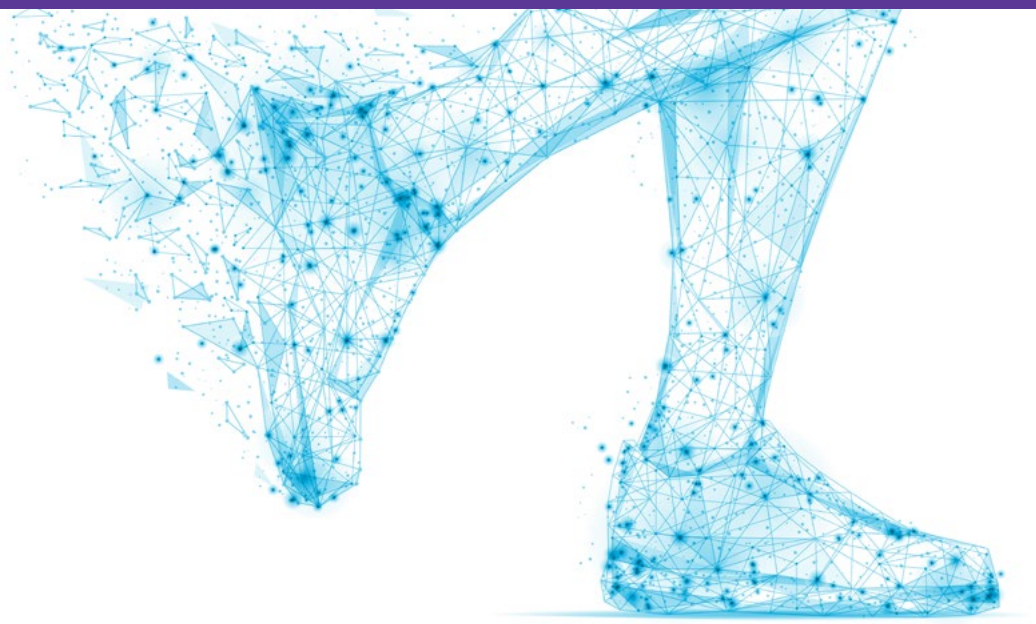
World Cancer Research Fund

American Institute for Cancer Research

CUP Continuous Update Project

Analysing research on cancer prevention and survival



Physical activity
and the risk of cancer

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 WCRF 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. Physical activity and the risk of cancer 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

See **Glossary** for definitions of terms highlighted in *italics*.

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

Executive summary

Background and context

In this part of the Third Expert Report from our Continuous Update Project (CUP) – the world's largest source of scientific research on cancer prevention and survivorship through diet, nutrition and physical activity – we analyse global research on how physical activity affects the risk of developing cancer.[1] This includes new studies as well as those included in the 2007 Second Expert Report, Food, Nutrition, Physical Activity and the Prevention of Cancer: a Global Perspective [1].

Physical activity is defined as any movement that uses skeletal muscles and requires more *energy* than resting [2, 3]. *Aerobic physical activity*, such as running, increases oxygen uptake and improves cardiovascular function, whereas anaerobic physical activity, such as resistance training using weights, increases muscle strength and mass. Physical activity has an effect on several bodily systems including *endocrinologic*, immunologic and metabolic processes which can, in turn, affect the risk for development of several cancers. Being physically active also helps to maintain a healthy weight and protect against cancer.

In this Third Expert Report, physical activity is classified into three types: total physical activity, recreational physical activity and occupational physical activity. Physical activity can also be classified by intensity: vigorous, moderate or light. The combination of frequency, intensity and duration of different types of physical activity determines the total volume of physical activity.

The intensity of physical activity is sometimes stratified into levels according to *metabolic equivalents (METs)* which describe intensity as oxygen uptake relative to a person's *resting metabolic rate* – for example, vigorous such as running and fast cycling (≥ 6 METs); moderate, such as brisk walking and vacuuming (3 to 5.9 METs); or light (< 3 METs), such as standing and walking at a slow pace.

Sedentary behaviour is defined as any waking behaviour characterised by an energy expenditure ≤ 1.5 METs while in a sitting or reclining posture [4]. New technologies have encouraged people to increase the time they spend engaging in sedentary behaviours, such as sitting in cars and watching television as well as using computers, electronic entertainment and mobile phones. The World Health Organization estimates that in 2010, globally about 23 per cent of adults did less than the recommended level of activity of at least 150 minutes of moderate-intensity aerobic physical activity per week [5]. The proportion of adults in high-income countries not meeting the recommended level of activity is higher [5].

Insufficient levels of physical activity have been linked to a number of health problems including cardiovascular disease, stroke, diabetes, *obesity*, poor bone health and depression [6].

[1] Cancers at the following sites are reviewed in the CUP: mouth, pharynx and larynx; nasopharynx; oesophagus; lung; stomach; pancreas; gallbladder; liver; colorectum; breast; ovary; endometrium; cervix; prostate; kidney; bladder; and skin.

How the research was conducted

The global scientific research on diet, nutrition, physical activity and the risk of cancer was systematically gathered and analysed, and then independently assessed by a panel of leading international scientists to draw conclusions about which factors increase or decrease the risk of developing the disease (see Judging the evidence).

This Third Expert Report presents in detail findings for which the Panel considered the evidence strong enough to make Cancer Prevention Recommendations (where appropriate) and highlights areas where more research is required (where the evidence is suggestive of a causal or protective relationship but is limited in terms of amount or by methodological flaws). Evidence that was considered by the Panel but was too limited to draw firm conclusions is not covered in detail in this Third Expert Report.

Findings

There is strong evidence that:

- **being physically active decreases the risk of cancers of the colon, breast (postmenopause) and endometrium**
- **undertaking physical activity of vigorous-intensity decreases the risk of pre and postmenopausal breast cancer**

The evidence implies that, in general, the more physically active people are, the lower the risk of some cancers.

The Panel has used this strong evidence on physical activity when making Recommendations (see below) designed to reduce the risk of developing cancer.

There is also other evidence on physical activity that is limited (either in amount or by methodological flaws), but is suggestive of a decreased risk of oesophageal, lung and liver cancers. In addition, there is evidence on sedentary behaviours that is limited but is suggestive of an increased risk of endometrial cancer. Further research is required, and the Panel has not used this evidence to make recommendations.

Recommendations

Our Cancer Prevention Recommendations – for preventing cancer in general – include maintaining a healthy weight, being physically active and eating a healthy diet. It is important to be physically active as part of everyday life and reduce the amount time spent sitting. The recommendations are listed on the inside back cover.

References

[1] World Cancer Research Fund/American Institute for Cancer Research. *Food, Nutrition, Physical Activity, and the Prevention of Cancer: a Global Perspective*. Washington DC: AICR, 2007. Available from wcrf.org/about-the-report

[2] The National Cancer Institute. Physical Activity and Cancer. 2017. Accessed 19/10/2017; available from https://www.cancer.gov/about-cancer/causes-prevention/risk/obesity/physical-activity-fact-sheet - q4

[3] Physical Activity Guidelines Advisory Committee. Physical Activity Guidelines Advisory Committee Report. 2008.

[4] Sedentary Behaviour Research Network. Letter to the editor: standardized use of the terms “sedentary” and “sedentary behaviours”. Appl Physiol Nutr Metab 2012; 37: 540–2.

[5] World Health Organisation. Global status report on noncommunicable diseases 2014.

[6] WHO. Global recommendations on physical activity for health. 2010.

1. Physical activity and the risk of cancer: a summary matrix

PHYSICAL ACTIVITY AND THE RISK OF CANCER					
WCRF/AICR GRADING		DECREASES RISK		INCREASES RISK	
		Exposure	Cancer site	Exposure	Cancer site
STRONG EVIDENCE	Convincing	**Physical activity[1]**	**Colorectum (colon) 2017[2]**		
	Probable	**Physical activity[1]**	**Breast (postmenopause) 2017[3]** **Endometrium 2013**		
		Vigorous-intensity physical activity	**Breast (premenopause) 2017[3]** **Breast (postmenopause) 2017[3]**		
LIMITED EVIDENCE	Limited – suggestive	Physical activity[1]	Oesophagus 2016[4] Lung 2017 Liver 2015 Breast (premenopause) 2017[3]	Sedentary behaviours	Endometrium 2013[5]
STRONG EVIDENCE	Substantial effect on risk unlikely	None identified			

1 The exposure of physical activity includes evidence for all types of activity and all intensity levels.
2 The evidence for physical activity and colorectum is for colon cancer only – no conclusion was drawn for rectal cancer.
3 In addition to physical activity, there was sufficient evidence for the Panel to make a separate judgement for vigorous-intensity physical activity and breast cancer (pre and postmenopause).
4 The evidence for physical activity and oesophageal cancer includes unspecified, adenocarcinoma and squamous cell carcinoma.
5 The evidence for sedentary behaviours and endometrial cancer was marked by sitting time.

Throughout this Third Expert Report, the year given for each cancer site is the year the CUP cancer report was published, apart from those for nasopharynx, cervix and skin, where the year given is the year the systematic literature review was last reviewed. Updated CUP cancer reports for nasopharynx and skin will be published in the future.

Definitions of World Cancer Research Fund (WCRF)/American Institute for Cancer Research (AICR) grading criteria

'Strong evidence': Evidence is strong enough to support a judgement of a convincing or probable causal (or protective) relationship and generally justify making public health recommendations.

'Convincing': Evidence is strong enough to support a judgement of a convincing causal (or protective) relationship, which justifies making recommendations designed to reduce the risk of cancer. The evidence is robust enough to be unlikely to be modified in the foreseeable future as new evidence accumulates.

'Probable': Evidence is strong enough to support a judgement of a probable causal (or protective) relationship, which generally justifies goals and recommendations designed to reduce the risk of cancer.

'Limited evidence': Evidence is inadequate to support a probable or convincing causal (or protective) relationship. The evidence may be limited in amount or by methodological flaws, or there may be too much inconsistency in the direction of effect (or a combination), to justify making specific public health recommendations.

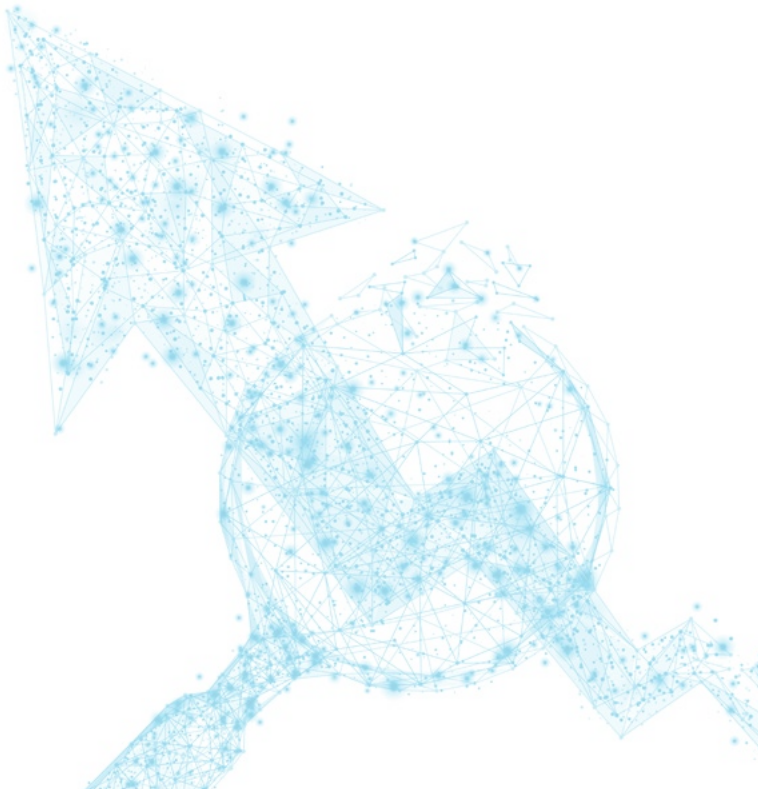
'Limited – suggestive': Evidence is inadequate to permit a judgement of a probable or convincing causal (or protective) relationship, but is suggestive of a direction of effect. The evidence may be limited in amount, or by methodological flaws, but shows a generally consistent direction of effect. This judgement generally does not justify making recommendations.

'Limited – no conclusion': There is enough evidence to warrant Panel consideration, but it is so limited that no conclusion can be made. The evidence may be limited in amount, by inconsistency in the direction of effect, by methodological flaws, or any combination of these. Evidence that was judged to be 'limited – no conclusion' is mentioned in Evidence and judgements **(Section 5)**.

'Substantial effect on risk unlikely': Evidence is strong enough to support a judgement that a particular lifestyle factor relating to diet, nutrition, body fatness or physical activity is unlikely to have a substantial causal (or protective) relation to a cancer outcome.

For further information and to see the full grading criteria agreed by the Panel to support the judgements shown in the matrices, please see **Appendix 1**.

The next section describes which evidence the Panel used when making Recommendations.



2. Summary of Panel judgements

The conclusions drawn by the CUP Panel are based on the evidence from both epidemiological and mechanistic studies relating specific data on physical activity to the risk of development of particular cancer types. Each conclusion on the likely causal relationship between physical activity and a cancer forms a part of the overall body of evidence that is considered during the process of making Cancer Prevention Recommendations. Any single conclusion does not represent a recommendation in its own right. The Cancer Prevention Recommendations are based on a synthesis of all these separate conclusions, as well as other relevant evidence, and can be found at the end of this Third Expert Report.

The CUP Panel concluded:

STRONG EVIDENCE

Convincing

- **Decreased risk**
  - **Physical activity:**[1] Being physically active convincingly protects against colon cancer.[2]

Probable

- **Decreased risk**
  - **Physical activity:**[1] Being physically active probably protects against postmenopausal breast cancer[3] and endometrial cancer.
  - **Vigorous-intensity physical activity:** Physical activity of vigorous intensity probably protects against pre and postmenopausal breast cancer.[3]

The evidence implies that, in general, the more physically active people are, the lower the risk of some cancers.

The Panel used this strong evidence on physical activity when making Recommendations designed to reduce the risk of developing cancer (see Recommendations and public health and policy implications, Section 2: Recommendations for Cancer Prevention).

LIMITED EVIDENCE

Limited – suggestive

- **Decreased risk**
  - **Physical activity:**[1] The evidence suggesting that being physically active decreases the risk of cancers of the following types is limited: oesophagus;[4] lung; liver; and breast (premenopause).[3]
- **Increased risk**
  - **Sedentary behaviours:** The evidence suggesting that sedentary behaviour increases the risk of endometrial cancer[5] is limited.

The Panel did not use the limited evidence when making Recommendations designed to reduce the risk of developing cancer. Further research is required into these possible effects on the risk of cancer.

See Definitions of WCRF/AICR grading criteria (**Section 1**: Physical activity and the risk of cancer: a summary matrix) for explanations of what the Panel means by 'strong evidence', 'convincing', 'probable', 'limited evidence' and 'limited – suggestive'.

[1] The exposure of physical activity includes evidence for all types of activity and all intensity levels.
[2] The evidence for physical activity and colorectum is for colon cancer only – no conclusion was drawn for rectal cancer.
[3] In addition to physical activity, there was sufficient evidence for the Panel to make a separate judgement for vigorous-intensity physical activity and breast cancer (pre and postmenopause).
[4] The evidence for physical activity and oesophageal cancer includes unspecified, adenocarcinoma and squamous cell carcinoma.
[5] The evidence for sedentary behaviours and endometrial cancer was marked by sitting time.

3. Definitions and patterns

3.1 Physical activity (including vigorous-intensity physical activity)

Physical activity is defined as any movement that uses skeletal muscles and requires more *energy* than resting [2, 3]. Physical activity utilises energy and is therefore an important factor in *energy balance*. *Aerobic physical activity*, such as running, increases oxygen uptake and improves cardiovascular function, whereas anaerobic physical activity, such as resistance training using weights, increases muscle strength and mass. Definitions of physical activity and physical activity of vigorous intensity vary between studies; for the definitions used in the CUP, see **Section 4.2.1.1**.

Physical activity has an effect on several bodily systems including *endocrinologic*, immunologic and metabolic processes which can, in turn, affect the risk for development of several cancers. Being physically active also helps to maintain a healthy weight and protect against cancer (see Energy balance and body fatness literature review 2017).

3.1.1 Type of physical activity

In this Third Expert Report, physical activity is classified into three types (see **Table 3.1**).

Insufficient levels of physical activity have been linked to a number of health problems including cardiovascular disease, stroke, diabetes, obesity, poor bone health and depression [6].

Table 3.1: Types of physical activity

Type	Includes
Total physical activity	All types of physical activity including recreational and occupational as well as transport (walking and travelling by bicycle, for example, in commuting to work) and household (cooking, shopping, cleaning, vacuuming, sweeping and washing).
Recreational	Exercise, sports and other forms of physical training. Recreational physical activity may be aerobic, such as walking, running, cycling, dancing and other activities that increase oxygen uptake, or anaerobic, such as resistance training using weights, which increases muscle strength and mass [7].
Occupational	Any physical activity at work. Occupations may be sedentary or involve light, moderate or vigorous-intensity physical activity.

3.1.2 Total volume of physical activity

Physical activity can be classified by intensity: vigorous, moderate or light (see **Table 3.2** and **Box 1**). The combination of the frequency, intensity and duration of different types of physical activity determines the total volume of physical activity. One hour of light physical activity uses about the same total amount of *energy* as 30 minutes of moderate or 20 minutes of vigorous activity.

Table 3.2: Intensity of physical activity according to the Department of Health in the UK [8]

Intensity	Examples
Vigorous	Aerobic dancing, fast cycling (12 to 14 miles per hour), swimming, tennis and running
Moderate	Brisk walking, vacuuming, painting or decorating, mowing the lawn and cycling (10 to 12 miles per hour)
Light	Standing, ironing, cleaning or dusting, and walking at a slow pace

Box 1: Measures of physical activity or sedentary behaviours

3.1.2.1 Metabolic equivalents

The total amount of *energy* a person uses during a particular activity is determined by a combination of the duration and intensity of the activity, and the amount of lean mass of the person. *Metabolic equivalents (METs)* describe intensity as oxygen uptake relative to a person's resting metabolic rate. The energy costs of any particular activity vary, depending on a person's *basal energy expenditure* and their age, sex, size, skill and level of fitness. MET values take these factors into account.

High total energy expenditure can be produced by performing low-intensity activity for a long duration or higher-intensity activity for a shorter duration. However, these two types of activity may have different physiological effects. The intensity of physical activity is therefore sometimes stratified into levels, such as vigorous (≥ 6 METs), moderate (3 to 5.9 METs), or light (< 3 METs) [6]. Sedentary behaviour is defined as ≤ 1.5 METs [4].

The combined contribution of multiple types of physical activity can be characterised in terms of MET-hours. METs are usually converted to MET-hours per day or per week, which are calculated as the sum of the MET level for each activity multiplied by the duration that the activity was performed.

3.1.2.2 Change in heart rate

Physical activity of vigorous intensity can also be defined as that which increases heart and breathing rates up to 80 per cent or more of their maximum (during vigorous-intensity physical activity *anaerobic metabolism* is needed to provide *energy*). Moderate physical activity increases heart and breathing rates to about 60 to 75 per cent of their maximum (and the energy requirement can usually be met by *aerobic metabolism* using the body's stores of glycogen and then fats). Light physical activity has only minor effects on heart and breathing rates. Sedentary activity involves no noticeable effort: heart and breathing rates are not raised perceptibly above 'resting' levels [9].

3.2 Sedentary behaviours

Sedentary behaviour is defined as any waking behaviour characterised by an energy expenditure ≤ 1.5 METs while in a sitting or reclining posture [4]. Examples include television viewing, video game playing, computer use, reading, talking on the telephone and sitting while commuting.

New technologies have encouraged people to increase the time spent engaging in sedentary behaviours such as sitting in cars and watching television as well as using computers, electronic entertainment and mobile phones.

The World Health Organization estimates that in 2010, about 23 per cent of adults did less than the recommended level of activity of at least 150 minutes of moderate-intensity *aerobic physical activity* per week [6]. Physical inactivity increases with age, is higher in women than men and is increased in *high-income* compared with *low-income countries* [6]. There are data to suggest that while occupational physical activity is generally decreasing, recreational physical activity is increasing in high-income countries [10].

Evidence that sedentary behaviours increase the risk of being overweight and obese is summarised in Energy balance and body fatness literature review 2017. For the definition of sedentary behaviours in the CUP, see **Section 4.2.1.2**.

4. Interpretation of the evidence

4.1 General

For general considerations that may affect interpretation of the evidence in the CUP, see Judging the evidence.

'Relative risk' (RR) is used in this Third Expert Report to denote ratio measures of effect, including 'risk ratios', 'rate ratios', 'hazard ratios' and *'odds ratios'*.

4.2 Specific

Specific factors that the Panel bears in mind when interpreting evidence on whether being physically active increases or decreases the risk of developing cancer are described in this section. Factors that are relevant to specific cancers are presented here too.

4.2.1 Exposures

4.2.1.1 Physical activity (including vigorous-intensity physical activity)

Definitions. Among the studies reviewed in the CUP, there was no generally agreed classification of different levels of overall physical activity, with quantified degrees of activity corresponding to terms such as 'active' and physically active'.

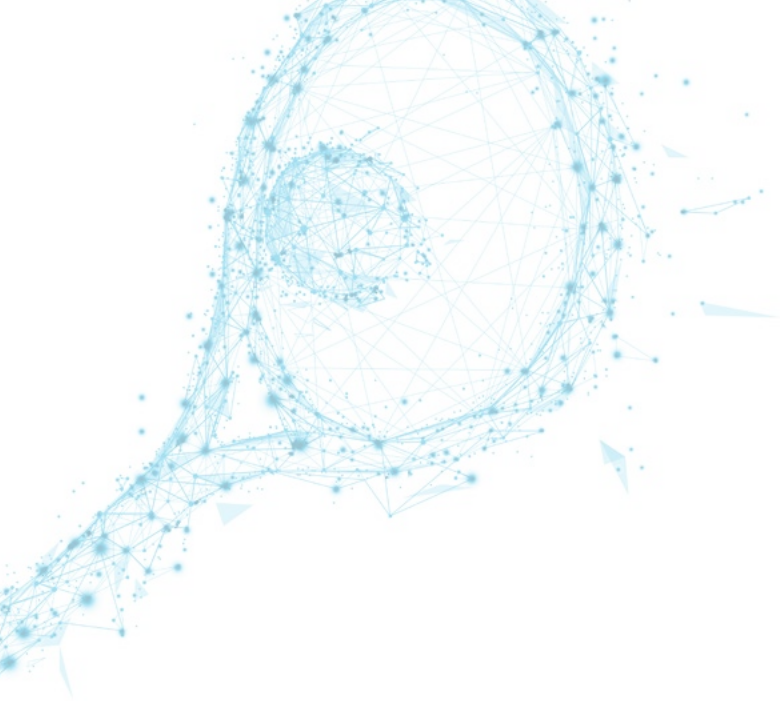
In the highest versus lowest analyses in the CUP, highest physical activity in the individual studies was generally defined as 'active', a measure in MET-hours per week or a MET score. Lowest physical activity was generally defined as 'inactive', a lower number of MET-hours per week or a lower MET score. There was wide variation in the highest and lowest levels between studies. Other measures used included minutes of physical activity a day and number of days the participant was physically active per week, as well as more qualitative measures. Dose–response meta-analyses conducted for physical activity used the increment of 10 MET-hours per week. Individual studies classified activities as vigorous intensity, which tended to be reported as hours per week of vigorous-intensity physical activity.

Confounding. In *high-income countries*, people who are physically active also tend to be health conscious and so, for example, are more likely to be non-smokers and to choose diets they believe to be healthy. This may confound findings that show associations with the risk of cancer.

Measurement. Physical activity is rarely measured precisely. Ideally, studies would record the frequency, intensity and duration of people's physical activity over an extended period – day and night. However, studies are generally not designed to obtain this information. Objective measures such as pedometers and microcomputer sensors are not usually feasible in large studies. Instead, questionnaires are most frequently used, which can be interviewer- or self-administered [3].

Different methods of measuring physical activity reported in the literature make comparison between studies difficult. Hence it is often not possible to conduct dose–response meta-analyses, or where it is possible many studies may be excluded. When dose–response meta-analysis is not possible, an analysis of highest versus lowest exposure category is conducted as part of the CUP. A summary estimate may be presented; however, the absolute value is likely to be inaccurate as the levels for highest and lowest exposure vary between studies. This type of analysis is nonetheless useful in determining the direction of effect of the studies.

Reporting bias. Questionnaires measure some forms of physical activity more accurately than others. Thus, people tend to recall vigorous



and recreational, and other voluntary activities, with relative accuracy. However, these activities are generally performed for relatively short periods of time and may amount to a smaller than perceived proportion of a person's total physical activity.

Patterns and ranges. Large studies of physical activity are mainly undertaken in high-income countries. Such studies tend to pay most attention to voluntary recreational activity and may therefore have limited relevance to populations in *lower-income countries*. In lower-income countries, overall activity levels may be higher and physical activity is mostly of the type classed as occupational, household or transport. The analyses on colorectal and breast cancer included a few studies from Asia, although the majority were from North America and Europe.

4.2.1.2 Sedentary behaviours

Definitions. Sedentary behaviour in the CUP was inferred from the amount of self-reported sitting time in many of the studies on physical activity.

Confounding. In *high-income countries*, people who report high levels of sedentary behaviour such as spending a lot of time watching television also tend to be less health conscious and so, for example, are more likely to smoke and to have an unhealthy diet. This may confound findings that show associations with the risk of cancer.

For further details on these topics, see sections on Measurement, Reporting bias and Patterns and ranges under **Section 4.2.1.1**.

4.2.2 Cancers

The information provided here on 'Other established causes' of cancer is based on judgements made by the International Agency for Research on Cancer (IARC) [11], unless a different reference is given. For more information on findings from the CUP on diet, nutrition, physical activity and the risk of cancer, see other parts of this Third Expert Report.

4.2.2.1 Oesophagus

Definition. The oesophagus is the muscular tube through which food passes from the pharynx to the stomach.

Classification. The oesophagus is lined over most of its length by squamous *epithelial* cells, where *squamous cell carcinomas* arise. The portion just above the gastric junction (where the oesophagus meets the stomach) is lined by columnar epithelial cells, from which *adenocarcinomas* arise. The oesophageal-gastric junction and gastric cardia are also lined with columnar *epithelial* cells.

Globally, squamous cell carcinoma is the most common type and accounts for 87 per cent of cases [12]; however, the proportion of adenocarcinomas is increasing dramatically in affluent nations. Squamous cell carcinomas have different geographic and temporal trends from adenocarcinomas and follow a different disease path. Different approaches or definitions in different studies are potential sources of heterogeneity.

Other established causes. Other established causes of oesophageal cancer include the following:

Smoking tobacco, chewing tobacco and snuff

Smoking tobacco (or use of smokeless tobacco, sometimes called 'chewing tobacco' or 'snuff') is a cause of oesophageal cancer. *Squamous cell carcinoma* is more strongly associated with smoking tobacco than *adenocarcinoma* [13]. It is estimated that 42 per cent of deaths of oesophageal cancer are attributable to tobacco use [14].

Infection

Between 12 and 39 per cent of oesophageal squamous cell carcinomas worldwide are related to carcinogenic types of human papilloma virus [15]. Helicobacter pylori infection, an established risk factor for *non-cardia stomach cancer*, is associated with a 41 to 43 per cent decreased risk of oesophageal adenocarcinoma [16, 17].

Other diseases

Risk of adenocarcinoma of the oesophagus is increased by gastro-oesophageal reflux disease, a common condition in which stomach acid damages the lining of the lower part of the oesophagus [13]. This type of oesophageal cancer is also increased by a rare condition, oesophageal achalasia (in which the valve at the end of the oesophagus called the 'cardia' fails to open and food gets stuck in the oesophagus) [13].

Family history

Tylosis A, a late-onset, inherited *familial* disease characterised by thickening of the skin of the palms and soles (hyperkeratosis), is associated with a 25 per cent lifetime incidence of oesophageal squamous cell carcinoma [18].

Confounding. Smoking tobacco is a potential *confounder*. People who smoke tend to have less healthy diets, less physically active ways of life and lower body weight than those who do not smoke. Therefore a central task in assessing the results of studies is to evaluate the degree to which observed associations in people who smoke may be due to residual confounding effects by smoking tobacco; that is, not a direct result of the *exposure* examined.

4.2.2.2 Lung

Definition. The lungs are part of the respiratory system and lie in the thoracic cavity. Air enters the lungs through the trachea, which divides into two main bronchi, each of which is subdivided into several bronchioles, which terminate in clusters of alveoli.

Classification. The two main types of lung cancer are small-cell lung cancer (SCLC) and non-small-cell lung cancer (NSCLC).

NSCLC accounts for 85 to 90 per cent of all cases of lung cancer and has three major subtypes: *squamous cell carcinoma*, *adenocarcinoma* and *large-cell carcinoma*. Adenocarcinoma and squamous cell carcinoma are the most frequent histologic subtypes, accounting for 50 per cent and 30 per cent of NSCLC cases, respectively [19].

SCLC accounts for 10 to 15 per cent of all lung cancers; this form is a distinct pathological entity characterised by aggressive biology, propensity for early *metastasis* and overall poor prognosis.

Other established causes. Other established causes of lung cancer include the following:

Smoking tobacco

Smoking tobacco is the main cause of lung cancer and increases the risk of all the main subtypes. However, *adenocarcinoma* is the

most common subtype among those who have never smoked. It is estimated that over 90 per cent of cases among men and over 80 per cent among women worldwide are attributable to smoking tobacco [20]. Passive smoking (inhalation of tobacco smoke from the surrounding air) is also a cause of lung cancer.

Previous lung disease

A history of emphysema, *chronic* bronchitis, tuberculosis or pneumonia is associated with an increased risk of lung cancer [21].

Other exposures

Occupational exposure to asbestos, crystalline silica, radon, mixtures of polycyclic aromatic hydrocarbons and some heavy metals is associated with an increased risk of lung cancer [22], as is exposure to indoor air pollution from wood and coal burning for cooking and heating [23].

Confounding. Smoking tobacco is the main cause of lung cancer. People who smoke also tend to have less healthy diets, less physically active ways of life and lower body weight than those who do not smoke. Therefore a central task in assessing the results of studies is to evaluate the degree to which observed associations in people who smoke may be due to residual *confounding* effects by smoking tobacco; that is, not a direct result of the exposure examined.

However, this evaluation may not completely mitigate the problem. Stratification by smoking status (for example, dividing the study population into people who smoke, those who used to smoke and those who have never smoked) can be useful, but typically the number of lung cancers in people who have never smoked is limited. Moreover, if an association is observed in people who currently smoke but not in people who have never smoked, residual confounding effects in the former group may be an explanation, but it is also plausible that the factor is only operative in ameliorating or enhancing the effects of tobacco smoke.

It is also important to differentiate residual confounding effects from a true effect limited to people who smoke. Because smoking tobacco is such a strong risk factor for lung cancer, residual confounding effects remain a likely explanation, especially when the estimated risks are of moderate magnitudes.

4.2.2.3 Liver

Definition. The liver is the largest internal organ in the body. It processes and stores nutrients and produces cholesterol and proteins such as albumin, clotting factors and the lipoproteins that carry cholesterol. It also secretes bile and performs many metabolic functions, including detoxification of several classes of *carcinogens*.

Classification. Most of the available data are on *hepatocellular carcinoma*, the best characterised and most common form of liver cancer. However, different outcomes are reported for unspecified primary liver cancer than for hepatocellular carcinoma and *cholangiocarcinoma,* so the different types of liver cancer may be a cause of heterogeneity among the study results.

Other established causes. Other established causes of liver cancer include the following:

Disease

Cirrhosis of the liver increases the risk of liver cancer [24].

Medication

Long-term use of oral contraceptives containing high doses of *oestrogen* and *progesterone* increases the risk of liver cancer [25].

Infection

Chronic infection with the hepatitis B or C virus is a cause of liver cancer [26].

Smoking tobacco

Smoking tobacco increases the risk of liver cancer generally, but there is a further increase in risk among people who smoke and have the hepatitis B or hepatitis C virus infection and also among people who smoke and consume large amounts of alcohol [27, 28]. It is estimated that 14 per cent of deaths worldwide from liver cancer are attributable to smoking tobacco [14].

Confounding. Smoking tobacco and hepatitis B and C viruses are possible *confounders* or *effect modifiers*.

The Panel is aware that alcohol is a cause of *cirrhosis*, which predisposes to liver cancer. Studies identified as focusing exclusively on patients with hepatic cirrhosis (including only patients with cirrhosis), hepatitis B or C viruses, alcoholism or history of alcohol abuse were not included in the CUP.

4.2.2.4 Colon and rectum

Definition. The *colon* (large intestine) is the lower part of the intestinal tract, which extends from the *caecum* (an intraperitoneal pouch) to the *rectum* (the final portion of the large intestine which connects to the anus).

Classification. Approximately 95 per cent of colorectal cancers are *adenocarcinomas*. Other types of colorectal cancers include *mucinous carcinomas* and *adenosquamous carcinomas*. *Carcinogens* can interact directly with the cells that line the colon and rectum.

Other established causes. Other established causes of colorectal cancer include the following:

Other diseases

Inflammatory bowel disease (Crohn's disease and ulcerative colitis) increases the risk of, and so may be seen as a cause of, colon cancer [29].

Smoking tobacco

There is an increased risk of colorectal cancer in people who smoke tobacco. It has been estimated that 12 per cent of cases of colorectal cancer are attributable to smoking cigarettes [30].

Family history

Based on twin studies, up to 45 per cent of colorectal cancer cases may involve a heritable component [31]. Between five and 10 per cent of colorectal cancers are consequences of recognised hereditary conditions [32]. The two major ones are *familial* adenomatous polyposis (FAP) and hereditary non-polyposis colorectal cancer (HNPCC, also known as Lynch syndrome). A further 20 per cent of cases occur in people who have a family history of colorectal cancer.

Confounding. Smoking tobacco is a possible *confounder*. In postmenopausal women, *menopausal hormone therapy* (MHT) use decreases the risk of colorectal cancer and is a potential confounder.

For more detailed information on adjustments made in CUP analyses on physical activity, see Evidence and judgements **(Section 5.1.1)**.

4.2.2.5 Breast

Definition. Breast tissue comprises mainly fat, glandular tissue (arranged in lobes), ducts and connective tissue. Breast tissue develops in response to *hormones* such as *oestrogens*, *progesterone*, insulin and growth factors. The main periods of development are during puberty, pregnancy and lactation. The glandular tissue atrophies after *menopause*.

Classification. Breast cancers are almost all *carcinomas* of the *epithelial* cells lining the breast ducts (the channels in the breast that carry milk to the nipple). Fifteen per cent of breast cancers are lobular carcinoma (from lobes); most of the rest are ductal carcinoma. Although breast cancer can occur in men, it is rare (less than one per cent of cases) and thus is not included in the CUP.

Breast cancers are classified by their receptor type; to what extent the cancer cells have receptors for the sex *hormones* oestrogen and progesterone and the growth factor human epidermal growth factor (hEGF), which can affect the growth of the breast cancer cells. Breast cancer cells that have oestrogen receptors are referred to as oestrogen receptor-positive (ER-positive or ER+), while those containing progesterone receptors are called progesterone receptor-positive (PR-positive or PR+) cancers, and those with receptors for hEGF are HER2 receptor-positive (HER2-positive or HER2+). Hormone-receptor-positive cancers are the most common subtypes of breast cancer but vary by population (60 to 90 per cent of cases). They have a relatively better prognosis than hormone-receptor-negative cancers, which are likely to be of higher pathological grade and can be more difficult to treat.

Most data come from *high-income countries*. Breast cancer is hormone related, and factors that modify risk may have different effects on cancers diagnosed in the pre and postmenopausal periods. Due to the importance of menopausal status as an *effect modifier*, studies should stratify for *menopause* status, but many do not.

Breast cancer is now recognised as a heterogeneous disease, with several subtypes according to hormone receptor status or molecular intrinsic markers. Although there is growing evidence that these subtypes have different causes, most studies have limited statistical power to evaluate effects by subtype.

There is growing evidence that the impact of *obesity* and dietary exposures on the risk of breast cancer may differ according to these particular molecular subtypes of cancer, but currently there is no information on how nutritional factors might interact with these characteristics.

Other established causes. Other established causes of breast cancer include the following:

Life events

Early *menarche* (before the age of 12), late natural *menopause* (after the age of 55), not bearing children and first pregnancy over the age of 30 all increase lifetime exposure to *oestrogen* and progesterone and the risk of breast cancer [33–35]. The reverse also applies: late menarche, early menopause, bearing children and pregnancy before the age of 30 all reduce the risk of breast cancer [33, 34].

Because nutritional factors such as obesity can influence these life course processes, their impacts on breast cancer risk may depend on the maturational stage at which the exposure occurs. For instance, obesity before the menopause is associated with reduced breast cancer risk, probably due to reduced ovarian progesterone production, while in post menopausal women, in whom ovarian oestrogen production is low, obesity increases breast cancer risk by increasing production of oestradiol through the action of aromatase in adipose tissue.

Radiation

Exposure to ionising radiation from medical treatment such as X-rays, particularly during puberty, increases the risk of breast cancer [36, 37].

Medication

MHT (containing oestrogen or progesterone) increases the risk of breast cancer [38]. Oral contraceptives containing both oestrogen and progesterone also cause a small increased risk of breast cancer in young women, among current and recent users only [39].

Family history

Some inherited mutations, particularly in BRCA1, BRCA2 and p53, result in a very high risk of breast cancer. However, germline mutations in these genes are infrequent and account for only two to five per cent of all cases of breast cancer [40].

Confounding. Use of MHT is an important possible *confounder* or *effect modifier* in postmenopausal breast cancer. High-quality studies adjust for age, number of reproductive cycles, age at which children were born and the use of hormone-based medications.

For more detailed information on adjustments made in CUP analyses, see Evidence and judgements, physical activity (**Section 5.1.2**) and vigorous physical activity (**Sections 5.2.1** and **5.2.2**).

4.2.2.6 Endometrium

Definition. The endometrium is the lining of the uterus (womb). It is subject to a process of cyclical change during the fertile years of a woman's life.

Classification. The majority of cancers that occur in the body of the uterus are endometrial cancers, mostly *adenocarcinomas* [41]. Because endometrial cancer is *hormone* related, factors that modify risk might have different effects at different times of life.

Other established causes. Other established causes of endometrial cancer include the following:

Life events

Not bearing children and late natural *menopause* (after the age of 55) both increase the risk of endometrial cancer [42]. The reverse also applies: bearing children and early menopause both reduce the risk of endometrial cancer [43–47].

Medication

Oral contraceptives, which contain either a combination of *oestrogen* and *progesterone*, or progesterone only, protect against endometrial cancer [46, 48]. Menopausal oestrogen hormone therapy unaccompanied by progesterone is a cause of this cancer. Menopausal oestrogen-only hormone therapy is normally prescribed only to women who have had a hysterectomy [46, 48]. Tamoxifen, a hormonal therapy used for breast cancer, can also increase the risk of endometrial cancer.

Family history

Women with a family history of endometrial or colorectal cancer have a higher risk of endometrial cancer [49]. Lifetime risk of endometrial cancer in women with Lynch syndrome mutations MLH1 or MSH2 is approximately 40 per cent, with a median age of 49. Women with MSH6 mutations have a similar risk of endometrial cancer but a later age of diagnosis [50].

Confounding. Including data on women who were at high risk of endometrial cancer who have had hysterectomies may have influenced the results. MHT is an effect modifier; in women who have never used MHT there is a stronger association between body mass index and endometrial cancer than in women who have ever used it [51].

For more detailed information on adjustments made in CUP analyses on physical activity see Evidence and judgements (**Section 5.1.3**).

5. Evidence and judgements

For information on study types, methods of assessment of exposures and methods of analysis used in the CUP, see Judging the evidence.

Full systematic literature reviews (SLRs) for each cancer are available online. For most cancer sites considered in the CUP,[1] there is also a CUP cancer report. CUP cancer reports summarise findings from the SLRs, again focusing on specific cancer sites. This section also presents findings from the SLRs, but from a different perspective: it brings together all of the key findings on physical activity and the risk of cancer.

Note that, throughout this section, if *Egger's test*, *non-linear analysis* or stratified analyses are not mentioned for a particular exposure and cancer, it can be assumed that no such analyses were conducted. This is often because there were too few studies with the required information.

5.1 Physical activity

Table 5.1 summarises the main findings from the CUP highest versus lowest meta-analyses of cohort studies on physical activity and the risk of cancer. Dose–response meta-analyses could not be conducted in the CUP for most types of physical activity as a variety of measures were used to collect the data. Physical activity types presented in this section include total physical activity, recreational physical activity and occupational physical activity.

Evidence for cancers of the following types was discussed in the CUP but was too limited to draw a conclusion[2]: mouth, pharynx and larynx (2018); stomach (2016); pancreas (2012); ovary (2014); prostate (2014); kidney (2015); bladder (2015); and skin (2017).

The strong evidence on the effects of physical activity on the risk of types of cancer is described in the following subsections. This strong evidence includes analyses performed in the CUP and/or other published analyses and information on mechanisms that could plausibly influence the risk of cancer.

For more information on the evidence for physical activity and the risk of cancer that was graded by the Panel as 'limited – suggestive' and suggests a direction of effect, see the following CUP documents:

- CUP oesophageal cancer report 2016: Section 7.6 and CUP oesophageal cancer SLR 2015: Section 6.1.1.2.
- CUP lung cancer report 2017: Section 7.13 and CUP lung cancer SLR 2015: Section 6.1.
- CUP liver cancer report 2015: Section 7.5 and CUP liver cancer SLR 2014: Section 6.1.
- CUP breast cancer report 2017: Section 7.6 and CUP breast cancer SLR 2017: Section 6.1.

Also, for information on mechanisms that could plausibly influence the risk of cancer, see **Appendix 2**.

Please note that the information on mechanisms included in the following subsections and in the appendix supersedes that in CUP cancer reports published before this Third Expert Report.

[1] Cancers at the following sites are reviewed in the CUP: mouth, pharynx and larynx; nasopharynx; oesophagus; lung; stomach; pancreas; gallbladder; liver; colorectum; breast; ovary; endometrium; cervix; prostate; kidney; bladder; and skin. CUP cancer reports not are currently available for nasopharynx, cervix and skin.

[2] **'Limited – no conclusion'**: There is enough evidence to warrant Panel consideration, but it is so limited that no conclusion can be made. The evidence may be limited in amount, by inconsistency in the direction of effect, by methodological flaws, or by any combination of these.

Table 5.1: Summary of CUP highest versus lowest meta-analyses of physical activity[1] and the risk of cancer

Cancer	Type of physical activity	Total no. of studies	No. of studies in meta-analysis	No. of cases	Risk estimate (95% CI)	Conclusion[2]	Date of CUP cancer report[3]
Colorectum (colon)[4]	Total	13	12	8,396	0.80 (0.72–0.88)	**Convincing: Decreases risk**	2017
	Recreational	21	20	10,258	0.84 (0.78–0.91)		
Breast (postmenopause)[5]	Total	9	8	11,798	0.87 (0.79–0.96)	**Probable: Decreases risk**	2017
	Recreational[6] (dose–response)	22	5	18,486	0.98 (0.97–0.99)		
	Recreational	22	17	> 24,253	0.87 (0.81–0.94)		
	Occupational	9	8	22,352	0.89 (0.83–0.96)		
Endometrium	Recreational	9	9	3,600	0.73 (0.58–0.93)	**Probable: Decreases risk**	2013
	Occupational	5	5	5,826	0.79 (0.71–0.88)		
Oesophagus[7]	Recreational	5	4	1,366	0.85 (0.72–1.01)	**Limited – suggestive: Decreases risk**	2016
Lung	Total	5	5	1,457	0.90 (0.77–1.04)	**Limited – suggestive: Decreases risk**	2017
Liver[8]	Different types of physical activity	3	–	–	Significant decreased risk in two studies	**Limited – suggestive: Decreases risk**	2015
Breast (premenopause)[5]	Total	4	4	1,837	0.93 (0.79–1.08)	**Limited – suggestive: Decreases risk**	2017
	Recreational[6] (dose–response)	12	3	2,331	0.96 (0.90–1.03)		
	Recreational	12	10	> 3,901	0.93 (0.74–1.16)		
	Occupational	6	6	4,494	0.82 (0.59–1.15)		

1 The exposure of physical activity includes evidence for all types of activity and all intensity levels.

2 See Definitions of WCRF/AICR grading criteria (**Section 1**: Physical activity and the risk of cancer: a summary matrix) for explanations of what the Panel means by 'convincing', 'probable', and 'limited – suggestive'.

3 Throughout this Third Expert Report, the year given for each cancer site is the year the CUP cancer report was published, apart from for nasopharynx, cervix and skin, where the year given is the year the SLR was last reviewed. Updated CUP cancer reports for nasopharynx and skin will be published in the future.

4 The evidence for physical activity and colorectum is for colon cancer only – no conclusion was drawn for rectal cancer.

5 In addition to physical activity, there was sufficient evidence for the Panel to make a separate judgement for vigorous-intensity physical activity and breast cancer (pre and postmenopause). For more information see **Section 5.2**.

6 Dose–response meta-analyses (per 10 metabolic equivalent [MET]-hours/week) were conducted for recreational physical activity and breast cancer (pre and postmenopause). Heterogeneity (I^2) was 69% and 0%, respectively.

7 The evidence for physical activity and oesophageal cancer includes unspecified, adenocarcinoma and squamous cell carcinoma.

8 A dose–response or highest versus lowest meta-analysis of cohort studies could not be conducted in the CUP for physical activity and the risk of liver cancer as the studies reported on different types of physical activity. Three studies were identified [52–54]. Two of the three studies reported a statistically significant decreased risk when comparing the highest with the lowest level of recreational physical activity (Relative risk [RR] 0.88 [0.81–0.95]; n = 169 diagnoses [53]) or walking (RR 0.70 [0.54–0.91] for men and RR 0.54 [0.37–0.78] for women; n = 377 deaths and 143 deaths, respectively [54]).

5.1.1 Colorectum (colon)

(Also see CUP colorectal cancer report 2017: Section 7.13 and CUP colorectal cancer SLR 2016: Sections 6.1 and 6.1.1.2.)

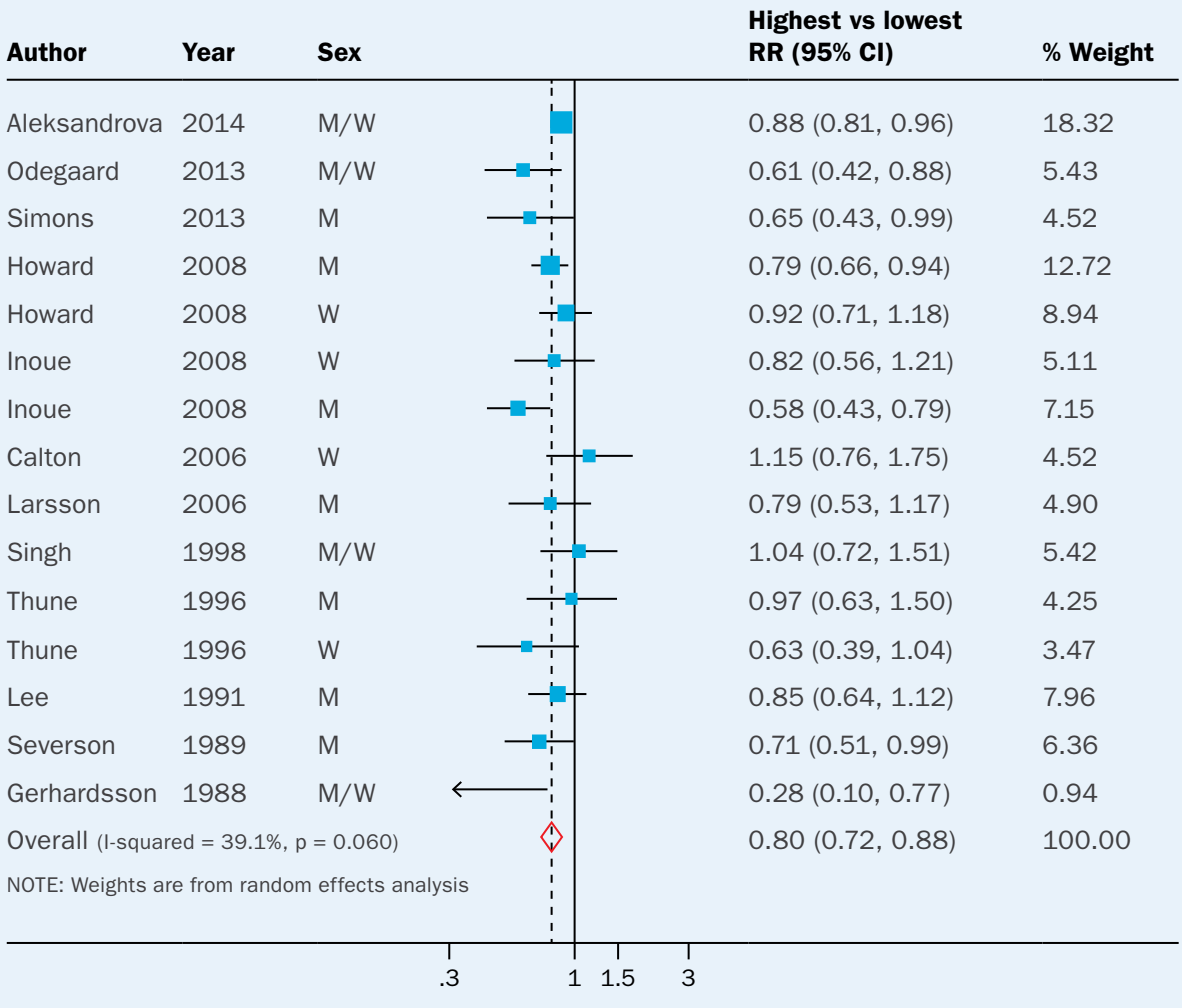
The evidence for total and recreational physical activity is presented in the following subsections. For information on walking, see CUP colorectal cancer SLR 2016, Section 6.1.1.2.

5.1.1.1 Total physical activity

5.1.1.1.1 CUP highest versus lowest meta-analysis

Twelve of 13 identified studies were included in the highest versus lowest meta-analysis, which showed a statistically significant decreased risk of colon cancer for the highest compared with the lowest level of total physical activity (RR 0.80 [95% CI 0.72–0.88]; n = 8,396 cases) (see **Figure 5.1**).

Figure 5.1: CUP highest versus lowest meta-analysis[1] for total physical activity and the risk of colon cancer



Source: Aleksandrova, 2014 [55]; Odegaard, 2013 [56]; Simons, 2013 [57]; Howard, 2008 [58]; Inoue, 2008 [52]; Calton, 2006 [59]; Larsson, 2006 [60]; Singh, 1998 [61]; Thune, 1996 [62]; Lee, 1991 [63]; Severson, 1989 [64]; Gerhardsson, 1988 [65].

[1] A total of 12 studies were analysed in the CUP highest versus lowest meta-analysis. In some studies, the relative risk for men and women was reported separately.

All studies included in the highest versus lowest meta-analysis adjusted for age and sex, or conducted analyses for men and women separately, most adjusted for *body mass index* (BMI) and many adjusted for tobacco smoking, diet, alcohol and family history of colorectal cancer cancers. Two studies accounted for age and sex only [63, 65]. For information on the adjustments made in individual studies, see CUP colorectal cancer SLR 2016, Table 299.

5.1.1.1.2 Published pooled analyses and meta-analyses

No published pooled analyses and no other published meta-analyses on total physical activity and the risk of colon cancer were identified.

5.1.1.2 Recreational physical activity

5.1.1.2.1 CUP highest versus lowest meta-analysis

Twenty of 21 identified studies were included in the highest versus lowest meta-analysis, which showed a statistically significant decreased risk of colon cancer for the highest compared with the lowest level of recreational physical activity (RR 0.84 [95% CI 0.78–0.91]; n = 10,258 cases) (see **Figure 5.2**).

All studies included in the highest versus lowest meta-analysis adjusted for age and sex, or conducted analyses for men and women separately, and many adjusted for BMI, tobacco smoking and alcohol. Four studies accounted for age and sex only [65, 71, 77, 80]. For information on the adjustments made in individual studies, see CUP colorectal cancer SLR 2016, Table 307.

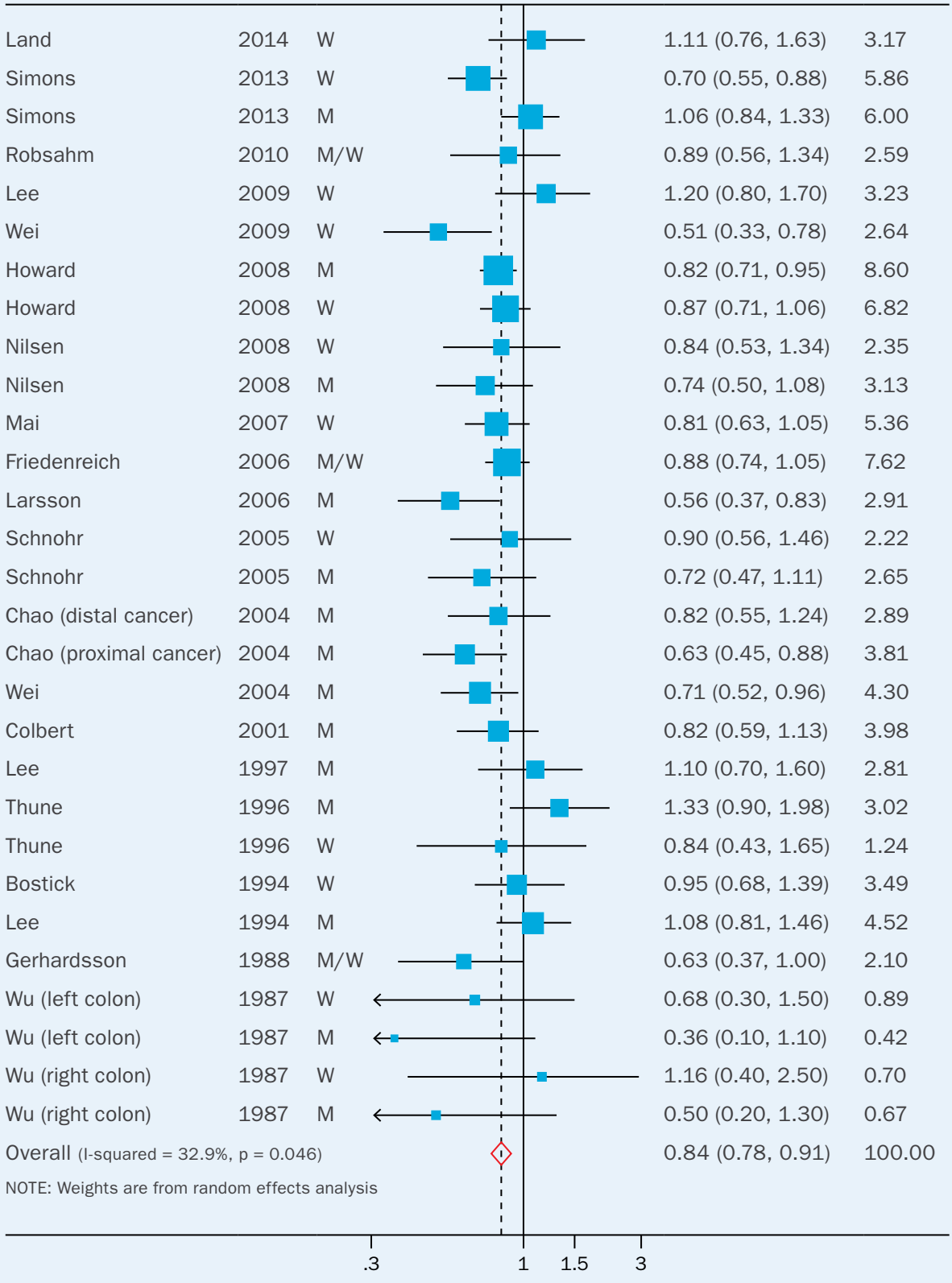
5.1.1.2.2 Published pooled analyses and meta-analyses

No published pooled analyses were identified. Three other published meta-analyses on recreational physical activity and the risk of colon cancer have been identified, which mainly reported a statistically significant decreased risk for the highest compared with the lowest level of recreational physical activity [81–83]. One meta-analysis of cohort and case-control studies reported a significant decreased risk in men and women combined (proximal colon cancer RR 0.73 [95% CI 0.66–0.81] and distal colon cancer RR 0.74 [95% 0.68–0.80]) [81]. The other two meta-analyses of cohort studies both reported a significant decreased risk for men (RR 0.74 [95% CI 0.61–0.90] [82] and RR 0.80 [95% CI 0.67–0.96]) [83], but only one analysis reported a significant decreased risk for women (RR 0.86 [95% CI 0.76–0.98]) [83].

5.1.1.3 Mechanisms

The information on mechanisms is based on both human and animal studies, with a preference for human studies whenever possible. This section covers the primary hypotheses that are currently prevailing and is not based on a systematic or exhaustive search of the literature.

Figure 5.2: CUP highest versus lowest meta-analysis[1] for recreational physical activity and the risk of colon cancer



Source: Land, 2014 [66]; Simons, 2013 [57]; Robsahm, 2010 [67]; Lee, 2009 [68]; Wei, 2009 [69]; Howard, 2008 [58]; Nilsen, 2008 [70]; Mai, 2007 [71]; Friedenreich, 2006 [72]; Larsson, 2006 [60]; Schnohr, 2005 [73]; Chao, 2004 [74]; Wei, 2004 [75]; Colbert, 2001 [76]; Lee, 1997 [77]; Thune, 1996 [62]; Bostick, 1994 [78]; Lee, 1994 [79]; Gerhardsson, 1988 [65]; Wu, 1987 [80].

[1] A total of 20 studies were analysed in the CUP highest versus lowest meta-analysis. In some studies, the relative risk for men and women and/or the anatomical location of the cancer was reported separately.

For further information on general processes involved in the development of cancer, see The cancer process.

Physical activity reduces body fatness and therefore has a beneficial effect on colorectal cancer risk, possibly through a reduction in *insulin resistance* and *inflammation* – both of which have been linked to colorectal cancer development [84–86]. However, it is unclear whether physical activity that is not accompanied by weight loss or maintenance of a healthy weight has a significant impact on these pathways. Other mechanisms by which physical activity may lower colorectal cancer risk include stimulating digestion and reducing transit time through the intestine [87], though robust data to support this mechanism in humans are limited. Overall, mechanistic data to support a link between physical activity and colorectal cancer are moderate in strength.

5.1.1.4 CUP Panel's conclusion

The evidence was strong and consistent and showed a significant decreased risk of colon cancer for the highest compared with the lowest level of total and recreational physical activity. For recreational physical activity, three other published meta-analyses mainly reported a significant decreased risk. There is robust evidence for mechanisms operating in humans. However, dose–response relationships could not be determined.

The CUP Panel concluded:

- **Being physically active convincingly protects against colon cancer.**

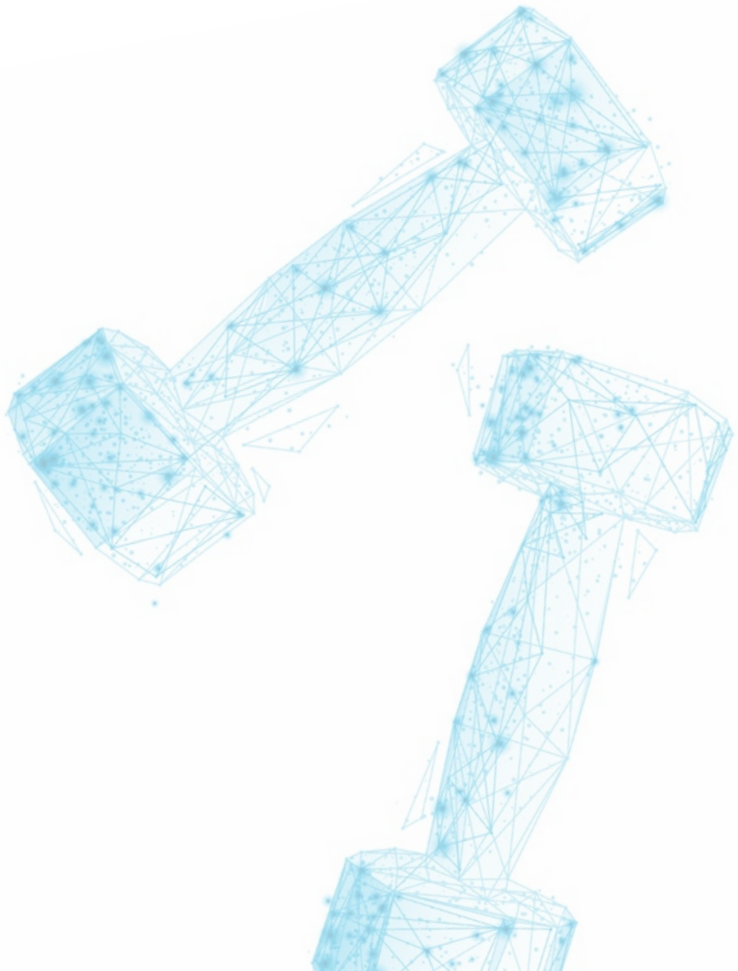
5.1.2 Breast (postmenopause)

(Also see CUP breast cancer report 2017: Section 7.6 and CUP breast cancer SLR 2017: Sections 6.1, 6.1.1.1 and 6.1.1.2.)

The evidence for total, recreational and occupational physical activity is presented in the following subsections. For evidence specifically on vigorous-intensity physical activity and postmenopausal breast cancer, see **Section 5.2.2**. For information on walking and household activity, see CUP breast cancer SLR 2017, Sections 6.1.1.2 and 6.1.1.3, respectively.

In addition to a highest versus lowest meta-analysis for recreational physical activity, a dose–response meta-analysis was also conducted as a sufficient number of studies reported in comparable measurement units.

Few studies evaluated associations by *hormone receptor subtype*, so it was not possible to conduct stratified analyses by breast cancer subtype.



5.1.2.1 Total physical activity

5.1.2.1.1 CUP highest versus lowest meta-analysis

Eight of nine identified studies were included in the highest versus lowest meta-analysis, which showed a statistically significant decreased risk of postmenopausal breast cancer for the highest compared with the lowest level of total physical activity (RR 0.87 [95% CI 0.79–0.96]; n = 11,798 cases) (see **Figure 5.3**).

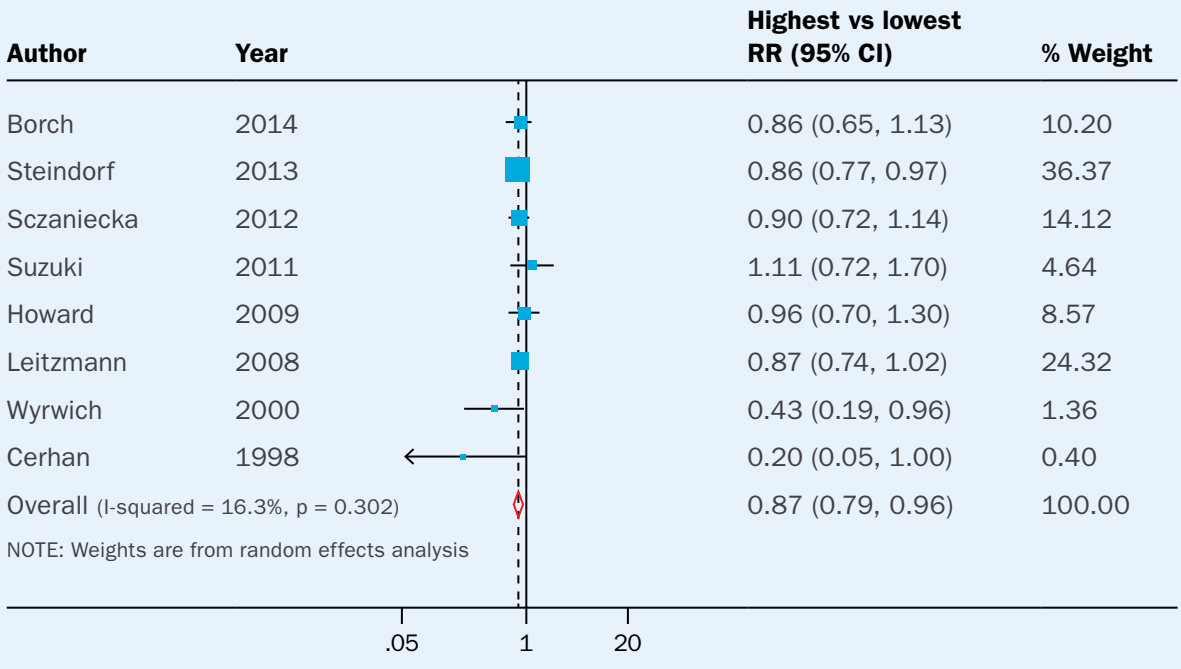
One published study that contributed 36 per cent weight in the highest versus lowest meta-analysis for total physical activity and the risk of postmenopausal breast cancer reported results by BMI category [89]. A statistically significant decreased risk was observed for active women compared with inactive women among those who had a healthy weight (RR 0.79 [95% CI 0.67–0.91]), but not for women who were overweight or obese [89]. No significant association was reported in the two studies that examined joint *hormone receptor subtypes* [88, 91].

Most studies included in the highest versus lowest meta-analysis adjusted for age, BMI, alcohol intake, reproductive factors and *menopausal hormone therapy (MHT)*. One study adjusted for age only [90]. For information on the adjustments made in individual studies, see CUP breast cancer SLR 2017, Table 441.

5.1.2.1.2 Published pooled analyses and meta-analyses

No published pooled analyses were identified. One other published meta-analysis on total physical activity and the risk of postmenopausal breast cancer was identified; it showed a statistically significant decreased risk for the highest compared with the lowest level of activity (RR 0.87 [95% CI 0.87–0.92]) [96].

Figure 5.3: CUP highest versus lowest meta-analysis for total physical activity and the risk of postmenopausal breast cancer



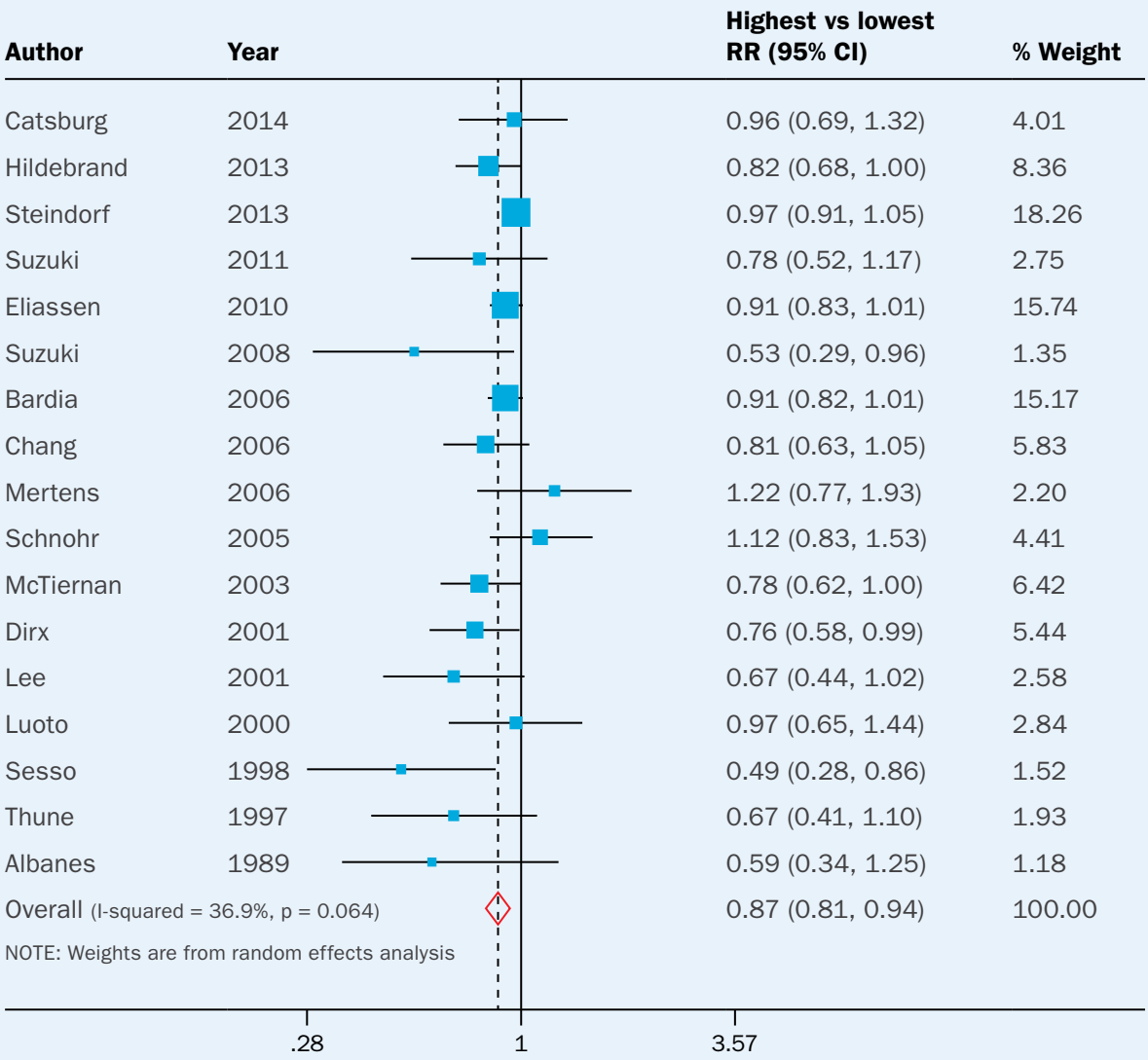
Source: Borch, 2014 [88]; Steindorf, 2013 [89]; Sczaniecka, 2012 [90]; Suzuki, 2011 [91]; Howard, 2009 [92]; Leitzmann, 2008 [93]; Wyrwich, 2000 [94]; Cerhan, 1998 [95].

5.1.2.2 Recreational physical activity

5.1.2.2.1 CUP highest versus lowest meta-analysis

Seventeen of 22 identified studies were included in the highest versus lowest meta analysis, which showed a statistically significant decreased risk of postmenopausal breast cancer for the highest compared with the lowest level of recreational physical activity (RR 0.87 [95% CI 0.81–0.94]; n > 24,253 cases) (see **Figure 5.4**).

Figure 5.4: CUP highest versus lowest meta-analysis for recreational physical activity and the risk of postmenopausal breast cancer



Source: Catsburg, 2014 [97]; Hildebrand, 2013 [98]; Steindorf, 2013 [89]; Suzuki, 2011 [91]; Eliassen, 2010 [99]; Suzuki, 2008 [100]; Bardia, 2006 [101]; Chang, 2006 [102]; Mertens, 2006 [103]; Schnohr, 2005 [73]; McTiernan, 2003 [104]; Dirx, 2001 [105]; Lee, 2001 [106]; Luoto, 2000 [107]; Sesso, 1998 [108]; Thune, 1997 [109]; Albanes, 1989 [110].

Many studies included in the highest versus lowest meta-analysis adjusted for age, BMI, alcohol intake, reproductive factors and MHT. For information on the adjustments made in individual studies, see CUP breast cancer SLR 2017, Table 469.

5.1.2.2.2 CUP dose–response meta-analysis

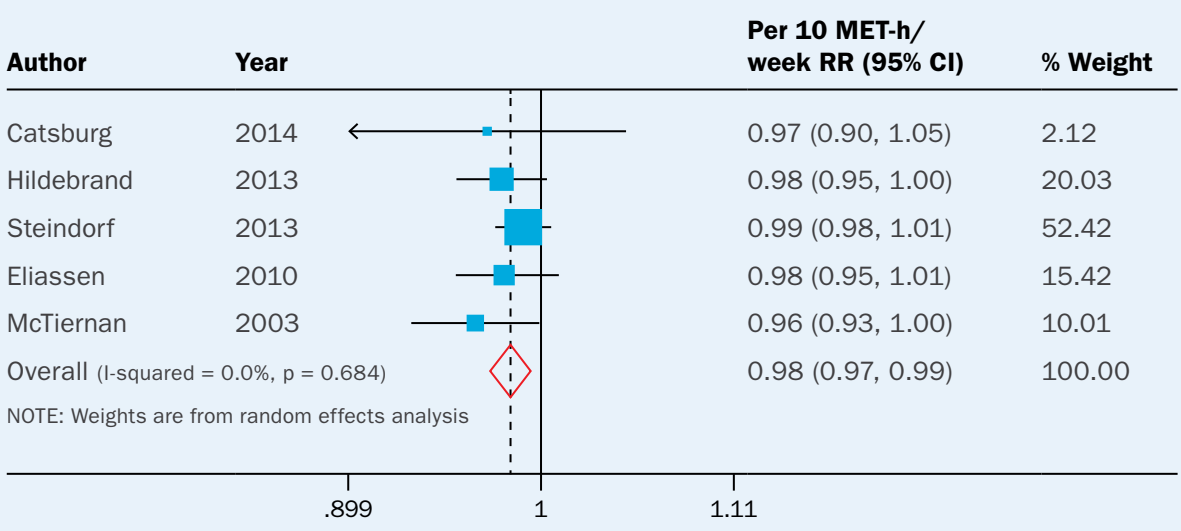
Five of 22 identified studies were included in the dose–response meta-analysis, which showed a statistically significant two per cent decreased risk of postmenopausal breast cancer per 10 MET-hours increase in recreational physical activity per week (RR 0.98 [95% CI 0.97–0.99]; n = 18,486 cases) (see **Figure 5.5**). No *heterogeneity* was observed and there was no evidence of small study bias with *Egger's test* (p = 0.12).

One published study that contributed 18 per cent weight in the highest versus lowest meta-analysis and 52 per cent weight in the dose–response meta-analysis for recreational physical activity and the risk of postmenopausal breast cancer reported results by BMI category [89]. No statistically significant association was observed in women who had a healthy weight, who were overweight or who were obese [89].

There was evidence of a non-linear dose–response relationship (p = 0.05; see **Figure 5.6**). The decreased risk was more pronounced after 25 MET-hours per week.

All studies included in the dose–response meta-analysis adjusted for age, BMI, alcohol intake, reproductive factors and MHT. For information on the adjustments made in individual studies see CUP breast cancer SLR 2017, Table 469.

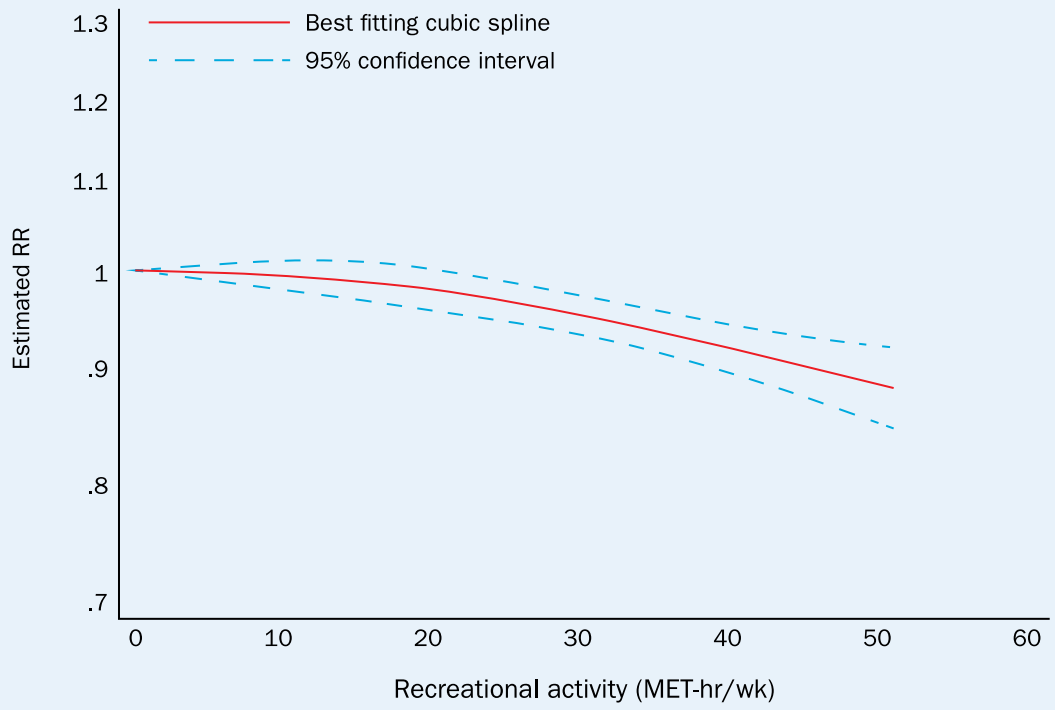
Figure 5.5: CUP dose–response meta-analysis[1] for the risk of postmenopausal breast cancer, per 10 MET-hours increase in recreational physical activity per week



Source: Catsburg, 2014 [97]; Hildebrand, 2013 [98]; Steindorf, 2013 [89]; Eliassen, 2010 [99]; McTiernan, 2003 [104].

[1] Seventeen studies could not be included in the dose–response meta-analysis, mainly because results were not reported in MET-hours. For further details, see CUP breast cancer SLR 2017, Tables 469 and 470.

Figure 5.6: CUP non-linear dose–response association of recreational physical activity and the risk of postmenopausal breast cancer



5.1.2.2.3 Published pooled analyses and meta-analyses

No published pooled analyses and no other published meta-analyses on recreational physical activity and the risk of postmenopausal breast cancer were identified.

5.1.2.3 Occupational physical activity

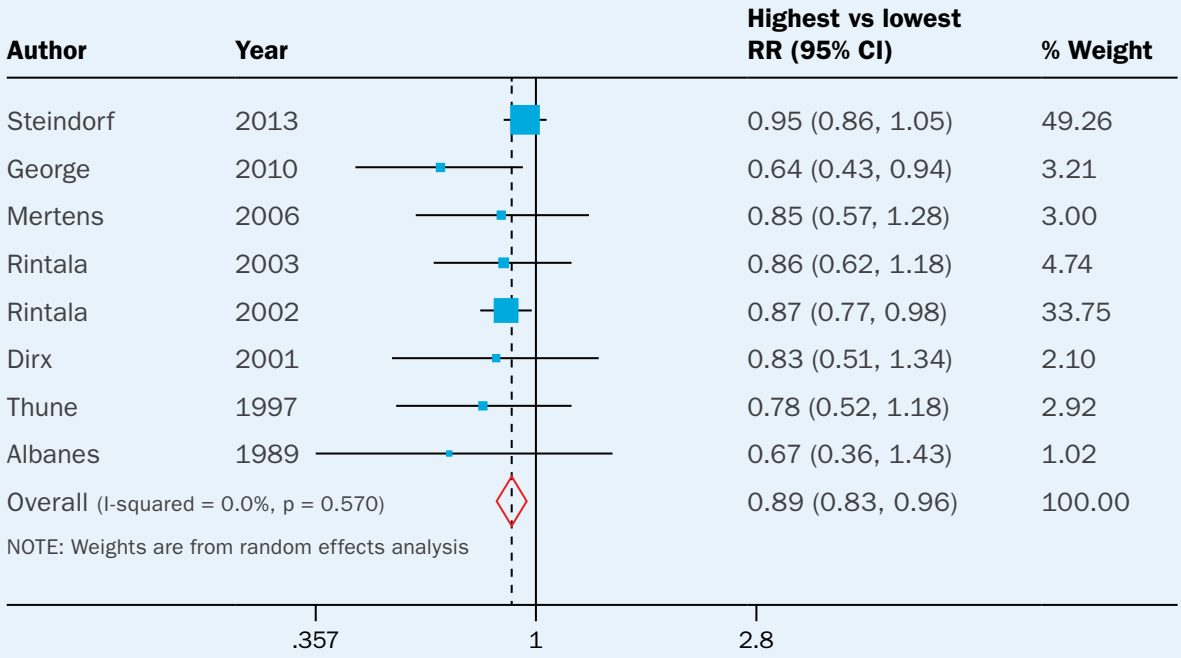
5.1.2.3.1 CUP highest versus lowest meta-analysis

Eight of nine identified studies were included in the highest versus lowest meta-analysis, which showed a statistically significant decreased risk of postmenopausal breast cancer for the highest compared with the lowest level of occupational physical activity (RR 0.89 [95% CI 0.83–0.96]; n = 22,352 cases) (see **Figure 5.7**).

One published study that contributed 49 per cent weight in the highest versus lowest meta-analysis for occupational physical activity and the risk of postmenopausal breast cancer reported results by BMI category [89]. No statistically significant association was observed in women who had a healthy weight, who were overweight or who were obese [89].

Most studies included in the highest versus lowest meta-analysis adjusted for age and reproductive factors, some studies adjusted for BMI, alcohol intake and MHT. For information on the adjustments made in individual studies, see CUP breast cancer SLR 2017, Table 455.

Figure 5.7: CUP highest versus lowest meta-analysis for occupational physical activity and the risk of postmenopausal breast cancer



Source: Steindorf, 2013 [89]; George, 2010 [111]; Mertens, 2006 [103]; Rintala, 2003 [112]; Rintala, 2002 [113]; Dirx, 2001 [105]; Thune, 1997 [109]; Albanes, 1989 [110].

5.1.2.3.2 Published pooled analyses and meta-analyses

No published pooled analyses and no other published meta-analyses on occupational physical activity and the risk of postmenopausal breast cancer were identified.

5.1.2.4 Mechanisms

The information on mechanisms is based on both human and animal studies, with a preference for human studies whenever possible. This section covers the primary hypotheses that currently prevail and is not based on a systematic or exhaustive search of the literature.

For further information on general processes involved in the development of cancer, see The cancer process.

Physical activity affects a diverse array of metabolic, hormonal and immunologic pathways. Regular physical activity reduces body fatness and therefore has a beneficial effect on breast cancer risk, possibly through reductions in circulating *oestrogen* levels, *insulin resistance* and *inflammation* – all of which have been linked to postmenopausal breast cancer development. However, it is unclear whether physical activity that is not accompanied by weight loss has a significant impact on these pathways.

Physical activity improves *insulin* sensitivity and reduces fasting insulin levels, which are linked to higher breast cancer risk in humans [114, 115]. Exercise may also affect breast cancer risk through its effects on *insulin-like growth factors* (IGFs) [116], because high levels of circulating IGF-I are associated with increased risk of several cancers, including breast cancer [117]. In

addition, physical activity has been shown to have immunomodulatory effects in humans, improving innate and acquired *immune response*, and promoting tumour surveillance [115, 118]. Studies have also shown that *aerobic exercise* can decrease oxidative stress and enhance DNA repair mechanisms in humans and would therefore be expected to suppress *carcinogenesis* [118]. Physically active individuals also tend to have higher sunlight exposure and consequently higher levels of vitamin D, which may modify cell proliferation [119].

5.1.2.5 CUP Panel's conclusion

The evidence was generally consistent and the meta-analysis of eight studies showed a statistically significant decreased risk of postmenopausal breast cancer for the highest compared with the lowest level of total physical activity. A significant decreased risk was also observed for occupational physical activity and recreational physical activity. A non-linear dose–response relationship was detected for recreational physical activity, where a larger decrease in risk was observed for physical activity levels of > 20 MET-hours per week. In addition, in support of the CUP finding, one published meta-analysis also reported a significant decreased risk of postmenopausal breast cancer for the highest compared with the lowest level of total physical activity. There is robust evidence for mechanisms operating in humans.

The CUP Panel concluded:

- **Being physically active probably protects against postmenopausal breast cancer.**

5.1.3 Endometrium

(Also see CUP endometrial cancer report 2013: Section 7.3 and CUP endometrial cancer SLR 2012: Sections 6.1.1.1, 6.1.1.2 and 6.1.1.4).

The evidence for recreational and occupational physical activity is presented in the following subsections. For information on walking or biking (mainly for transportation), exercise or sport, and vigorous-intensity physical activity, see CUP endometrial cancer SLR 2012, Sections 6.1.1.4, 6.1.1.5 and 6.1.3, respectively.

5.1.3.1 Recreational physical activity

5.1.3.1.1 CUP highest versus lowest meta-analysis

All nine identified studies were included in the highest versus lowest meta-analysis, which showed a statistically significant decreased risk of endometrial cancer for the highest compared with the lowest level of recreational

physical activity (RR 0.73 [95% CI 0.58–0.93]; n = 3,600 cases) (see **Figure 5.8**).

In analyses restricted to studies that adjusted for BMI, there was a statistically significant decreased risk of endometrial cancer for the highest compared with the lowest level of recreational physical activity (RR 0.80 [95% CI: 0.69–0.92]).

Most studies included in the highest versus lowest meta-analysis adjusted for age and reproductive factors, and some studies adjusted for BMI and tobacco smoking.

5.1.3.1.2 Published pooled analyses and meta-analyses

No published pooled analyses were identified. One other published meta-analysis on recreational physical activity and the risk of endometrial cancer has been identified [129]. The meta-analysis included the same studies that were in the CUP and therefore the results were the same.

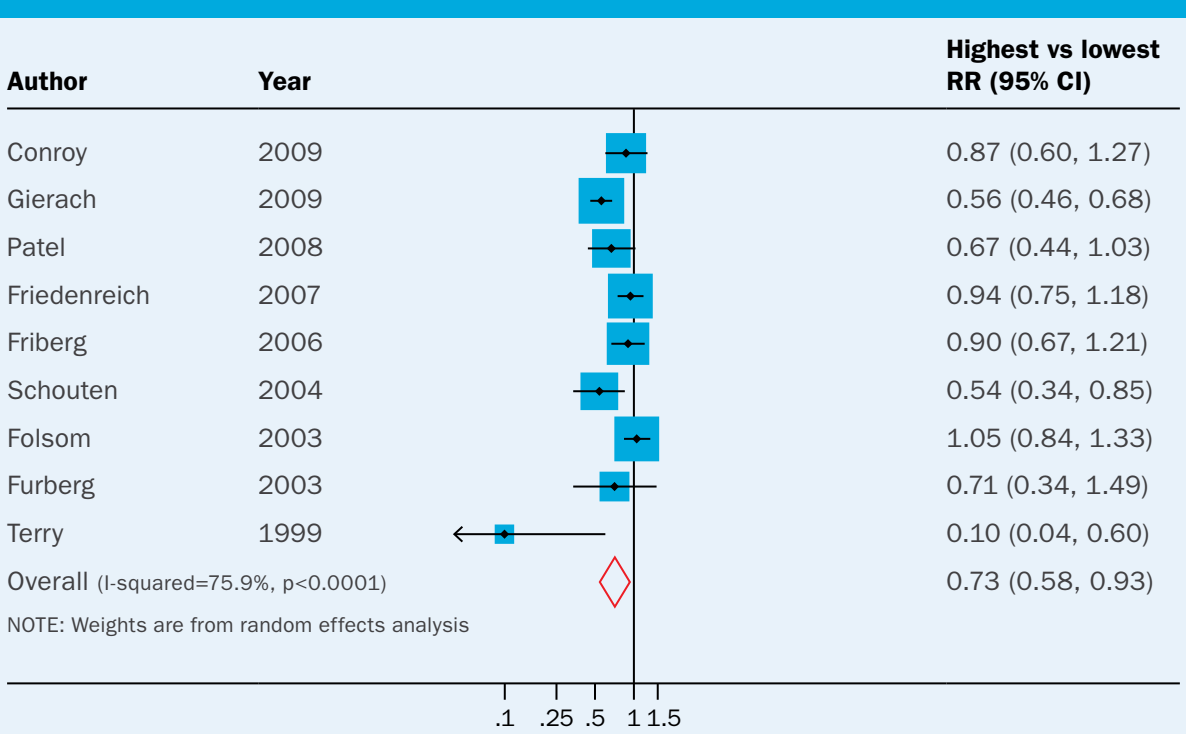
5.1.3.2 Occupational physical activity

5.1.3.2.1 CUP highest versus lowest meta-analysis

All five identified studies were included in the highest versus lowest meta-analysis, which showed a statistically significant decreased risk of endometrial cancer for the highest compared with the lowest level of occupational physical activity (RR 0.79 [95% CI 0.71–0.88]; n = 5,826 cases) (see **Figure 5.9**).

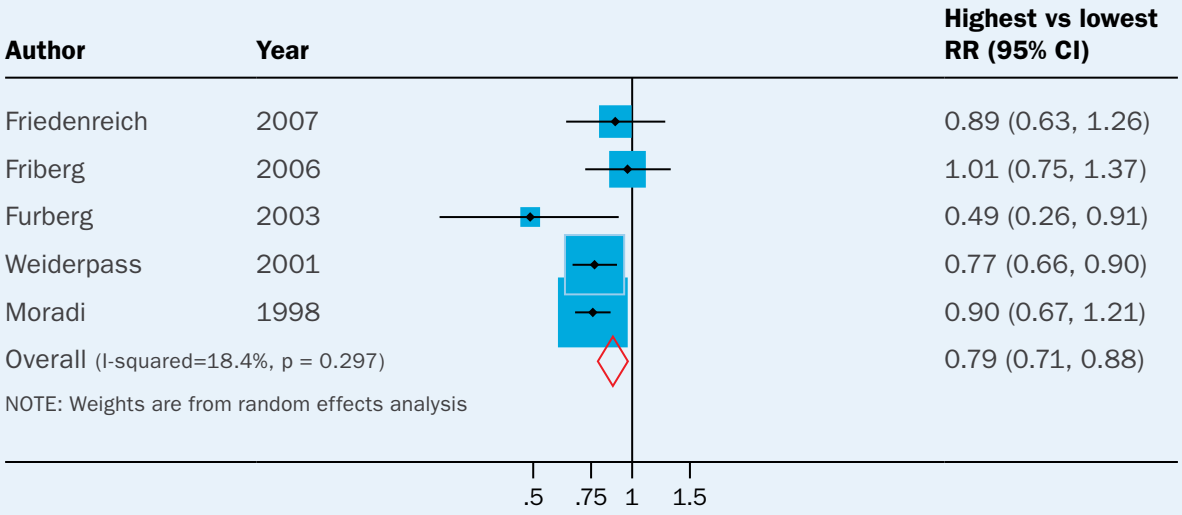
Three of five identified studies controlled for BMI [123, 124, 127]. No statistically significant association with BMI was observed in two of the studies [123, 124], but the risk of endometrial cancer was significantly decreased for the highest compared with the lowest level of occupational physical activity in obese women in the third (RR 0.22 [95% CI 0.08–0.66]) [127].

Figure 5.8: CUP highest versus lowest meta-analysis for recreational physical activity and the risk of endometrial cancer



Source: Conroy, 2009 [120]; Gierach, 2009 [121]; Patel, 2008 [122]; Friedenreich, 2007 [123]; Friberg, 2006 [124]; Schouten, 2004 [125]; Folsom, 2003 [126]; Furberg, 2003 [127]; Terry, 1999 [128].

Figure 5.9: CUP highest versus lowest meta-analysis for occupational physical activity and the risk of endometrial cancer



Source: Friedenreich, 2007 [123]; Friberg, 2006 [124]; Furberg, 2003 [127]; Weiderpass, 2001 [130]; Moradi, 1998 [131].

Most studies included in the highest versus lowest meta-analysis adjusted for age and reproductive factors, and some studies adjusted for BMI and tobacco smoking.

5.1.3.2.2 Published pooled analyses and meta-analyses

No published pooled analyses and no other published meta-analyses on occupational physical activity and the risk of endometrial cancer were identified.

5.1.3.3 Mechanisms

The information on mechanisms is based on both human and animal studies, with a preference for human studies whenever possible. This section covers the primary hypotheses that currently prevail and is not based on a systematic or exhaustive search of the literature.

For further information on general processes involved in the development of cancer, see The cancer process.

Physical activity reduces body fatness and therefore has a beneficial effect on endometrial cancer risk, possibly through reductions in circulating *oestrogen* levels, *insulin resistance* and *inflammation* – all of which have been linked to endometrial cancer development. Physical activity has been shown to decrease oestradiol levels [132], improve insulin sensitivity [133], and reduce chronic inflammation [115, 134] – all pathways which have been linked to endometrial cancer development [135–139].

5.1.3.4 CUP Panel's conclusion

The evidence was generally consistent and showed a significant decreased risk of endometrial cancer for the highest compared with the lowest level of recreational and occupational physical activity. For recreational physical activity, one other published meta-analysis reported significant decreased risk. There is robust evidence of mechanisms operating in humans. However, dose–response relationships could not be determined.

The CUP Panel concluded:

- **Being physically active probably protects against endometrial cancer.**

5.2 Vigorous-intensity physical activity

Table 5.2 summarises the main findings from the CUP highest versus lowest and dose–response meta-analyses of cohort studies on vigorous-intensity physical activity and the risk of cancer.

Evidence for cancers of the following types was discussed in the CUP but was too limited to draw a conclusion[1]: oesophagus (2015), stomach (2015) and endometrium (2012).

Table 5.2: Summary of CUP highest versus lowest and dose–response meta-analyses of vigorous-intensity physical activity[1] and the risk of cancer

Cancer	Analysis type	Total no. of studies	No. of studies in meta-analysis	No. of cases	Risk estimate (95% CI)	Increment	I^2 (%)	Conclusion[2]	Date of CUP cancer report[3]
Breast (premenopause)[4]	Highest vs. lowest	6	6	4,452	0.83 (0.73–0.95)	–	–	**Probable: Decreases risk**	2017
	Dose–response		3	1,473	0.91 (0.83–1.01)	30 mins/day	0		
Breast (postmenopause)[4]	Highest vs. lowest	12	11	20,171	0.90 (0.85–0.95)	–	–	**Probable: Decreases risk**	2017
	Dose–response		3	3,293	0.94 (0.86–1.02)	30 mins/day	0		

1 The exposure of vigorous-intensity physical activity includes evidence for all types of activity performed at a vigorous level of intensity.

2 See Definitions of WCRF/AICR grading criteria (**Section 1**: Physical activity and the risk of cancer: a summary matrix) for explanations of what the Panel means by 'probable'.

3 Throughout this Third Expert Report, the year given for each cancer site is the year the CUP cancer report was published, apart from for nasopharynx, cervix and skin, where the year given is the year the SLR was last reviewed. Updated CUP cancer reports for nasopharynx and skin will be published in the future.

4 In addition to vigorous-intensity physical activity, the Panel made a separate judgement for physical activity and breast cancer (pre and postmenopause). For more information, see **Section 5.1**.

The strong evidence on the effects of vigorous-intensity physical activity on the risk of types of cancer is described in the following subsections. This strong evidence includes analyses performed in the CUP and/or other published analyses, and information on mechanisms that could plausibly influence the risk of cancer.

Please note that the information on mechanisms included in the following subsections and in the appendix (see **Appendix 2**) supersedes that in CUP cancer reports published before this Third Expert Report.

5.2.1 Breast premenopause

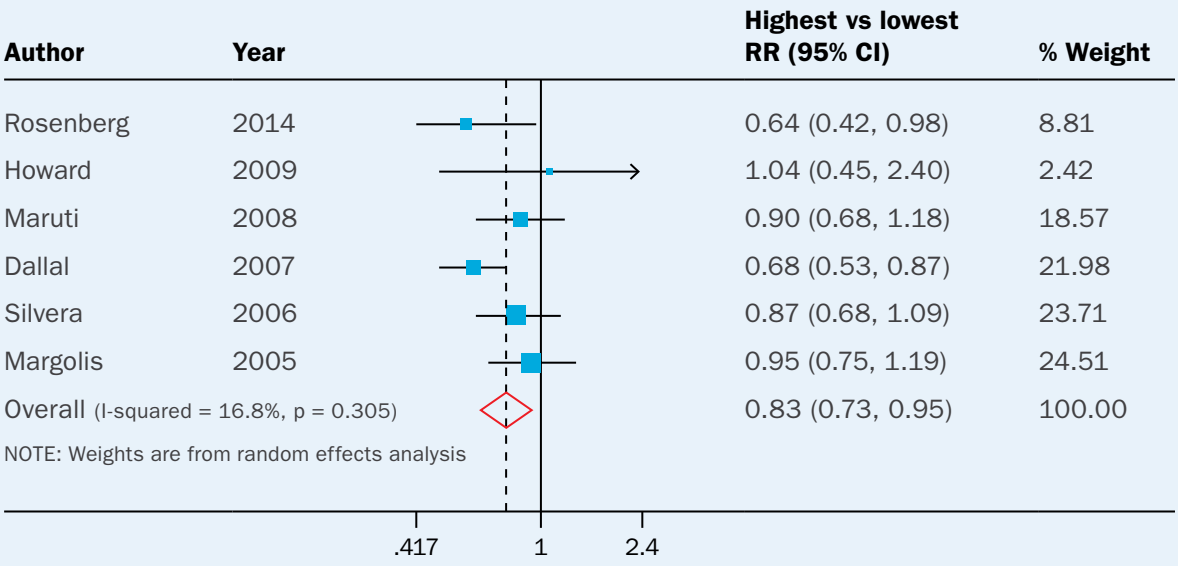
(Also see CUP breast cancer report 2017: Section 7.7 and CUP breast cancer SLR 2017: Sections 6.1.3).

The evidence specifically for vigorous-intensity physical activity is presented in the following section. For information on total, recreational and occupational physical activity as well as walking and household activity, see CUP breast cancer SLR 2017, Section 6.1 and subsections.

5.2.1.1 CUP highest versus lowest meta-analysis

All six identified studies were included in the highest versus lowest meta-analysis, which showed a statistically significant decreased risk of premenopausal breast cancer for the highest compared with the lowest level of vigorous-intensity physical activity (RR 0.83 [95% CI 0.73–0.95]; n = 4,452 cases) (see **Figure 5.10**).

Figure 5.10: CUP highest versus lowest meta-analysis for vigorous-intensity physical activity and the risk of premenopausal breast cancer



Source: Rosenberg, 2014 [140]; Howard, 2009 [92]; Maruti, 2008 [141]; Dallal, 2007 [142]; Silvera, 2006 [143]; Margolis, 2005 [144].

[1] **'Limited – no conclusion'**: There is enough evidence to warrant Panel consideration, but it is so limited that no conclusion can be made. The evidence may be limited in amount, by inconsistency in the direction of effect, by methodological flaws, or by any combination of these.

All except two studies [140, 141] included in the highest versus lowest meta-analysis adjusted for age, BMI, alcohol intake and reproductive factors. For information on the adjustments made in individual studies, see CUP breast cancer SLR 2017, Table 495.

5.2.1.2 Dose–response meta-analysis

Three of six identified studies were included in the dose–response meta-analysis, which showed no statistically significant association between the risk of premenopausal breast cancer and vigorous-intensity physical activity, (RR 0.91 [95% CI 0.83–1.01]; per 30-minute increase in vigorous-intensity physical activity per day; n = 1,473 cases) (see **Figure 5.11**). No *heterogeneity* was observed.

One study [92] included in the dose–response meta-analysis adjusted for age, BMI, alcohol intake and reproductive factors. For information on the adjustments made in individual studies see CUP breast cancer SLR 2017, Table 495.

5.2.1.3 Published pooled analyses and meta-analyses

No published pooled analyses and no other published meta-analyses on vigorous-intensity physical activity and the risk of premenopausal breast cancer were identified.

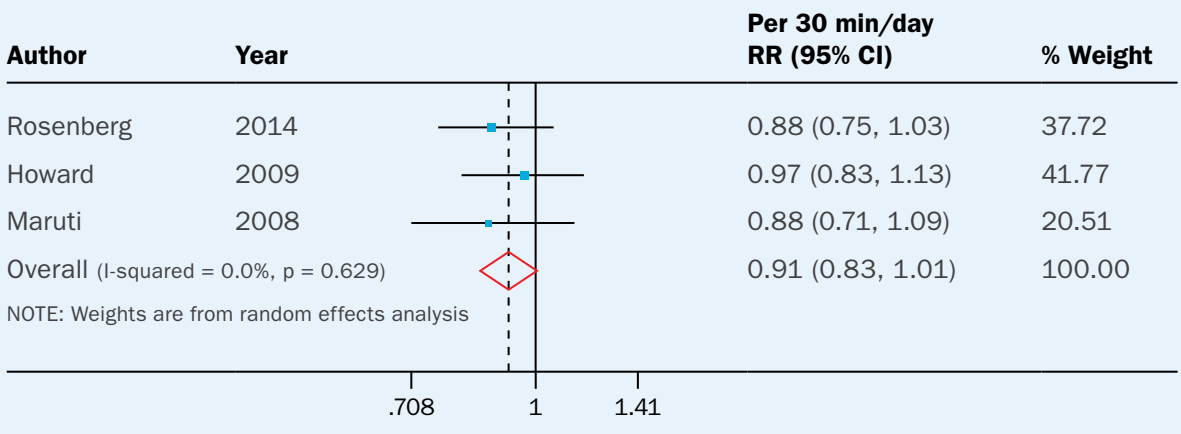
5.2.1.4 Mechanisms

The information on mechanisms is based on both human and animal studies, with a preference for human studies whenever possible. This section covers the primary hypotheses that currently prevail and is not based on a systematic or exhaustive search of the literature.

For further information on general processes involved in the development of cancer, see The cancer process.

No specific mechanisms have been identified for vigorous-intensity physical activity and premenopausal breast cancer, beyond those described for physical activity (see **Appendix 2**).

Figure 5.11: CUP dose–response meta-analysis[1] for the risk of premenopausal breast cancer, per 30 minute increase in vigorous-intensity physical activity per day



Source: Rosenberg, 2014 [140]; Howard, 2009 [92]; Maruti, 2008 [141].

[1] Three studies could not be included in the dose–response meta-analysis, mainly because sufficient information was not provided. For further details, see CUP breast cancer SLR 2017, Table 495.

5.2.1.5 CUP Panel's conclusion

The evidence for vigorous-intensity physical activity and the risk of premenopausal breast cancer was generally consistent, and the meta-analysis of six studies showed a statistically significant decreased risk for the highest compared with the lowest levels of vigorous-intensity physical activity. A dose–response meta-analysis of fewer studies observed no significant association, although the summary estimate was in the direction of a decreased risk. There is robust evidence for mechanisms operating in humans.

The CUP Panel concluded:

- **Physical activity of vigorous intensity probably protects against premenopausal breast cancer.**

5.2.2 Breast postmenopause

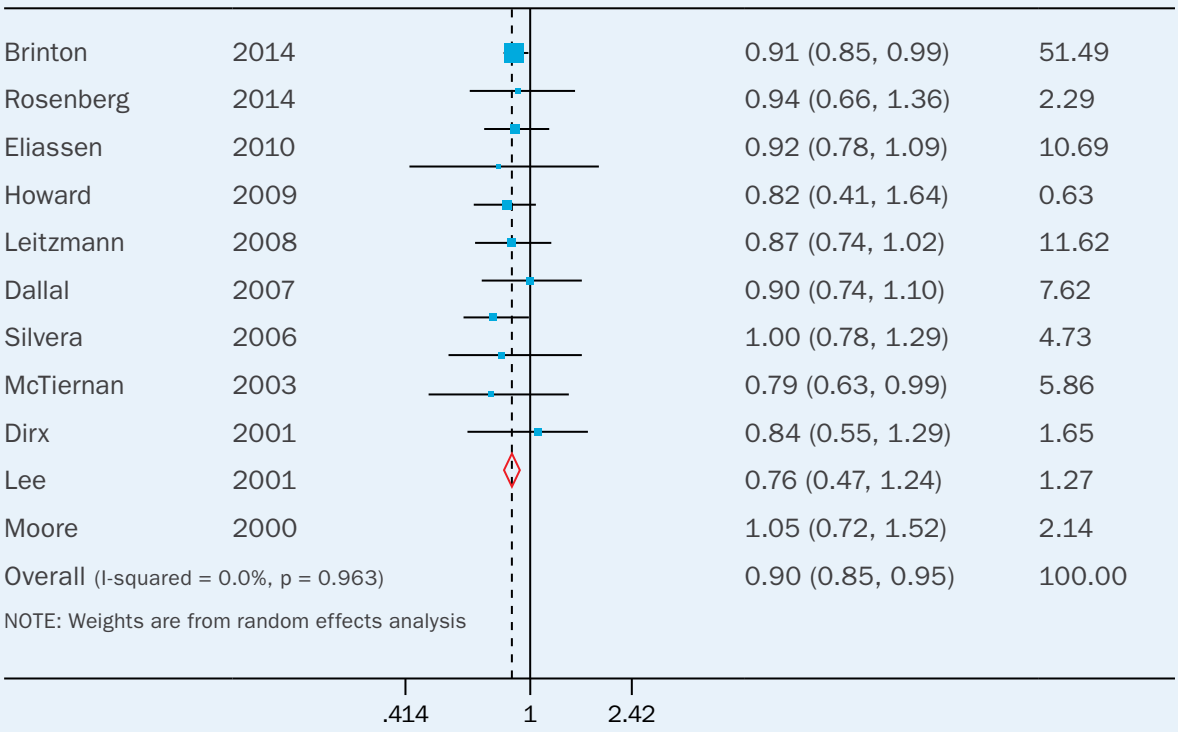
(Also see CUP breast cancer report 2017: Section 7.7 and CUP breast cancer SLR 2017: Sections 6.1.3)

The evidence specifically for vigorous-intensity physical activity is presented in the following subsections. For evidence on physical activity and postmenopausal breast cancer, see **Section 5.1.2**.

5.2.2.1 CUP highest versus lowest meta-analysis

Eleven of 12 identified studies were included in the highest versus lowest meta-analysis, which showed a statistically significant decreased risk of postmenopausal cancer for the highest compared with the lowest level of vigorous-intensity physical activity (RR 0.90 [95% CI 0.85–0.95]; n = 20,171 cases) (see **Figure 5.12**).

Figure 5.12: CUP highest versus lowest meta-analysis for vigorous-intensity physical activity and the risk of postmenopausal breast cancer



Source: Brinton, 2014 [145]; Rosenberg, 2014 [140]; Eliassen, 2010 [99]; Howard, 2009 [92]; Leitzmann, 2008 [93]; Dallal, 2007 [142]; Silvera, 2006 [143]; McTiernan, 2003 [104]; Dirx, 2001 [105]; Lee, 2001 [106]; Moore, 2000 [146].

All except three studies [105, 140, 146] included in the highest versus lowest meta-analysis adjusted for age, BMI, alcohol intake and reproductive factors. For information on the adjustments made in individual studies, see CUP breast cancer SLR 2017, Table 499.

5.2.2.2 CUP dose–response meta-analysis

Three of 12 identified studies were included in the dose–response meta-analysis, which showed no statistically significant association between the risk of postmenopausal breast cancer and vigorous-intensity physical activity (RR 0.94 [95% CI 0.86–1.02]; per 30-minute increase in vigorous-intensity physical activity per day; n = 3,293 cases) (see **Figure 5.13**). No *heterogeneity* was observed.

One published study [93] reported a statistically significant decreased risk of postmenopausal breast cancer for the highest compared with the lowest level of vigorous-intensity physical activity in women with a healthy weight (RR 0.68 [95% CI 0.54–0.85]), but not in women who were overweight or obese. Another published study [147] observed a significant decreased risk for women who were overweight or obese (RR 0.86 [95% CI 0.77–0.96]), but not for women with a healthy weight.

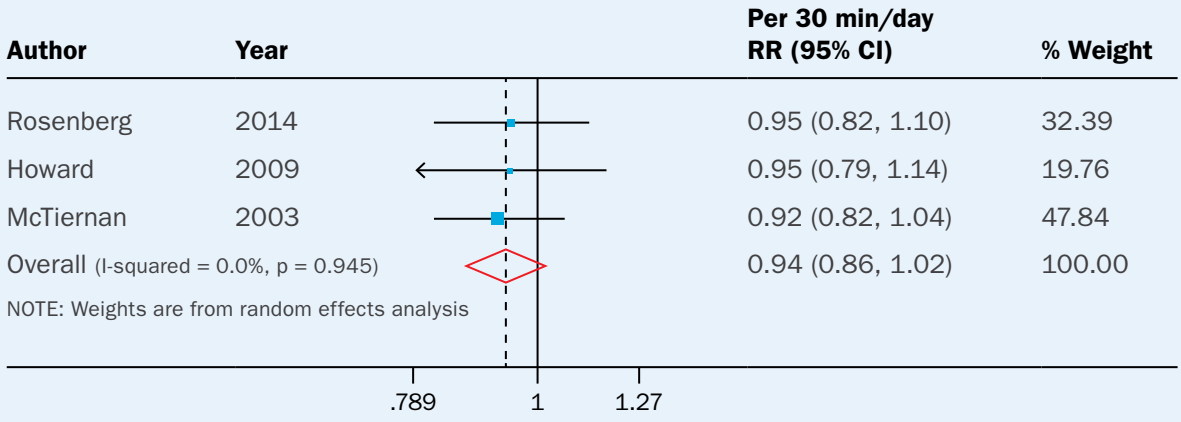
Four published studies [93, 106, 148, 149] reported results by *hormone receptor subtype*. Two studies observed no significant association with any subtype [93, 106] and two studies [148, 149] reported a significant decreased risk with high moderate or vigorous-intensity physical activity compared with none for oestrogen-receptor-positive (ER-positive) breast cancer only (RR 0.77 [95% CI 0.64–0.92] and RR 0.88 [95% CI 0.79–0.98], respectively).

All except one study [140] included in the dose–response meta-analysis adjusted for age, BMI, alcohol intake and reproductive factors. For information on the adjustments made in individual studies, see CUP breast cancer SLR 2017, Table 499.

5.2.2.3 Published pooled analyses and meta-analyses

No published pooled analyses and no other published meta-analyses on vigorous-intensity physical activity and the risk of postmenopausal breast cancer were identified.

Figure 5.13: CUP dose–response meta-analysis[1] for the risk of postmenopausal breast cancer, per 30-minute increase in vigorous-intensity physical activity per day



Source: Rosenberg, 2014 [140]; Howard, 2009 [92]; McTiernan, 2003 [104].

[1] Nine studies could not be included in the dose–response meta-analysis, mainly because results were not results were not reported in minutes or hours, or sufficient information was not provided. For further details, see CUP breast cancer SLR 2017, Table 499.

5.2.2.4 Mechanisms

The information on mechanisms is based on both human and animal studies, with a preference for human studies whenever possible. This section covers the primary hypotheses that currently prevail and is not based on a systematic or exhaustive search of the literature.

For further information on general processes involved in the development of cancer, see The cancer process.

No specific mechanisms have been identified for vigorous-intensity physical activity and postmenopausal breast cancer, beyond those described for physical activity (see **Section 5.1.2.4**).

5.2.2.5 CUP Panel's conclusion

The evidence was generally consistent and the meta-analysis of 11 studies showed a statistically significant decreased risk for the highest compared with the lowest level of vigorous-intensity physical activity. A dose–response meta-analysis of fewer studies observed no significant association, although the summary estimate was in the direction of a decreased risk. There is robust evidence for mechanisms operating in humans.

The CUP Panel concluded:

- **Physical activity of vigorous intensity probably protects against postmenopausal breast cancer.**

5.3 Sedentary behaviours

Table 5.3 summarises the main findings from the CUP highest versus lowest meta-analysis of cohort studies on sedentary behaviours and the risk of endometrial cancer. A dose–response meta-analysis could not be conducted in the CUP because different measures were used in the studies.

Evidence for cancers of the following types was discussed in the CUP but was too limited to draw a conclusion[1]: oesophagus (2016), stomach (2016), liver (2015), breast (pre and postmenopause; 2017) and kidney (2015).

Table 5.3: Summary of CUP highest versus lowest meta-analysis of sedentary behaviours and the risk of endometrial cancer

Cancer	Total no. of studies	No. of studies in meta-analysis	No. of cases	Risk estimate (95% CI)	Conclusion[1]	Date of CUP cancer report[2]
Endometrium[3]	3	3	1,579	1.46 (1.21–1.76)	**Limited – suggestive: Increases risk**	2013

1 See Definitions of WCRF/AICR grading criteria (**Section 1**: Physical activity and the risk of cancer: a summary matrix) for explanations of what the Panel means by 'limited – suggestive'.

2 Throughout this Third Expert Report, the year given for each cancer site is the year the CUP cancer report was published, apart from for nasopharynx, cervix and skin, where the year given is the year the SLR was last reviewed. Updated CUP cancer reports for nasopharynx and skin will be published in the future.

3 The evidence for sedentary behaviours and endometrial cancer was marked by sitting time.

[1] **'Limited – no conclusion'**: There is enough evidence to warrant Panel consideration, but it is so limited that no conclusion can be made. The evidence may be limited in amount, by inconsistency in the direction of effect, by methodological flaws, or by any combination of these.

For more information on the evidence for sedentary behaviours and the risk of cancer that was graded by the Panel as 'limited – suggestive', and suggests a direction of effect, see the following CUP documents:

- CUP endometrial cancer report 2013: Section 7.4 and CUP endometrial cancer SLR 2012: Section 6.2.

Also, for information on mechanisms that could plausibly influence the risk of cancer, see **Appendix 2**.

Please note that this information on mechanisms supersedes that in CUP cancer reports published before this Third Expert Report.

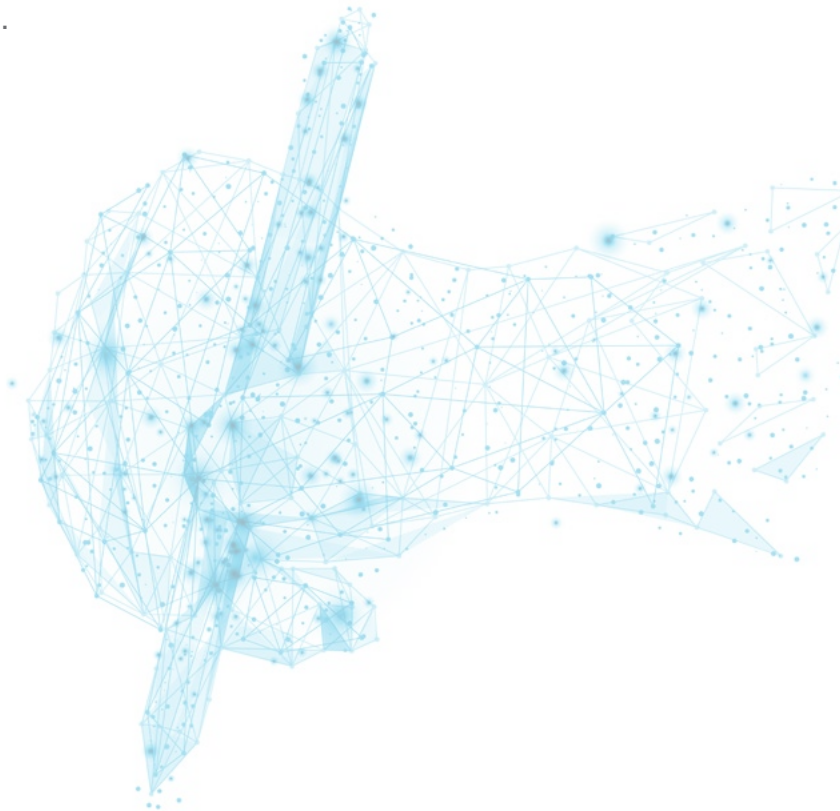
5.4 Other

The effect of other types of physical activity on the risk of cancer was evaluated, as well as those that were graded by the Panel as 'limited – suggestive', 'probable' or 'convincing'. These included walking, cycling and housework. However, data were either of too low quality or too inconsistent, or the number of studies too few to allow conclusions to be reached.

6. Comparison with the 2007 Second Expert Report

In the 2007 Second Expert Report, there was strong evidence that physical activity is protective against cancers of the colon, breast (postmenopause) and endometrium. The evidence for all of these cancers has stayed strong.

In this Third Expert Report, physical activity of vigorous intensity and the risk of breast cancer could be assessed for the first time, and there was strong evidence that it has a protective effect in both pre and postmenopausal women.



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Abbreviations

AICR	American Institute for Cancer Research
BMI	Body mass index
CI	Confidence interval
CUP	Continuous Update Project
ER-positive	Oestrogen-receptor positive
IGF-I	Insulin-like growth factor 1
MET	Metabolic equivalent
MHT	Menopausal hormone therapy
RR	Relative risk
SLR	Systematic literature review
WCRF	World Cancer Research Fund

Glossary

Adenocarcinoma
Cancer of glandular epithelial cells.

Adenosine triphosphate (ATP)
The principal molecule used for storage and transfer of energy in metabolic processes.

Adenosquamous carcinoma
A type of cancer that contains two types of cells: squamous cells (thin, flat cells that line certain organs) and gland-like cells.

Adjustment
A statistical tool for taking into account the effect of known confounders (see **confounder**).

Aerobic metabolism
The normal process of producing ATP (see **adenosine triphosphate**) as a source of energy using oxygen.

Aerobic physical activity/exercise
Relating to or denoting exercise taken to improve the efficiency of the body's cardiovascular system in absorbing and transporting oxygen.

Anaerobic metabolism
The process of producing ATP (see **adenosine triphosphate**) as a source of energy without oxygen, resulting in lactic acid accumulation.

Basal energy expenditure (see **basal metabolic rate**)

Basal metabolic rate (BMR)
The amount of energy required to maintain the essential body functions in resting and fasting conditions, expressed as megajoules, kilojoules or kilocalories per minute, hour or day.

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**).

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.

Caecum
A pouch connected to the junction of the small and large intestines.

Carcinogen
Any substance or agent capable of causing cancer.

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).

Case-control study
An epidemiological study in which the participants are chosen on the basis of their disease or condition (cases) or lack of it (controls), to test whether distant or recent history of an exposure such as tobacco smoking, genetic profile, alcohol consumption or dietary intake is associated with the risk of disease.

Cholangiocarcinoma
A malignant tumour in the ducts that carry bile from the liver to the small intestine.

Chronic
Describing a condition or disease that is persistent or long lasting.

Cirrhosis
A condition in which normal liver tissue is replaced by scar tissue (fibrosis), with nodules of regenerative liver tissue.

Cohort study
A study of a (usually large) group of people whose characteristics are recorded at recruitment (and sometimes later) and followed up for a period of time during which outcomes of interest are noted. Differences in the frequency of outcomes (such as disease) within the cohort are calculated in relation to different levels of exposure to factors of interest – for example, tobacco smoking, alcohol consumption, diet and exercise. Differences in the likelihood of a particular outcome are presented as the relative risk, comparing one level of exposure with another.

Colon
Part of the large intestine extending from the caecum to the rectum.

Confidence interval (CI)
A measure of the uncertainty in an estimate, usually reported as 95% confidence interval (CI), which is the range of values within which there is a 95% chance that the true value lies. For example, the association of tobacco smoking and relative risk of lung cancer may be expressed as 10 (95% CI 5–15). This means that the estimate of the relative risk was calculated as 10 and that there is a 95% chance that the true value lies between 5 and 15.

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.

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.

Dose–response
A term derived from pharmacology that describes the degree to which an association or effect changes as the level of an exposure changes, for instance, intake of a drug or food.

Effect modification
Effect modification (or effect-measure modification) occurs when the effect of an exposure differs according to levels of another variable (the modifier).

Egger's test
A statistical test for small study effects such as publication bias.

Endocrine
Referring to organs or glands that secrete hormones into the blood.

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.

Energy balance
The state in which the total energy absorbed from foods and drink equals total energy expended, for example, through basal metabolism and physical activity. Also the degree to which intake exceeds expenditure (positive energy balance) or expenditure exceeds intake (negative energy balance).

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.

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.

Familial
Relating to or occurring in a family or its members.

Hepatocellular carcinoma
Primary malignant tumour of the liver.

Heterogeneity
A measure of difference between the results of different studies addressing a similar question. In meta-analysis, the degree of heterogeneity may be calculated statistically using the I^2 test.

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'.

Hormone
A substance secreted by specialised cells that affects the structure and/or function of cells or tissues in another part of the body.

Hormone receptor status
Hormone receptors are proteins found in and on breast or other cells that respond to circulating hormones and influence cell structure or function. A cancer is called oestrogen-receptor-positive (ER+) if it has receptors for oestrogen, and oestrogen-receptor-negative (ER-) if it does not have the receptors for oestrogen.

Immune response
The production of antibodies or specialised cells, for instance, in response to foreign proteins or other substances.

Inflammation
The immunologic response of tissues to injury or infection. Inflammation is characterised by accumulation of white blood cells that produce several bioactive chemicals (cytokines), causing redness, pain, heat and swelling. Inflammation may be acute (such as in response to infection or injury) or chronic (as part of several conditions, including obesity).

Insulin
A protein hormone secreted by the pancreas that promotes the uptake and utilisation of glucose, particularly in the liver and muscles. Inadequate secretion of, or tissue response to, insulin leads to diabetes mellitus.

Insulin-like growth factor (IGF)
Polypeptides with high sequence similarity to insulin that are part of a complex system that cells use to communicate with their physiologic environment. IGF-I is the main mediator of growth **hormone** activity.

Insulin resistance
A pathological condition in which cells fail to respond normally to the hormone insulin.

Large cell carcinoma
A term used to describe a microscopically identified variant of certain cancers, for example, lung cancers, in which the abnormal cells are particularly large.

Low-income countries
As defined by the World Bank, countries with an average annual gross national income per capita of US$1,005 or less in 2016. This term is more precise than and used in preference to 'economically developing countries'.

Menarche
The start of menstruation.

Menopausal hormone therapy (MHT)
Treatment with oestrogens and progesterones with the aim of alleviating menopausal symptoms or osteoporosis. Also known as hormone replacement therapy.

Menopause
The cessation of menstruation.

Meta-analysis
The process of using statistical methods to combine the results of different studies.

Metabolic equivalent (MET)
One MET equals the resting metabolic rate, measured as the rate of oxygen consumption, which is approximately 3.5 millilitres of oxygen per kilogram of body weight per minute. Equivalent to physical activity ratio.

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

Mucinous carcinoma
A type of cancer that begins in cells that line certain internal organs and produce mucin (the main component of mucus).

Non-cardia stomach cancer
A subtype of stomach cancer that occurs in the lower portion of the stomach.

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.

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.

Odds ratio
A measure of the risk of an outcome such as cancer, associated with an exposure of interest, used in case-control studies; approximately equivalent to relative risk.

Oestrogen
The female sex hormones, produced mainly by the ovaries during reproductive life and also by adipose tissue.

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.

Progesterone
Female sex hormone, produced mainly by the ovaries during reproductive life and by the placenta during pregnancy.

Rectum
The final section of the large intestine, terminating at the anus.

Relative risk (RR)
The ratio of the rate of an outcome (for example, disease (incidence) or death (mortality)) among people exposed to a factor, to the rate among the unexposed, usually used in cohort studies.

Resting metabolic rate
Metabolic rate in a fasting subject sitting quietly (also see **basal metabolic rate**).

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.

Statistical significance
The probability that any observed result has or has not occurred by chance. Conventionally, a probability of less than five per cent ($p < 0.05$) that a study result has occurred by chance is considered 'statistically significant' (see **confidence interval**).

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

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Appendix 1: Criteria for grading evidence for cancer prevention

Adapted from Chapter 3 of the 2007 Second Expert Report [1]. Listed here are the criteria agreed by the Panel that were necessary to support the judgements shown in the matrices. The grades shown here are 'convincing', 'probable', 'limited – suggestive', 'limited – no conclusion', and 'substantial effect on risk unlikely'. In effect, the criteria define these terms.

These criteria were used in a modified form for breast cancer survivors (see CUP Breast cancer survivors report 2014).

CONVINCING (STRONG EVIDENCE)

Evidence strong enough to support a judgement of a convincing causal (or protective) relationship, which justifies making recommendations designed to reduce the risk of cancer. The evidence is robust enough to be unlikely to be modified in the foreseeable future as new evidence accumulates.

All of the following are generally required:

- Evidence from more than one study type.
- Evidence from at least two independent cohort studies.
- No substantial unexplained *heterogeneity* within or between study types or in different populations relating to the presence or absence of an association, or direction of effect.
- Good-quality studies to exclude with confidence the possibility that the observed association results from random or systematic error, including *confounding*, measurement error and *selection bias*.
- 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.
- Strong and plausible experimental evidence, either from human studies or relevant animal models, that typical human exposures can lead to relevant cancer outcomes.

PROBABLE (STRONG EVIDENCE)

Evidence strong enough to support a judgement of a probable causal (or protective) relationship, which generally justifies recommendations designed to reduce the risk of cancer.

All of the following are generally required:

- Evidence from at least two independent cohort studies or at least five case-control studies.
- No substantial unexplained *heterogeneity* between or within study types in the presence or absence of an association, or direction of effect.
- Good-quality studies to exclude with confidence the possibility that the observed association results from random or systematic error, including confounding, measurement error and *selection bias*.
- Evidence for biological plausibility.

LIMITED – SUGGESTIVE

Evidence that is too limited to permit a probable or convincing causal judgement but is suggestive of a direction of effect. The evidence may be limited in amount or by methodological flaws, but shows a generally consistent direction of effect. This judgement is broad and includes associations where the evidence falls only slightly below that required to infer a probably causal association through to those where the evidence is only marginally strong enough to identify a direction of effect. This judgement is very rarely sufficient to justify recommendations designed to reduce the risk of cancer; any exceptions to this require special, explicit justification.

All of the following are generally required:

- Evidence from at least two independent cohort studies or at least five case-control studies.
- The direction of effect is generally consistent though some unexplained heterogeneity may be present.
- Evidence for biological plausibility.

LIMITED – NO CONCLUSION

Evidence is so limited that no firm conclusion can be made. This judgement represents an entry level and is intended to allow any exposure for which there are sufficient data to warrant Panel consideration, but where insufficient evidence exists to permit a more definitive grading. This does not necessarily mean a limited quantity of evidence. A body of evidence for a particular exposure might be graded 'limited – no conclusion' for a number of reasons. The evidence may be limited by the amount of evidence in terms of the number of studies available, by inconsistency of direction of effect, by methodological flaws (for example, lack of *adjustment* for known *confounders*) or by any combination of these factors.

When an exposure is graded 'limited – no conclusion', this does not necessarily indicate that the Panel has judged that there is evidence of no relationship. With further good-quality research, any exposure graded in this way might in the future be shown to increase or decrease the risk of cancer. Where there is sufficient evidence to give confidence that an exposure is unlikely to have an effect on cancer risk, this exposure will be judged 'substantial effect on risk unlikely'.

There are also many exposures for which there is such limited evidence that no judgement is possible. In these cases, evidence is recorded in the full CUP SLRs on the World Cancer Research Fund International website (dietandcancerreport.org). However, such evidence is usually not included in the summaries.

SUBSTANTIAL EFFECT ON RISK UNLIKELY (STRONG EVIDENCE)

Evidence is strong enough to support a judgement that a particular food, nutrition or physical activity exposure is unlikely to have a substantial causal relation to a cancer outcome. The evidence should be robust enough to be unlikely to be modified in the foreseeable future as new evidence accumulates.

All of the following are generally required:

- Evidence from more than one study type.
- Evidence from at least two independent cohort studies.
- Summary estimate of effect close to 1.0 for comparison of high- versus low-exposure categories.
- No substantial unexplained heterogeneity within or between study types or in different populations.
- Good-quality studies to exclude, with confidence, the possibility that the absence of an observed association results from random or systematic error, including inadequate power, imprecision or error in exposure measurement, inadequate range of exposure, confounding and selection bias.
- Absence of a demonstrable biological gradient ('dose–response').
- Absence of strong and plausible experimental evidence, from either human studies or relevant animal models, that typical human exposure levels lead to relevant cancer outcomes.

Factors that might misleadingly imply an absence of effect include imprecision of the exposure assessment, insufficient range of exposure in the study population and inadequate *statistical power*. Defects such as these and in other study design attributes might lead to a false conclusion of no effect.

The presence of a plausible, relevant biological mechanism does not necessarily rule out a judgement of 'substantial effect on risk unlikely'. But the presence of robust evidence from appropriate animal models or humans that a specific mechanism exists or that typical exposures can lead to cancer outcomes argues against such a judgement.

Because of the uncertainty inherent in concluding that an exposure has no effect on risk, the criteria used to judge an exposure 'substantial effect on risk unlikely' are roughly equivalent to the criteria used with at least a 'probable' level of confidence. Conclusions of 'substantial effect on risk unlikely' with a lower confidence than this would not be helpful and could overlap with judgements of 'limited – suggestive' or 'limited – no conclusion'.

SPECIAL UPGRADING FACTORS

These are factors that form part of the assessment of the evidence that, when present, can upgrade the judgement reached. An exposure that might be deemed a 'limited – suggestive' causal factor in the absence, for example, of a biological gradient, might be upgraded to 'probable' if one were present. The application of these factors (listed below) requires judgement, and the way in which these judgements affect the final conclusion in the matrix are stated.

Factors may include the following:

- 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.
- A particularly large summary effect size (an odds ratio or relative risk of 2.0 or more, depending on the unit of exposure) after appropriate control for *confounders*.
- Evidence from randomised trials in humans.
- Evidence from appropriately controlled experiments demonstrating one or more plausible and specific mechanisms actually operating in humans.
- Robust and reproducible evidence from experimental studies in appropriate animal models showing that typical human exposures can lead to relevant cancer outcomes.

Appendix 2: Mechanisms

The evidence on mechanisms has been based on human and animal studies. Though not a systematic or exhaustive search, the expert reviews represent the range of currently prevailing hypotheses.

Physical activity

Colorectum (colon)

Physical activity reduces body fatness and therefore has a beneficial effect on colorectal cancer risk, possibly through a reduction in *insulin resistance* and *inflammation* – both of which have been linked to colorectal cancer development [84–86]. However, it is unclear whether physical activity that is not accompanied by weight loss or maintenance of a healthy weight has a significant impact on these pathways. Other mechanisms by which physical activity may lower colorectal cancer risk include stimulating digestion and reducing transit time through the intestine [87], though robust data to support this mechanism in humans is limited. Overall, mechanistic data to support a link between physical activity and colorectal cancer are moderate in strength.

Breast (postmenopause)

Physical activity affects a diverse array of metabolic, hormonal, and immunologic pathways. Regular physical activity reduces body fatness and therefore has a beneficial effect on breast cancer risk, possibly through a reduction in circulating *oestrogen* levels, *insulin resistance* and *inflammation* – all of which have been linked to postmenopausal breast cancer development. However, it is unclear whether physical activity that is not accompanied by weight loss has a significant impact on these pathways.

Physical activity improves insulin sensitivity and reduces fasting *insulin* levels, which are linked to higher breast cancer risk in humans [114, 115]. Exercise may also affect breast cancer risk through its effects on *insulin-like growth factors* (IGFs) [116], because high levels of circulating IGF-I are associated with increased risk of several cancers, including breast cancer [117]. In addition, physical activity has been shown to have immunomodulatory effects in humans, improving innate and acquired *immune response*, and promoting tumour surveillance [115, 118]. Studies have also shown that *aerobic exercise* can decrease oxidative stress and enhance DNA repair mechanisms in humans and would therefore be expected to suppress *carcinogenesis* [118]. Physically active individuals also tend to have higher sunlight exposure and consequently higher levels of vitamin D, which may modify cell proliferation [119].

Endometrium

Physical activity reduces body fatness and therefore has a beneficial effect on endometrial cancer risk, possibly through a reduction in circulating *oestrogen* levels, *insulin resistance* and *inflammation* – all of which have been linked to endometrial cancer development. Physical activity has been shown to decrease oestradiol levels [132], improve insulin sensitivity [133] and reduce chronic inflammation [115, 134] – all pathways which have been linked to endometrial cancer development [135–139].

Oesophagus

Physical activity reduces body fatness and therefore has a beneficial effect on oesophageal cancer risk. Long-term moderate physical activity also lowers *insulin resistance* and *inflammation* – both of which have been linked to oesophageal cancer development.

Lung

Physical activity affects a diverse array of metabolic, hormonal, and immunologic pathways. Physical activity reduces *insulin resistance* and *inflammation* – both of which have been linked to lung cancer development [150], [151, 152]. In addition, physical activity has been shown to have immunomodulatory effects, enhancing the innate and acquired *immune response*, and promoting tumour surveillance [115], [118]. Exercise can also decrease oxidative stress and enhance DNA repair mechanisms over the long term and would therefore be expected to suppress *carcinogenesis* [118]. Physical activity has also been associated with up-regulation of enzymatic systems and co-factors such as glutathione that detoxify chemical *carcinogens* and protect the lungs [153].

Liver

The underlying biological mechanisms of the observed cancer-protective effects of physical activity are not well defined and likely to be largely similar across different anatomical cancer sites. These potential mechanisms include reduced body fatness, lower *insulin resistance* and *inflammation*; changes in *obesity*-related and sex hormone levels; and regulation of immune function and improved immune surveillance [154, 155].

Breast (premenopause)

Physical activity impacts upon a diverse array of metabolic, hormonal, and immunologic pathways. Critically, physical activity contributes to the ability to optimize *energy balance* and maintain a healthy weight ([156, 157]). Regular physical activity may possibly act through a reduction in circulating *oestrogen* levels, *insulin resistance* and *inflammation*/immune status – all of which have been linked to postmenopausal breast cancer development. However, it is unclear whether physical activity that is not accompanied by weight loss has a significant impact on these pathways.

Human epidemiologic studies have shown that greater exposure to *oestrogens* increases the risk of breast cancer in both premenopausal and postmenopausal women [158, 159]. Physical activity has been shown to decrease levels of oestrogens and androgens in postmenopausal women, and some trials have also shown reductions in circulating oestrogens, increased menstrual cycle length, and decreased ovulation in premenopausal women with a high level of physical activity. In addition, physical activity has been shown to have immunomodulatory effects, improving innate and acquired *immune response*, and promoting tumour surveillance [115, 118]. Studies have also shown that *aerobic exercise* can decrease oxidative stress and enhance DNA repair mechanisms in humans and would therefore be expected to suppress *carcinogenesis* [118]. Physically active individuals also tend to have higher sunlight exposure and consequently increased vitamin D, which may affect cancer risk [119].

Physical activity of vigorous intensity

Breast (premenopause)

No specific mechanisms have been identified for vigorous-intensity physical activity and premenopausal breast cancer, beyond those described for physical activity.

Breast (postmenopause)

No specific mechanisms have been identified for vigorous-intensity physical activity and postmenopausal breast cancer, beyond those described for physical activity.

Sedentary behaviours

Endometrium

Sedentary habits result in increased adiposity, and therefore mechanisms associated with body fatness (sex hormones, *insulin*, *inflammation*) may explain a large part of the association between sedentary habits and endometrial cancer risk [160]. There is also suggestive evidence that sedentary behaviour such as longer television-viewing time is associated with lower levels of vitamin D [161, 162] but so far the evidence regarding an increased risk of endometrial cancer in women with low levels of vitamin D has been limited [163].

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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