized for multiple assays; *3)* appropriate quality control standards need to be incorporated to evaluate reproducibility; and *4)* methods must be standardized for extraction, sequencing, and bioinformatics for pooling and meta-analyses. At present, however, the degree of standardization required for translation to large-scale studies is relatively early in development. Several methodologic issues have plagued epidemiologic studies of human microbiome and cancer, including specimen collection, storage, quality control, measurement, bioinformatics processing, and data analysis techniques (50). Currently, there are concerted efforts to standardize collection of stable samples (51–53). Furthermore, the Microbiome Quality Control (MBQC) Study was completed to identify sources of variation across and within labs for 16s gene sequencing in 19 participating laboratories (50).

Key research priorities are to incorporate additional tools and resource development; to incorporate non-bacterial components of the microbiome; to increase training for bioinformatics, computation biology and data science; to standardize sample and data collection protocols; and to create large databases and repositories for increasing volume of complex data (54). These concerns are particularly relevant in cancer epidemiology where additional issues exist such as small sample sizes, and possible sources of bias from limited sampling or the cross-sectional nature of numerous studies, thus, necessitating the need for multiple prospective studies to address bias and temporality (55).

Metabolomics and biomarkers of dietary exposure

State of the science—Metabolomics holds promise as a tool for the discovery of biomarkers that may be measured as objective assessments of dietary exposures. There are around 28,000 known metabolites derived from foods alone, collectively referred to as the "food metabolome" (56). The overall workflow for biomarker discovery by metabolomics involves selection of study design, profiling of biospecimens (high and low consumers) for identification of signals associated with food intake, and annotation of these signals. Intervention and observational studies complement each other for biomarker discovery and

validation. In addition, the choice of biospecimen is critical and different dietary assessment methods cover different timeframes. A recent accomplishment is the use of high-resolution liquid chromatography mass spectrometry, the analytical instrumentation used to help unlock the metabolome's chemical diversity. For example, metabolomics is currently being applied in the European Prospective Investigation into Nutrition and Cancer (57) cross-sectional study to find biomarkers of coffee intake. Reported coffee intake was found to be correlated with levels of several coffee-derived metabolites in diverse European consumers. Therefore, different assessments of exposure can be obtained if concentrations of coffee-derived metabolites rather than coffee intake in volume are measured. Other existing European initiatives on food-derived metabolites include the Phenol-Explorer database, which includes data on metabolites of important polyphenol rich foods (58), the Exposome-Explorer database on biomarkers of food and environmental exposures (59) and the Food Biomarkers Alliance (FoodBALL) which aims to identify and quantify new dietary biomarkers to improve nutritional assessment and research.

Human feeding studies provide an important context for intake biomarker development and validation. A recent report describes a novel feeding study design in which participants were provided a diet approximating their usual diet for a two week period, with various blood and urine measures for intake variations among study participants, resulting in identification of suitable biomarkers for several nutritional variables (17). Specimens from this study are currently undergoing extensive metabolomic profiling to identify additional intake biomarkers.

Research priorities—Recent major advances in metabolomics research include the measurement of known metabolites derived from foods (56) and improvements in analytic instruments to quantify the metabolome. Key research priorities include validation studies because many biomarkers proposed have not been confirmed to reflect exposure in in community dwelling populations. Furthermore, some 'validation' studies have regarded dietary self-report data as the true intakes in metabolomics-based biomarker development. These approaches may be circular due to the limitations of available self-report intake data that drives the need for intake biomarkers. New population-based studies should utilize standard reference materials for different types of biological samples (plasma, serum, urine). Other types of biospecimens such as teeth, hair, tissues, and RBCs may be very useful because of their utility in specific research questions. Additionally, where the tissue originates in the body is also going to be important. For example, Mayers et al. (60) have shown that tissue of origin dictates differences in branched-chain amino acid (BCAAs) metabolism. For pancreatic ductal carcinoma (PDAC) and non-small cell lung carcinoma (NSCLC) the same initiating event is *Kras* activation and *Trp53* deletion, but these tumors use BCAAs differently. NSCLC incorporate free BCAAs into tissue protein and use BCAAs as a nitrogen source, but PDAC tumors have decreased BCAA uptake (60), showing that the tissue origin is important in the metabolic determinant of cancer. In other situations, rather than focus on individual-level biomarkers, there is a need to incorporate biomarker panels and these should be prioritized for major questions in cancer epidemiology. Quite often, there is long-term storage of samples from epidemiology studies and the impact of storage and sample processing could also be important. Other priorities include bringing together

open-source tools and databases to facilitate biomarker discovery. Importantly, there is a need for additional human feeding studies to identify metabolomics-based intake biomarkers (61).

Emerging technologies for measuring diet

State of the science—New technology is critical to enable researchers to refine the associations between diet and disease prevention. For FFQs, development and use of an optical reader in a scanner that could process thousands of completed questionnaires from cohort participants was an innovative breakthrough. As the tool successfully transitioned from paper to digital formats additional advances could be made (using static images to aid respondents, missed question responses, and allowing for automated datasets to be created) (62, 63).

Advances in 24-hour dietary recall (24HR) through tools such as the Automated Self-Administered 24-hour recall (ASA24) (64) allow for their application, from primarily studies for surveillance, to broaden into epidemiological cohorts. Intake estimates from 24HRs appear to be less biased relative to a measure of true intake than estimates from FFQs (65, 66), although many days of recording may be needed for some variables, and this approach allows for additional informative context, such as time of eating, duration of eating, and geographical context.

Few groups in the world are working on automated systems of dietary assessment. New mobile methods such as image-assisted approaches are under development and can supplement dietary records or 24HRs. Image-based approaches capture all eating occasions by images as the primary record of dietary intake (67). The French web-based dietary record (Etude Nutrinet Santé) is a good model for biomarker testing, but a majority of the respondents likely are doing a recall. At least one study showed that wearable cameras reduced the magnitude of misreporting of energy (vs DLW) in men and women (68). It is possible that wearable cameras with high definition sensors could enhance the accuracy of self-reports by providing objective information on diet consumption. Researchers are currently developing smartphone apps and other wearable technologies that could lead to more objective and accurate ways to assess food intake. Metabolomics is also emerging as an important tool for the identification of dietary biomarkers and also for identifying biomarkers of dietary patterns (16).

How the information is collected about what people eat continues to be highly relevant, especially as questions are posed regarding multidimensionality and dynamism across the cancer continuum. When information is collected about what people eat, the data can be analyzed using dietary patterns, episodically consumed foods, nutrients, and/or bioactive components. To help address this need, and in response to calls for innovative methodological efforts on dietary patterns to enhance epidemiologic analyses (69), the Dietary Patterns Methods Project was formed to standardize dietary patterns research and strengthen the scientific evidence based on dietary patterns. This research harmonized food dietary patterns across three different cohorts to represent men and women and five ethnic groups. Collectively, the reduction in risk of mortality from cancer ranged from 11 to 24%

(70). The results strongly supported a high-quality diet being associated with lower risk of mortality from cancer.

Research priorities—Major advances include the transitioning of many FFQs from paper to digital formats as web or mobile apps. Concurrently, the 24HR dietary recall was translated to web- and mobile apps with the same advances adopted by FFQs. Studies, to date, support these new tools working as well as their original labor intensive counterparts (71, 72). Results suggest these innovations enhance participant cooperation and may reduce research costs (66, 73). In general, the use of technology, including wearable devices (passive collection) and image-based apps (active collection) to assess diet is in its infancy. Key research priorities include assessing willingness of people to use these methods for an extended duration of time. Few peer-reviewed studies have assessed the quality of dietary results from the passive or active mobile methods using unbiased biomarkers. Improved methods and measures to capture dietary intake and context of eating are important issues to assess in diverse groups. Biomarkers need to be included as part of validation/calibration testing and usability. For methods using images captured in real-time, cross-disciplinary teams should be used to pursue automation of food identification and volume estimation of the foods in the images.

Emerging technologies for measuring PA and sedentary behavior

State of the science—Epidemiologic studies of questionnaires to assess long-term participation in moderate-vigorous intensity PA (e.g. in past year) and sitting behaviors have provided evidence that subjects that do not accumulate sufficient time doing PA is associated with increased risk for early mortality and cardiometabolic diseases (74, 75), and many types of cancer (76). Instruments used in these studies have most often focused on leisure-time PA (i.e., exercise and recreation) and there is substantial evidence that self-reported exercise participation is associated with less adiposity, higher levels of cardiorespiratory fitness and more favorable metabolic health (77, 78) supporting the utility of these instruments. Although self-reports of PA have been instrumental in identifying many activity-disease associations leading to the development of PA Guidelines for Americans (74), and recommendations from the American Cancer Society (79), they have two basic limitations that have left major gaps in our knowledge and limit further advances.

First, questionnaires measuring habitual PA are known to have measurement error (80). In prospective studies, these errors are expected to result in the underestimation of the strength of observable associations and false negative results. Thus, we may underestimate the actual impact of PA on cancer prevention. Although measurement error correction techniques (81, 82) may mitigate these effects, they cannot obviate type II errors, so they may only be a partial solution to the problem. A second less commonly discussed limitation is that questionnaires used in most cohorts investigating cancer risk do not attempt to comprehensively assess the full spectrum of activities of everyday living, or sedentary behaviors that account for 50% or more of the waking day for adults (83, 84). Thus, we know much less about potential risks linked to sedentary behavior or benefits associated with lower intensity activities, common in daily life.

The revolution in mobile communication and wearable sensor technologies in the last decade has radically changed our ability to quantify human behavior in large-scale epidemiologic studies and these new tools may offer solutions to the measurement problems noted above (85). Both previous day recalls (84, 86–87) and accelerometer-based measures (88) have greater validity than PA questionnaires (89), and they both measure the full range of sedentary and active behaviors (e.g., light, moderate, vigorous intensity). Previous-day recall methods have been developed and refined and are now being applied to internet-based and mobile computing platforms that can be automated and are thus highly scalable in large cohorts at lower cost than interviewer-based alternatives (80, 90). Importantly, initial estimates suggest that a modest number of replicate recalls (e.g., 4 to 6) over a one-year period may be sufficient to minimize the impact of day-to-day (intra-individual) variation (80). Given that smartphones are now an elemental part of daily life for many - 74% of United States households own smartphones (2.4 devices/household) and 91% of users plan to purchase another one (91) - they offer an excellent opportunity to capture high quality self-reported PA information in new ways.

Research-grade accelerometers available for the last 20 years have recently become much more advanced and are now capable of collecting high-dimensional raw acceleration data (e.g., 80 Hz) for weeks at a time and increasingly sophisticated calibration methods are being developed to translate movement data into relevant exposure metrics (92–94). Large prospective cohorts capable of studying cancer risk in the near term have begun to employ these accelerometers worn on the wrist (95) and waist (85, 96); these studies promise to generate new insights. Indeed, the initial plan for the 1,000,000 person NIH Precision Medicine Initiative Cohort (now the “All of Us Cohort”) is to capture physical activity behavior from wearable devices (97).

Although more work is needed to establish the validity of accelerometer-based devices in community dwelling studies using strong reference measures such as doubly labeled water, direct observation, or other high quality objective measures,(98, 99) recent accelerometer-mortality studies from NHANES have already started to fill gaps in our knowledge and have provided initial evidence that lower intensity PA and sedentary time are associated with mortality, in addition to the established relation with moderate-vigorous intensity activity (100, 101). We need to extend this work to cancer prevention studies.

Taking advantage of new technologies to apply better measures in future studies (90) could lead to a better understanding of the relationship of PA and cancer risk and provide intervention opportunities that extend and strengthen current efforts to increase participation in moderate-vigorous intensity exercise, and ultimately the development of new and more precise cancer prevention recommendations.

Research priorities—Although questionnaires have been useful in establishing important associations, they have inherent limitations and new better measurement approaches are needed to facilitate future advances (80, 90, 102). Use of mobile communication tools such as smart phones and wearable sensors to capture the full spectrum of PA and sedentary behavior could help fill current knowledge gaps. In addition, new technologies to support and deliver behavioral interventions to increase PA are also promising. These technologies

have strengths and limitations. Key research priorities for cancer studies in population-based settings, in addition to validation, include research to optimize the usability, feasibility, and acceptability of these technologies over long periods of time. Prospective cohort studies will be needed to understand the usefulness of these technologies, in cancer prevention, etiology and survival. For epidemiology studies, the impact of behavioral variability on specific technologies will also be required to optimize cancer epidemiology protocols. In terms of the existing and emerging technologies, additional questions include whether the total activity (volume) or the intensity of the activity is important and whether circadian patterns (sleep/wake cycles) are associated with cancer risk.

Hormones and cancer

State of the science—Hormones have important roles in mediating the impacts of nutrition, physical activity and obesity and have been implicated in the etiology of several common cancers including endometrium, breast, ovary and prostate. Several review papers have been published on the role of both endogenous and exogenous hormones and cancer risk (103–109). For endogenous hormones, the Nurses' Health Study (NHS) and NHS II provided the earliest prospective data to show that circulating sex hormones were associated with postmenopausal breast cancer risk (110). For exogenous hormones, large randomized placebo controlled trials in the Women's Health Initiative showed postmenopausal breast cancer risk to be elevated with widely used combined estrogens plus progestin, but transiently reduced with the same estrogens alone, pointing to biological complexities in hormone and cancer relationships.

Research priorities—Although much research has been published on hormones and cancer, to conduct epidemiologic studies of hormone biomarkers and cancer risk, large numbers of study participants are needed to provide adequate power for hypothesis testing. Pooling of hormone biomarkers from prospective cohort studies is a key approach for risk estimation including by ethnicity and other population subgroups (111). The problem is that for pooling projects standardized methods for hormone measurement is ideal. Other priorities would be to investigate whether dietary factors and PA are associated with patterns of hormonal profiles in humans to understand whether hormonal mechanism is important through which diet and PA operate. In the NHS II, dietary fat and fiber intakes were not associated with patterns of urinary estrogen metabolites in premenopausal women (112).

Gene-Environment (GxE) Interactions

State of the science—It is well-known that cancer risk is influenced by the biology that results from the interplay of genetic and environmental factors. The era of genome-wide association studies (GWAS) identified hundreds of genetic variants associated with cancer, but the effects of most of the variants have been small (odds ratios: 1.1-1.4) (113). A National Cancer Institute Think Tank Report addressed several studies that have tested for GxE interactions for GWAS identified loci and noted most of these studies have not observed statistically significant interactions (113).

Research priorities—Research on the interactions between genes and the environment has been a priority area for NCI. However, despite massive research investment, the impact

of GxE in cancer risk has not been impressive. Genetic research tools have become more high-throughput and precise, but results from GWAS studies have not been easy to interpret because a vast majority of GWAS-identified single nucleotide polymorphisms (SNPs) are located in non-coding regions of the genome (114). There is a need to understand the functional significance of these SNPs. There have to be more precise and accurate ways to measure environmental exposures because exposure assessment errors contribute to inabilities to consistently detect GxE interactions. This paper describes innovation in technologies for measuring diet and physical activity, as well as the areas of metabolomics and microbiomics. Large-scale epidemiology cohorts have to be leveraged utilizing computational tools and innovative statistical modeling to address gene-gene and gene-environment interactions.

Epigenetics

State of the science—As noted above, the vast majority of SNPs associated with cancer risk are located in non-coding regions of genes or their promoters that do not produce functional proteins. It is now believed that these non-coding DNA, previously thought to be "junk" DNA have importance in epigenomics (115). Epigenetics refer to non-heritable changes in gene expression observed in the absence of changes in DNA sequence. The epigenome interacts with the non-coding regions of the genome in carcinogenesis (115). Observational studies provide support for a link between epigenetic alterations and cancer (116, 117). There is also evidence that diet is directly related to epigenetic alterations (117). The idea that dietary factors can affect epigenetic alterations and these epigenetic alterations affect human cancer risk is based on animal experiments (117).

Research priorities—Epigenetic alterations such as DNA methylation of normal cells occurs as part of the ageing process and it is known as epigenetic drift (118). There is a need to understand the difference between epigenetic drift and epigenetic alterations due to modifiable environmental risk factors such as diet or other factors such as obesity. In terms of the impact of modifiable environmental factors on the epigenome, there is also a need to understand which of the three classes of epigenetic molecule, DNA methylation, modifications of histone and other chromosomal proteins and noncoding RNAs, would be ideal candidate biomarkers (117). Multiple epigenetics measurements over time prior to disease onset should be integrated into prospective cancer epidemiology cohorts to investigate whether and to what extent diet and other modifiable factors drive epigenetic alterations.

Implementation of what we already know

Despite known limitations in measurement of food and nutrient intake, and PA, assessment methods and analytic approaches are continually being improved, and evidence-based recommendations on food, nutrition, PA, and cancer prevention have been made. Examples include the Dietary Guidelines for Americans, the American Cancer Society guidelines on nutrition and PA for cancer prevention, and the World Cancer Research Fund and American Institute for Cancer Research (119) recommendation on Food, Nutrition, PA, and the Prevention of Cancer. In addition, IARC has assessed that red and processed meat consumption increases cancer risk. These assessments and recommendations are based on a

large body of epidemiologic (predominantly prospective cohort) studies, buttressed by other studies, including animal and other mechanistic studies. Implementation science would be helpful, even though outstanding issues remain, to ensure that the knowledge already generated benefits the most people possible (120).

CONCLUSION

The very large international and ethnic differences in cancer rates are minimally explained by genetic factors and demonstrate the huge potential for cancer prevention. Many important relations have been documented between diet, PA, and obesity, and incidence of cancers. A substantial portion of these differences in cancer rates can be explained by modifiable factors, and much more is possible with the incorporation of newer technologies and studies that include long follow-up and evaluation of effects across the life cycle. An important part of cancer incidence is explained by excess adiposity, but additional contributions from diet and PA across the lifecycle have only been partly investigated. In addition to the obesity cancer burden, there is strong potential for further reduction in cancer by diet, PA, and their influence on the microbiome. It seems likely that diet may act on cancer by impacting the type and diversity of microbes in the gut, which in turn mediate cancer risk, but the mediating associations have not been explored in cancer epidemiologic studies. Rapid new advances have been made using technologies such as metabolomics and PA monitors to assess diet, PA, respectively, and even obesity/adiposity, and newer innovative technologies are being tested. However, several challenges and research priorities (see Table 1) remain as outlined in this commentary. The research priorities identified in this paper highlight the work that needs to be conducted to move the science forward to decrease the cancer burden.

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Table 1.

Summary of key area-specific priorities for cancer research and proposed actions.

Area-specific priorities for cancer research	Actions
Nutrition and cancer epidemiology Expand research across the life course, improve diet measurements, and utilize biological samples.	• Investigate the impact of diet across the life course, especially gaps in early life. • Investigate long latencies between exposure and diagnosis of cancer. • Investigate dose-response relationships with better categorization of dietary components. • Study molecular effects of different dietary components/patterns. • Integrate genomics, microbiomics, metabolomics and epigenomics with nutrition. • Leverage emerging technologies and integrate objective measures such as metabolomics for identification of dietary biomarkers and patterns. • Strengthen the development and application of intake biomarkers from body fluids, particularly blood and urine. • Link to infrastructural resources of health care settings to investigate diet and cancer prognosis and related outcomes. • Expand studies outside the industrialized world to capture current demographic transition. • Utilize short-term feeding studies for biomarker assessment for use in cohorts.
Physical activity (PA) and cancer epidemiology Expand research on PA and sedentary behaviors across the life course, improve measurements, and utilize biological samples.	• Expand research across the cancer spectrum to cover cancer sites and subtypes that have not adequately been studied. • Study effect modification by adiposity, diet, age, race/ethnicity, comorbidities, etc. • Expand research on PA in older adults. • Study PA type, frequency, intensity, dose, and timing in life. • Improve measures with applicable emerging technologies. • Focus on biologic mechanisms of action of PA-cancer relationships.
Obesity and cancer epidemiology Expand research on the impact of weight gain across the life course and measures of adiposity.	• Evaluate whether “obesity paradox” observed for certain cancer sites is due to methodological limitations. • Expand investigations of the impact of obesity and/or weight gain across the life course, including earlier in life. • Improve approaches to modeling of weight gain across the life course and cancer. • Confirm validity of adiposity measurements by age, race/ethnicity. • Investigate whether more precise measurement of fat compartments and body fat distribution have advantages beyond simple BMI. • Investigate obesity and/or weight trajectory on cancer survivors, including pediatric cancer survivors, and study the impact of obesity on second primary cancers and cancer recurrence. • Study whether obesity phenotypes are important for metabolic health. • Investigate trans-generational impact of obesity on cancer. • Investigate and identify mechanistic targets and intervention strategies to offset effects of obesity on chemotherapeutic drugs among cancer survivors. • Evaluate whether intentional weight loss following chronic obesity reverses the carcinogenic effects of obesity. • Evaluate effective methods to translate evidence-based methods to reducing obesity (i.e., healthy diet, PA) at both the individual and societal levels.
Gut Microbiome Expand prospective studies of the microbiome and cancer, and improve current methodological limitations.	• Incorporate additional tools and resource development. • Expand and incorporate non-bacterial components of the microbiome. • Standardize sample and data collection protocols. • Utilize large databases and repositories for increasing volume of complex data. • Increase human resources and training for bioinformatics and computational biology.
Metabolomics and biomarkers of dietary exposures Expand prospective studies of the metabolome and cancer, and improve current methodological limitations.	• Utilize validation studies because many biomarkers proposed are not necessarily informative in community dwelling populations. • Utilize standard reference materials for different types of biological samples (e.g., plasma, serum, and urine). • Expand studies to include other types of biospecimens (e.g. teeth, hair, and other tissues). • Incorporate biomarker panels. • Evaluate impact of long-term storage and subsequent sample processing of biospecimens. • Consolidate open-source tools and databases. • Conduct studies to identify metabolomics-based dietary intake biomarkers.
Emerging technologies for measuring diet Expand studies on emerging technologies to improve accuracy and precision of assessment of dietary intake.	• Evaluate the utility and validity of dietary assessment apps in mobile devices, wearable sensors, and other emerging technologies. • Improve methods and measures to capture dietary intake and context of eating in diverse groups. • Incorporate biomarkers as part of validation/calibration testing for emerging technologies. • Expand studies to include usability and cross-disciplinary teams to pursue automation of food identification and volume estimation.
Emerging technologies for measuring PA and sedentary behavior Expand studies on emerging technologies to improve accuracy and	• Evaluate usability, feasibility, and acceptability of mobile devices, wearable sensors, and other emerging technologies that measure PA and sedentary behavior. • Evaluate technologies in participants of large, prospective cohort studies.

Area-specific priorities for cancer research	Actions
precision of assessment of PA and sedentary behaviors.	• Evaluate impact of behavioral variability on use of specific technologies. • Improve systems and scalability for implementation of accelerometer-based measures.
Hormones and cancer Expand pooling projects to test homone cancer relationships.	• Pool hormone biomarkers from prospective cohort studies to understand cancer risk by ethnicity and other population subgroups. • Standardize methods for hormone measurements. • Expand human studies to investigate whether dietary factors and PA are associated with patterns of hormonal profiles.
Gene-Environment (GxE) Interactions Interpret the impact of GWAS-identified single nucleotide polymorphisms (SNPs) located in non-coding regions of the genome.	• There is a need to understand the functional significance of GWAS identified SNPs in the non-coding regions of the genome. • More precise and accurate ways to measure environmental exposures are needed because exposure assessment errors contribute to inabilities to consistently detect GxE interactions.
Epigenetics SNPs associated with cancer risk in non-coding regions of genes or their promoters that do not produce functional proteins may have importance in epigenomics.	• There is a need to understand the difference between epigenetic drift and epigenetic alterations due to modifiable environmental risk factors such as diet. • For impact of environmental factors on the epigenome, there is a need to understand which of the three classes of epigenetic molecules, DNA methylation, modifications of histone or other chromosomal proteins and noncoding RNAs, would be ideal candidate biomarkers in cancer risk assessment.
Implementation of what we already now Implement evidence based knowledge such as national guidelines on food, nutrition, PA, and cancer prevention.	• Expand implementation science efforts to ensure that knowledge already generated benefits the most people possible.