



# Diet, nutrition, physical activity and **prostate cancer**

2014

Revised 2018

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# 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.

## 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. **Diet, nutrition, physical activity and prostate cancer** is one of many parts that make up the CUP Third Expert Report: for a full list of contents, see **[dietandcancerreport.org](http://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.

## HOW TO CITE THIS REPORT

This part: World Cancer Research Fund/American Institute for Cancer Research. Continuous Update Project Expert Report 2018. **Diet, nutrition, physical activity and prostate cancer**. Available at **[dietandcancerreport.org](http://dietandcancerreport.org)**

The whole report: World Cancer Research Fund/American Institute for Cancer Research. *Diet, Nutrition, Physical Activity and Cancer: a Global Perspective*. Continuous Update Project Expert Report 2018. Available at **[dietandcancerreport.org](http://dietandcancerreport.org)**

## KEY

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

## EXECUTIVE SUMMARY

### Background and context

Prostate cancer is the second most common cancer among men worldwide, and the most common cancer in males in 84 countries [1]. Occurring more frequently in the developed world, rates have also been increasing in the developing world; and - as a result of the large number of cases of prostate cancer detected by screening – it is estimated that in just over a decade prostate cancer will overtake lung cancer as the most common form of cancer in men around the globe [2].

Prostate cancer becomes more common as men age – in the USA 97% of all prostate cancers are diagnosed in men 50 years or older - so as life expectancy increases we are likely to see more cases of the disease.

Incidence rates of prostate cancer vary more than 25 fold between different parts of the world, with the highest rates in Australia, New Zealand, Northern and Western Europe and North America – a disparity which is, in part, the result of some countries employing screening methods which pick up large numbers of early cancers.

In addition, men with a family history of the disease or of African heritage are more at risk of developing the disease; for example, in the USA, African American men are 1.6 times more likely to develop prostate cancer than Caucasian men.

Early prostate cancer usually has no symptoms but can be detected by screening - although it may remain latent in the body without ever causing harm. With more advanced cases of the disease, men may experience weak or interrupted urine flow; the inability to urinate or difficulty starting or stopping urine flow; the need to urinate frequently, especially at night; blood in the urine; or pain or burning with urination. However, these symptoms are not specific to prostate cancer and can also be due to benign conditions such as prostatic hyperplasia.

World Cancer Research Fund International's Continuous Update Project report on prostate is the most rigorous, systematic, global analysis of the scientific research currently available on prostate cancer and how certain lifestyle factors affect the risk of developing the disease.

The report is the latest from our Continuous Update Project - the world's largest source of scientific research on cancer prevention and survivorship through diet, weight and physical activity - and builds on our 2007 Second Expert Report [3] on the links between lifestyle and cancer.

In this summary we provide an overview of the scientific findings and conclusions of the report.

## How the research was conducted

The global scientific research on diet, weight, physical activity and the risk of prostate cancer was gathered and analysed, and then independently assessed by a panel of leading international scientists in order to draw conclusions about which of these factors increase or decrease the risk of developing prostate cancer.

In the report advanced prostate cancer is defined as cancers reported in any of the following ways:

- advanced cancer
- metastatic cancer
- fatal cancer (prostate specific mortality)
- high stage or grade
- stage C or D on the Whitmore/Jewett scale
- Gleason grade  $\geq 7$
- stage 3-4 on the American Joint Committee on Cancer (AJCC) 1992 classification

The total number of men in the 104 global studies reviewed was over nine million (9,855,000); and the total number of prostate cancer cases in the studies analysed for the report was 191,000.

To ensure consistency, the methodology for the Continuous Update Project (CUP) remains largely unchanged from that used previously for our 2007 Second Expert Report [3].

## Findings

### There is strong evidence that:

- There is strong evidence that being overweight or obese increases the risk of advanced prostate cancer (being overweight or obese is assessed by body mass index (BMI), waist circumference and waist-hip ratio).
- There is strong evidence that developmental factors in the womb, childhood, and adolescence that influence growth are linked to an increased risk of prostate cancer (the taller a man is, the greater his risk of prostate cancer).
- There is strong evidence that consuming beta-carotene (either through food or supplements) is unlikely to have a substantial effect on the risk of prostate cancer.

The findings on being overweight or obese, and adult height in this report are new; those for beta-carotene remain unchanged from our 2007 Second Expert Report [3].

### There is some evidence that:

- The evidence that a higher consumption of dairy products increases the risk of prostate cancer is limited.
- The evidence that diets high in calcium increase the risk of prostate cancer is limited.
- The evidence that low plasma alpha-tocopherol concentration (vitamin E) increases the risk of prostate cancer is limited.
- The evidence that low plasma (blood) selenium concentrations increases risk of prostate cancer is limited.

### Findings that have changed since our 2007 Second Expert Report

- The conclusion for diets high in calcium has been downgraded from strong evidence of an increased risk of prostate cancer, to limited evidence.
- The conclusion for selenium has been downgraded from strong evidence that it lowers the risk of prostate cancer, to limited evidence - and refers to low blood levels of selenium rather than foods containing selenium.
- In addition the links between prostate cancer risk and foods containing lycopene and selenium supplements have been downgraded from strong evidence of a decreased risk, to no conclusion possible.

## Why some findings have changed since our 2007 Second Expert Report

In the seven years since the publication of our 2007 Second Expert Report [3], a considerable amount of global research on prostate cancer has been conducted, providing a more nuanced insight into the links between diet, weight, physical activity and the risk of developing the disease. For example, as more evidence has accumulated, it has become clear that not all prostate cancers are the same. Whereas previous research tended to group all prostate cancers together, more studies are now focusing on specific types of prostate cancer - for example, fatal, advanced and early (non-advanced) prostate cancers. While this nuancing has made interpreting the evidence between some lifestyle factors and the different types of prostate cancer more difficult, it has also served to clarify the evidence in other areas.

So the evidence on being overweight or obese is now clearer, but for other factors, links that were apparent previously are now less so. This does not mean that no link exists, for example, between foods containing lycopene and prostate cancer, but rather that if there is a link, the nature of the research conducted - because of variations in diagnosis and classifications of the disease - has made it more difficult to see. To provide more insight, better designed studies are required.

## Recommendations

Our Cancer Prevention Recommendations – for preventing cancer in general – include maintaining a healthy weight, being physically active and eating a healthy diet. The Cancer Prevention Recommendations are listed on the inside back cover of this report, with full details available in [Recommendations and public health and policy implications](#).

## References

- [1] Stewart, B.W. and Wild, C.P. eds., 2014. World Cancer Report 2014. International Agency for Cancer Research. Available from: <http://www.iarc.fr/en/publications/books/wcr/index.php>
- [2] Ferlay J et al. GLOBOCAN 2012 v1.0, Cancer Incidence and Mortality Worldwide: IARC CancerBase No. 11. 2014; Available from <http://globocan.iarc.fr>
- [3] 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 at [wcrf.org/about-the-report](http://wcrf.org/about-the-report)

2014	DIET, NUTRITION, PHYSICAL ACTIVITY AND PROSTATE CANCER		
		DECREASES RISK	INCREASES RISK
STRONG EVIDENCE	Convincing		
	Probable		<b>Body fatness (advanced prostate cancer)<sup>1,2</sup></b> <b>Adult attained height<sup>3</sup></b>
LIMITED EVIDENCE	Limited – suggestive		Dairy products Diets high in calcium Low plasma alpha-tocopherol concentrations Low plasma selenium concentrations
	Limited – no conclusion	Cereals (grains) and their products, dietary fibre, potatoes, non-starchy vegetables, fruits, pulses (legumes), processed meat, red meat, poultry, fish, eggs, total fat, saturated fatty acids, monounsaturated fatty acids, polyunsaturated fatty acids, plant oils, sugar (sucrose), sugary foods and drinks, coffee, tea, alcoholic drinks, carbohydrate, protein, vitamin A, retinol, alpha carotene, lycopene, folate, thiamin, riboflavin, niacin, vitamin C, vitamin D, vitamin E supplements, gamma-tocopherol, multivitamins, selenium supplements, iron, phosphorus, calcium supplements, zinc, physical activity, energy expenditure, vegetarian diets, Seventh-day Adventist diets, individual dietary patterns, body fatness (non-advanced prostate cancer), birth weight, energy intake	
STRONG EVIDENCE	Substantial effect on risk unlikely	<b>Beta-carotene<sup>4,5</sup></b>	

- 1 Body fatness is marked by body mass index (BMI), waist circumference and waist-hip ratio. The effect was observed in advanced prostate cancer only.
- 2 Advanced in this report includes advanced, high grade, and fatal prostate cancers (see section 5.2).
- 3 Adult attained height is unlikely to directly influence the risk of cancer. It is a marker for genetic, environmental, hormonal, and also nutritional factors affecting growth during the period from preconception to completion of linear growth.
- 4 Includes both foods naturally containing the constituent and foods which have the constituent added.
- 5 The evidence includes studies using supplements at doses of 20, 30, and 50 mg/day.

# 1. Summary of Panel judgements

Overall the Panel notes the strength of the evidence that body fatness is probably a cause of advanced prostate cancer only and developmental factors (marked by adult attained height) are probably a cause of prostate cancer.

## **The CUP Panel judges as follows:**

- **Greater body fatness (marked by BMI, waist circumference, and waist-hip ratio) is probably a cause of advanced prostate cancer.**
- **Developmental factors leading to greater linear growth (marked by adult attained height) are probably a cause of prostate cancer.**
- **Consuming beta-carotene in supplements or foods containing beta-carotene is unlikely to have substantial effect on the risk of prostate cancer.**
- **For a higher consumption of dairy products, the evidence suggesting an increased risk of prostate cancer is limited.**
- **For diets high in calcium, the evidence suggesting an increased risk of prostate cancer is limited.**
- **For low plasma alpha-tocopherol concentrations, the evidence suggesting an increased risk of prostate cancer is limited.**
- **For low plasma selenium concentrations, the evidence suggesting an increased risk of prostate cancer is limited.**

The Panel judgements are shown in the matrix on **page 9**.

## 2. Trends, incidence, and survival

The prostate is a walnut sized gland in men that surrounds the top of the urethra just below the bladder outlet; it produces seminal fluid. Male hormones, such as testosterone, control its growth and function.

Prostate cancer is the second most common cancer worldwide, and the fifth most common cause of cancer death among men [1]. Almost all cases are adenocarcinoma, a glandular malignancy. Around 1.1 million new cases were recorded worldwide in 2012, accounting for 15% of all new cases of cancer in men.

Prostate cancer is more common as men age, in the US 97% of all prostate cancers are diagnosed in men 50 years or older [2]. Incidence rates of prostate cancer vary by more than 25-fold in different parts of the world; the highest rates are in Australia and New Zealand, Northern and Western Europe and North America [1]. A proportion of the variation in incidence rates can be explained by differences in screening practices, notably screening for prostate-specific antigen (PSA).

Early prostate cancer detected by screening usually has no symptoms [2]. With more advanced disease men may experience weak or interrupted urine flow; the inability to urinate or difficulty starting or stopping urine flow; the need to urinate frequently, especially at night; blood in the urine; or pain or burning with urination, but these symptoms may also be due to a common condition called benign prostatic hyperplasia. Prostate cancer that has spread often presents as bone pain. The 5- and 10-year survival is high in Europe and North America, but lower in some Asian and African countries. For further information see **box 1**.

### Box 1: Cancer incidence and survival

**The cancer incidence rates and figures given here are those reported by cancer registries, now established in many countries. These registries record cases of cancer that have been diagnosed. However, many cases of cancer are not identified or recorded: some countries do not have cancer registries; regions of some countries have few or no records; records in countries suffering war or other disruption are bound to be incomplete; and some people with cancer do not consult a physician. Altogether, this means that the actual incidence of cancer is higher than the figures given here. The cancer survival information given here and elsewhere are usually global averages. Survival rates are generally higher in high-income countries and other parts of the world where there are established services for screening and early detection of cancer and well established treatment facilities. Survival is often a function of the stage at which a cancer is detected and diagnosed. The symptoms of some cancers are often evident only at a late stage, which accounts for the relatively low survival rates.**



### 3. Pathogenesis

The disease usually develops slowly and dysplastic lesions may precede cancer by many years or even decades. The prevalence of latent prostate cancer at autopsy is high and increases with age. Overt and clinically relevant disease is less common. The introduction of PSA screening has contributed to the detection of cancer at an earlier stage. Although this likely contributes to a reduction in mortality, because a significant number of indolent lesions (see section 5.2 for further information) that might never progress to become clinically overt are also detected, many of which are treated, it also leads to the phenomenon of over treatment.

Adenocarcinoma of the prostate is thought to arise primarily from an in situ proliferation of neoplastic prostatic epithelial cells [3]. Metastasis of prostatic adenocarcinoma is mainly to the lymph nodes and to bone.

Non-modifiable risk factors are age, race and familial history. Elevated blood concentrations of insulin-like growth factor (IGF)-1 have been implicated as a potentially modifiable risk factor [4, 5]. Other modifiable risk factors have been suggested but the evidence has been inconsistent.

Genetic susceptibility has been linked to African heritage and familial disease [1]. In the US, African American men are 1.6 times more likely to develop prostate cancer than Caucasian men. A large number of single-nucleotide polymorphisms that modestly affect risk have also been identified [6].

### 4. Other established causes

There are no other established causes of prostate cancer.

## 5. Interpretation of the evidence

### 5.1 General

For general considerations that may affect interpretation of the evidence, see [Judging the evidence](#).

‘Relative risk’ (RR) is used in this report to denote ratio measures of effect, including ‘risk ratios’, ‘rate ratios’, ‘hazard ratios’, and ‘odds ratios’.

## 5.2 Specific

Considerations specific to cancer of the prostate include:

### Prostate-specific antigen (PSA) screening

Prostate cancer leads to an elevated blood concentration of PSA. Although it is highly sensitive for prostate cancer, it is not specific. Levels may be raised due to non-malignant disease, for example benign prostatic hyperplasia. Further more, when only modestly raised, PSA alone cannot distinguish between early stage or indolent tumours which may never be of clinical significance, and more aggressive or later stage cancers. Thus, a decision on initial therapy should be based upon a careful interpretation of prostate biopsy results and considerations of risks and benefits.

Cancers detected at an older age with indolent features can be monitored by a process called active surveillance. Consequently studies of the natural history of screen detected cancers, and of prostate cancers generally in screened populations, will be dominated by the behaviour of the more common but less clinically relevant low grade or indolent tumours. In some populations, such as the US, PSA screening is widely used. However, in other populations, such as Europe, PSA screening is less common. The number of cases of prostate cancer identified by PSA screening is not consistently reported in studies, and few report epidemiological results based upon the grade or stage of cancer detected.

### Prostate cancer heterogeneity

The clinical course of diagnosed prostate cancer varies considerably. Although prostate cancer can spread locally and metastasise, and may be fatal, many men, especially at older ages, are found to have previously undetected and presumably asymptomatic prostate cancers at autopsy. There are several ways of characterising prostate cancers according to grade (aggression) or stage – and while these are related they are not the same. The term ‘advanced’ prostate cancer is sometimes employed in epidemiologic studies and variably defined as higher grade, later stage, and presence of metastatic disease or death. Further research is needed to better define the biological potential of newly diagnosed prostate cancer.

For the purpose of this report advanced prostate cancer is defined as cancers reported in any of the following ways:

- stage 3-4 on the American Joint Committee on Cancer (AJCC) 1992 classification
- advanced cancer
- advanced or metastatic cancer
- metastatic cancer
- stage C or D on the Whitmore/Jewett scale
- fatal cancer (prostate specific mortality)
- high stage or grade
- Gleason grade  $\geq 7$



## **Mortality**

Death from prostate cancer as an outcome in epidemiological studies is also problematic. There is significant competing mortality from other chronic diseases due to prolonged survival after a diagnosis of prostate cancer. Most critically, other cancers and cardiovascular diseases may be associated with similar risk factors (thus a confounder). In addition, death in the metastatic setting during long-term therapy may be recorded as cardiovascular disease or other event.

## **6. Methodology**

To ensure consistency, the methodology for the Continuous Update Project (CUP) remains largely unchanged from that used previously for the Second Expert Report [7]. However, based upon the experience of conducting the systematic literature reviews (SLRs) for the Second Expert Report, some modifications to the methodology were made. The literature search was restricted to Medline and included only randomised controlled trials (RCTs), cohort and case-control studies. Due to their methodological limitations, case-control studies were not included in the Prostate Cancer SLR 2014, unlike the 2005 SLR for the Second Expert Report.

Where possible in the Prostate Cancer SLR 2014 meta-analyses for incidence and mortality were conducted separately. However, analyses combining studies on prostate cancer incidence and mortality were also conducted to explore if this outcome can explain any heterogeneity. Where possible, in addition to total prostate cancer (all types of prostate cancer), stratified analyses were conducted for advanced, non-advanced and fatal prostate cancers.

Studies reporting mean difference as a measure of association are not included in the Prostate Cancer SLR 2014, as relative risks estimated from the mean differences are not adjusted for possible confounders, and thus not comparable to adjusted relative risks from other studies.

Non-linear meta-analysis was applied when the data suggested that the dose-response curve is non-linear, and when detecting a threshold of exposure might be of interest. Details about the non-linear meta-analyses can be found in the Prostate Cancer SLR 2014.

The Prostate Cancer SLR 2014 included studies published up to 30th April 2013. For more information on methodology see the full Prostate Cancer SLR 2014 ([wcrf.org/prostate-cancer-slr](http://wcrf.org/prostate-cancer-slr)).

### **6.1 Mechanistic evidence**

The evidence for mechanisms is summarised under each exposure. These summaries were developed from mechanistic reviews conducted for the Second Expert Report [1], updates from CUP Panel members and published reviews.

*Update: The evidence for site specific mechanisms of carcinogenesis has been updated for the WCRF/AICR Diet, Nutrition, Physical Activity and Cancer: A Global Perspective report 2018 (our Third Expert Report, available at [dietandcancerreport.org](http://dietandcancerreport.org)). The evidence is based on both human and animal studies. It covers the primary hypotheses that are currently prevailing and is not based on a systematic or exhaustive search of the literature. A signpost to the relevant section in the Third Expert Report which summarises the updated mechanisms evidence can be found under each exposure within this report.*

## 7. Evidence and judgements

The following sections summarise the evidence identified in the Prostate Cancer SLR 2014, the Panel's conclusions, and a comparison with the findings from the Second Expert Report. It also includes a brief description of potential mechanisms for each exposure.

For information on the criteria for grading the epidemiological evidence see the Appendix in this report. References to studies added as part of the CUP have been included; for details of references to other studies from the Second Expert Report [7], see the Prostate Cancer SLR 2014.

### 7.1 Dairy products

*(Also see Prostate Cancer SLR 2014: Section 2.7 and 2.7.1)*

#### **Total dairy products**

The Prostate Cancer SLR 2014 identified 14 new or updated studies (15 articles) [8-21] giving a total of 21 studies (25 articles) in the CUP (see Prostate Cancer SLR 2014 table 58 for a full list of references). Of 15 studies (15 estimates) reporting on total prostate cancer incidence, 13 reported a positive association, four of which were significant, and two reported a non-significant inverse association when comparing the highest versus the lowest categories of intake (see Prostate Cancer SLR 2014 figure 59).

Fifteen of the 21 studies were included in the dose-response meta-analysis ( $n = 38,107$ ), which showed a statistically significant 7% increased risk per 400 g of dairy products per day (RR 1.07 (95% CI 1.02-1.12)) (see Prostate Cancer SLR 2014 figure 60). Moderate heterogeneity was observed ( $I^2 = 44\%$ ).

When stratified by prostate cancer type, the dose-response meta-analyses showed no significant association per 400 g per day for non-advanced, advanced, or fatal prostate cancer (see **table 1** and Prostate Cancer SLR 2014 figure 63).

**Table 1: Summary of CUP stratified dose-response meta-analysis – dairy products**

Cancer type	Increment	RR (95% CI)	I <sup>2</sup>	No. Studies	No. Cases
<b>CUP 2014 Non-advanced</b>	Per 400g/day	1.09 (1.00-1.18)	53%	8	16,749
<b>CUP 2014 Advanced</b>	Per 400g/day	0.97 (0.91-1.05)	0%	10	4,465
<b>CUP 2014 Fatal</b>	Per 400g/day	1.11 (0.92-1.33)	20%	5	898

Four studies were not included in any of the CUP analyses due to three reporting insufficient data and one reporting a non-specific exposure.

The Prostate Cancer SLR 2014 findings were similar to the dose-response meta-analysis from the 2005 SLR for total prostate cancer, which included eight studies and showed a statistically significant 6% increased risk per serving per day (RR 1.06 (95% CI 1.01-1.11);  $n = 7,367$ ;  $I^2 = 53\%$ ), but the Prostate Cancer SLR 2014 included 15 studies, more cases of prostate cancer, and had less heterogeneity. There was no stratified analysis for the 2005 SLR.

### Published meta-analyses

The results from two published meta-analyses on dairy products and prostate cancer were identified in the Prostate Cancer SLR 2014 [22, 23]. Both studies reported a statistically significant positive association (RR 1.11 (95% CI 1.03-1.19);  $n = 10,952$  and RR 1.18 (95% CI 1.07-1.30);  $n = 6,708$ , respectively) when comparing highest versus lowest categories of intake.

### Milk

The Prostate Cancer SLR 2014 identified eight new studies (eight articles) [9, 12, 14, 15, 18, 24-26] giving a total of 22 studies (22 articles) in the CUP (see Prostate Cancer SLR 2014 table 62 for a full list of references). Of 15 studies (15 estimates) reporting on total prostate cancer incidence, 12 reported a positive association, three of which were statistically significant, two reported a non-significant inverse association, and one reported no effect (RR 1.00) when comparing the highest versus the lowest categories of intake (see Prostate Cancer SLR 2014 figure 64).

Fourteen of the 22 studies were included in the dose-response meta-analysis ( $n = 11,151$ ), which showed no significant association per 200 g of milk per day (RR 1.03 (95% CI 1.00-1.06)) (see Prostate Cancer SLR 2014 figure 65). Low heterogeneity was observed ( $I^2 = 9\%$ ). There was evidence of non-linearity ( $p = 0.01$ ) with a slight flattening of the dose-response curve at a higher intake (see Prostate Cancer SLR 2014 figure 69 and table 63).

When stratified by prostate cancer type, the dose-response meta-analyses showed no significant association per 200 g per day for non-advanced, advanced, or fatal prostate cancer (see **table 2** and Prostate Cancer SLR 2014 figure 68).

**Table 2: Summary of CUP stratified dose-response meta-analysis – milk**

Cancer type	Increment	RR (95% CI)	I <sup>2</sup>	No. Studies	No. Cases
<b>CUP 2014 Non-advanced</b>	Per 200g/day	1.06 (1.00-1.13)	0%	4	4,092
<b>CUP 2014 Advanced</b>	Per 200g/day	0.98 (0.89-1.09)	0%	4	1,072
<b>CUP 2014 Fatal</b>	Per 200g/day	1.04 (0.73-1.50)	68%	2	253

Six studies were not included in any of the CUP analyses due to five reporting insufficient data, and one reporting a non-specific exposure.

The Prostate Cancer SLR 2014 findings for total prostate cancer were similar to the dose-response meta-analysis from the 2005 SLR, which included eight studies and showed no significant association per serving (RR 1.05 (95% CI 0.98-1.14); *n* = 1,469; I<sup>2</sup> = 25%), but the Prostate Cancer SLR 2014 included 14 studies and over seven times more cases of prostate cancer. There was no stratified analysis for the 2005 SLR.

### Published meta-analyses

The results from two published meta-analyses on milk and prostate cancer were identified in the Prostate Cancer SLR 2014 [22, 23]. Both studies reported a non-significant positive association (RR 1.06 (95% CI 0.91-1.23); *n* = 4,452 and RR 1.21 (95% CI 1.00-1.47); *n* = 1,579) when comparing highest versus lowest categories of intake.

### Other dairy product exposures

The Prostate Cancer SLR 2014 conducted dose-response meta-analyses for whole milk, low-fat milk, cheese and yoghurt and total prostate cancer (see **table 3**). Statistically significant positive associations were found for low fat milk and cheese, and no significant associations were found for whole milk and yoghurt.

**Table 3: Summary of CUP dose-response meta-analysis – other dairy product exposures**

Cancer type	Increment	RR (95% CI)	I <sup>2</sup>	No. Studies	No. Cases
<b>CUP 2014 Whole milk</b>	Per 200g/day	0.98 (0.95-1.01)	0%	8	19,664
<b>CUP 2014 Low-fat milk</b>	Per 200g/day	1.06 (1.01-1.11)	67%	6	19,430
<b>CUP 2014 Cheese</b>	Per 50g/day	1.09 (1.02-1.18)	0%	11	22,950
<b>CUP 2014 Yoghurt</b>	Per 100g/day	1.08 (0.93-1.24)	82%	6	18,282



## Mechanisms

High calcium intake down regulates the formation of 1,25-dihydroxy vitamin D<sub>3</sub>, thereby increasing cell proliferation in the prostate [27]. Prostate cancer tumours in rats treated with 1,25-dihydroxy vitamin D<sub>3</sub> were significantly smaller and presented fewer lung metastases [28]. Also consumption of milk increases blood levels of IGF-1, which has been associated with increased prostate cancer risk in recent pooled and meta-analyses [4, 5, 29].

*Update: As part of the WCRF/AICR Diet, Nutrition, Physical Activity and Cancer: A Global Perspective report, published in 2018, this section on mechanisms has been reviewed and updated. Please see [Exposures: Meat, fish and dairy products](#) (Appendix – Mechanisms) for the updated mechanisms summary.*

### CUP Panel's conclusion:

The evidence for total dairy products showed a significant increased risk per 400 g per day, but the relationship was unclear when stratified by prostate cancer type. For milk, there was evidence of a non-linear dose-response. The CUP Panel concluded:

**For a higher consumption of dairy products, the evidence suggesting an increased risk of prostate cancer is limited.**

## 7.2 Diets high in calcium

*(Also see Prostate Cancer SLR 2014: Section 5.6.3)*

The Prostate Cancer SLR 2014 identified 11 new or updated studies (11 articles) [8, 10-12, 14, 18, 19, 26, 30-32] giving a total of 16 studies (18 articles) in the CUP (see Prostate Cancer SLR 2014 table 223 for a full list of references). Of 15 studies (15 estimates) reporting on total prostate cancer incidence, 13 reported a positive association, of which three were statistically significant, and two reported a non-significant inverse association when comparing the highest versus the lowest categories of intake of dietary calcium (see Prostate Cancer SLR 2014 figure 241).

Fifteen of 16 studies were included in the dose-response meta-analysis ( $n = 38,749$ ), which showed a statistically significant 5% increased risk per 400 mg of dietary calcium per day (RR 1.05 (95% CI 1.02-1.09)) (see Prostate Cancer SLR 2014 figure 242). Moderate heterogeneity was observed ( $I^2 = 49%$ ).

When stratified by prostate cancer type, the dose-response meta-analysis showed statistically significant increased risk per 400 mg per day for non-advanced prostate cancer, and non-significant increased risk per 400 mg per day for advanced prostate cancer (see **table 4** and Prostate Cancer SLR 2014 figure 245).

**Table 4: Summary of CUP stratified dose-response meta-analysis – diets high in calcium**

Cancer type	Increment	RR (95% CI)	I <sup>2</sup>	No. Studies	No. Cases
<b>CUP 2014 Non-advancement</b>	Per 400 mg/day	1.07 (1.03-1.12)	7%	8	9,048
<b>CUP 2014 Advanced</b>	Per 400 mg/day	1.02 (0.93-1.12)	55%	10	3,999

Nine of the 13 studies published after 2003 provided information on PSA testing in the study populations. There was no clear modification of the association between calcium and prostate cancer by PSA testing.

Seven studies investigated dairy sources of calcium and four studies examined non-dairy sources of calcium. The relationship was only significant for dairy calcium (RR 1.06 (95% CI 1.02-1.09); *n* = 10,493; I<sup>2</sup> = 33%).

The Prostate Cancer SLR 2014 findings for total prostate cancer were similar to the dose-response meta-analysis from the 2005 SLR, which included eight studies and showed a significant positive association per 1,000 mg per day (RR 1.27 (95% CI 1.09-1.48); *n* = 7,288) with moderate heterogeneity (I<sup>2</sup> = 46%), but the association was not as strong. The Prostate Cancer SLR 2014 included nearly double the number of studies and more of cases of prostate cancer. There was no stratified analysis for the 2005 SLR.

#### **Published meta-analyses**

The results from two published meta-analyses on dietary calcium and prostate cancer were identified in the Prostate Cancer SLR 2014 [22, 33]. Both meta-analyses on total prostate cancer included five studies (three studies are included in both) and reported statistically significant positive associations when comparing highest versus lowest categories of intake (RR 1.15 (95% CI 1.02-1.30); *n* = 8,327 and RR 1.38 (95% CI 1.04-1.83); *n* = 6,970; I<sup>2</sup> = 54%, respectively). One of the meta-analyses also conducted analysis for four studies on advanced prostate cancer, and reported a non-significant positive association (RR 1.46 (95% CI 0.65-3.25); *n* = 6,834; I<sup>2</sup> = 72%) when comparing highest versus lowest intake categories.

#### **Other calcium exposures**

The Prostate Cancer SLR 2014 included a total of nine cohort studies on calcium supplements. Dose-response meta-analysis of four studies on total, advanced, and non-advanced prostate cancer showed no significant association (see Prostate Cancer SLR 2014 figure 250). Two studies were included in the dose-response meta-analysis on fatal prostate cancer and calcium supplements, which showed a significant positive effect (RR 1.29 (95% CI 1.08-1.54) see Prostate Cancer SLR 2014 figure 250). One RCT was included in the CUP, which showed a non-significant inverse association. See Section 5.6.3 of the Prostate Cancer SLR 2014 for further information.



## Mechanisms

Calcium can be taken to be a marker for dairy product intake in high-income populations. In areas outside the USA, Europe and Oceania, dairy products are not as widely consumed, and the range of calcium intakes is smaller.

High calcium intake down regulates the formation of 1,25-dihydroxy vitamin D<sub>3</sub>, thereby increasing cell proliferation in the prostate. Prostate cancer tumours in rats treated with 1,25-dihydroxy vitamin D<sub>3</sub> were significantly smaller and presented fewer lung metastases [27]. Also, consumption of milk increases blood levels of IGF-1, which has been associated with increased prostate cancer risk in some studies [28].

*Update: As part of the WCRF/AICR Diet, Nutrition, Physical Activity and Cancer: A Global Perspective report, published in 2018, this section on mechanisms has been reviewed and updated. Please see [Exposures: Meat, fish and dairy products](#) (Appendix – Mechanisms) for the updated mechanisms summary.*

### CUP Panel's conclusion:

There was evidence of a dose-response relationship between dietary calcium and total prostate cancer. However, in the stratified analyses the association was not significant for advanced prostate cancer, whereas it was for non-advanced prostate cancer. No conclusion could be drawn for calcium supplements. The CUP Panel concluded:

**For diets high in calcium, the evidence suggesting an increased risk of prostate cancer is limited.**

## 7.3 Beta-carotene

(Also see Prostate Cancer SLR 2014: Section 5.5.1.2)

### Dietary beta-carotene

The Prostate Cancer SLR 2014 identified six new or updated studies (six articles) [34-39] giving a total of 11 studies (13 articles) in the CUP (see Prostate Cancer SLR 2014 table 163 for a full list of references). Of eight studies reporting on total prostate cancer incidence, four reported a non-significant positive association, and four a non-significant inverse association when comparing the highest versus the lowest categories of intake (see Prostate Cancer SLR 2014 figure 177). Of two studies reporting on prostate cancer mortality, one reported a non-significant positive association, and one a non-significant inverse association when comparing the highest versus the lowest categories of intake.

Ten of the 11 studies were included in the dose-response meta-analysis ( $n = 12,219$ ), which showed no effect per 700 µg of dietary beta-carotene per day (RR 1.00 (95% CI 0.99-1.00)) (see **figure 1** (Prostate Cancer SLR 2014 figure 178)). No heterogeneity was observed.

**Figure 1: Dose-response meta-analysis of dietary beta-carotene and total prostate cancer, per 700 µg/day**



One study was not included in any of the CUP analyses due to reporting insufficient data.

The Prostate Cancer SLR 2014 findings strengthened the findings of the dose-response meta-analysis from the 2005 SLR, which included six studies and showed no association per 700 µg per day (RR 1.00 (95% CI 0.99-1.01);  $n = 2,101$ ), but the Prostate Cancer SLR 2014 included more cohort studies and more cases of prostate cancer.

### Serum beta-carotene

The Prostate Cancer SLR 2014 identified six new or updated studies (six articles) [40-45], giving a total of 14 studies (17 articles) in the CUP (see Prostate Cancer SLR 2014 table 172 for a full list of references). Of 13 studies (13 estimates) reporting on total prostate cancer incidence, four reported a positive association, one of which was statistically significant, and nine reported an inverse association, of which one was statistically significant when comparing the highest versus the lowest categories (see Prostate Cancer SLR 2014 figure 185).

Nine of the 14 studies were included in the dose-response meta-analysis ( $n = 3,449$ ), which showed no significant association per 10 µg per 100 ml of serum beta-carotene (RR 0.99 (95% CI 0.95-1.04)) (see Prostate Cancer SLR 2014 figure 186). Moderate heterogeneity was observed ( $I^2 = 38%$ ).

When stratified by outcome, the dose-response meta-analysis showed no significant association per 10 µg per 100 ml (RR 0.97 (95% CI 0.85-1.12);  $n = 639$ ;  $I^2 = 70\%$ ) for three studies on advanced prostate cancer (see Prostate Cancer SLR 2014 figure 189).

One study was not included in any of the CUP analyses due to reporting insufficient data.

The Prostate Cancer SLR 2014 findings were similar to the dose-response meta-analysis from the 2005 SLR, which included six studies and showed no association per 10 µg per 100 ml (RR 1.00 (95% CI 0.91-1.09);  $n = 1,499$ ) with moderate heterogeneity ( $I^2 = 44\%$ ), but the Prostate Cancer SLR 2014 included nine cohort studies and more cases of prostate cancer. There was no stratified analysis in the 2005 SLR.

### Beta-carotene supplements

The Prostate Cancer SLR 2014 identified three new cohort studies (three articles) [35, 39, 42], giving a total of five cohort studies (five articles) in the CUP (see Prostate Cancer SLR 2014 table 164 for a full list of references). The main analyses reported no significant association between beta-carotene supplements and total prostate cancer. No dose-response meta-analysis was possible.

Three RCT studies (five articles) were included in the 2005 SLR, all reported no significant association (see **table 5** below).

**Table 5: Summary of randomised controlled trials – beta-carotene supplements**

Trial Name	No. Participants	Intervention	Length of intervention	Length of follow-up	RR (95% CI)
<b>Beta-carotene and Retinol Efficacy Trial (CARET) [46] [47]</b>	18,314 at high risk of developing lung cancer	30 mg beta-carotene and 25,000 IU retinyl palmitate	4 years (trial ended early)	5 years	1.01 (0.80-1.27)
<b>Physicians' Health Study (PHS)[48]</b>	22,071	50 mg beta-carotene taken on alternate days	13 years		1.00 (0.90-1.10)
<b>Alpha-Tocopherol Beta-Carotene Cancer Prevention (ATBC) Study (male smokers) [49] [50]</b>	29,133	20 mg of beta-carotene only or with 50 mg of alpha-tocopherol	5-8 years	6-8 years	1.26 (0.98-1.62) for the 1985-1993 follow-up period

### CUP Panel's conclusion:

There is strong evidence from good quality cohort studies on dietary intake, serum levels and supplement use, which consistently fail to demonstrate an association. There was no evidence of an adverse or protective effect using supplements at doses of 20, 30, and 50 mg/day. The CUP Panel concluded:

**Consuming beta-carotene in supplements or foods containing beta-carotene is unlikely to have substantial effect on the risk of prostate cancer.**

## 7.4 Low plasma alpha-tocopherol concentrations

(Also see *Prostate Cancer SLR 2014: Section 5.5.11*)

The Prostate Cancer SLR 2014 identified five new or updated studies (five articles) [41-43, 51, 52] giving a total of 12 studies (17 articles) in the CUP (see Prostate Cancer SLR 2014 table 210 for a full list of references). Of 11 studies (11 estimates) reporting on total prostate cancer incidence, three reported a non-significant positive association, and eight reported an inverse association, two of which were significant when comparing the highest versus the lowest alpha-tocopherol concentrations (see Prostate Cancer SLR 2014 figure 226).

Nine of the 12 studies were included in the dose-response meta-analysis ( $n = 4,989$ ), which showed no significant association per 1 mg/L of plasma alpha-tocopherol (RR 0.99 (95% CI 0.98-1.00)) (see Prostate Cancer SLR 2014 figure 227). No heterogeneity was observed.

When stratified by prostate cancer type, the dose-response meta-analysis showed no significant association per 1 mg/L (RR 0.98 (95% CI 0.97-1.00);  $n = 948$ ; 4 studies) for advanced prostate cancer (see Prostate Cancer SLR 2014 figure 230). Low heterogeneity was observed ( $I^2 = 22\%$ ).

One study was not included in any of the CUP analyses due to insufficient data.

The Prostate Cancer SLR 2014 findings for total prostate cancer were similar to the dose-response meta-analysis from the 2005 SLR, which included seven studies and showed no significant association per 1 mg/L (RR 0.98 (95% CI 0.97-1.00);  $n = 1,482$ ) with no heterogeneity, but the Prostate Cancer SLR 2014 included two more studies and more cases of prostate cancer. There was no stratified analysis in the 2005 SLR.

### Other vitamin E exposures

The Prostate Cancer SLR 2014 conducted dose-response meta-analyses for dietary vitamin E, dietary alpha-tocopherol, serum gamma-tocopherol, vitamin E supplements, and total prostate cancer. No significant associations were found (see **table 6**).

For dietary alpha-tocopherol, four studies ( $n = 14,141$ ) were included in the CUP, but no meta-analysis was possible.



**Table 6: Summary of CUP dose-response meta-analysis – other vitamin E exposures**

Exposure	Increment	RR (95% CI)	I <sup>2</sup>	No. Studies	No. Cases
<b>CUP 2014 Dietary vitamin E</b>	Per 10 mg/day	1.01 (0.96-1.06)	20%	5	11,112
<b>CUP 2014 Serum gamma-tocopherol</b>	Per 1 mg/L	0.97 (0.91-1.04)	52%	7	2,742
<b>CUP 2014 Vitamin E supplements</b>	Per 100 IU/day	1.00 (0.99-1.01)	0%	7	21,862

### Mechanisms

Alpha-tocopherol is the most biologically potent of the eight naturally occurring isomers of vitamin E. Vitamin E is an antioxidant that has been reported to prevent deoxyribonucleic acid (DNA) damage, enhance DNA repair, prevent lipid peroxidation, and prevent activation of carcinogens such as nitrosamines. In addition to acting as a free radical scavenger, vitamin E enhances the body's immune response, which may play a role in cancer defences.

*Update: As part of the WCRF/AICR Diet, Nutrition, Physical Activity and Cancer: A Global Perspective report, published in 2018, this section on mechanisms has been reviewed and updated. Please see [Exposures: Other dietary exposures \(Appendix – Mechanisms\)](#) for the updated mechanisms summary.*

### CUP Panel's conclusion:

The evidence was generally consistent with little or no heterogeneity. No conclusion could be drawn for serum gamma-tocopherol and vitamin E from diet and supplements. The CUP Panel concluded:

**For low plasma alpha-tocopherol concentrations, the evidence suggesting an increased risk of prostate cancer is limited.**

## 7.5 Low plasma selenium concentrations

(Also see *Prostate Cancer SLR 2014: Section 5.6.4*)

The Prostate Cancer SLR 2014 identified four new studies (four articles) [40, 43, 53, 54] giving a total of 17 studies (17 articles) in the CUP (see Prostate Cancer SLR 2014 table 241 for a full list of references). Three studies reported on plasma selenium and 14 on serum selenium. Of 10 studies (10 estimates) reporting on total prostate cancer incidence, seven reported an inverse association, two of which were statistically significant, and three reported a non-significant positive association when comparing the highest versus the lowest categories (see Prostate Cancer SLR 2014 figure 262).

Nine of the 17 were included in the dose-response meta-analysis ( $n = 3,559$ ), which showed no significant association per 10  $\mu\text{g/L}$  of plasma selenium (RR 0.95 (95% CI 0.91-1.00)) (see Prostate Cancer SLR 2014 figure 263). Low heterogeneity was observed ( $I^2 = 29\%$ ). Egger's test for publication bias was statistically significant ( $p < 0.01$ ). Asymmetry in the funnel plot suggests small studies showing a positive association have not been published (see Prostate Cancer SLR 2014 figure 264).

When stratified by prostate cancer types the dose-response meta-analysis showed no significant association for non-advanced and advanced prostate cancers per 10  $\mu\text{g/L}$  (see table 7 and Prostate Cancer SLR 2014 figure 266).

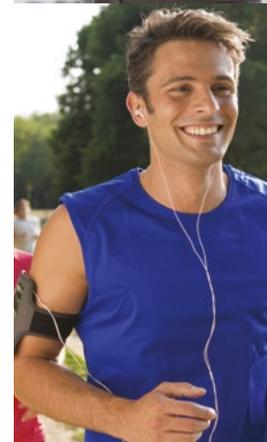
**Table 7: Summary of CUP stratified dose-response meta-analysis – low plasma selenium concentration**

Cancer type	Increment	RR (95% CI)	$I^2$	No. Studies	No. Cases
<b>CUP 2014 Non-advanced</b>	Per 10 $\mu\text{g/L}$	0.99 (0.95-1.03)	0%	4	1,879
<b>CUP 2014 Advanced</b>	Per 10 $\mu\text{g/L}$	0.95 (0.89-1.00)	0%	5	1,500

There was evidence of non-linearity for advanced prostate cancer ( $p = 0.04$ ). The slope was steeper at lower concentrations of serum selenium (see Prostate Cancer SLR 2014 figure 267 and table 242).

Seven studies were not included in any of the CUP analyses due to insufficient data.

The Prostate Cancer SLR 2014 findings on total prostate cancer were similar to the dose-response meta-analysis from the 2005 SLR, which showed no significant association per 10  $\mu\text{g/L}$  (RR 0.95 (95% CI 0.89-1.00);  $n = 1,329$ ;  $I^2 = 58\%$ ), but the Prostate Cancer SLR 2014 included more studies, more than double the number of cases of prostate cancer, and had less heterogeneity. For advanced prostate cancer, the 2005 SLR showed a statistically significant inverse association per 10  $\mu\text{g/L}$  (RR 0.87 (95% CI 0.79-0.97);  $n = 835$ ;  $I^2 = 0\%$ ), differing from the non-significant finding in the Prostate Cancer SLR 2014 that included three more studies and more cases of prostate cancer.



## Published meta-analyses

The results from one published meta-analysis on plasma or serum selenium and prostate cancer was identified in the Prostate Cancer SLR 2014 [55]. For total prostate cancer, the non-linear dose-response analysis of seven cohorts and two case-control studies ( $n = 3,579$ ) reported a significant inverse association at 135  $\mu\text{g/L}$  (RR 0.85 (95% CI 0.74-0.97)) and 170  $\mu\text{g/L}$  (RR 0.75 (95% CI 0.65-0.86)). Two studies included in the Prostate Cancer SLR 2014 were not included in this meta-analysis. For advanced prostate cancer, the non-linear dose-response analysis of six cohort studies ( $n = 876$ ) reported a significant inverse association at 135  $\mu\text{g/L}$  (RR 0.60 (95% CI 0.45-0.81)) and 170  $\mu\text{g/L}$  (RR 0.50 (95% CI 0.36-0.68)). Another meta-analysis of two cohorts and one case-control study reported a significant inverse association (RR 0.29 (95% CI 0.14-0.61)) between prostate cancer and a toenail selenium concentration between 0.85 and 0.94  $\mu\text{g/g}$ .

## Other selenium exposures

The Prostate Cancer SLR 2014 included a total of five studies in the CUP on selenium supplements, but no meta-analysis was possible. One new RCT was identified (SELECT trial), giving a total of two RCTs. SELECT reported that selenium supplements, taken alone or with vitamin E, did not reduce risk of prostate cancer. See Section 5.6.4 of the Prostate Cancer SLR 2014 for further information.

## Mechanisms

Dietary selenium deficiency has been shown to cause a lack of selenoprotein expression. Twenty-five selenoproteins have been identified in animals and a number of these have important anti-inflammatory and antioxidant properties. Four are glutathione peroxidases, which protect against oxidative damage to biomolecules such as lipids, lipoproteins, and DNA. Three are thioredoxin reductases; among other functions these reduce oxidised ascorbic acid to its active antioxidant form.

In addition, selenoproteins are involved in testosterone production, which is an important regulator of both normal and abnormal prostate growth.

*Update: As part of the WCRF/AICR Diet, Nutrition, Physical Activity and Cancer: A Global Perspective report, published in 2018, this section on mechanisms has been reviewed and updated. Please see [Exposures: Other dietary exposures](#) (Appendix – Mechanisms) for the updated mechanisms summary.*

## CUP Panel's conclusion:

There was evidence of a non-linear dose-response relationship showing an inverse relationship between plasma selenium and prostate cancer at low plasma concentrations. No conclusion could be drawn for selenium supplements. The CUP Panel concluded:

**For low plasma selenium concentrations, the evidence suggesting an increased risk of prostate cancer is limited.**

## 7.6 Body fatness (advanced prostate cancer)

(Also see *Prostate Cancer SLR 2014: Sections 8.1.1, 8.2.1, and 8.2.3*)

Analyses were performed for body fatness and total, advanced, and non-advanced prostate cancer, but conclusions could only be drawn for advanced prostate cancer.

The Panel interpreted body mass index (BMI), waist circumference, and waist-hip ratio as measures of body fatness. The Panel is aware that these anthropometric measures are imperfect and cannot distinguish between lean mass and fat mass.

### Body mass index (BMI)

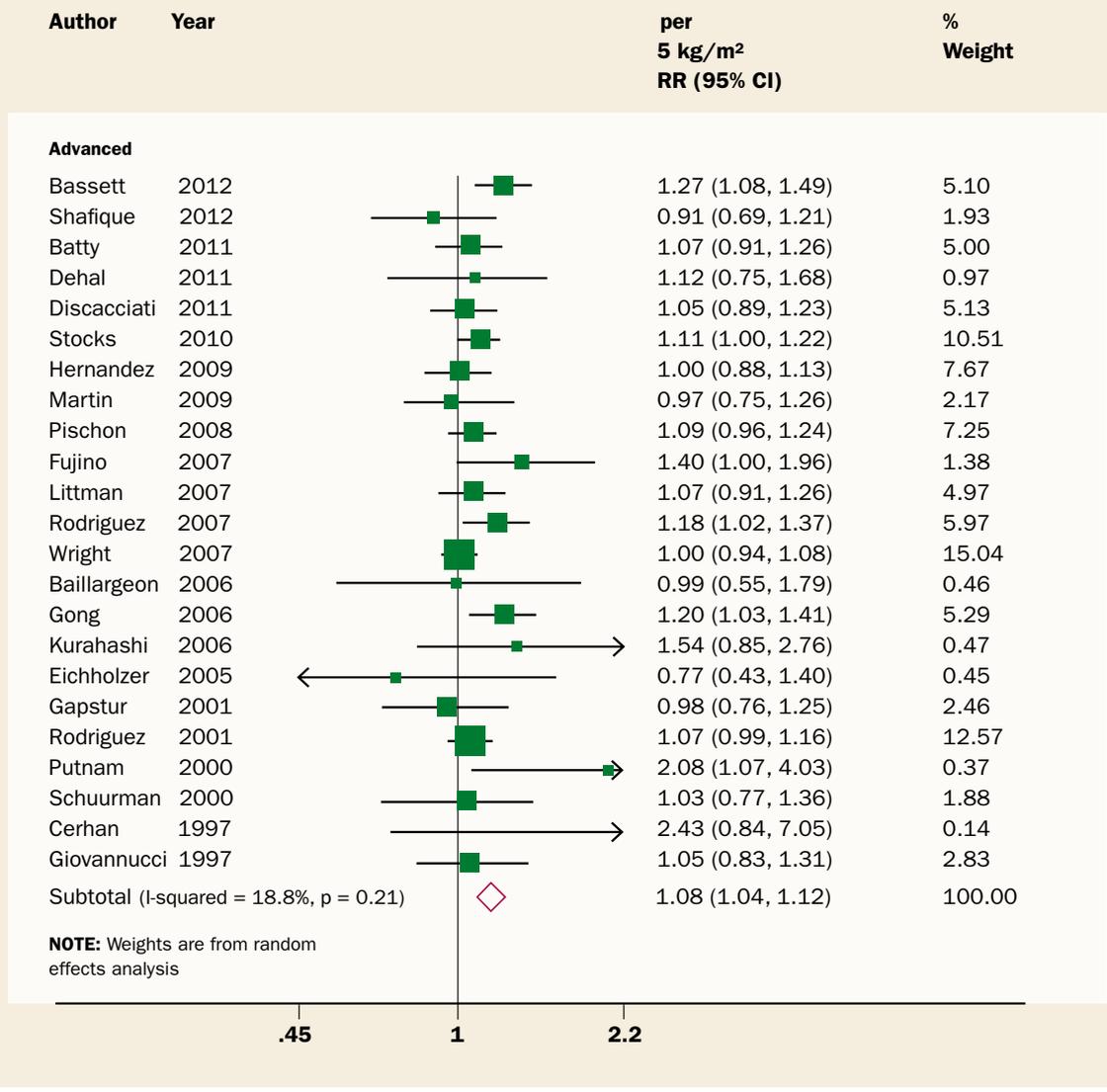
The CUP identified 18 new or updated studies (19 articles) [37, 56-73], giving a total of 24 studies (26 articles) on advanced prostate cancer in the CUP (see *Prostate Cancer SLR 2014 table 257* for a full list of references). Of 15 studies (15 estimates) reporting on advanced prostate cancer incidence, 13 reported a positive association, of which two were statistically significant, and two reported an inverse association, of which one was statistically significant when comparing the highest versus the lowest categories (see *Prostate Cancer SLR 2014 figure 284*). Six studies (six estimates) reported on prostate cancer mortality, of which three reported a non-significant positive association, two reported a non-significant inverse association, and one reported no association (RR 1.00) for the highest versus the lowest categories.

Twenty-three of 24 studies on advanced prostate cancer were included in the dose-response meta-analysis ( $n = 11,149$ ), which showed a statistically significant 8% increased risk per 5 kg/m<sup>2</sup> (RR 1.08 (95% CI 1.04-1.12)) (see **figure 2** (*Prostate Cancer SLR 2014 figure 285*)). Low heterogeneity was observed ( $I^2 = 19%$ ).

For prostate cancer mortality, the dose-response meta-analysis of 12 studies showed statistically significant 11% increased risk per 5 kg/m<sup>2</sup> (RR 1.11 (95% CI 1.06-1.17);  $n = 9,820$ ;  $I^2 = 20%$ ) (see *Prostate Cancer SLR 2014 figure 282*).



**Figure 2 Dose-response meta-analysis of BMI and advanced prostate cancer, per 5 kg/m<sup>2</sup>**



Five of the studies on advanced prostate cancer investigated the influence of PSA tests and no studies identified a modification of the association. Three of the studies reported a lower proportion of screening or PSA testing in obese men.

The Prostate Cancer SLR 2014 findings on advanced prostate cancer were in contrast to the dose-response meta-analysis from the 2005 SLR that included two studies and showed a non-significant inverse association per 5 kg/m<sup>2</sup> (RR 0.99 (95% CI 0.96-1.01); *n* = 633; *I*<sup>2</sup> = 0%), but the Prostate Cancer SLR 2014 included more studies and cases of advanced prostate cancer.

## Published meta-analyses

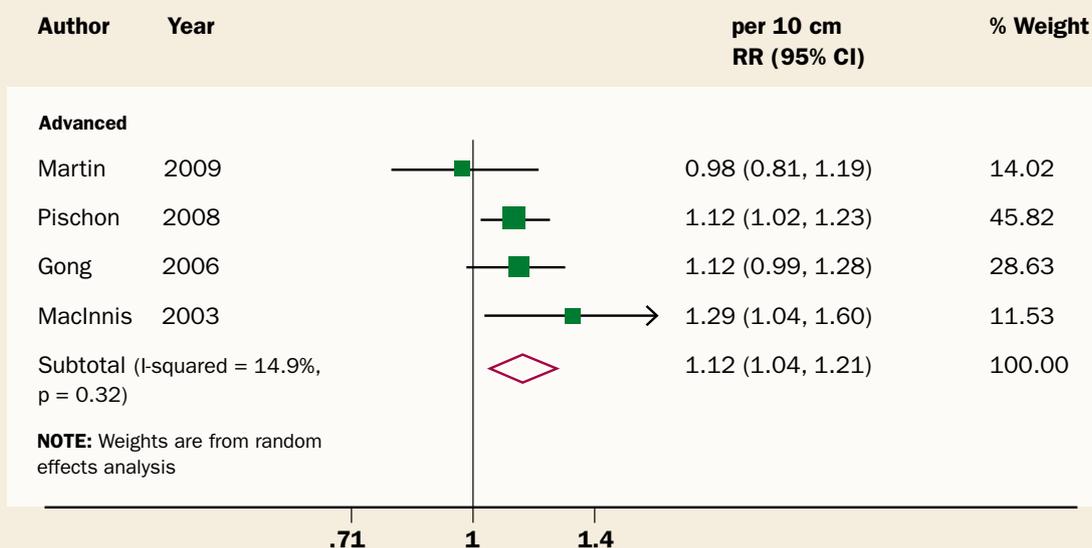
The results from two published meta-analyses on BMI and advanced prostate cancer were identified in the Prostate Cancer SLR 2014 [74, 75]. One meta-analysis included 13 studies and the other included six studies; both reported a statistically significant positive association per 5 kg/m<sup>2</sup> (RR 1.09 (95% CI 1.02-1.25); *n* = 7,067; I<sup>2</sup> = 38% and RR 1.15 (1.06-1.25); *n* = 6,817; I<sup>2</sup> = 59%).

## Waist circumference

The Prostate Cancer SLR 2014 identified three new studies (four articles) [58, 59, 63, 76], giving a total of five studies (six articles) on advanced prostate cancer in the CUP (see Prostate Cancer SLR 2014 table 271 for a full list of references). Of three studies (three estimates) reporting on advanced prostate cancer incidence, all three reported a non-significant positive association when comparing the highest versus the lowest categories (see Prostate Cancer SLR 2014 figure 305).

Four of the five studies on advanced prostate cancer were included in the dose-response meta-analysis (*n* = 1,781), which showed a statistically significant 12% increased risk per 10 cm (RR 1.12 (95% CI 1.04-1.21)) (see **figure 3** (Prostate Cancer SLR 2014 figure 306)). Low heterogeneity was observed (I<sup>2</sup> = 15%).

**Figure 3 Dose-response meta-analysis of waist circumference and advanced prostate cancer, per 10 cm**



The Prostate Cancer SLR 2014 strengthened the 2005 SLR findings on advanced prostate cancer, in which one study showed a non-significant positive relationship (RR 1.04 (95% CI 0.98-1.10); *n* = 423) per 10 cm, but the Prostate Cancer SLR 2014 included four studies and more cases of advanced prostate cancer.

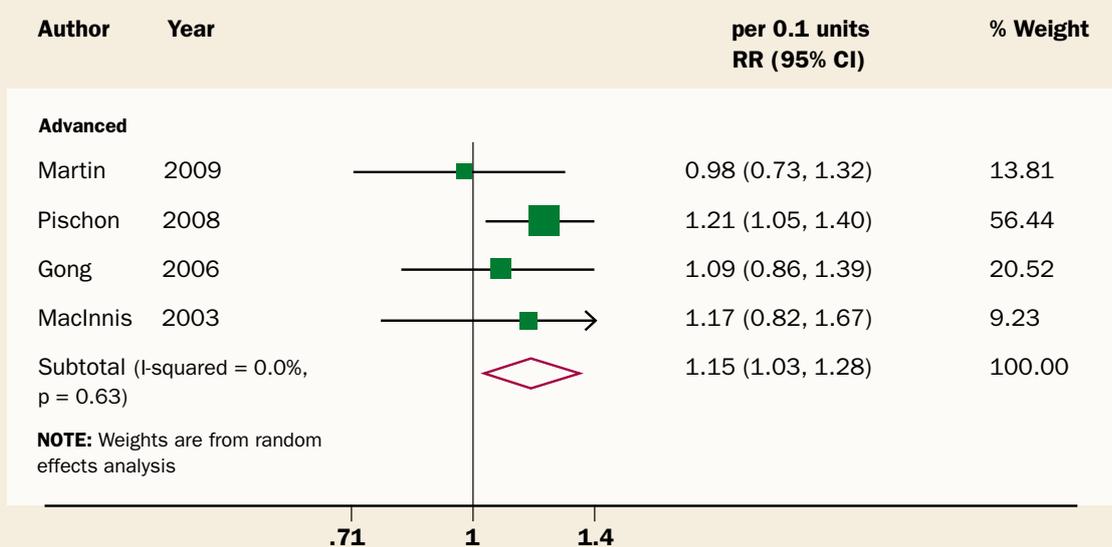


## Waist-hip ratio

The Prostate Cancer SLR 2014 identified three new studies (three articles) [58, 59, 63] giving a total of four studies (four articles) on advanced prostate cancer in the CUP (see Prostate Cancer SLR 2014 table 276 for a full list of references). Of three studies (three estimates) reporting on advanced prostate cancer incidence, three reported a positive association, of which one was statistically significant when comparing the highest versus the lowest categories (see Prostate Cancer SLR 2014 figure 312).

All four studies on advanced prostate cancer were included in the dose-response meta-analysis ( $n = 1,781$ ), which showed a statistically significant 15% increased risk per 0.1 units (RR 1.15 (95% CI 1.03-1.28)) (see **figure 4** (Prostate Cancer SLR 2014 figure 313)). No heterogeneity was observed.

**Figure 4 Dose-response meta-analysis of waist-hip ratio and advanced prostate cancer, per 0.1 units**



The Prostate Cancer SLR 2014 strengthened the 2005 SLR findings on advanced prostate cancer, in which one study showed a non-significant positive relationship (RR 1.03 (95% CI 0.93-1.14)) per 0.1 unit, the Prostate Cancer SLR 2014 included four studies and more cases of advanced prostate cancer.

## Mechanisms

Obesity influences the levels of a number of hormones and growth factors [77]. Insulin and leptin are elevated in obese people, and can promote the growth of cancer cells. In addition, insulin resistance is increased, in particular by abdominal fatness, and the pancreas compensates by increasing insulin production. This hyperinsulinaemia increases the risk of cancers of the colon and endometrium, and possibly of the pancreas and kidney.

Sex steroid hormones, including oestrogens, androgens, and progesterone, are likely to play a role in obesity and cancer [77]. In men, obesity is related to lower serum testosterone levels, which in turn may be associated with enhanced risk of or adverse outcome in advanced prostate cancer. Because testosterone plays an important role in determining the differentiation status of the prostate epithelium, decreased levels of testosterone may facilitate the growth of a less differentiated, aggressive prostate cancer phenotype [78].

Obesity is associated with a low-grade chronic inflammatory state. Obese adipose tissue is characterised by macrophage infiltration and these macrophages are an important source of inflammation. The adipocyte (fat cell) produces pro-inflammatory factors, and obese individuals have elevated concentrations of circulating tumour necrosis factor (TNF)-alpha, interleukin (IL)-6, and C-reactive protein, compared with lean people, as well as of leptin, which also functions as an inflammatory cytokine. Such chronic inflammation can promote cancer development [79].

*Update: As part of the WCRF/AICR Diet, Nutrition, Physical Activity and Cancer: A Global Perspective report, published in 2018, this section on mechanisms has been reviewed and updated. Please see [Exposures: Body fatness and weight gain](#) (Appendix – Mechanisms) for the updated mechanisms summary.*

### CUP Panel's conclusions

The evidence was consistent for a dose-response relationship for advanced prostate cancer. There is also evidence of plausible mechanisms. No conclusion could be drawn for total or non-advanced prostate cancer. The CUP Panel concluded:

**Greater body fatness (marked by BMI, waist circumference, and waist-hip ratio) is probably a cause of advanced prostate cancer.**

## 7.7 Adult attained height

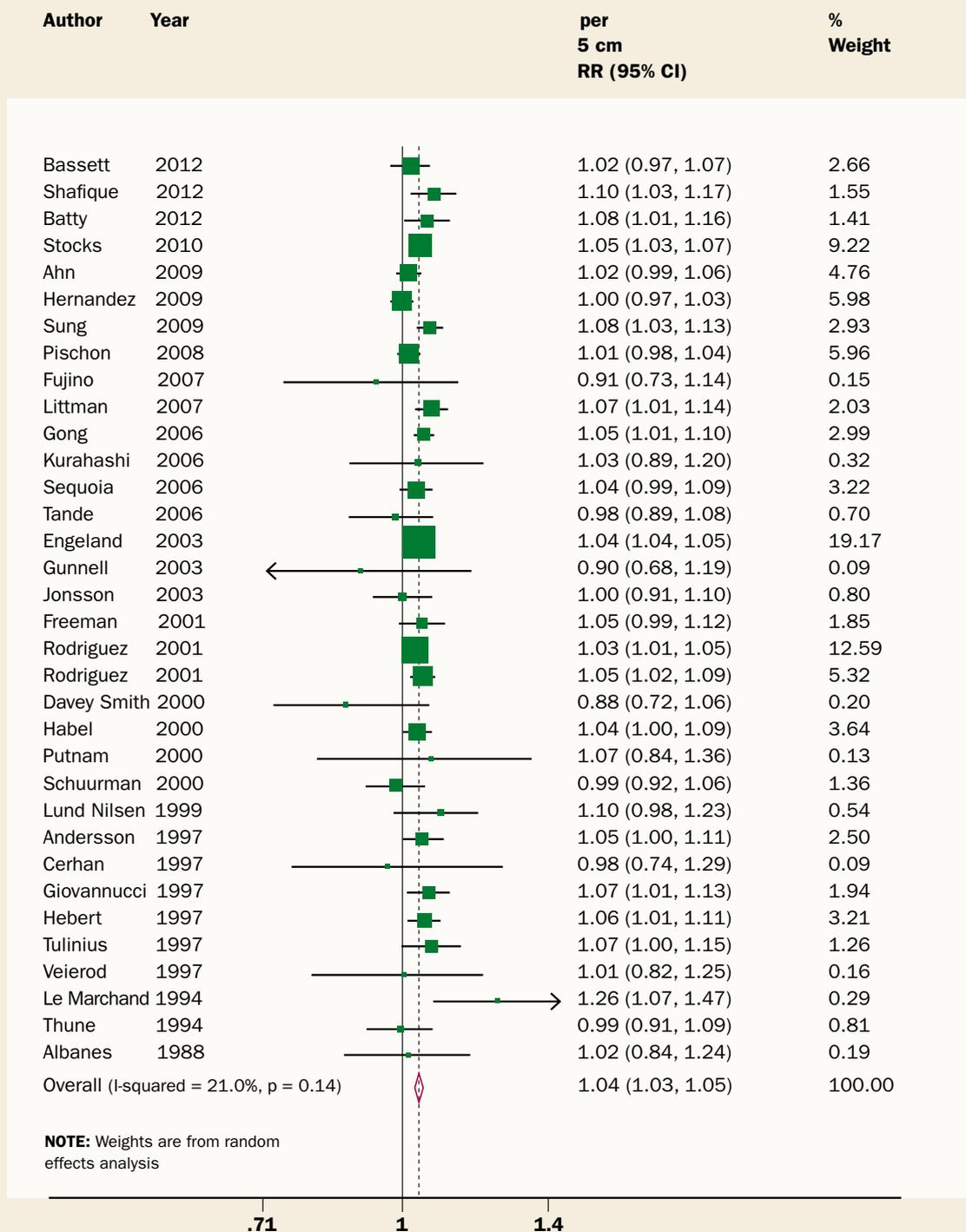
*(Also see Prostate Cancer SLR 2014: Section 8.3.1)*

The Prostate Cancer SLR 2014 identified 17 new or updated studies (20 articles) [24, 37, 42, 56, 59-61, 63, 64, 66, 67, 69, 72, 76, 80-85] giving a total of 42 studies (53 articles) in the CUP (see Prostate Cancer SLR 2014 table 280 for a full list of references). Of 25 studies (25 estimates) reporting on total prostate cancer incidence, 22 reported a positive association, five of which were statistically significant, two showed a non-significant negative association and one showed no association (RR 1.00) when comparing the highest versus the lowest categories (see Prostate Cancer SLR 2014 figure 314). Of five studies (five estimates) reporting on prostate cancer mortality, four reported a positive association, two of which were significant, and one reported a non-significant inverse association when comparing the highest versus lowest categories.



Thirty-four of the 42 studies were included in the dose-response meta-analysis ( $n = 79,387$ ), which showed a statistically significant 4% increased risk per 5 cm (RR 1.04 (95% CI 1.03-1.05)) (see **figure 5** (Prostate Cancer SLR 2014 figure 315)). Low heterogeneity was observed ( $I^2 = 21\%$ ).

**Figure 5: Dose-response meta-analysis of height and prostate cancer, per 5 cm**



When stratified by prostate cancer outcome the dose-response meta-analysis showed statistically significant increased risk per 5 cm for non-advanced, advanced and fatal prostate cancer (see **table 8** and Prostate Cancer SLR 2014 figures 318 and 320). There was evidence for non-linearity for total and advanced prostate cancer ( $p = 0.01$  and  $p < 0.01$ , respectively), but not for non-advanced prostate cancer (see Prostate Cancer SLR 2014 figures 322 and 323 and tables 281 and 282). For total prostate cancer there was evidence of a greater slope at shorter heights and for advanced prostate cancer there was evidence for a greater slope at taller heights.

**Table 8: Summary of CUP stratified dose-response meta-analysis – height**

Cancer type	Increment	RR (95% CI)	I <sup>2</sup>	No. Studies	No. Cases
<b>CUP 2014 Non-advanced</b>	Per 5 cm	1.03 (1.01-1.05)	19%	10	16,749
<b>CUP 2014 Advanced</b>	Per 5 cm	1.04 (1.02-1.06)	47%	19	4,465
<b>CUP 2014 Fatal</b>	Per 5 cm	1.04 (1.01-1.06)	36%	9	898

Eight studies were not included in any of the CUP analyses due to insufficient data.

The Prostate Cancer SLR 2014 findings were in contrast to the dose-response meta-analysis from the 2005 SLR, which included 23 studies and showed a non-significant positive association per 10 cm (RR 1.02 (95% CI 0.97-1.08);  $n = 46,729$ ) with high heterogeneity ( $I^2 = 86%$ ), but the Prostate Cancer SLR 2014 included more studies and more cases of prostate cancer.

#### Published pooled and meta-analyses

The results from two published pooled analyses and one meta-analysis on height and prostate cancer were identified in the Prostate Cancer SLR 2014 [86-88]. One pooled analysis reported a statistically significant positive association, which is consistent with the Prostate Cancer SLR 2014. The second pooled analysis reported a non-significant positive association, but included only 274 cases. Results are presented in **table 9**. The published meta-analysis included 31 studies and reported a statistically significant positive association per 10 cm (RR 1.09 (95% CI 1.06-1.12);  $n = 1,357$ ;  $I^2 = 23%$ ).



**Table 9: Summary of CUP meta-analysis and pooled analyses – height**

Analysis	Increment	RR (95% CI)	I <sup>2</sup>	No. Studies	No. Cases	Factors adjusted for
<b>CUP Prostate Cancer SLR 2014</b>	Per 5 cm	1.04 (1.03-1.05)	21%	34	79,387 incidence & mortality	
<b>Emerging Risk Factor Collaboration [88]</b>	Per 6.5 cm	1.07 (1.02-1.11)	9%	121	2,818 mortality	Age, sex, smoking, year of birth
<b>Asia Pacific Cohort Studies Collaboration [87]</b>	Per 6 cm	1.06 (0.95-1.18)	-	38	274 mortality	Age, study, year of birth

### Mechanisms

Factors that lead to greater adult attained height, or their consequences, are a cause of a number of cancers. Adult height is related to the rate of growth during fetal life and childhood [89, 90]. Health and nutrition status in the neonatal period and childhood may impact on the age of sexual maturity. These processes are mediated by changes in the hormonal microenvironment that may have both short- and long-term effects on circulating levels of growth factors, insulin, and other endocrine or tissue specific mediators that may influence cancer risk [91].

*Update: As part of the WCRF/AICR Diet, Nutrition, Physical Activity and Cancer: A Global Perspective report, published in 2018, this section on mechanisms has been reviewed and updated. Please see [Exposures: Height and birthweight](#) (Appendix – Mechanisms) for the updated mechanisms summary.*

### CUP Panel’s conclusions

The evidence was consistent for a dose-response relationship for total, non-advanced, advanced and fatal prostate cancers. There is also evidence of plausible mechanisms. The CUP Panel concluded:

**Developmental factors leading to greater linear growth (marked by adult attained height) are probably a cause of prostate cancer.**

## 7.8 Other

Other exposures were evaluated. However, data were either of too low quality, too inconsistent, or the number of studies too few to allow conclusions to be reached. This list of exposures judged as ‘Limited-no conclusion’ is summarised in the matrix on **page 9**.

The evidence for foods containing lycopene and for selenium supplements previously judged as ‘probable’ decreases risk in the Second Expert Report was limited (see section 5.2) and the Panel could not draw any conclusions on the updated evidence.

The evidence for pulses (legumes), and alpha-tocopherol supplements previously judged as ‘limited - suggestive’ decreases risk and processed meat as ‘limited - suggestive’ increases risk in the Second Expert Report, was less consistent and the Panel could not draw any conclusions on the updated evidence.

Evidence for the following exposures previously judged as ‘limited-no conclusion’ in the Second Expert Report, remain unchanged after updating the analyses with new data identified in the Prostate Cancer SLR 2014: non-starchy vegetables, fruits, red meat, poultry, fish, eggs, total fat, saturated fatty acids, monounsaturated fatty acids, polyunsaturated fatty acids, coffee, tea, alcoholic drinks, carbohydrate, retinol, alpha-carotene, vitamin C, vitamin D, vitamin E supplements, gamma-tocopherol, multivitamins, physical activity, birth weight, vegetarian diets, and energy intake.

The following exposures, also previously too limited to draw conclusions in the Second Expert Report and not updated as part of the Prostate Cancer SLR 2014 due to a lack of new evidence, remain ‘limited - no conclusion’: Cereals (grains) and their products, dietary fibre, potatoes, plant oils, sugar (sucrose), sugary foods and drinks, protein, vitamin A, thiamin, riboflavin, niacin, iron, phosphorus, zinc, energy expenditure, and Seventh-day Adventist diets.

In addition, evidence for the following new exposures, for which no judgement was made in the Second Expert Report, is too limited to draw any conclusions: folate, and individual dietary patterns.

## 8. Comparison with the Second Expert Report

The Panel, for the first time, concluded there is strong evidence that body fatness (marked by BMI, waist circumference, and waist-hip ratio) is a cause of advanced prostate cancer only and developmental factors (marked by adult attained height) are a cause of prostate cancer. The increase in amount and quality of the evidence has highlighted the variability in diagnosis and classification of disease (see section 5.2). In some cases, where it was possible to stratify by grade or stage of disease it has allowed stronger conclusions to be drawn, and for others it has highlighted the need for further research.



## 9. Conclusions

### The CUP Panel judges as follows:

- Greater body fatness (marked by BMI, waist circumference, and waist-hip ratio) is probably a cause of advanced prostate cancer.
- Developmental factors leading to greater linear growth (marked by adult attained height) are probably a cause of prostate cancer.
- Consuming beta-carotene in supplements or foods containing beta-carotene is unlikely to have substantial effect on the risk of prostate cancer.
- For a higher consumption of dairy products, the evidence suggesting an increased risk of prostate cancer is limited.
- For diets high in calcium, the evidence suggesting an increased risk of prostate cancer is limited.
- For low plasma alpha-tocopherol concentrations, the evidence suggesting an increased risk of prostate cancer is limited.
- For low plasma selenium concentrations, the evidence suggesting an increased risk of prostate cancer is limited.

The Cancer Prevention Recommendations were reviewed by the CUP Panel and published in 2018. Please see [Recommendations and public health and policy implications](#) for further details.

Each conclusion on the likely causal relationship between an exposure and the risk of 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 2018 Cancer Prevention Recommendations are based on a synthesis of all these separate conclusions, as well as other relevant evidence.

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## Abbreviations

<b>AICR</b>	American Institute for Cancer Research
<b>ATBC</b>	Alpha-Tocopherol Beta-Carotene Cancer Prevention Study
<b>BMI</b>	Body Mass Index
<b>CARET</b>	Beta-carotene and Retinol Efficacy Trial
<b>CI</b>	Confidence Interval
<b>CUP</b>	Continuous Update Project
<b>DNA</b>	Deoxyribonucleic Acid
<b>IGF</b>	Insulin-like Growth Factor
<b>IL</b>	Interleukin
<b><i>n</i></b>	Number of Cases
<b>PHS</b>	Physicians' Health Study
<b>PSA</b>	Prostate-Specific Antigen
<b>RCT</b>	Randomised Controlled Trial
<b>RR</b>	Relative Risk
<b>SLR</b>	Systematic Literature Review
<b>TNF</b>	Tumour Necrosis Factor
<b>WCRF</b>	World Cancer Research Fund

## Glossary

### **Adenocarcinoma**

Cancer of glandular epithelial cells.

### **Adjustment**

A statistical tool for taking into account the effect of known confounders.

### **Antioxidants**

Any substance that inhibits oxidation or traps or quenches reactive oxygen species generated during metabolism.

### **Anthropometric measures**

Measures of body dimensions.

### **Bias**

In epidemiology, deviation of an observed result from the true value in a particular direction (systematic error) due to factors pertaining to the observer or to study design or analysis.

### **Body mass index (BMI)**

Body weight expressed in kilograms divided by the square of height expressed in metres ( $BMI = \text{kg}/\text{m}^2$ ). It provides an indirect measure of body fatness. Also called Quetelet's Index.

### **Carcinogen**

Any substance or agent capable of causing cancer.

### **Carcinoma**

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

### **Carcinoma in situ**

The first stage of carcinoma in which the malignant tumour has not spread beyond the epithelium.

### **Case-control study**

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

### **Chronic disease**

A disease that develops or persists over a long period of time. Includes non-communicable diseases such as cancer, cardiovascular disease, and diabetes, and some infectious diseases such as tuberculosis.

### **Cohort study**

A study of a (usually large) group of people whose characteristics are recorded at recruitment (and sometimes later), 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 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 to another.

### **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 effect of smoking on the relative risk of lung cancer in one study may be expressed as 10 (95% CI 5–15). This means that in this particular analysis, 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**

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

**Confounding factor** (see confounder)

### **Deoxyribonucleic acid (DNA)**

The double-stranded, helical molecular chain found within the nucleus of each cell that carries the genetic information.

### **Egger's test**

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

### **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.

### **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.

### **Hormone**

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

### **Immune response**

The production of antibodies or specialised cells in response to foreign proteins or other substances.

### **Incidence rates**

The number of new cases of a condition appearing during a specified period of time expressed relative to the size of the population, for example 60 new cases of breast cancer per 100,000 women per year.

**Inflammation**

The immunologic response of tissues to injury or infection. Inflammation is characterised by accumulation of white blood cells that produce several bioactive chemicals, causing redness, pain, and swelling.

**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.

**Lesion**

A general term for any abnormality of cells or tissues, including those due to cancerous change.

**Malignant**

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

**Meta-analysis**

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

**Metastasis**

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

**Oxidative damage**

Damage to cells or structures in cells caused by oxidation, either by chemicals or by radiation. Some oxidants are generated in the normal course of metabolism. Oxidation of DNA is one cause of mutation.

**Pathogenesis**

The origin and development of disease. The mechanisms by which causal factors increase the risk of disease.

**Polymorphisms**

Common variations (more than 1 per cent of the population) in the DNA sequence of a gene.

**Pooled analysis** (see pooling)**Pooling**

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

**Publication bias**

A bias in the overall balance of evidence in the published literature due to selective publication. Not all studies carried out are published, and those that are may differ from those that are not. Publication bias can be tested for with either Begg's or Egger's tests.

**Randomised controlled trial (RCT)**

A study in which a comparison is made between one intervention (often a treatment or prevention strategy) and another (control). Sometimes the control group receives an inactive agent (a placebo). Groups are randomised to one intervention or the other, so that any difference in outcome between the two groups can be ascribed with confidence to the intervention. Neither investigators nor subjects usually know to which condition they have been randomised; this is called 'double-blinding'.

**Relative risk (RR)**

The ratio of the rate of disease or death among people exposed to a factor, compared to the rate among the unexposed, usually used in cohort studies.

**Selection bias**

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

**Statistical significance**

The probability that any observed result might not have occurred by chance. In most epidemiologic work, a study result whose probability is less than 5% ( $p < 0.05$ ) is considered sufficiently unlikely to have occurred by chance to justify the designation **'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.

**Tocopherol**

A form of vitamin E.

**Waist-hip circumference ratio**

A measure of body shape indicating fat distribution.

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## Appendix: Criteria for grading evidence for cancer prevention

See also [Judging the evidence](#), section 8.

Adapted from Chapter 3 of the 2007 Second Expert Report. 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](http://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.

## 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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