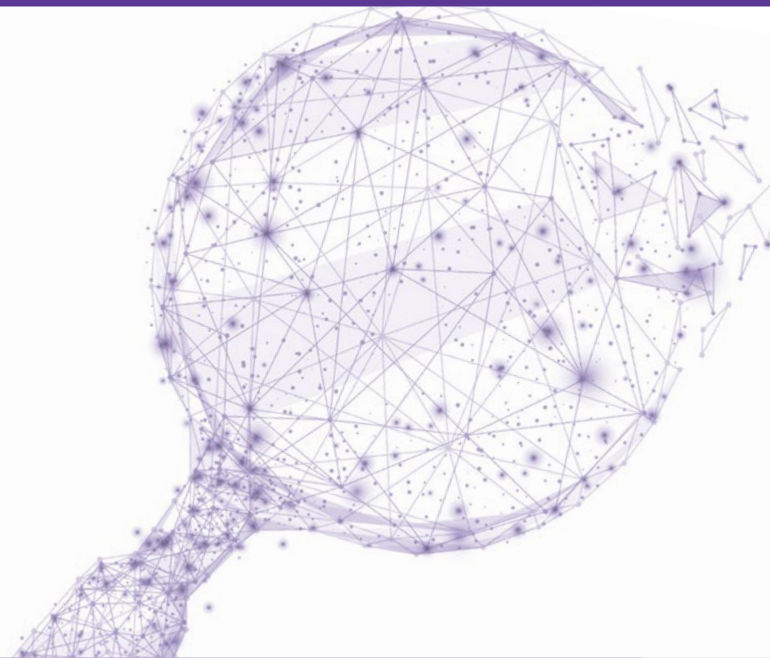
World Cancer Research Fund

American Institute for Cancer Research

CUP Continuous Update Project

Analysing research on cancer prevention and survival



Future research directions

2018

World Cancer Research Fund International

World Cancer Research Fund UK

Wereld Kanker Onderzoek Fonds

World Cancer Research Fund 世界癌症研究基金會

Contents

WORLD CANCER RESEARCH FUND NETWORK

Our Vision

We want to live in a world where no one develops a preventable cancer.

Our Mission

We champion the latest and most authoritative scientific research from around the world on cancer prevention and survival through diet, weight and physical activity, so that we can help people make informed choices to reduce their cancer risk.

As a network, we influence policy at the highest level and are trusted advisors to governments and to other official bodies from around the world.

Our Network

World Cancer Research Fund International is a not-for-profit organisation that leads and unifies a network of cancer charities with a global reach, dedicated to the prevention of cancer through diet, weight and physical activity.

The World Cancer Research Fund network of charities is based in Europe, the Americas and Asia, giving us a global voice to inform people about cancer prevention.

CUP Continuous Update Project

Analysing research on cancer prevention and survival

THIRD EXPERT REPORT

Our Continuous Update Project (CUP)

The Continuous Update Project (CUP) is the World Cancer Research Fund (WCRF) Network's ongoing programme to analyse cancer prevention and survival research related to diet, nutrition and physical activity from all over the world. Among experts worldwide it is a trusted, authoritative scientific resource which informs current guidelines and policy on cancer prevention and survival.

Scientific research from around the world is continually added to the CUP's unique database, which is held and systematically reviewed by a team at Imperial College London. An independent panel of experts carries out ongoing evaluations of this evidence, and their findings form the basis of the WCRF Network's Cancer Prevention Recommendations (see inside back cover).

Through this process, the CUP ensures that everyone, including policymakers, health professionals and members of the public, has access to the most up-to-date information on how to reduce the risk of developing cancer.

The launch of the World Cancer Research Fund Network's Third Expert Report, *Diet, Nutrition, Physical Activity and Cancer: a Global Perspective*, in 2018 brings together the very latest research from the CUP's review of the accumulated evidence on cancer prevention and survival related to diet, nutrition and physical activity. Future research directions is one of many parts that make up the CUP Third Expert Report: for a full list of contents, see dietandcancerreport.org

The CUP is led and managed by World Cancer Research Fund International in partnership with the American Institute for Cancer Research, on behalf of World Cancer Research Fund UK, Wereld Kanker Onderzoek Fonds and World Cancer Research Fund HK.

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Key

References to other parts of the Third Expert Report are highlighted in purple.

Introduction

Identifying opportunities

Cancer prevention has been a fundamental focus for the World Cancer Research Fund (WCRF) and the American Institute for Cancer Research (AICR) since their inception. The WCRF/AICR Cancer Prevention Recommendations represent the most comprehensive and up-to-date evidence-based strategies to reduce cancer risk through diet, nutrition and physical activity (see Recommendations and public health and policy implications). However, the evidence linking these factors and cancer varies in strength and quality.

This part of the Third Expert Report outlines several future research directions that the Continuous Update Project (CUP) Panel (see Judging the evidence) identified as broad areas in which progress would further enhance future recommendations and improve our understanding of the mechanisms by which diet, nutrition and physical activity alter cancer risk and outcomes. New methods of research and new issues to study are always being developed; these advances will likely further strengthen our confidence in some of the existing recommendations, but may also necessitate revision of others in the future.

Changing paradigms

The CUP and its predecessors, the First and Second Expert Reports [1, 2], have identified specific foods (such as processed meat) and components of foods and drinks (such as ethanol in alcoholic drinks) in the human diet that increase or decrease the risk of one or more specific cancers. In recent years, there has been a shift in emphasis on the part of the Panel and the broader research community towards a more holistic approach. In humans, as with all organisms, the normal physiological and metabolic state is subject to external and endogenous challenges (stresses). Good nutritional state is an important component of the body's capacity to withstand these stresses and maintain health. The Panel consider that a more holistic approach to the dietary and nutritional determinants of resilience to external and endogenous challenges will account more effectively for the potential synergy of dietary factors and their interaction with behaviours that are often highly correlated.

The accumulating results of the CUP increasingly point to the importance of the systemic metabolic milieu of the body – as reflected in anthropometric measures such as growth and development in early life, and body fatness – as being a critical determinant of cancer susceptibility. Whereas the evidence for the impacts of some specific exposures, such as red and processed meat, alcohol and wholegrains, is strong, specific individual foods, drinks, nutrients or other components of foods appear increasingly less likely to be important singular factors in causing or protecting against cancer. Instead, patterns of diet and physical activity combine to create a metabolic state that is more, or less, conducive to the acquisition of the genetic and epigenetic changes that lead to the alterations in cells characterised as the hallmarks of cancer [3, 4] (see The cancer process, Section 2).

This Third Expert Report has highlighted many examples of strong evidence that are judged to be sufficient to support recommendations. However, it has also highlighted the many factors for which the evidence is judged to be too limited in amount, quality or consistency to draw firm conclusions (see Judging the evidence). Each of these factors, especially those in the 'limited – suggestive' category, represents an opportunity to resolve the uncertainty of their role in cancer causation or prevention. In addition, the Panel acknowledges that even when the epidemiological evidence is strong, the corresponding specific mechanistic evidence may be inadequate.

The Panel discussions over the last 10 years have identified six critical areas of research:

1. **Biological mechanisms by which diet, nutrition and physical activity affect cancer processes**

2. **The impact of diet, nutrition and physical activity throughout the life course on cancer risk**

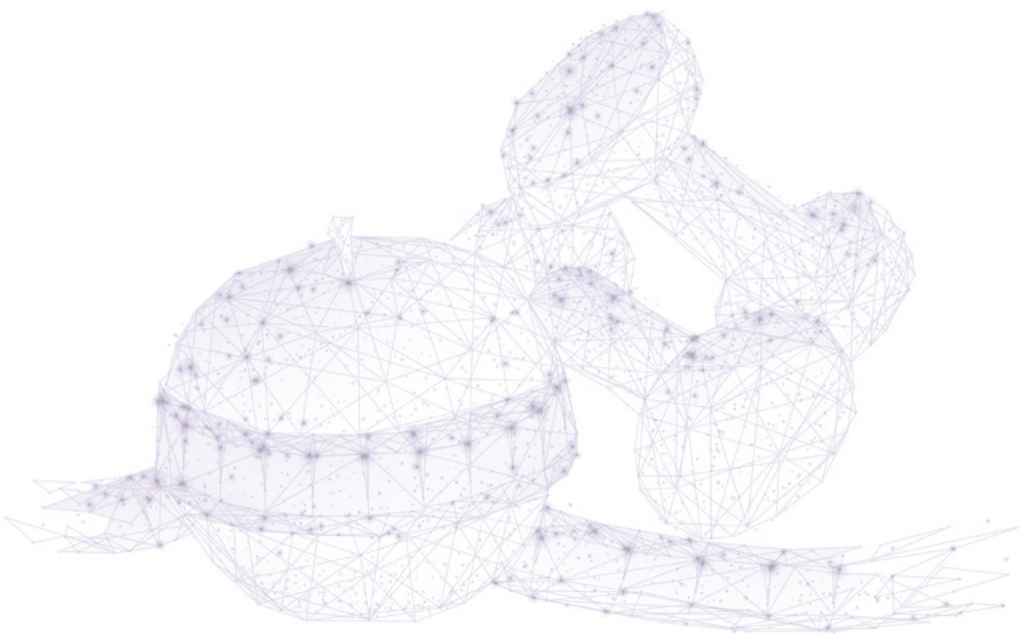
3. **Better characterisation of diet, nutrition, body composition and physical activity exposures**

4. **Better characterisation of cancer-related outcomes**

5. **Stronger evidence for the impact of diet, nutrition and physical activity on outcomes in cancer survivors**

6. **Globally representative research on specific exposures and cancer**

These areas are outlined in detail over the following sections and are for consideration by the research community and funding organisations generally. A summary of the themes can also be found in the Summary of the Third Expert Report.



1. Biological mechanisms by which diet, nutrition and physical activity affect cancer processes

The associations between diet, nutrition and physical activity and cancer are sufficiently consistent and strong to propose recommendations. However, the biological mechanisms through which these factors operate are less clearly defined. The CUP Panel emphasised the need for greater insights into the biological mechanisms by which diet, nutrition and physical activity influence cancer risk.

In recent years there has been a rapid advancement in understanding of the complex and interacting intracellular and intercellular processes that lead to cancer; the biological characteristics that distinguish tumours from normal tissues have been eloquently summarised as the hallmarks of cancer [3, 4] (see The cancer process, Section 1.2.3). However, despite compelling evidence implicating diet, nutrition and physical activity-related factors as key determinants of cancer risk in populations, the mechanisms by which these factors lead to the acquisition of the hallmarks of cancer remain to be fully elucidated.

All biological processes depend on a supply of the energy and nutrients that are necessary for normal function. The development of a cancer occurs in cells within a specific microenvironment, which is influenced by nutritional factors at the local and systemic levels. However, little research has been devoted to characterising methodically the demands for energy or specific nutrients placed on cells and the body by these biological processes, or the metabolic and other consequences of energy and nutrient supply that does not match these demands, in the context of cancer development.

The majority of common cancer types arise in epithelial tissues. Examining the impacts of diet, nutrition and physical activity on epithelial tissue and in the emerging tumour microenvironment offers opportunities to reveal the mechanisms by which diet, nutrition and physical activity might both potentiate and prevent the development of cancer [5–9]. Each epithelial niche comprises many cell types that are exquisitely sensitive to microenvironmental signals. The metabolic and phenotypic plasticity (ability to change function and cellular identity) of cells, including immune cells and adipocytes, in microenvironmental niches, is critical for the fate of potentially malignant cells [10]. Plausible mechanisms for how diet, nutrition and physical activity may affect the regulation of tissue microenvironments have been proposed, but conclusive demonstrations of such effects are largely lacking.

Dissecting the biological mechanisms through which diet, nutrition and physical activity enable the acquisition of the hallmarks of cancer will require the systematic integration of *in vitro*, *in vivo* (human and animal) and epidemiological research approaches. Understanding the roles of diet, nutrition and physical activity in maintaining or perturbing appropriate metabolism and function and how this leads to cancer is an urgent research priority.

2. The impact of diet, nutrition and physical activity throughout the life course on cancer risk

There is strong evidence, mainly from animal models, that there are critical periods of susceptibility to the effects of diet, nutrition and physical activity on cancer risk. Observational evidence from humans strongly implicates events occurring early in life as important determinants of cancer risk. However, reliable data on exposures in people throughout the life course is scarce and the mechanisms through which such windows of susceptibility operate are poorly understood.

Early growth and development

The risk of several adult cancers varies according to markers of growth and development in early life – including birthweight, age at menarche and adult attained height – as well as with body mass index (BMI) during or at the end of childhood growth (see Exposures: Height and birthweight). Nutritional factors are key determinants of patterns of growth and limitation of energy or nutrient supply during particular periods of growth, including in utero exposures, can act as a potential constraint on growth, leading to adaptations in the foetus or the child that may persist into adulthood, with consequences for adult phenotype. Such phenotypical alterations include susceptibility to cardiometabolic disease and may also include susceptibility to cancer.

Periods of heightened cancer susceptibility are known for several adverse exposures (such as ionising radiation and ultraviolet light); therefore, any variations in risk associated with the timing of exposures throughout the life course are important considerations when making recommendations [11, 12]. For instance, women who are overweight or obese in young adulthood (18 to 30 years) are at a reduced risk of both pre- and postmenopausal breast cancer, but being overweight or obese in later adulthood increases the risk of postmenopausal breast cancer [13]. This observation presents challenges regarding the interpretation of the evidence and its impact on public health messaging. However, understanding and resolving the mechanisms through which these effects are mediated would provide a basis for the development of alternative strategies to reduce the risk of cancer in general as well as of other non-communicable diseases (NCDs). Identifying the developmental factors that are responsible for the association of height with cancer risk has important implications for recommendations on child growth.

Changes in body weight and composition

Although there is strong evidence that adult weight gain and obesity are causes of breast cancer, the evidence that intentional weight loss later in life modifies cancer risk is limited. Research is needed to determine whether intentional weight loss in people living with overweight and obesity reduces cancer risk, just as cessation of tobacco use reduces later risk [14]. The impact of potential latency of risk reduction following weight loss and of the duration of overweight and obesity also need further study.

The impact of body composition, including loss of lean mass and sarcopenic obesity are areas of increasing interest for research. The wider availability of methods for objective measures of body composition and the secondary uses of clinical imaging provide opportunities to enhance our understanding of these factors [15].

Diet

For many dietary components and nutrients, the evidence is currently suggestive of a possible effect, but too limited to draw firm conclusions that would support recommendations, either because of the amount, quality or consistency of the evidence. In light of the acknowledged latency between exposure and the development of cancer, improving the assessment of overall dietary exposures over time and during critical periods of proposed susceptibility is a research priority. In addition, exposure to dietary factors and nutrients may have different effects during specific developmental phases or stages in carcinogenesis and progression [12]. For example, the impact of typical folate intakes on cancer risk may depend on age and the presence or absence of pre-neoplastic or pre-malignant cellular changes.

Alcohol

Alcohol intake is associated with an increased risk of six types of cancers: mouth, pharynx and larynx, oesophagus (squamous cell carcinoma), stomach, liver, colorectal and breast cancer (see Exposures: Alcoholic drinks). However, it is uncertain whether intakes and patterns of intake during particular life periods confer particularly elevated risks; for example, binge drinking in early adulthood may have stronger effects than total lifetime exposure [16]. Understanding the impact of intakes during each phase, total duration and the benefits of cessation for each cancer type will help ensure that future recommendations are optimally effective [17].

Physical activity and sedentary behaviour

Physical activity is associated with significant reductions in risk of colorectal, postmenopausal breast and endometrial cancers (see Exposures: Physical activity). These cancer types are also strongly associated with increased body fatness. However, there is strong evidence that increased body fatness is a cause of ovarian, prostate (advanced) stomach (cardia), gallbladder, pancreatic, kidney and liver cancers; the evidence for the role of physical activity in these cancers is limited. Therefore, understanding the role of physical activity, independent of body fatness, is a priority. Furthermore, it is not known whether there are critical periods during which being physically active is most beneficial. For example, does physical activity contribute more strongly to retarding the progression of early neoplastic changes or the earlier malignant transformation? Similarly, a greater understanding is needed of the role of sedentary behaviour overall, as a risk factor for obesity and at potentially critical periods during the life course.

Transgenerational impact

There is substantial *in vivo* data to suggest that both early exposures and transgenerational impacts are highly plausible in people, but the current evidence is limited by methodological challenges [18]. Understanding the impacts of specific exposures on pre-malignant and invasive disease, throughout the life course and in a range of cancer sites, is a high priority.

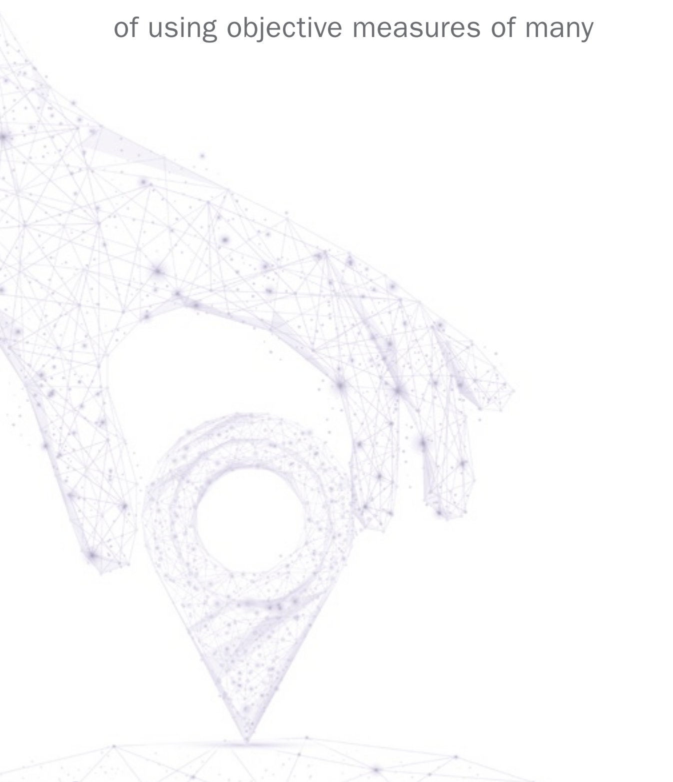
3. Better characterisation of diet, nutrition, body composition and physical activity exposures

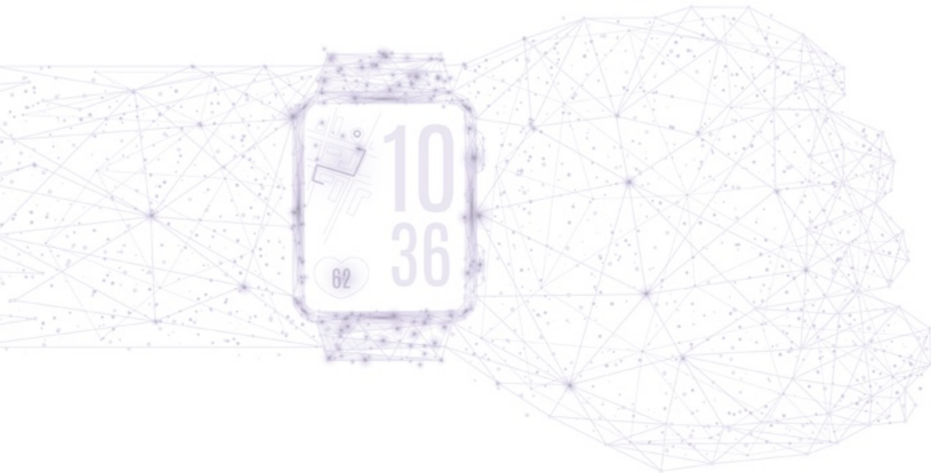
The estimated impact of diet, nutrition and physical activity on cancer risk, in the current literature, has most commonly been determined from self-reported exposures at a single time point. The recent availability of objective measures to accurately capture such exposures provides opportunities to enhance research in this area.

The quality of research that seeks to investigate the impact of an exposure on an outcome, such as the development of cancer, is dependent on reliable measures of that exposure. However, lifestyle exposures such as diet, nutrition, composition and physical activity have been difficult to measure accurately and precisely, often relying on self-reports, and are subject to several potential biases and measurement error [19–21].

In the CUP, the systematic collation and interpretation of the evidence available in published literature has highlighted the limitations of previously available methods for characterising dietary intake, body composition, relevant metabolic processes and physical activity. Recent technological advances have improved the feasibility of using objective measures of many lifestyle exposures. However, the volume and complexity of the data from these new methods demands the development of validated statistical methods for the processing and analysis of such data. Biomarkers of dietary exposures can be used to validate self-reported dietary exposures to reduce misclassification of exposures and increase statistical power. However, the pursuit of more holistic approaches to the characterisation of diet will require biomarkers that can provide corresponding integrated measures of dietary exposures.
The technique of Mendelian randomisation also offers opportunities for exploring how cancer risk differs with genetic variations that mimic different levels of exposure, but with less likelihood of confounding.

The burden of cancer is growing most rapidly in low- to middle-income countries [22] and these nations may help by providing a wider range of exposures to be studied but do not have the resources to support many of the new technologies for exposure measurement. Therefore, it is important to develop environmental and lifestyle exposure assessment tools for cancer epidemiology research in low-resource settings [23], as well as to forge collaborations with centres of excellence in high-income countries, to help build capacity. Low- to middle-income countries potentially offer opportunities to examine a broader distribution of exposures as well as the impact of the nutrition transition [24].





The advent of inexpensive activity tracking devices is already transforming our ability to quantify physical activity [25]. Further application of these devices in research and the development of tools and approaches to efficiently analyse the resultant data will be critical for enhancing our understanding of the role of physical activity in cancer prevention and survival.

Similarly, objective measures of body composition such as dual-energy X-ray absorptiometry ('dexa' scan), computer tomographic (CT) scans and magnetic resonance imaging (MRI) can provide accurate measures of body composition beyond anthropometric measures such as BMI, waist circumference and waist-hip ratio. BMI is currently the most commonly used measure of adiposity. However, BMI is an indirect measure and there is substantial variation in body composition between people with the same BMI [26], in addition to ethnic differences in risk associated with overweight and obesity [27, 28]. Changes in body composition over time, often through reductions in lean mass or increased adiposity, may be an important determinant of cancer risk that is not captured by measures taken at a single time point. Longitudinal data, ideally using objective measures of lean mass, adiposity and distribution of adipose tissue over time, will enable researchers to examine body composition and its relationship with cancer risk more completely.

For alcohol consumption, further research is needed on the role of patterns of drinking (for example, bingeing or social drinking) and the benefits of stopping, especially in moderate drinkers. Understanding the contribution of acute, chronic or lifetime exposure, including pooled analyses of former versus never drinkers versus periods of abstinence and cumulative exposure – analogous to the pack-years used in tobacco exposure – would help inform future public health messaging.

4. Better characterisation of cancer-related outcomes

Tumours are increasingly classified by molecular features in addition to traditional anatomic and histological features. The differential impact of risk factors on molecularly defined subtypes of some cancers demands that molecular features are accurately reported and available to researchers. Long-term survival in cancer patients demands an increased focus on non-cancer outcomes.

The establishment of comprehensive registries makes cancer unique among non-communicable diseases. In many jurisdictions, the reporting of cancer diagnoses is legally mandated and conducted to a high level of completeness, accuracy and timeliness of reporting, but such infrastructure lags behind the increasing burden of cancer in many low- to middle-income countries. The diagnosis, characterisation and treatment of cancer has become more and more complex. Emerging molecular phenotypes define cancers beyond simple anatomic classifications. The CUP has recognised the increasing stratification of cancer diagnoses by molecular features and the growing evidence that the different molecular subtypes may be associated with specific risk factor profiles that influence cancer risk, prognosis and treatment selection and subsequent outcomes. Therefore, comprehensive characterisation of the molecular features of tumours, of the treatment selected on the basis of the tumour features and of the potential evolution of tumour phenotype will all need to be addressed in future research.

Improvements in cancer survival make it necessary to consider long-term outcomes. Recurrence, progression, co-morbidities and late effects of therapy all have significant impacts on patients and health services. The potential for diet to affect treatment efficacy, both positively and negatively, demands that further research be conducted to identify any potential interactions. As cancer survival improves, the duration of follow-up of people living with and beyond cancer needs to increase so that the full spectrum of the impact of the disease, its treatment and the impact of lifestyle on those outcomes can be adequately addressed. The impacts of diet, nutrition and physical activity on cancer-related outcomes, in addition to cancer-specific and overall mortality, need to be fully characterised so that their role in overall health can be appropriately assessed.

5. Stronger evidence for the impact of diet, nutrition and physical activity on outcomes in cancer survivors

The dramatic increase in cancer survivorship has led to intense research into the impact of diet, nutrition and physical activity on outcomes after a diagnosis of cancer. However, the current evidence is not sufficiently strong to support specific recommendations for cancer survivors beyond advice to follow the recommendations for cancer prevention. Research is needed to determine whether interventions that change body composition, dietary intake or levels of physical activity can improve patient outcomes after a cancer diagnosis.

The dramatic increase in the number of cancer survivors over the past four decades has led to progress in research showing that factors related to diet, nutrition and physical activity can predict various cancer outcomes and suggesting that healthy lifestyle choices might positively affect outcomes after a diagnosis of cancer. Consequently, in addition to a longstanding focus on cancer prevention, WCRF/AICR now also aims to provide robust evidence-based recommendations on diet, nutrition and physical activity after a cancer diagnosis. However, in the only cancer survivor CUP report completed so far, for breast cancer, there were no factors for which the evidence was strong enough to support specific recommendations. Although many factors were predictive of outcome, the quality of the evidence was too limited (for example, inadequate control for confounding by treatment or disease stage) to have confidence that changes in these factors would necessarily lead to change in outcome, and so they were categorised as 'limited – suggestive' (see CUP Breast cancer survivors report 2014 and Survivors of breast and other cancers).

There is emerging but limited data on the effect of diet, nutritional status and physical activity on outcomes for survivors of breast and other cancers, including prognosis and quality of life during and after treatment. The phase of survivorship (see Survivors of breast and other cancers) is critical when considering research needs regarding the roles of diet, nutrition and physical activity in cancer survivorship. Cancer survivors may provide a more feasible setting in which to conduct intervention studies of relevant exposure owing to the higher event rate and more focused window of exposure. Furthermore, cancer survivors may be more willing to change diet or levels of activity. Future research will need to address each phase of survivorship and the potential to positively affect outcomes in people living with and beyond cancer.

There is currently considerable uncertainty regarding the roles of body composition and weight management in the context of cancer survival. For several cancer sites

there appears to be an advantage to being overweight at diagnosis but for others outcomes are less favourable [27]. However, to address the potential impact of disease on body composition and outcomes, future research must account for peri-diagnostic weight trajectories.

Diet, nutrition and physical activity and their interaction with genetic, epigenetic and hormonal factors may play an important role in influencing response to treatment, quality of life during and after treatment, and risk of metastasis and recurrence, as well as overall and cancer-specific mortality.

The role of physical activity in potentially improving outcomes in people living with and beyond cancer is an area of intense research interest. However, there is substantial danger of reverse causality in observational studies due to the likelihood that disease stage and symptoms may limit participation in physical activity. In addition to cancer-specific outcomes, the role of physical activity in improving overall survival, fatigue and quality of life are important research priorities.

6. Globally representative research on specific exposures and cancer

Cancer is a global disease, but the majority of research to date has been conducted in high-income countries. The rapidly increasing burden of cancer and the change in the pattern of cancer in low- to middle-income countries, as well as differences in diet, nutrition and physical activity between diverse populations, mean that existing research cannot simply be generalised to those populations. Context-specific research is necessary to understand the impact of these exposures in diverse global populations.

The majority of epidemiological studies have been conducted in high-income countries such as the UK, other European countries, the USA and Australia. Good-quality data on specific exposures and cancer sites was very limited for many countries, especially low- to middle-income countries. Patterns of cancer incidence and relevant exposures vary considerably according to geographical region. In addition, different racial and ethnic responses to exposures may lead to disparities in cancer risk and outcomes within geographic regions with shared exposures.

Currently, the burden of cancer in the developing world is driven by tobacco use and infectious agents such as human papillomavirus, hepatitis B and *Helicobacter pylori* [29]. However, the rates of cancers associated with overweight, obesity and decreasing physical activity are increasing and are expected to increase further [30]. A range of socioeconomic and cultural factors are driving obesity rates in low- to middle-income countries, such as urbanisation, unemployment, inadequate educational levels and low breastfeeding rates, as well as unsound complementary feeding practices [31]. Measures of exposures and the distribution of outcomes may differ in different settings [32]; careful validation of exposure assessment instruments is needed to ensure that future research is equipped to address the cancer challenge, particularly in low-resource settings [23].

For people living with and beyond cancer, the healthcare context in which they are diagnosed and treated has a dramatic impact on outcome. Almost all research on the impacts of diet, nutrition and physical activity has occurred in countries with a high Human Development Index (HDI). If cancer outcomes differ between countries with different HDI, then the impacts of diet, nutrition and physical activity may also differ. Therefore, understanding their roles and any potential barriers to improving adherence to recommendations for cancer prevention in low HDI settings is an urgent priority.

Summary

In the same way that cancer treatments do not benefit patients equally, the efficacy of cancer prevention measures varies between people and between populations. Understanding and predicting those differences will provide opportunities for targeted and more effective preventive strategies for well-defined or high-risk groups [33]. However, current knowledge regarding variability in individual or population-based responses to cancer prevention recommendations is limited. The current 'one size fits all' approach is based on the best available evidence, but it is likely that more targeted approaches could yield substantial benefits.

Addressing the areas of research identified by the CUP will enhance knowledge of many inter-related aspects of cancer risk and outcomes. Dissecting the biological mechanisms will provide opportunities to further evaluate the relationship between exposures and outcomes through controlled intervention studies, particularly among high-risk groups and in cancer survivors.

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Abbreviations

AICR	American Institute for Cancer Research
BMI	Body mass index
CT	Computer tomographic
CUP	Continuous Update Project
HDI	Human development index
MRI	Magnetic resonance imaging
NCD	Non-communicable disease
WCRF	World Cancer Research Fund

Glossary

Adipocytes
Cells of adipose tissue, where fats (triglycerides) are stored.

Adipose tissue
Body fat. Tissue comprising mainly cells containing triglyceride (adipocytes). It acts as an energy reserve, provides insulation and protection, and secretes metabolically active hormones.

Adiposity
Degree of body fatness; can be measured indirectly in a variety of ways including body mass index (see **body mass index**) and percentage body fat.

Alcohol
An organic compound that contains a hydroxyl group bound to a carbon atom. Releases energy when metabolised in the body. Commonly ethanol C_6H_5OH.

Anthropometric measures
Measures of body dimensions.

Bias
In epidemiology, consistent deviation of an observed result from the true value in a particular direction (systematic error) due to factors pertaining to the observer or to the study type or analysis (see **selection bias**).

Biological mechanisms
System of causally interacting processes that produce one or more effects.

Biomarker
A naturally occurring molecule, gene or characteristic by which a particular pathological or physiological process can be identified.

Body composition
The composition of the body in terms of the relative proportions of water and adipose and lean tissue. Can also be described as the proportions of fat (lipid) and fat-free mass. May also include the content of micronutrients, such as iron, and the distribution of adipose tissue, for example, central/peripheral or visceral/subcutaneous.

Body mass index (BMI)
Body weight expressed in kilograms divided by the square of height expressed in metres ($BMI = kg/m^2$). Provides an indirect measure of body fatness.

Cancer
Any disorder of cell growth that results in the invasion and destruction of surrounding healthy tissue by abnormal cells and which may spread to distant sites. Cancer cells arise from normal cells whose nature is permanently changed.

Carcinogenesis
The process by which a malignant tumour is formed.

Carcinoma
Malignant tumour derived from epithelial cells, usually with the ability to spread into the surrounding tissue (invasion) and produce secondary tumours (metastases).

Cardia stomach cancer
A sub-type of stomach cancer that occurs in the cardia, near the gastro-oesophageal junction

Cell
Structural and functional unit of most living organisms. Can exist independently or as part of a tissue or organ.

Confounder/confounding factors
A variable that is associated with both an exposure and a disease but is not in the causal pathway from the exposure to the disease. If not adjusted for within a specific epidemiological study, this factor may distort the apparent exposure–disease relationship. An example is that tobacco smoking is related both to coffee drinking and to risk of lung cancer, and thus unless accounted for (adjusted) in studies, might make coffee drinking appear falsely as a cause of lung cancer.

CT scans
A computerised tomography (CT) scan combines a series of X-ray images taken from different angles and uses computer processing to create cross-sectional images, or slices, of the bones, blood vessels and soft tissues inside the body.

Diet, nutrition and physical activity
In the CUP, these three exposures are taken to mean the following: **diet**, the food and drink people habitually consume, including dietary patterns and individual constituent nutrients as well as other constituents, which may or may not have physiological bioactivity in humans; **nutrition**, the process by which organisms obtain energy and nutrients (in the form of food and drink) for growth, maintenance and repair, often marked by nutritional biomarkers and body composition (encompassing body fatness); and **physical activity**, any body movement produced by skeletal muscles that requires energy expenditure.

Dietary supplement
A substance, often in tablet or capsule form, which is consumed in addition to the usual diet. Dietary supplements typically refer to vitamins or minerals, though phytochemicals or other substances may be included.

Endogenous
Substances or processes that originate from within an organism, tissue or cell.

Energy
Energy, measured as calories or joules, is required for all metabolic processes. Fats, carbohydrates, proteins and alcohol from foods and drinks release energy when they are metabolised in the body.

Epigenetics
Relating to the control of gene expression through mechanisms that do not depend on changes in the nucleotide sequence of DNA, for example, through methylation of DNA or acetylation of histone.

Epithelial (see **epithelium**)

Epithelium
The layer of cells covering internal and external surfaces of the body, including the skin and mucous membranes lining body cavities such as the lung, gut and urinary tract.

Ethanol
An organic compound in which one of the hydrogen atoms of water has been replaced by an alkyl group. See **alcohol**.

Exposure
A factor to which an individual may be exposed to varying degrees, such as intake of a food, level or type of physical activity, or aspect of body composition.

Fat
Storage lipids of animal tissues, mostly triglyceride esters. See **adipose tissue**.

Folate
A salt of folic acid. Present in leafy green vegetables, peas and beans, and fortified breads and cereals.

Hallmarks of cancer
Key phenotypic characteristics in structure and function that represent an essential part of the biology of a cancer cell.

Helicobacter pylori (H. pylori)
A gram-negative bacterium that lives in the human stomach. It colonises the gastric mucosa and elicits both inflammatory and lifelong immune responses.

Hepatitis
Inflammation of the liver, which can occur as the result of a viral infection or autoimmune disease, or because the liver is exposed to harmful substances, such as alcohol.

High-income countries
As defined by the World Bank, countries with an average annual gross national income per capita of US$12,236 or more in 2016. This term is more precise than and used in preference to 'economically developed countries'.

In vitro
Processes that occur outside the body, in a laboratory apparatus.

In vivo
Describing biological processes as they are observed to occur within living organisms.

Incidence
Frequency of occurrence of new cases of a disease in a particular population during a specified period.

Life course approach
The long-term effects on later health or disease risk of physical or social exposures during pre-conception, gestation, childhood, adolescence, young adulthood and later adult life.

Low- and middle-income countries
As defined by the World Bank, low-income countries are countries with an average annual gross national income per capita of US$1,005 or less in 2016. Middle-income countries, are countries with an average annual gross national income per capita of between US$1,006 and US$12,235 in 2016. These terms are more precise than and used in preference to 'economically developing countries'.

Malignant
A tumour with the capacity to spread to surrounding tissue or to other sites in the body.

Menarche
The start of menstruation.

Mendelian randomisation
A method of using natural variation in genes of known function to mimic a potential causal effect of a modifiable exposure on disease. The design helps to avoid problems from reverse causation and confounding.

Menopause
The cessation of menstruation.

Metabolism
The sum of chemical reactions that occur within living organisms.

Metastasis/metastatic spread
The spread of malignant cancer cells to distant locations around the body from the original site.

Neoplastic
Referring to abnormal new growth of tissue that persists in the absence of the original stimulus.

Non-communicable diseases (NCDs)
Diseases which are not transmissible from person to person. The most common NCDs are cancer, cardiovascular disease, chronic respiratory diseases, and diabetes.

Nutrient
A substance present in food and required by the body for maintenance of normal structure and function, and for growth and development.

Nutrition
Process by which organisms obtain energy and nutrients (in the form of food and drink) for growth, maintenance and repair.

Obesity
Excess body fat to a degree that increases the risk of various diseases. Conventionally defined as a BMI of 30 kg/m^2 or more. Different cut-off points have been proposed for specific populations.

Phenotype
The observable characteristics displayed by an organism; depends on both the genotype (the genetic makeup of a cell) and environmental factors.

Physical activity
Any movement using skeletal muscles that requires more energy than resting.

Policy
A course of action taken by a governmental body including, but not restricted to, legislation, regulation, guidelines, decrees, standards, programmes and fiscal measures. Policies have three interconnected and evolving stages: development, implementation and evaluation. Policy development is the process of identifying and establishing a policy to address a particular need or situation. Policy implementation is a series of actions taken to put a policy in place, and policy evaluation is the assessment of how the policy works in practice.

Pooled analysis
In epidemiology, a type of study in which original individual-level data from two or more original studies are obtained, combined and re-analysed.

Processed meat
Meats transformed through salting, curing, fermentation, smoking or other processes to enhance flavour or improve preservation (see Exposures: Meat, fish and dairy products).

Resilience
Property of a tissue or of a body to resume its former condition after being stressed or disturbed.

Reverse causality
When the true relationship between two variables is actually occurring in the opposite direction to how they are being studied; instead of the exposure leading to the outcome, the variable being measured as the outcome is causing the variable being measured as the exposure.

Selection bias
Bias arising from the procedures used to select study participants and from factors influencing participation.

Squamous cell carcinoma
A malignant cancer derived from squamous epithelial cells.

Statistical power
The power of any test of statistical significance, defined as the probability that it will reject a false null hypothesis.

Stress
A state of physiological or psychological strain caused by adverse stimuli that tends to disturb the functioning of an organism.

Systematic literature review (SLR)
A means of compiling and assessing published evidence that addresses a scientific question with a predefined protocol and transparent methods.

Systemic
Describing something that occurs throughout the body, not just locally.

Tissue

A collection of one or more types of cells of similar structure organised to carry out particular functions.

Tumour

A mass of neoplastic and other cells.

Waist–hip ratio (WHR)

A measure of body shape indicating central (abdominal) fat distribution.

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Our Cancer Prevention Recommendations

Be a healthy weight
Keep your weight within the healthy range and avoid weight gain in adult life

Be physically active
Be physically active as part of everyday life – walk more and sit less

Eat a diet rich in wholegrains, vegetables, fruit and beans
Make wholegrains, vegetables, fruit, and pulses (legumes) such as beans and lentils a major part of your usual daily diet

Limit consumption of 'fast foods' and other processed foods high in fat, starches or sugars
Limiting these foods helps control calorie intake and maintain a healthy weight

Limit consumption of red and processed meat
Eat no more than moderate amounts of red meat, such as beef, pork and lamb. Eat little, if any, processed meat

Limit consumption of sugar sweetened drinks
Drink mostly water and unsweetened drinks

Limit alcohol consumption
For cancer prevention, it's best not to drink alcohol

Do not use supplements for cancer prevention
Aim to meet nutritional needs through diet alone

For mothers: breastfeed your baby, if you can
Breastfeeding is good for both mother and baby

After a cancer diagnosis: follow our Recommendations, if you can
Check with your health professional what is right for you

Not smoking and avoiding other exposure to tobacco and excess sun are also important in reducing cancer risk.

Following these Recommendations is likely to reduce intakes of salt, saturated and trans fats, which together will help prevent other non-communicable diseases.

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