

Diet, nutrition, physical activity and body weight for people living with and beyond breast cancer

The latest evidence, our guidance for patients, carers and health professionals, and recommendations for future research

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Citation: World Cancer Research Fund International. Diet, nutrition, physical activity and body weight for people living with and beyond breast cancer. The latest evidence, our guidance for patients, carers and health professionals, and recommendations for future research. 2024. Available at: <https://www.wcrf.org/diet-activity-and-cancer/global-cancer-update-programme/cancer-survivors/>

Introduction

This report:

- Outlines the prevalence of breast cancer and the growing population of people surviving breast cancer
- Describes how we are developing guidance and recommendations in the Global Cancer Update Programme, including how we have incorporated input from health professionals and patients
- Reports the current evidence relating to the impact of diet, nutrition, physical activity and body weight on outcomes after a breast cancer diagnosis
- Reports the Global Cancer Update Programme expert panel judgements on the evidence in those living with and beyond breast cancer
- Discusses research gaps and recommendations for future research
- Presents guidance and makes recommendations for those living with and beyond breast cancer

This report focuses on those living with and beyond breast cancer, we have produced an accompanying report with guidance for those living with and beyond colorectal cancer.



World Cancer Research Fund network

OUR VISION

Our vision is a world where no one develops a preventable cancer, and people living with and beyond cancer are enabled to live longer, healthier lives.

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 lifestyle choices to reduce their cancer risk.

OUR NETWORK

As an international network of charities, we've been funding life-saving research into cancer prevention and survival, influencing global healthcare policy, and educating the public since 1982. WCRF Network comprises: American Institute for Cancer Research (AICR) in the US, Wereld Kanker Onderzoek Fonds (WKOF) in the Netherlands, World Cancer Research Fund (WCRF) in the UK and a presence in Asia with a science ambassador based in Hong Kong. Together, we help people worldwide live longer, healthier lives, free from the devastating effects of cancer.



Global Cancer Update Programme

The Global Cancer Update Programme (CUP Global) analyses global research on how diet, nutrition, physical activity and body weight affect cancer risk and survival. It is produced by World Cancer Research Fund International (WCRF International) in partnership with American Institute for Cancer Research (AICR), World Cancer Research Fund in the UK (WCRF) and Wereld Kanker Onderzoek Fonds (WKOF) in the Netherlands.

This report is from WCRF International's CUP Global - the world's largest source of scientific research on cancer prevention and survivorship focused upon analysing the evidence related to diet, nutrition, physical activity and body weight. The research in this report builds on the 2014 (updated 2018) report *Diet, nutrition, physical activity and breast cancer survivors* which was published as part of the Third Expert Report produced by WCRF/ AICR titled *Diet, Nutrition, Physical Activity and Cancer: a Global Perspective* [1].

Many world-renowned experts contribute to CUP Global. An expert panel evaluates the strength of the evidence from systematic reviews, develops guidance and recommendations, makes recommendations for future research and provides input on the direction of the work. Topic-specific expertise for key areas of work is provided via expert committees; of particular relevance to the current report is the cancer survivors expert committee. Additional expertise is provided via formal observers to the panel, representing key organisations in the field (World Health Organization, International Agency for Research on Cancer, National Cancer Institute and Union for International Cancer Control). See page 37 for a full list of contributors to the work in this report.



Key aims of CUP Global

The transition period in 2020/21 enabled WCRF International to develop 7 key aims for the new programme of research under the new name of the Global Cancer Update Programme (CUP Global):



Development of population or disease-specific guidance and recommendations – for specific stages of life (eg children, young adults, older adults), specific populations (eg childhood and adult cancer survivors) and specific cancer subtypes (eg ER, PR positive and triple-negative breast cancer, Lynch syndrome, cancers with a genetic component vs sporadic).



Clarification of existing knowledge to develop greater understanding of cancer prevention and survivorship – eg the role and impact of specific dietary patterns, the biological mechanisms that cause or prevent cancer.



Efficient and targeted approaches and keeping the evidence current – eg through the application of automated approaches and analytical tools, and the use of a dedicated scanning exercise and data prioritisation (including rapid reviews) to target or trigger an evidence update.



Collaborations and input from experts and external stakeholders – utilising experts from across the world, as well as continuing to work in collaboration with the research team at Imperial College London.



Varied and targeted outputs – to enable greater reach and scope within the scientific community (through academic papers), as well as targeted communications for other audiences (including dissemination events).



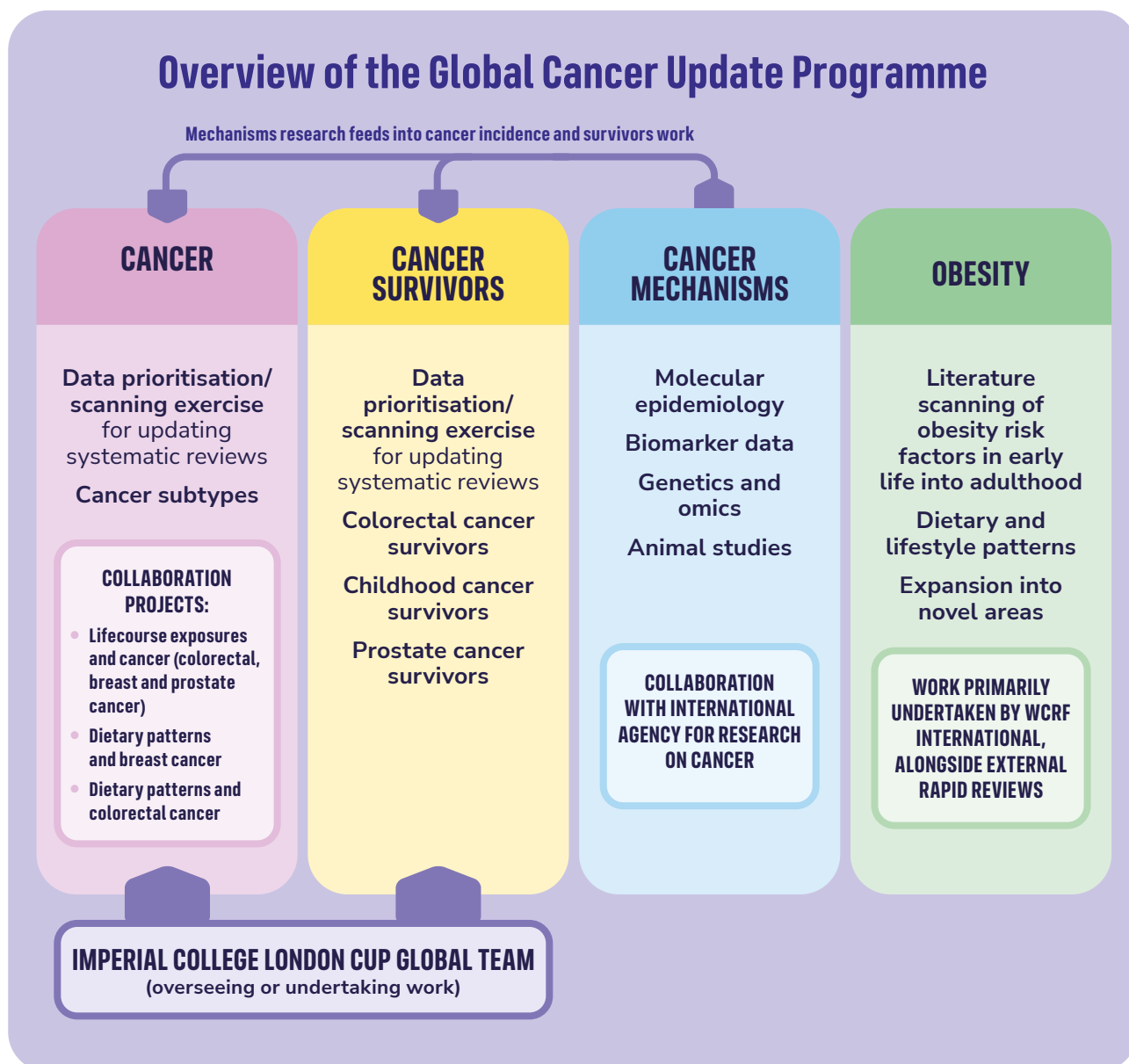
Globally representative research – most epidemiological studies are conducted in high-income countries, such as those in Europe, the US and Australia, with limited or no data from other countries, especially low- and middle-income countries. Cancer incidence and prevalence vary considerably according to geographical region, making the case for future CUP Global studies to address the limited data from low- and middle-income countries.



Strong public involvement – we recognise the importance of user involvement at all stages of the work, from identifying research priorities, promoting involvement in funded research and selecting successful research funding applications, to making recommendations and disseminating findings.

Areas of research focus in CUP Global

The current work is organised into 4 areas: cancer incidence, cancer survivors, cancer mechanisms and obesity. The mechanisms work supports the cancer incidence and survivors work through developing a clearer understanding of the biological processes that underpin associations between diet, nutrition, physical activity, body weight and cancer. This current report is part of the cancer survivors work area, with the systematic reviews conducted by the CUP Global team at Imperial College London.



Executive summary

Background

Breast cancer is the most common cancer in women and the second most common cancer overall, accounting for 1 in 9 (11.6%) new cancer cases worldwide in 2022. At the same time, progress in early detection and treatment has significantly increased the number of years lived after a diagnosis. Survival rates differ between countries, but worldwide there are an estimated 7.8 million women who have survived at least 5 years after a diagnosis of breast cancer. There is increasing demand for reliable, evidence-based guidance on diet and physical activity from health professionals and people living with and beyond cancer.

This report is from World Cancer Research Fund International's Global Cancer Update Programme (CUP Global) - the world's largest source of scientific research on cancer prevention and survivorship through diet, nutrition, physical activity and body weight. The research in this report builds on the 2014 (updated 2018) report *Diet, nutrition, physical activity and breast cancer survivors* which was published as part of the Third Expert Report produced by WCRF/ AICR on *Diet, Nutrition, Physical Activity and Cancer: a Global Perspective*. At that time, research on cancer survival was limited, but there was enough evidence to conclude that people living with and beyond cancer should follow our Cancer Prevention Recommendations. These outline an integrated pattern of behaviours that the evidence consistently shows is linked to reduced cancer risk.

The increasing recognition of the importance of diet, nutrition, physical activity and body weight in cancer survival provides the rationale for the current work.

Aims of this report

This report summarises the latest research on diet, nutrition, physical activity and body weight for people living with and beyond breast cancer. It also presents guidance for patients and recommendations for future research. This information can be used to develop materials for those responsible for the care of patients and patients themselves. We intend for this work to supplement our existing Cancer Prevention Recommendations. Whilst we recommend that people living with and beyond cancer follow these as much as they can, they were not specifically developed for this group. Our new guidance adds to these recommendations by highlighting specific behaviours which evidence suggests may be beneficial for people living with and beyond breast cancer.

The evidence underpinning this report

The Global Cancer Update Programme research team at Imperial College London carried out a comprehensive analysis investigating the extent to which certain modifiable risk factors impact mortality (cancer-specific and all-cause), risk of cancer recurrence and health-related quality of life in women after a breast cancer diagnosis. Four systematic reviews were carried out. Review 1 analysed data from 108 studies on diet and breast cancer outcomes and there were 2 reviews on physical activity (the first included 20 studies on breast cancer outcomes and the second included 79 studies on health-related quality of life outcomes). The fourth review focused on body weight and breast cancer outcomes and included 225 studies.

An independent panel of experts graded the strength of the evidence from each review using WCRF International's pre-determined criteria to give a final evidence judgement for each exposure.

The panel judged the strength of much of the evidence as 'limited' which hampered the expert panel's ability to develop recommendations. Despite this, we consider it important that people living with and beyond cancer can access reliable information based on the latest evidence that has been judged by our expert panel. The recommendations and guidance described here have been developed using a robust and transparent process, incorporating input from expert clinicians and scientists, along with user input from health professionals and patients.

As an evidence-based organisation, we have used the best available evidence to develop this process and produce practical guidance on diet, physical activity and body weight for people living with and beyond breast cancer.



Recommendations for future research

WCRF International, our panel of experts and the cancer survivors expert committee are continually discussing how the evidence base within survivorship research can be strengthened. We have agreed upon several key areas:

- Well-designed clinical trials and prospective cohorts are needed. These studies should account for differences in cancer sub-types, treatment types and other patient characteristics.
- Studies should aim to use the most accurate methods possible for assessing diet, nutrition, physical activity and body weight within populations living with and beyond cancer. They should include more accurate reporting of the timing of exposures.
- Novel methods for understanding the biological processes and mechanisms that underpin the associations we find in our cancer survivorship research are much needed.
- Research should aim to study more diverse populations.

By highlighting gaps in the evidence base, current research enables us to look to the future with insights on where further (high quality) research is needed. Observational studies can also help to identify promising exposures for testing in randomised-controlled trials. This allows us to develop new areas of investigation, with the aim of future new findings being used to develop specific recommendations for this group and to further confirm the benefits of following our recommendations and guidance.

Recommendations and guidance for people living with and beyond breast cancer

The below recommendations and guidance have been developed using the best available evidence and consultation with experts in the field and individuals living with and beyond breast cancer.

Evidence comes from the 4 systematic reviews described in the full report, along with previous evidence reviewed for the Third Expert Report which led to the development of WCRF/AICR's Cancer Prevention Recommendations.



Please note: We recommend that individuals living with and beyond cancer speak to their healthcare team before making any changes related to diet, nutrition, physical activity or body weight. Any healthcare professionals using this guidance should consider where a patient is in their cancer journey and interpret the guidance appropriately to suit each person's individual needs.



Summary of our recommendations and guidance for those living with and beyond breast cancer

EVIDENCE	RECOMMENDATIONS/GUIDANCE
 <p>General guidance WCRF/AICR's recommendations for cancer prevention</p>	
<p>Nutritional factors and physical activity appear to predict outcomes in people living with beyond cancer, but there is insufficient evidence that changing these improves outcomes.</p>	<p>We suggest that people consider following as many of WCRF/AICR's cancer prevention recommendations as they are able to.</p>
<p>New specific recommendation on physical activity</p>	
<p> Physical activity</p> <p>Increasing physical activity improves health-related quality of life after a diagnosis of breast cancer. People who are more physically active have better health outcomes, but it is uncertain whether increasing physical activity will improve health outcomes.</p>	<p>We recommend that people are physically active. However, physical activity should be increased under the supervision of health care professionals.</p>
<p>New specific guidance on diet and body weight</p>	
<p> Diet</p> <p>Dietary fibre</p> <p>People who eat more dietary fibre have better health outcomes after a diagnosis of breast cancer. But it is uncertain that increasing dietary fibre improves these outcomes.</p>	<p>We suggest that people consider increasing their dietary fibre intake.</p>
<p>Soy</p> <p>There is limited evidence suggesting that people who eat more soy foods have better health outcomes after a diagnosis of breast cancer. There have previously been concerns over soy foods increasing the risk of developing breast cancer, but systematic reviews show no consistent evidence of a link between soy foods and breast cancer risk.</p>	<p>The current evidence does not support guidance to consume more soy foods (or to introduce soy foods if these are not currently part of the diet) after a diagnosis of breast cancer, but for those who already consume them, there is no need to stop.</p>
<p>Vitamin D</p> <p>This review found limited evidence suggesting that those with higher vitamin D status have better health outcomes after a diagnosis of breast cancer, but there was no evidence of any benefit from vitamin D supplements.</p>	<p>We are not making specific guidance about vitamin D supplements to improve outcomes after a breast cancer diagnosis.</p>
<p> Body weight</p> <p>Those with body weight in the 'healthy range' after a diagnosis of breast cancer have the best health outcomes. But it is uncertain that deliberate weight loss by people with overweight or obesity improves these outcomes.</p>	<p>We suggest that people who are not underweight aim to avoid gaining weight during and after treatment.</p>

Recommendations are based on strong evidence.

Guidance is based on evidence graded as 'limited suggestive'. Limitations in the evidence meant that the panel could not be confident that associations were causal, so we cannot be sure that changing the exposures would change the outcomes. Despite the limitations in the evidence, this represents the best advice based on the current evidence and expert opinion.

Outcomes are health outcomes (including all-cause mortality and cancer outcomes) and health-related quality of life.

Background

Incidence and survival from breast cancer

The global burden of cancer is increasing due to a growing and aging population alongside increases in risk factors, most notably obesity; other contributing risk factors include smoking, physical inactivity and unhealthy dietary patterns [2]. In recent decades, progress in the early detection and treatment of cancer has led to a dramatic increase in the number of people living with and beyond cancer (LWBC). In addition, therapeutic control of tumour growth and progression in patients with recurrent disease has led to a diagnosis becoming a prolonged chronic condition with a long lifespan and acceptable quality of life. Within this report, we define this group as all people who have been diagnosed with cancer, including before, during and after treatment [3].

Breast cancer is the most common cancer in women and the second most common type of cancer overall, accounting for 1 in 9 (11.6%) new cancer cases worldwide in 2022 [4]. Survival rates differ between countries, but worldwide there are an estimated 7.8 million women who have survived at least five years after a diagnosis of breast cancer [5].

It is essential that the long-term health needs of people LWBC, beyond those directly related to their cancer, be considered. Cancer prevention is a crucial component of the World Health Organization's (WHO) global target of a 25% reduction in deaths from cancer and other non-communicable diseases (NCDs) in people aged 30 to 69 by 2025 [6]. However, achieving this target (referred to as 25 x 25) requires the deployment of more effective health systems to improve survival, alongside more effective prevention [7].

Research has historically focused on understanding exposures influencing cancer development. Despite growing numbers of people LWBC, until recently there has been relatively little available research focused on diet, nutrition, physical activity and body weight as levers for improving post-diagnostic survival and quality of life. Although there has been a substantial growth in research, the increase in people LWBC has resulted in greater demand for reliable, evidence-based guidance for health professionals and people LWBC concerning diet, physical activity and body weight. Our work with researchers, health professionals and patients has also highlighted the need for more tailored advice for people LWBC. Numerous studies have explored the views of people LWBC about their needs, preferences and experiences of accessing dietary information (including weight-related information). Studies commonly show a preference for receiving information directly from health-professionals, however, people also report that information can be too generic and sometimes conflicting [8].

Our current report aims to help fill this gap by providing information based on the latest available research.

Our previous work and recommendations

WCRF/AICR previously produced a set of Cancer Prevention Recommendations (see **Appendix 1**), based on evidence judgements made by a panel of independent experts and published in 2018 as part of The Third Expert Report *Diet, Nutrition, Physical Activity and Cancer: a Global Perspective* [9]. The panel concluded that following these recommendations would ‘*convincingly or probably*’ contribute to reducing cancer risk. These recommendations were based on evidence for reducing the risk of developing cancer and did not specifically focus on studies including patients following a cancer diagnosis.

The first report on cancer survivors was published in 2014; this examined literature linking diet, nutrition, physical activity and body weight to survival and occurrence of new primary cancers in people living with and beyond breast cancer [1]. At the time, the panel was unable to draw firm conclusions on the effect of diet, nutrition, physical activity or body weight upon outcomes in this group. The lack of evidence was especially apparent in relation to the reduction of mortality (from breast cancer or any other cause) or risk of developing second primary breast cancer. However, the panel agreed that the conclusions underpinning the Cancer Prevention Recommendations were also likely to be relevant for people LWBC and recommended that, as far as possible, they should aim to follow these recommendations once acute treatment had finished. In addition, the panel judged that following these recommendations was unlikely to be harmful to people LWBC who have completed treatment. However, the evidence was inadequate to make specific recommendations for this group with confidence. The current work builds upon this and signals an increasing focus for the WCRF Network in the cancer survivorship area.



About this report

Purpose of the report

This report brings together the findings from a series of new systematic reviews along with interpretation of the evidence by our panel of experts. This has been used to develop recommendations and guidance. The systematic reviews, carried out by the CUP Global team at Imperial College London, examine how diet, nutrition, physical activity and body weight affect survival and recurrence after a breast cancer diagnosis [10-13]. A further review examined how physical activity affects health-related quality of life for women living with and beyond breast cancer [14].

As the evidence base for people LWBC continues to develop, we hope to expand our guidance to include information for different cancer types. Further to this, as the evidence base improves in quality, we hope to develop cancer survival recommendations to accompany those we have for cancer prevention.

Who the report is for

The information included in this report is aimed at those with an interest in improving the survival and quality of life of people living with and beyond breast cancer. This group includes:

- Healthcare professionals involved in the clinical and supportive care of people living with and beyond breast cancer at various stages of their cancer journey. This could be: oncologists; surgeons; cancer nurse specialists; nurse practitioners; dietitians; physiotherapists; other medical professionals; pharmacists; nutritionists and nutritional therapists; and any other relevant healthcare professionals.
- Civil society, patient and charitable organisations (eg cancer charities).
- Researchers working in the areas of diet, nutrition, physical activity, body weight and cancer.
- Policymakers in public health settings.
- People living with and beyond cancer. We will be developing resources specifically for patients and their families, but these reports can be accessed by anyone wanting to read more about the science underpinning the recommendations and guidance.



This report aims to inform:

- The development of appropriate public-facing outputs and resources for people living with and beyond breast cancer including patients who have completed the acute phase of their cancer treatment.
- The development of resources for healthcare professionals working with patients living with and beyond breast cancer.
- How the quality and interpretation of future research can be improved to make it more relevant to the specific considerations of people LWBC.
- Policymakers about the strength and limitations of current evidence on diet, nutrition, physical activity and body weight and key outcomes within this group.

Approach

WCRF International's Global Cancer Update Programme (CUP Global) has a robust process for reviewing and interpreting evidence to ensure that our recommendations and guidance are supported by the best available research. Recommendations for the public are generally developed from evidence judged as 'strong' by the independent expert panel. The literature on how diet, nutrition, physical activity and body weight influence long-term health for people LWBC is, despite growth in recent years, in its infancy compared with that for cancer incidence. Researching the modifiable behaviours that might influence health-related outcomes among those LWBC is also highly complex.

The term 'cancer survivor' (or 'living with and beyond cancer' (LWBC)) covers a wide variety of circumstances beginning at diagnosis through cancer treatment to the end of life. In this report, the term 'living with and beyond cancer' (LWBC) will be used. The definition LWBC here does not include people living with a diagnosis of benign tumour or conditions defined as premalignant, such as premalignant breast lesions. Using a single term to cover people LWBC to encompass all of these stages cannot do justice to the heterogeneous, complex and emotional reality of living with cancer. Each stage of survivorship has its own particular characteristics, and the impact of interventions or exposures, including those related to diet, nutrition, physical activity and body weight, can vary considerably. The experience of LWBC also varies depending upon the site-specific cancer diagnosed. That is why, when it comes to survival-related information, we are producing guidance for individual cancers rather than cancer overall.

Despite the challenges, it is important that people LWBC can access sound information. Therefore, along with recommendations for how future research can address these challenges, it is important to maximise how the currently available evidence is used. The processes developed in CUP Global, and described in this report, utilise the evidence as it currently stands through a robust transparent process, incorporating input from expert clinicians and scientists, along with user input from health professionals and patients. This enables us to provide people LWBC with information based on the best available evidence while taking into account its limitations.

Using evidence to develop guidance and recommendations

Summary of steps taken



RECOMMENDATIONS- typically developed using strong evidence

GUIDANCE- developed using less strong evidence with input from expert clinicians, scientists and patients and their healthcare providers

Factors considered

- Is there potential patient benefit? (on cancer or other outcomes)
- Is there evidence of harm in this population?
- Are there specific population groups (eg age, sex, race and ethnicity, other socio-demographic characteristics) or clinical populations (eg cancer subtype, treatment) which need to be considered?
- Taking into account the broader context, is there possible harm/ benefit for other health outcomes or any environmental considerations?
- Does the current research allow for a degree of confidence?
- What is the likely impact of a recommendation/ guidance?

What we mean by 'guidance' and 'recommendations'

Guidance in this report refers to statements developed with input from experts (scientists, health professionals and patients). This differs from clinical guidelines and our recommendations - which we developed based around a strong evidence base. The current guidance is a way of providing information for healthcare professionals and patients in areas where the evidence is less strong based on the judgement criteria. However, it is noteworthy that a substantial body of evidence was reviewed by the panel to be able to develop this guidance.

STEP 1

Gathering evidence through systematic reviews carried out by CUP Global team at Imperial College London

Four systematic reviews were carried out by the CUP Global team at Imperial College London: 3 reviews examined the effect of post-diagnosis diet, physical activity and body weight on all-cause mortality, breast and non-breast cancer-specific mortality, breast cancer recurrence and second primary cancers (referred to here as ‘health outcomes’). A further review examined the effect of physical activity on health-related quality of life outcomes.

The results from each review are summarised below; these are supported by a selection of forest plots to illustrate the results, see **Appendix 2**, please refer to the papers to access all of the results and forest plots.

Reviews on health outcomes

Published papers available here:

<https://onlinelibrary.wiley.com/toc/10970215/2023/152/4>

These studies focused on mortality and recurrence outcomes.

The protocol was developed by the research team at Imperial College London with input from the Protocol Expertise Group. The peer reviewed protocol is available online [15].

PubMed and Embase databases were searched from inception to 31st October 2021. Relevant exposures were any type of post-diagnosis physical activity, diet (food, food components, nutrients, dietary patterns, supplements) and adiposity¹ (body mass index (BMI), waist circumference, waist-to-hip ratio, changes in weight or BMI). Randomised controlled trials (RCTs) and observational longitudinal studies (or pooled analyses of individual data of these studies) were included if they reported outcome data on all-cause mortality, breast and non-breast cancer-specific mortality, breast cancer recurrence and/or second primary cancers. Most studies reported all-cause mortality, breast cancer-specific mortality and/ or breast cancer recurrence, with more limited data available for second primary cancers, non-breast cancer-specific mortality and cardiovascular mortality.

¹The term ‘body weight’ is used in this report hereafter as a simpler term for adiposity; it includes body mass index, waist circumference, waist-to-hip ratio

Physical activity findings

A total of 23 studies were included in the review (20 observational studies and follow ups from 3 RCTs). These comprised more than 39,000 women with breast cancer, of whom approximately 5,000 died, including 2,000 who died from breast cancer.

Most studies looked at the effect of recreational physical activity such as aerobics, walking and running, with limited data on other types of activity. Higher levels of recreational physical activity were associated with a lower risk of all-cause mortality and breast cancer-specific mortality.

Diet findings

A total of 108 studies were included in the review (104 observational studies and 4 RCTs). These comprised more than 151,000 women with breast cancer, of whom 14,900 died, including 5,900 who died of breast cancer.

Higher intake of soy foods was associated with lower all-cause mortality, breast cancer-specific mortality and breast cancer recurrence; higher intake of dietary fibre was associated with lower all-cause mortality only. Following certain healthier dietary and lifestyle patterns was associated with lower all-cause mortality. Higher vitamin D status (measured by serum 25-hydroxyvitamin D, 25(OH)D) was associated with lower all-cause mortality and breast cancer-specific mortality.

The results were not conclusive for other dietary exposures, including fruit and vegetables; wholegrains; meat, fish and eggs; milk and dairy products; carbohydrate, protein and fat; alcohol; dietary supplements. Few studies were found which reported the effect of dietary change – making it difficult to draw any conclusions from their results.



Body weight-related findings

A total of 226 studies were included in the review (225 observational studies and one RCT). These comprised more than 456,000 women with breast cancer, 36,000 of whom died, including 21,000 who died from breast cancer.

In general, greater BMI, waist circumference and waist-to-hip ratio were associated with a higher risk of adverse health outcomes. Few studies were found which reported the effect of BMI change or weight change – making it difficult to draw any conclusions from their results.

Review on health-related quality of life

Published paper available here:
<https://doi.org/10.1093/jncics/pkac072>

The peer reviewed protocol is available online [16]. PubMed and CENTRAL databases were searched from inception to 31st August 2019. Studies were included if they reported RCTs of exercise and physical activity interventions before, after or during primary treatment. Primary treatment included surgical treatment and/or (neo)adjuvant therapy (eg chemotherapy, radiotherapy and/or hormonal therapy) in the acute phase only, the extended use of hormonal therapy was excluded. Relevant outcomes were health-related quality of life (overall and its main functional domains - physical, emotional, mental) measured using validated tools.

Findings

The review included approximately 14,500 women taking part in 79 trials (reported in 92 publications), mainly in North America and Europe. The results from most of these trials (59 out of 92 publications) could be meta-analysed. Overall, the results showed that physical activity improved health-related quality of life. This was seen for global quality of life and specific quality of life domains (including physical and emotional functioning). The evidence was less clear on how frequency and amount of physical activity made a difference to health-related quality of life. There was some evidence that physical activity had a greater effect on health-related quality of life when it was started after treatment had ended compared with during it.



STEP 2

Evidence judged by the CUP Global panel

An independent panel of experts, convened by WCRF international, graded the strength of the evidence described above using pre-defined grading criteria (shown in **Appendix 3** and [1]). WCRF International's grading criteria are designed to judge, for observational studies, whether an association is causally linked to a particular health outcome, or, for RCTs, whether a specific intervention affects the risk of developing specific health outcomes. The panel considered several factors when judging the evidence, including: the amount of evidence; the consistency, magnitude and precision of the summary estimates; whether there was a dose-response relationship; study design and risk of bias; generalisability; the presence of biological plausibility and mechanisms. The evidence levels used within the grading criteria were 'strong' (either 'convincing' or 'probable') or 'limited' (either 'suggestive' or 'no conclusion'), with an additional 'strong' grading of 'substantial effect on risk unlikely' where there is strong evidence that the exposure does not affect the risk of an outcome.



Summary of panel judgements of evidence

The panel made the following judgements based on the evidence from the systematic reviews in relation to medical outcomes and health-related quality of life in people living with and beyond breast cancer (see **Appendix 4** for a summary of the evidence judgements).

Physical activity

- There was strong evidence (probable causality) that interventions for increasing physical activity result in improved health-related quality of life.
- There was insufficient evidence to draw conclusions on specific domains of quality of life (eg physical or emotional functioning or well-being) that may benefit from physical activity, or the types and doses of activity required for improving quality of life.
- Higher levels of recreational physical activity after diagnosis were associated with a lower risk of death overall and from breast cancer. The evidence was judged as limited (suggestive) because the panel could not be sure of the direction of these associations.

Diet

- There was limited (suggestive) evidence that higher consumption of soy foods (isoflavones and soy protein) reduces the risk of all-cause mortality, breast cancer mortality and breast cancer recurrence.
- There was limited (suggestive) evidence that higher consumption of dietary fibre reduces the risk of all-cause mortality.
- There was limited (suggestive) evidence that greater serum vitamin D [25(OH)D] reduces the risk of all-cause mortality and breast cancer mortality. Relevant here is that the evidence for vitamin D supplements impacting all-cause mortality, breast cancer mortality and breast cancer recurrence was limited (no conclusion).
- There was limited (suggestive) evidence that following certain healthy dietary and lifestyle patterns reduces the risk of all-cause mortality and other causes of death.

Body weight

- There was strong evidence (probable) that greater body weight (measured by body mass index, waist circumference, waist-to-hip ratio) increases the risk of all-cause mortality and breast cancer specific mortality, and that higher body mass index also increases the risk of a second primary breast cancer.
- There was limited (suggestive) evidence that greater body weight (measured by body mass index, waist circumference, waist-to-hip ratio) increases the risk of breast cancer recurrence, and that increased body mass index also increases the risk of non-breast cancer specific mortality and cardiovascular disease mortality.

STEP 3

Recommendations for future research

The work of the CUP Global panel in judging the evidence from these reviews highlighted a number of limitations that should be addressed in future research. In particular, it was agreed that there is a need not just for more research but also improved methodologies, so that future research can address these limitations. In other words, more of the same types of data or studies are unlikely to strengthen our understanding of the influence of modifiable behaviours related to diet, nutrition, physical activity and body weight on outcomes for people LWBC. Improved research would allow for stronger evidence conclusions, which could then be turned into information for the public. This work will help the WCRF Network to support those LWBC to live healthier and longer lives.

In addition, research that can more clearly define the potential health and economic benefits from intervening to improve diet, nutrition, physical activity and body weight in those LWBC may help to achieve greater buy-in from key decision makers.

It is also important that health professionals, researchers, policy makers and other relevant stakeholders are aware of the limitations of current research when offering advice or making decisions that may impact the long-term health of those LWBC.

The key issues that future research should aim to address include:

- Conducting well-designed clinical trials and prospective cohorts that account for differences in cancer sub-types (eg ER+ vs ER- breast cancer), timing and types of treatment (eg surgery, medication), and other patient characteristics (eg co-morbidities, age, race, ethnicity). These factors should be accurately reported.
- Using more accurate methods to assess 'usual' pre-diagnosis dietary intake, physical activity and body weight, with more accurate reporting of the timing of exposures, and accurate measurement of potential confounding factors.
- Providing further information on the biological pathways that may explain the relationships between diet, nutrition, physical activity, body weight and cancer/non-cancer outcomes.
- Increasing diversity and inclusivity of study populations and accurate characterisation of samples.

The above key issues are outlined in more detail in the table below, along with potential solutions. While many of these issues are generally applicable to research on diet, nutrition, physical activity and body weight involving those LWBC, where there are specific considerations for breast cancer these are noted.

It is also important to note that despite limitations, observational studies can help to identify promising exposures for testing in more robust study designs (eg appropriately conducted RCTs).

Research recommendations

RESEARCH CONSIDERATION Reverse causation

ISSUES AND POTENTIAL SOLUTIONS

The observational design of many studies on diet, physical activity and body weight makes it difficult to exclude the possibility of reverse causation. The disease and treatments received may affect a patient's dietary choices and ability to do physical activity, while their dietary and physical activity choices may also affect disease outcomes. Reverse causality is also a particular issue when interpreting associations between body weight and survival outcomes, and it is challenging to disentangle intentional and unintentional weight loss. This is an inherent problem for observational studies in cancer survivorship populations.

Future research could attempt to address this through:

- *Well-conducted intervention studies where the impact of specific diet, physical activity and/or weight management interventions on survival or other outcomes is the primary research question. However, such studies can be costly and challenging to conduct.*
- *More accurate reporting of the timing of exposures in studies (eg before, during and/or after treatment) and/or analyses of existing studies that account for treatment timing.*
- *Measuring body weight both pre- and post-diagnosis will enable better exploration of these associations. Collecting and reporting pre-diagnosis body weight data is challenging but is possible in cohort studies. However, depending on the type of cancer and treatment pathway, this may introduce bias.*
- *Methods for better understanding the impact of treatment on modifiable risk factors as well as outcomes should be considered. This includes how treatment might result in changes in diet, physical activity levels and body weight, as well as quality of life, morbidity and mortality.*
- *Stage of disease at diagnosis has a clear impact on outcomes, for example, whether the cancer is metastatic or has already impacted health (eg cachexia), by impacting behaviour and affecting treatment options and effectiveness. Future studies need to develop better ways of collecting stage data and including it within analysis.*



RESEARCH CONSIDERATION Residual confounding

ISSUES AND POTENTIAL SOLUTIONS

It is rarely possible to control for all factors that may affect the outcome of interest in cohort studies. Treatment-related factors may interact with behaviours (eg by changing the way that a person eats or the energy they have for recreational exercise) and make interpretation complicated. In addition, the presence of other co-morbidities among people with cancer, such as cardiovascular disease or type 2 diabetes, may also impact exposures and outcomes of interest.

Future research should consider how to better account for confounding factors. Suggestions for how future research could attempt to address this include:

- *Accurate reporting of disease state, presentation of disease, disease stage, treatment factors (treatment mode, completion, dose) and any co-morbidities.*
- *Accurate reporting and appropriate adjustment for confounders, including information on timing of confounders in relation to exposure and outcome of interest.*
- *Studies often use recalled data – this can introduce bias – novel ways of more accurately recording such data could be considered.*
- *The use of longitudinal data has the potential to overcome some of the limitations of current studies.*
- *Consideration of the impact of other factors on outcomes, including patient genetic cancer risk, as well as broader social determinants of health (eg socio-economic status, race and ethnicity).*
- *Consideration of whether some confounders also act as effect modifiers.*
- *Appropriate sample sizes to offer sufficient study power to account for confounders.*

Breast cancer specific considerations:

Better reporting within studies of breast cancer survivors would aid interpretation of studies, including specific information on:

- Biological subtype of tumour
- Treatment-induced menopause
- Type of treatment including hormonal therapy
- Invasive vs non-invasive breast cancer

RESEARCH CONSIDERATION Time-varying impacts

ISSUES AND POTENTIAL SOLUTIONS

There is a growing body of evidence demonstrating that the impact of a risk factor upon a health outcome changes over time and across the lifecourse. Considering this in future studies will allow for better understanding of potentially dynamic associations.

Repeated dietary, nutritional, physical activity or body weight assessments can account for changes in the exposure over time or changes in behaviour after diagnosis (eg cutting out unhealthy foods). This is important because a single measure post-diagnosis is unlikely to accurately capture 'usual' behaviour pre-diagnosis.

RESEARCH CONSIDERATION Indirect effects

ISSUES AND POTENTIAL SOLUTIONS

Some risk factors, such as body weight, may adversely affect outcomes by limiting the treatment options available to a patient. They may also alter the efficacy of treatment. For instance, breast cancer patients living with obesity experience more complications related to surgery, radiation and chemotherapy, resulting in worse outcomes.

One solution to overcome this may be to conduct trials in patients where more in-depth and repeated information on these factors is available. For example, there is potential to look at computed tomography (CT) derived body composition measurements in studies of metastatic cancer where patients have regular CTs.

RESEARCH CONSIDERATION More accurate data on diet, nutrition, physical activity and body weight

ISSUES AND POTENTIAL SOLUTIONS

Despite there now being large amounts of data collected related to cancer survival, the quality of published research in this area does not allow for strong conclusions to be drawn. Future studies should consider improving the quality and accuracy of the patient data they collect. Best practice and quality assurance within the research field could be considered. For example:

- *Ensuring that validated questionnaires (eg food frequency questionnaires) are used to collect dietary components. Dietary components also need to be appropriately defined to avoid misclassification. The development of online data collection software enables data to be collected more easily in large samples and should be considered.*
- *Objective measures of physical activity (eg accelerometry) should be considered to better capture the amount, intensity and type of activity, and any changes in patterns of activity over time.*
- *Most studies use BMI as a measure of adiposity, but this does not distinguish between lean body mass and fat mass and does not provide information about fat distribution. Future studies should consider collecting more detailed information on this in addition to BMI.*

RESEARCH CONSIDERATION Study cohorts specific to cancer survivorship

ISSUES AND POTENTIAL SOLUTIONS

Existing data are largely from cohorts not specifically designed to look at cancer survivorship but rather incidence. The level of information about exposures and other details of participants may therefore be insufficient to fully assess the impact of modifiable risk factors upon survivor-specific outcomes.

There are also different patterns of cancer recurrence based on the type of cancer (the 'natural history' of the disease) that can affect study outcomes. This should be considered in the study design.

Initiatives for establishing cancer survivor cohorts, to increase size and study power, have been discussed and some are currently underway. Given the increasing size of survivor populations – the inclusion of people LWBC in studies should be seen as a priority.

RESEARCH CONSIDERATION Increased diversity and inclusivity within research

ISSUES AND POTENTIAL SOLUTIONS

Research should aim to study more diverse populations as published research currently tends to focus on populations from countries in Europe, North America and China.

More inclusive and representative study populations are needed, including greater diversity in terms of geography, race and ethnicity, socio-economic status and other factors known to impact long-term health and life expectancy.

There is also a growing body of evidence that diverse research teams are better able to understand and overcome challenges within their work. Research organisations should consider the diversity of their research teams – and seek out diverse ways of thinking about research focused upon cancer survivorship.

RESEARCH CONSIDERATION More accurate characterisations of study populations

ISSUES AND POTENTIAL SOLUTIONS

Cancer patients represent a diverse group of individuals. Study populations should be well-characterised. This will help to improve the quality of the available data and the accuracy of study outcomes. Studies should better define and report on their study populations, including:

- Cancer sub-types
- Potential influence of disease-specific factors, such as treatment type, stage (eg metastatic vs early-stage), time since diagnosis
- Socio-demographic determinants (eg age, sex, race and ethnicity, socio-economic factors, menopausal status).



RESEARCH CONSIDERATION Improved understanding of underlying mechanisms

ISSUES AND POTENTIAL SOLUTIONS

Increased knowledge of the potential biological pathways underpinning the associations between exposures and outcomes seen in epidemiological studies would improve our understanding of causality. This is an active area of work within CUP Global.

For example, there are multiple mechanisms that underpin the associations between physical activity and cancer progression. These include the role of sex hormones, metabolic dysregulation, inflammation, immune function, oxidative stress and genetic mutations. It remains unclear if physical activity influences these pathways independently or if it exerts its action via reductions in adipose tissue.

Breast cancer specific considerations:

Weight gain during and after breast cancer treatment is common. Changes in body composition, such as increased fat mass or lean tissue atrophy, can increase the risk of co-morbidities, such as cardiovascular disease or type 2 diabetes, which consequently may influence survival.

RESEARCH CONSIDERATION More multi-disciplinary research collaborations

ISSUES AND POTENTIAL SOLUTIONS

There is a clear need for more collaboration between specialists so that expertise on cancer, diet, nutrition, physical activity and body weight can be brought together more effectively. As our understanding of biological mechanisms increases and becomes more complex – research teams will likely benefit from the inclusions of experts in this field.

Multidisciplinary teams and projects would help to address some of the key issues with the current research discussed here.



STEP 4

Development of guidance and recommendations with input from the panel, cancer survivors expert committee and users

WCRF International worked with the CUP Global panel and cancer survivors expert committee in 2023 to develop a process for producing guidance. The guidance presented in this document is based on evidence judged by the panel to be at least 'limited suggestive'. Oncology experts from the panel and expert committee provided direction on which evidence gradings were suitable for developing into guidance.

User input

Input from individuals living with and beyond breast cancer

When developing this report, we recognised the importance of getting input from those who would be directly using the public-facing information produced from it. This included those living with and beyond breast cancer and the health professionals who will be communicating and relaying the guidance to them. Involving direct users in the development of the guidance is important for enhancing patient care as it allows them to identify patient-focused issues and ensures it most closely matches their lived experience.

We recruited 8 people living with and beyond breast cancer to contribute, interviewees were identified using People in Research (NIHR) and Breast Cancer Now. Some of the interviewees had previous experience in reviewing patient materials through their work with other organisations, though for others, this was their first time doing such a review. Before the interview, each participant was sent a draft example of patient facing material which was intended to communicate our guidance. The interviewees were asked 2 sets of questions: one set on their experiences of accessing advice on health information (specifically around diet and physical activity) since their diagnosis, and the other more specifically on our guidance. Their feedback was used to develop the guidance within this report and will be used further by the WCRF Network when developing public-facing outputs based on this guidance.



They also gave feedback on the layout, highlighting the need for a clearer structure with greater use of bullet points. Multiple interviewees stressed the need for accessible and conversational language which was direct but also empowered the reader to take control of potential changes in behaviour. Several interviewees also suggested including examples of how others have incorporated the guidance into their lives and that these case studies should come from a range of backgrounds to bring the guidance to life and ensure inclusiveness.

Appendix 5 summarises their feedback and outlines how it has been incorporated into the guidance.



Input from health professionals:

In our ongoing conversations with healthcare professionals, it is clear that there is an unmet need for cancer-specific information about what those LWBC can do to improve their health and potentially outcomes. With this in mind, we sought input from healthcare professionals – firstly, about the need for our new guidance and, secondly, how they might use it.

We received feedback from clinical cancer nurse specialists and cancer dieticians, both in the UK and US, on a draft example of the information that we could provide them to support their conversations with patients LWBC. As a result of their feedback, the document was restructured for clarity. They further highlighted the importance of the “strong” evidence gradings on health-related quality of life and physical activity, and wanted to ensure that this was addressed separately from the rest of the guidance. They also noted that stronger evidence should come before limited evidence in information for the public.

Based on suggestions from the healthcare professionals reviewing the document, the wording around the recommendations/guidance for soy foods was revised. This ensured that patients would fully understand that soy consumed should be high in isoflavones and minimally processed. Clarity was added to the explanation of soy foods, as well as the need to choose unsweetened, fortified soya-based dairy alternatives.

Within our conversations with individuals LWBC and healthcare professionals it was noted that it would be useful to link to information that was already available. Therefore, references to other organisations, where possible, were included – for example, the WHO recommendations on the amount of physical activity required to confer a health benefit.

The reviewers, especially those not based in the UK, provided feedback on the need for language to be inclusive and have a consideration of global audiences. We will carefully consider this when we are developing public-facing outputs based on the current guidance.

Our recommendations and guidance for those living with and beyond breast cancer

Current evidence, as well as our recommendations and guidance for those living with and beyond breast cancer are provided below, these reflect the strength of the scientific evidence and expert opinion. Additional information on specific considerations for interpreting the recommendations and guidance statements is also provided. It is important that changes to diet, nutrition, physical activity and body weight are discussed with a healthcare professional, as appropriate.

Much of the evidence on which the guidance in this report is based comes from observational studies rather than intervention studies. This means that any associations found cannot confidently be assumed to be causal, for instance because of confounding or reverse causation. So, even if people who are found to experience a particular diet, physical activity or body weight exposure have better outcomes, if the exposure is not causal, then changing it cannot be assumed to change the outcome. This problem is a main reason why the evidence is regarded as weak and this guidance is less secure than our firm recommendations. Nevertheless it represents the best advice, based on current evidence and expert opinion.

In developing the guidance, we include a description of the association between the exposure (eg diet) and health outcomes, followed by a brief outline of our guidance. For each guidance statement, we have provided a supporting summary statement of the evidence grading.

These recommendations and guidance are based on the evidence described in this report; there is evidence for health-related quality of life, with other outcomes referred to collectively as 'health outcomes'. See steps 1 and 2 for information about the specific health outcomes.

Our existing WCRF/AICR recommendations for cancer prevention

WCRF/AICR have previously developed a set of 10 cancer prevention recommendations, these include following a healthy diet, being physically active and maintaining a healthy body weight. These are based on decades of research and many studies have now shown that following them reduces the risk of developing cancer, as well as reducing the risk of other chronic diseases [9].

One of these recommendations is that people LWBC follow the cancer prevention recommendations as much as possible (see **Appendix 1**). This recommendation was made by the expert panel, as part of the Third Expert Report, based on the best available evidence at the time. The panel made this recommendation with caution because, although nutritional factors and physical activity appear to predict outcomes in people LWBC, there was insufficient evidence that changing these improves outcomes for this group.

Guidance statement:

People who follow WCRF/AICR's Cancer Prevention Recommendations are predicted to have better outcomes after a breast cancer diagnosis.

We suggest that people consider following as many of these recommendations as they are able to.

The findings from the reviews described in this report (that healthy dietary and lifestyle patterns are associated with a lower risk of all-cause and non-breast cancer mortality) are consistent with this guidance.

In addition to this general guidance, we have used the more recent evidence from the current reviews to develop guidance and a recommendation specifically for people living with and beyond breast cancer. These are outlined below.

Physical activity

There is strong evidence that increasing physical activity after a diagnosis of breast cancer improves health-related quality of life. It was not possible to assess which types of physical activity were most beneficial or whether there was an optimal amount of physical activity for quality of life. However, there is little evidence that physical activity would cause increased harm in this group compared with the general population (eg injury from physical activity).

There is also limited evidence suggesting that higher levels of recreational physical activity might improve health outcomes.

Recommendation:

Increasing physical activity improves health-related quality of life after a diagnosis of breast cancer.

People who are more physically active have better health outcomes after a diagnosis of breast cancer, but it is uncertain whether increasing physical activity will improve these outcomes

We recommend that people are physically active. However, physical activity should be increased under the supervision of health care professionals.

There are numerous wider benefits of regular physical activity [17], including:

- Reducing the risk of developing other conditions, such as cardiovascular disease and type 2 diabetes
- Helping maintain a healthy body weight
- Reducing the risk of depression and anxiety
- Reducing the risk of falls, as well as hip and vertebral fractures, in older adults
- Helping improve sleep and cognitive health
- Helping keep joints and muscles healthy



Additional information:

International guidelines on physical activity from the World Health Organization (WHO) [17] recommend that adults (aged 19 to 64 years):

- Should do at least **150–300 minutes of moderate-intensity** aerobic physical activity, or at least **75–150 minutes of vigorous-intensity** aerobic physical activity (or an equivalent combination of these) throughout the week.
- Should also do **muscle-strengthening activities** (at moderate or greater intensity) that involve all major muscle groups on two or more days a week, as these provide additional health benefits.
- **May do more than 300 minutes** of moderate-intensity aerobic physical activity or more than 150 minutes of vigorous-intensity aerobic physical activity (or an equivalent combination of these) throughout the week **for additional health benefits.**
- **Should limit the amount of time spent being sedentary.** Replacing sedentary time with physical activity of any intensity (including light intensity) provides health benefits.

For adults aged 65 years and above, WHO additionally recommends:

- Doing varied multicomponent physical activity that emphasises functional balance and strength training at moderate or greater intensity, on 3 or more days a week, to enhance functional capacity and to prevent falls.

Please note that these general physical activity guidelines may not be applicable to all people.

Dietary fibre

There is limited evidence suggesting that higher consumption of dietary fibre might improve health outcomes.

Guidance statement:

People who eat more dietary fibre have better health outcomes after a diagnosis of breast cancer.

While it is uncertain that increasing dietary fibre improves these outcomes, we suggest that people consider increasing their dietary fibre intake.

Foods containing dietary fibre:

- Vegetables
- Fruits
- Wholegrain foods, such as oats, brown rice, bulgur wheat, wholegrain breakfast cereals, wholewheat pasta and wholemeal breads
- Pulses such as chickpeas, beans and lentils
- Nuts and seeds

Additional information:

People who increase their fibre intake should do so gradually. In general we are referring to natural food sources of fibre.



Soy foods

There is limited evidence suggesting that soy foods might reduce all-cause mortality, breast cancer mortality and breast cancer recurrence after a diagnosis of breast cancer.

People may have heard that eating soy foods can increase the risk of developing breast cancer and understandably may have concerns about eating these foods. This concern comes from the theoretical link between dietary isoflavones (of which soy is the main dietary source) and breast cancer. However, systematic reviews show no consistent evidence of a link² between soy foods and developing breast cancer, and there was no evidence from the current work that soy foods are harmful after diagnosis.

Therefore, although the evidence is currently insufficient to advise an increase in consumption of soy foods, those already consuming them do not need to stop.

Guidance statement:

The evidence does not support guidance to consume more soy foods (or to introduce soy foods if these are not currently part of the diet) after a diagnosis of breast cancer, but for those who already consume them, there is no need to stop.

Soy (or soya) foods include:

- Edamame (green soybeans)
- Tofu
- Tempeh
- Soy beverages and other dairy alternatives
- Roasted soy nuts



Additional information:

If soy alternatives to dairy are consumed, it is preferable to use products that are unsweetened and fortified with calcium and other essential nutrients, such as vitamin D and iodine (check the product label).

²Our expert panel previously judged the evidence for soy foods/isoflavones and breast cancer risk as 'limited no conclusion' in the Third Expert Report (<https://www.wcrf.org/wp-content/uploads/2021/02/Breast-cancer-report.pdf>)

Body weight

The review showed strong associations between body weight (measured by BMI, waist circumference and waist-to-hip ratio) and health outcomes. The panel concluded that these were unlikely to be caused by chance or bias and therefore judged these to be 'strong probable'. However, there was insufficient evidence on body weight change to make any guidance about weight loss. Therefore, a cautious approach has been taken, focusing on avoiding weight gain. This is important since women commonly gain weight during treatment for breast cancer.

Guidance statement:

Those with body weight in the 'healthy range' after a diagnosis of breast cancer have the best health outcomes. While it is uncertain that deliberate weight loss by people with overweight or obesity improves these outcomes, we suggest that people who are not underweight aim to avoid gaining weight during and after treatment.

Maintaining a healthy body weight can reduce the risk of the following conditions:

- Cardiovascular disease
- Type 2 diabetes
- Osteoarthritis

Underweight patients should discuss their nutritional needs with their medical team.



Vitamin D supplements

This review found limited evidence suggesting that higher vitamin D status reduces the risk of breast cancer-specific and all-cause mortality, but there was no evidence of any benefit from vitamin D supplements.

Therefore, we are not making specific guidance about vitamin D supplements to improve outcomes after a breast cancer diagnosis. People should take any supplements advised by their health care team, but should be cautious of taking over the counter vitamin D supplements if they are already being prescribed vitamin D or calcium supplements.



Please note: We recommend that individuals living with and beyond cancer speak to their healthcare team before making any changes related to diet, nutrition, physical activity or body weight. Any healthcare professionals using this guidance should consider where a patient is in their cancer journey and interpret the guidance appropriately to suit each person's individual needs.



Acknowledgments

Global Cancer Update Programme panel (developed guidance for people living with and beyond breast cancer)

Professor Lord John Krebs, University of Oxford, UK (Panel Chair); Professor Matty Weijnen, Maastricht University, NL (Panel Deputy Chair); Professor Monica Baskin, University of Pittsburgh, US (Chair of Expert Committee on Cancer Incidence); Professor Sarah Lewis, University of Bristol, UK (Chair of Expert Committee on Cancer Mechanisms); Professor Ellen Copson, University of Southampton, UK (Chair of Expert Committee on Cancer Survivors); Professor Jaap Seidell, VU University, NL (Chair of the Expert Committee on Obesity); Professor Rajiv Chowdhury, Florida International University, US (Global Representative); Lynette Hill, UK (Public Representative)

Formal observers to the Global Cancer Update Programme panel

Dr Carolina Espina, International Agency for Research on Cancer, FR; Dr Jason Montez, World Health Organization, CH; Professor Mathilde Touvier, French National Institute of Health and Medical Research, FR; Shalini Jayasekar Zürn, Union for International Cancer Control, CH; Dr Emily Tonorezos, National Cancer Institute, US

Global Cancer Update Programme cancer survivors expert committee (contributed to the development of guidance for people living with and beyond breast cancer)

Professor Ellen Copson, University of Southampton, UK (Chair); Professor Andrew Renehan, University of Manchester, UK (Deputy Chair); Professor Anne May, University Medical Centre Utrecht, NL; Professor Anne Tjonneland, Danish Cancer Society Research Centre, DK; Professor Galina Velikova, University of Leeds, UK; Professor Karen Steindorf, DKFZ and NCT, DE; Dr Martijn Bours, Maastricht University, NL; Dr Melissa Hudson, St. Jude Children's Research Hospital, US; Professor Rod Skinner, Newcastle University, UK; Professor Wendy Demark-Wahnefried, University of Alabama, US; Professor Folakemi Odedina, Mayo Clinic, US

CUP Transition panel (carried out judgement of breast cancer evidence and developed recommendation for physical activity and quality of life for people living with and beyond breast cancer)

Professor Alan Jackson, University of Southampton, UK; Professor Ed Giovannucci, Harvard T.H. Chan School of Public Health, US; Professor Anne McTiernan, Fred Hutchinson Cancer Research Center, US; Professor Ellen Kampman, Wageningen University, NL; Professor Marc Gunter, Imperial College London, UK; Dr Kostas Tsilidis, Imperial College London, UK; Professor Steven Clinton, Ohio State University, US; Dr Vivien Lund, UK (Public Representative)

Formal observers to CUP Transition panel

Professor Elio Riboli, Imperial College London, UK; Professor Amanda Cross, Imperial College London, UK

Imperial College London research team (carried out the systematic literature reviews)

Dr Kostas Tsilidis (co-Principal Investigator); Dr Doris Chan (co-Principal Investigator); Professor Amanda Cross, Dr Georgios Markozannes, Margarita Cariolou, Katia Balducci, Sonia Kiss, Sofia Cividini, Rita Vieira, Dr Dagfinn Aune, Dr Ahmad Jayedi, Dr Eduardo Seleiro (project manager), Lam Teng (database manager), Dr Darren C. Greenwood, University of Leeds, UK (statistical advisor)

Previously in Imperial College London research team:

Dr Teresa Norat (previously Principal Investigator CUP), Dr Nerea Becerra-Tomás, Dr Leila Abar, Dr Jakub Sobiecki, Neesha Nanu, Britta Talumaa, Victoria White, Dr Rui Vieira (database manager), Christophe Stevens (database manager), Yusuf O. Anifowoshe (database manager)

Protocol Expertise Group

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User involvement

Patients and health professionals providing feedback on the guidance and recommendation, including patient representatives via Breast Cancer Now and People in Research (NIHR)

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Other staff members have contributed previously, including:

Nicole Musuwo, Senior Research Interpretation Officer, WCRF International; Daphne Katsikioti, Senior Research Interpretation Officer, WCRF International; Deirdre McGinley-Gieser, Executive Vice President, AICR



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Appendix 1: WCRF/ AICR Cancer Prevention Recommendations

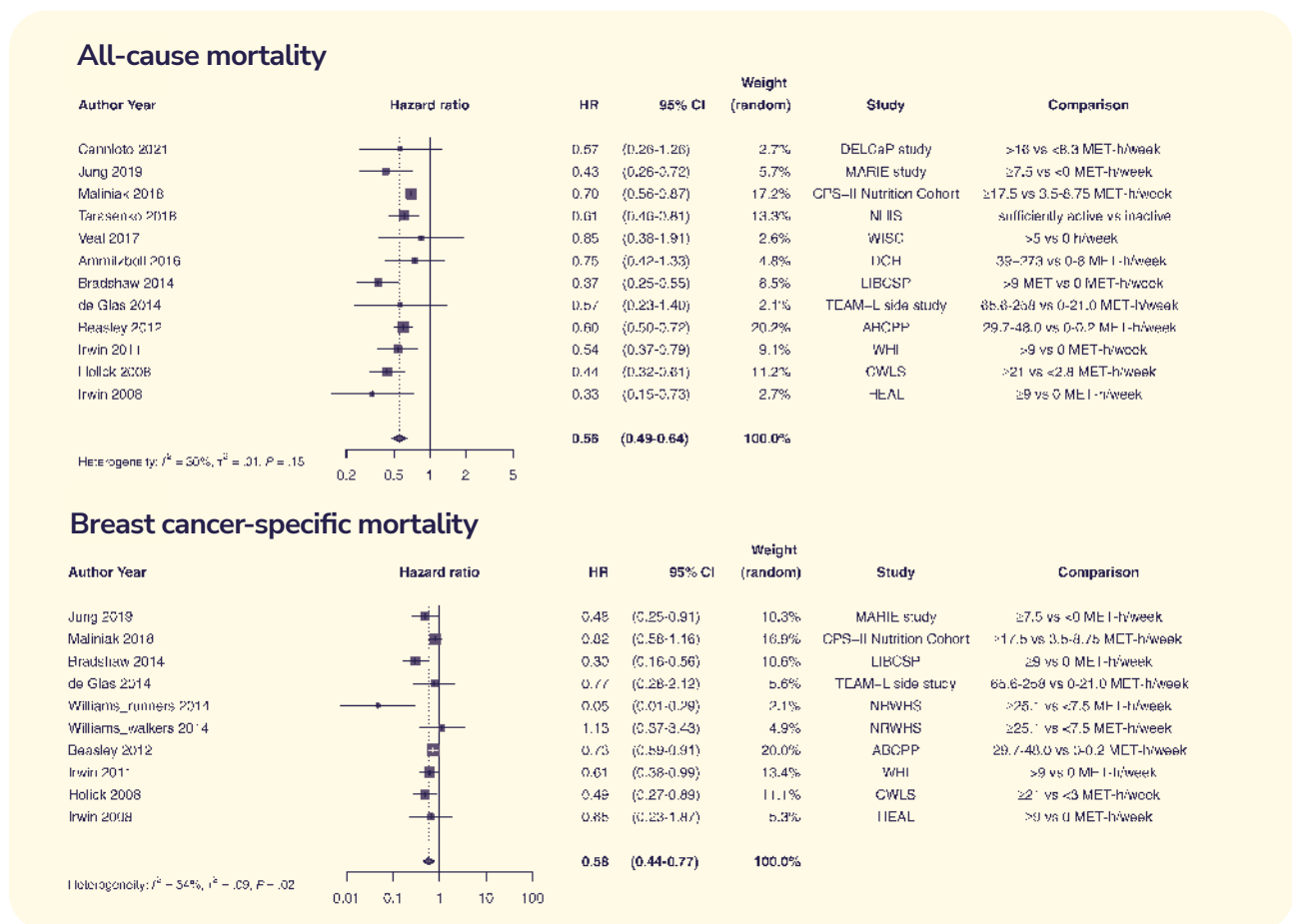


Appendix 2: Selection of forest plots illustrating findings from systematic reviews

The below forest plots are a selection shown to illustrate the results from the reviews, please refer to the papers to access all of the results and forest plots.

Health outcomes

Recreational physical activity after diagnosis and health outcomes



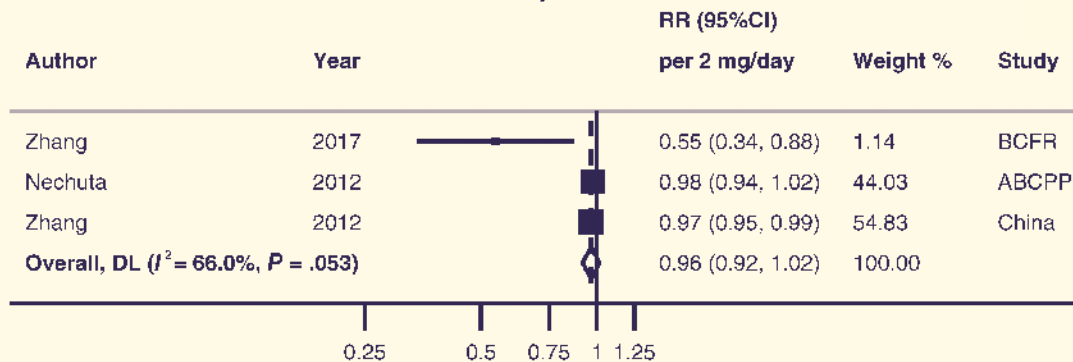
Footnote:

Summary hazard ratio estimate (95% CI) of all-cause mortality for the highest compared to the lowest level of recreational physical activity after diagnosis (top plot) and breast cancer-specific mortality for the highest compared to the lowest level of recreational physical activity after diagnosis (bottom plot). Forest plot shows results from the random effects model. Diamond represents the summary hazard ratio. Each square represents the hazard ratio estimate of each study and the horizontal line across each square represents the 95% confidence interval (CI) of the hazard ratio estimate. ABCPP (Beasley 2012) included data from three US cohorts that is, LACE, NHS, WHEL and one Chinese cohort SBCSS. For the CPS-II Nutrition Cohort (Maliniak 2018), the HR estimates for the two age groups reported were combined using fixed effects models before inclusion in the meta-analysis.

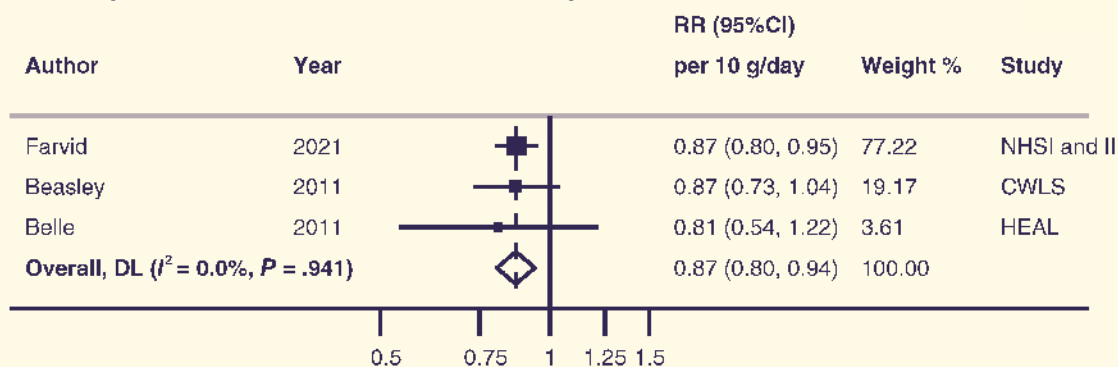
Citation: Cariolou M, Abar L, Aune D, Balducci K, Becerra-Tomás N, Greenwood DC, et al. Postdiagnosis recreational physical activity and breast cancer prognosis: Global Cancer Update Programme (CUP Global) systematic literature review and meta-analysis. *International Journal of Cancer*. 2023;152(4):600-15. (Plots B and D, taken from Figure 2)

Diet after diagnosis and health outcomes

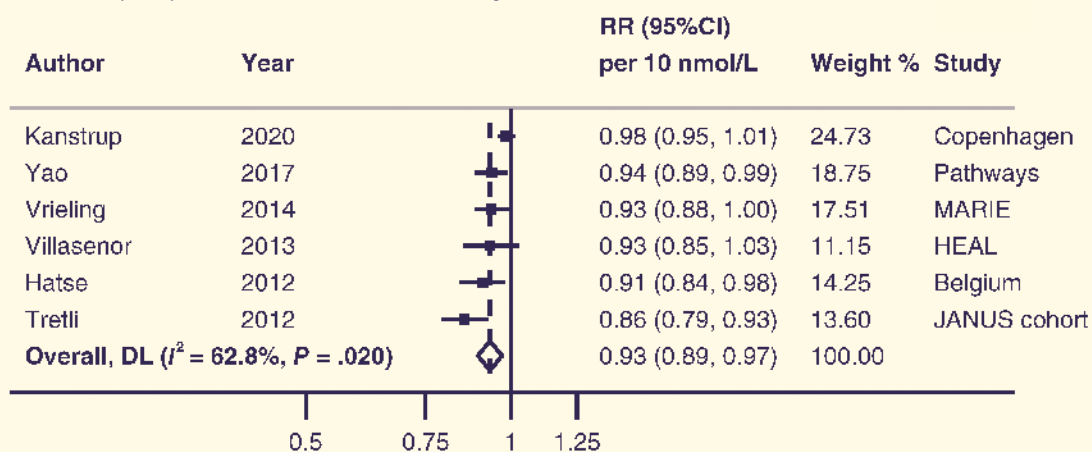
Isoflavone intake and all-cause mortality



Dietary fibre intake and all-cause mortality



Serum 25(OH)D and all-cause mortality

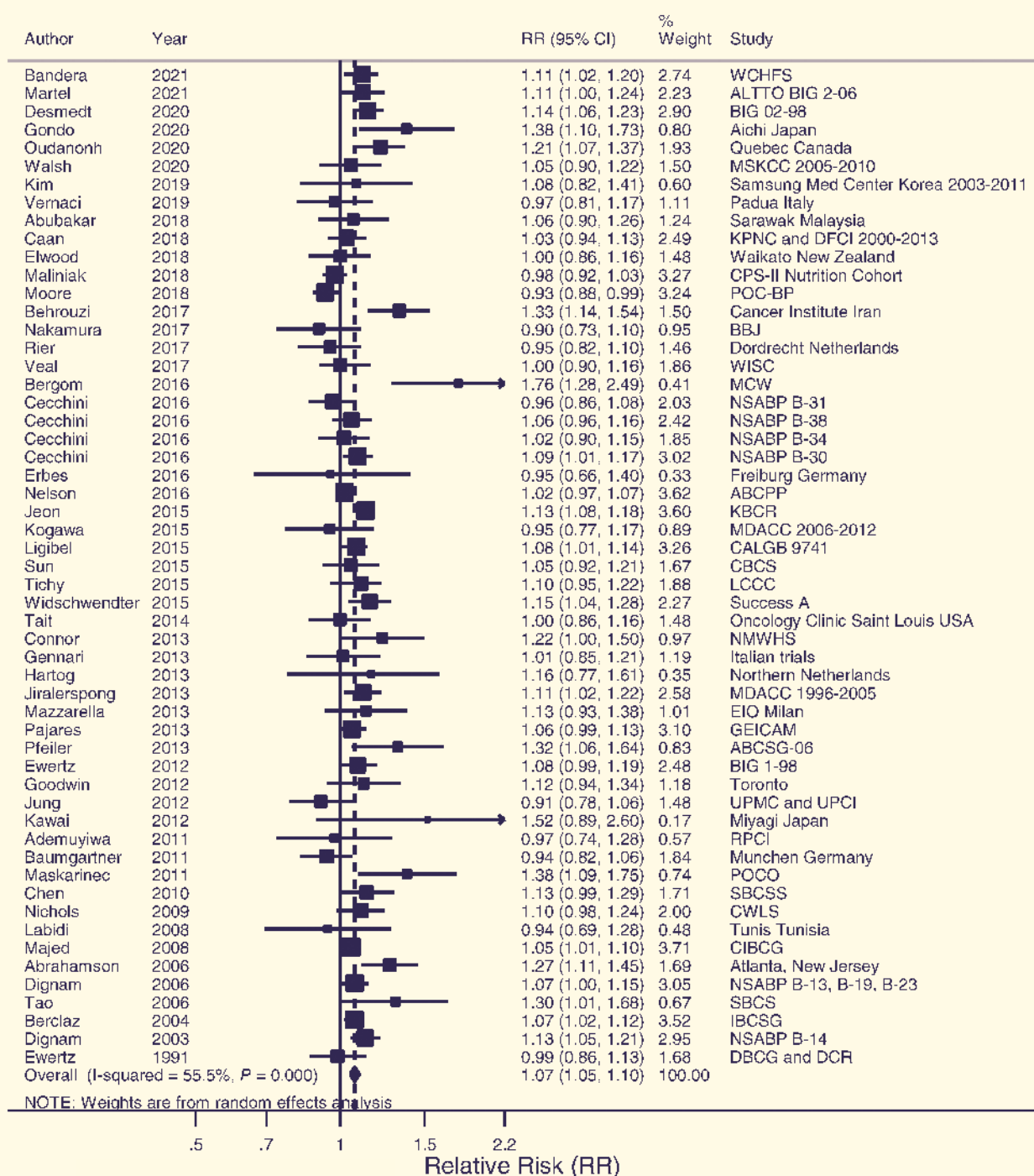


Footnote:

Linear dose-response meta-analyses on isoflavone intake, dietary fibre intake, serum 25(OH)D and all-cause mortality. Forest plots show the linear dose-response results from the inverse variance DerSimonian-Laird random-effects models. Diamonds represent the summary relative risk (RR) estimates. Each square represents the RR estimate of each study and the horizontal line across each square represents the 95% confidence interval (CI) of the RR estimate. The increment units were 2 mg/day (isoflavone intake), 10 g/day (dietary fibre intake), 10 nmol/L (serum 25(OH)D). Abbreviations: ABCPP, After Breast Cancer Pooling Project; BCFR, Breast Cancer Family Registry; CI, confidence interval; CWLS, Collaborative Women's Longevity Study; HEAL, Health, Eating, Activity, and Lifestyle Study; MARIE, Mammmary carcinoma risk factor Investigation; NHS, Nurses' Health Study; RR, Relative risk.

Citation: Becerra-Tomás N, Balducci K, Abar L, Aune D, Cariolou M, Greenwood DC, et al. Postdiagnosis dietary factors, supplement use and breast cancer prognosis: Global Cancer Update Programme (CUP Global) systematic literature review and meta-analysis. *International Journal of Cancer*. 2023;152(4):616-34. (Plots B, D and F, taken from Figure 3)

Body mass index after diagnosis and health outcomes (all-cause mortality)



Footnote:

Linear and nonlinear dose-response meta-analyses of postdiagnosis body mass index and all-cause mortality. Forest plot shows the linear dose-response results for postdiagnosis body mass index (BMI) and all-cause mortality from the inverse variance DerSimonian-Laird random-effects model. Diamond represents the summary relative risk (RR) estimate and its width as the 95% confidence interval (CI). Each square represents the RR estimate of each study and the horizontal line across each square represents the 95% CI of the RR estimate. The increment unit was per 5 kg/m². Nonlinear curve was estimated using restricted cubic spline regression with three knots at 10th, 50th and 90th percentiles of distribution of the exposure and pooled in random-effects meta-analysis. BMI at 20 kg/m² was selected as reference. The table shows selected BMI values and their corresponding RR (95% CI) estimated in the nonlinear dose-response meta-analysis.

Citation: Chan DSM, Vieira R, Abar L, Aune D, Balducci K, Cariolou M, et al. Postdiagnosis body fatness, weight change and breast cancer prognosis: Global Cancer Update Program (CUP global) systematic literature review and meta-analysis. *International Journal of Cancer*. 2023;152(4):572-99. (Figure 2)



Physical activity and health-related quality of life

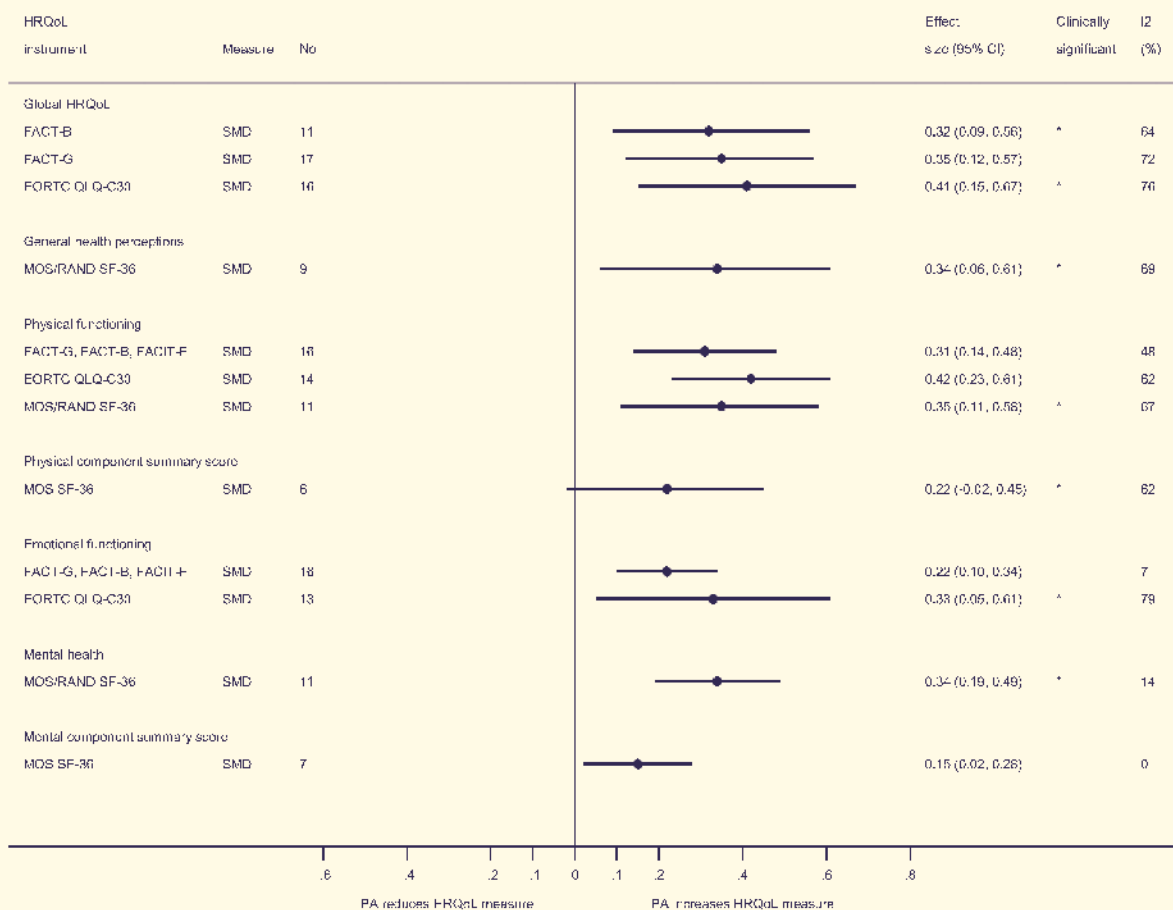


Figure 5. Summary standardized mean differences (95% confidence intervals) for physical activity and different domains of health-related quality of life. Effects that were considered clinically significant are marked with *. CI = confidence interval; EORTC QLQ-C30 = European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-C30; ES = effect size; FACT-B = Functional Assessment of Cancer Therapy-General and breast cancer; FACT-G = Functional Assessment of Cancer Therapy-General; FACIT-F = Functional Assessment of Chronic Illness Therapy-Fatigue; HRQoL = health-related quality of life; MOS/RAND SF-36 = Medical Outcomes Study and RAND Short Form-36; PA = physical activity; SMD = standardized mean difference.

Citation: Aune D, Markozannes G, Abar L, Balducci K, Cariolou M, Nanu N, et al. Physical Activity and Health-Related Quality of Life in Women With Breast Cancer: A Meta-Analysis. JNCI Cancer Spectrum. 2022;6(6):pkac072. (Figure 5)

Appendix 3: Summary of grading criteria

EVIDENCE GRADES	GRADING CRITERIA FOR EVIDENCE ON DIET, NUTRITION, PHYSICAL ACTIVITY AND SURVIVAL FOLLOWING CANCER				
			Het	PB	Mec
STRONG EVIDENCE	CONVINCING	Evidence of an effect from a meta-analysis of RCTs or at least 2 well-designed independent RCTs	NO	NO	DESIRABLE
	PROBABLE	Evidence of an effect from a meta-analysis of RCTs or 2 well-designed RCTs	SOME	NO	DESIRABLE
		OR Evidence of an effect from 1 well-designed RCT and 1 well-designed cohort study	NO	NO	REQUIRED
		OR Evidence from at least 1 well-designed pooled analysis of follow-up studies	NO	NO	REQUIRED
OR Evidence from at least 2 independent well-designed follow-up studies	NO	NO	REQUIRED		
LIMITED SUGGESTIVE	LIMITED SUGGESTIVE	Evidence from a meta-analysis of RCTs or at least 2 well-designed RCTs but the confidence interval may include the null	SOME	NO	NOT REQUIRED
		OR Evidence from 1 well-designed RCT but the confidence interval may include the null	NO	NO	REQUIRED
		OR Evidence of an effect from a pooled analysis of follow-up studies	SOME	NO	NOT REQUIRED
		OR Evidence from a pooled analysis of follow-up studies but the confidence interval may include the null	SOME	NO	REQUIRED
		OR Evidence of an effect from at least 1 follow-up study	NO	NO	REQUIRED
		OR Evidence of an effect from at least 2 follow-up studies	NO	NO	NOT REQUIRED
	OR Evidence from at least 2 follow-up studies but the confidence interval may include the null	SOME	NO	REQUIRED	
LIMITED - NO CONCLUSION	Any of the following reasons: - Too few studies available - Inconsistency of direction of effect - Poor quality of studies	-	-	-	
STRONG EVIDENCE	SUBSTANTIAL EFFECT ON RISK UNLIKELY	Evidence of the absence of an effect (a summary estimate close to 1.0) from any of the following: a. A meta-analysis of RCTs b. At least 2 well-designed independent RCTs c. A well-designed pooled analysis of follow-up studies d. At least 2 well-designed follow-up studies - Absence of a dose-response relationship (in follow-up studies)	NO	-	ABSENCE

Note: Special upgrading factors: (a) Presence of a plausible biological gradient ('dose response') in the association. Such a gradient need not be linear or even in the same direction across the different levels of exposure, so long as this can be explained plausibly. (b) A particularly large summary effect size (a relative risk of 2.0 or more, or 0.5 or less, depending on the unit of exposure), after appropriate control for confounders. (c) Evidence from appropriately controlled experiments demonstrating one or more plausible and specific mechanisms. (d) All plausible known residual confounders or biases including reverse causation would reduce a demonstrated effect, or suggest a spurious effect when results show no effect. Special considerations important for evidence for breast cancer survivors including the following potential confounding variables—the type of tumour, type of treatment, amount of treatment received and the dissemination of the disease.

Abbreviations: Het, substantial unexplained heterogeneity or some unexplained heterogeneity; PB, publication bias; Mec, strong and plausible mechanistic evidence is required, desirable but not required, not required or absent.

Appendix 4: Summary of panel conclusions

The below table summarises the evidence judgements made by the expert panel as part of our ongoing work to examine how diet, weight and physical activity exposures affect outcomes following a breast cancer diagnosis.

LIVING WITH AND BEYOND BREAST CANCER (HEALTH AND HEALTH-RELATED QUALITY OF LIFE OUTCOMES)					
2022	Post diagnosis diet, nutrition and physical activity for breast cancer survivors				
		DECREASES RISK		INCREASES RISK	
		EXPOSURE	OUTCOME	EXPOSURE	OUTCOME
STRONG EVIDENCE	CONVINCING				
	PROBABLE	Physical activity interventions	HR quality of life ¹	Body fatness ²	All mortality BC mortality 2nd BC
LIMITED EVIDENCE	LIMITED-SUGGESTIVE	Healthy dietary patterns ³	All mortality Non-cancer mortality	Body fatness ⁴	Recurrence Non-BC mortality CVD mortality
		Soy foods	All mortality BC mortality Recurrence		
		Dietary fibre	All mortality		
		Vitamin D status ⁵	All mortality BC mortality		
		Recreational physical activity	All mortality BC mortality		
	LIMITED-NO CONCLUSION	Post diagnosis BMI change or weight change Low-fat diet, predefined healthy dietary and lifestyle patterns (for breast cancer-specific mortality and cardiovascular disease death), data-driven dietary patterns, high-fat dietary pattern, alcoholic drinks, fruit and vegetables, cruciferous vegetables, dietary fibre (for breast cancer-specific mortality and recurrence), wholegrains, red and processed meats, fish, eggs, milk and dairy products, nutrients (fats, carbohydrate, animal protein, plant protein), supplements (multivitamins, antioxidants, vitamins, carotenoids), vitamin D (blood levels on recurrence)			
STRONG EVIDENCE	STRONG EVIDENCE	SUBSTANTIAL EFFECT ON RISK UNLIKELY			

Abbreviations:

HR quality of life, health-related quality of life; All mortality, all-cause mortality; BC mortality, breast cancer-specific mortality; 2nd BC, 2nd primary breast cancer; non-BC mortality, non-breast cancer related mortality; CVD mortality, cardiovascular disease mortality

Footnotes:

- 1 There was insufficient evidence to draw conclusions on specific domains of quality of life or the types and doses of physical activity
- 2 BMI, waist circumference, waist-hip ratio for all-cause mortality and BC mortality; BMI for 2nd BC
- 3 Refers to predefined healthy dietary and lifestyle patterns
- 4 BMI, waist circumference, waist-hip ratio for recurrence; BMI for non-BC related mortality and CVD mortality
- 5 Refers to blood level

Appendix 5: User input

Feedback on accessing advice on diet, physical activity and health:

- Participants consistently mentioned a lack of reliable, evidence-based information following their diagnosis.
- Participants reported that healthcare professionals were generally either too “afraid” to talk about diet and lifestyle changes, not aware of the changes that could be suggested, or seemed to lack the knowledge needed to offer such information.
- In some cases, the advice that was given by healthcare teams was not considered appropriate or necessarily evidence-based .
- Some reported cancer charities as offering very good general support, but not enough specific information about diet, physical activity and their health that was relevant to their cancer journey and cancer sub-type.
- Many participants reported that the information found on the internet or social media was generally unreliable and often conflicting.
- Patient forums were a popular source of support, but some participants doubted the accuracy of some of the advice from other survivors.
- Facebook support groups were also mentioned, although some included strong opinions from survivors that were seen as potentially misleading.
- Information and advice from appropriately qualified people with their own cancer diagnosis was one source considered relevant and trustworthy.

Feedback on the guidance:

- Guidance was considered accessible and easy to read.
- The use of clear sections and sub-titles was seen as helpful.
- The links to additional information were viewed positively.
- However, many participants said the example guidance needed to be more visual.
- Guidance also needed to be more inclusive to suit lower literacy levels, but also to consider different cultural and personal food preferences.
- Examples to ‘bring to life’ the guidance were needed, such as specific hints and tips, or quotes/ stories detailing the challenges that cancer survivors had faced to make it more personable and actionable.
- Specific consideration of some of the challenges following a diagnosis was needed (for example early-onset menopause for some breast cancer patients).
- There was a perceived need to set the guidance in the context of the potential broader health and wellbeing benefits (e.g. for mental health) or health challenges (e.g. other co-morbidities; physical impairment due to surgery or medication side effects) and also for the advice to feel more achievable (e.g. considering cost-of-living).
- Making the guidance more ‘empowering’ by emphasising the potential benefits of making even small changes to behaviour could be helpful.



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World Cancer Research Fund International's Global Cancer Update Programme is a global analysis of scientific research into the link between diet, nutrition, physical activity, weight and cancer. It is produced in partnership with American Institute for Cancer Research, World Cancer Research Fund in the UK and Wereld Kanker Onderzoek Fonds in The Netherlands.

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