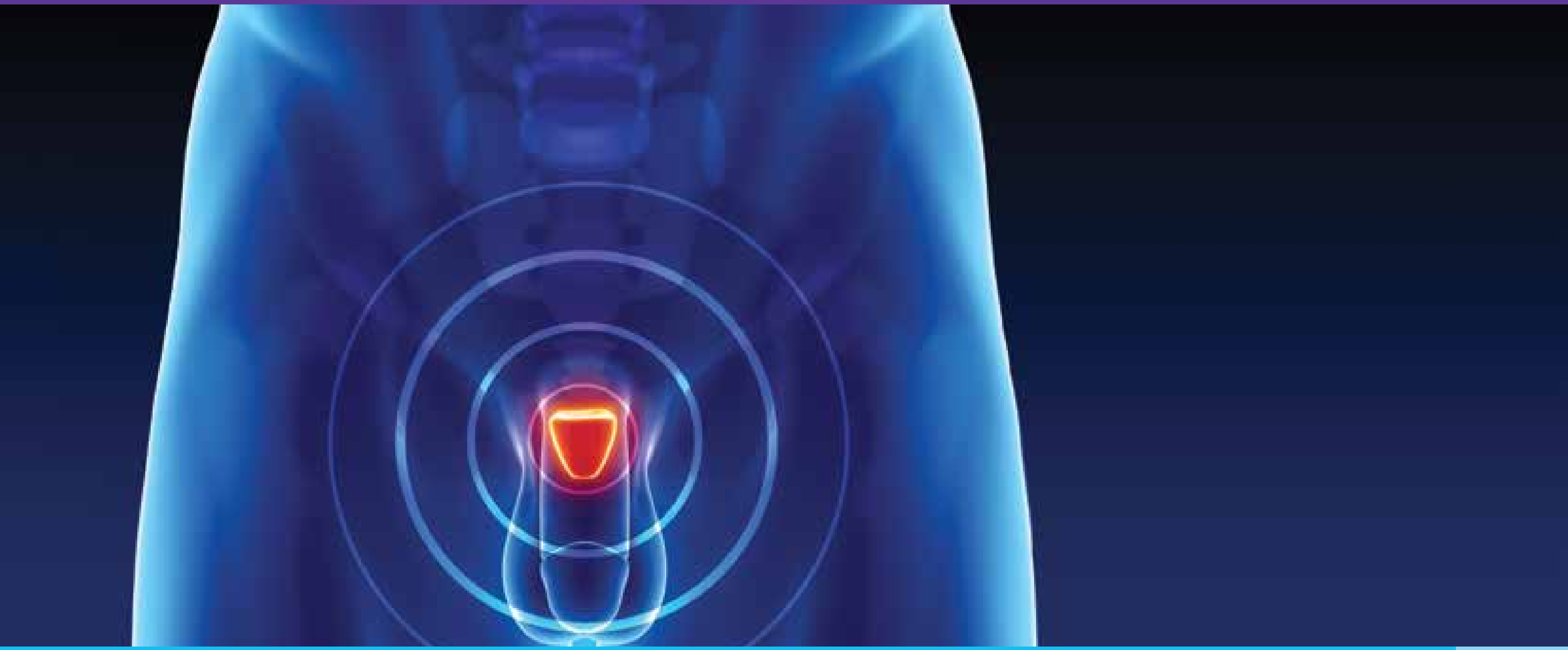
World Cancer Research Fund International

CUP Continuous Update Project

Analysing research on cancer prevention and survival



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

2014

In partnership with

American Institute for Cancer Research

World Cancer Research Fund

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WORLD CANCER RESEARCH FUND INTERNATIONAL

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 though 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)

World Cancer Research Fund International's Continuous Update Project analyses global cancer prevention and survival research linked to diet, nutrition, physical activity and weight. Among experts worldwide it is a trusted, authoritative scientific resource, which underpins current guidelines and policy for cancer prevention.

The Continuous Update Project is produced in partnership with the American Institute for Cancer Research, World Cancer Research Fund UK, World Cancer Research Fund NL and World Cancer Research Fund HK.

The findings from the Continuous Update Project are used to update our Recommendations for Cancer Prevention, which were originally published in *Food, Nutrition, Physical Activity, and the Prevention of Cancer: a Global Perspective* (our Second Expert Report). These ensure that everyone - from policymakers and health professionals, to members of the public - has access to the most up-to-date information on how to reduce the risk of developing the disease.

As part of the CUP, scientific research from around the world is collated and added to a database of epidemiological studies on an ongoing basis and systematically reviewed by a team at Imperial College London. An independent panel of world-renowned experts then evaluate and interpret the evidence to make conclusions based on the body of scientific evidence. Their conclusions form the basis for reviewing and, where necessary, revising our Recommendations for Cancer Prevention.

A review of the Recommendations for Cancer Prevention is expected to be published in 2017, once an analysis of all of the cancers being assessed has been conducted. So far, new CUP reports have been published with updated evidence on breast, colorectal, pancreatic, endometrial and ovarian cancers. In addition, our first ever CUP report on breast cancer survivors was published in October 2014.

This CUP report on prostate cancer updates the prostate cancer section of the Second Expert Report (section 7.14) and is based on the findings of the CUP Prostate Cancer Systematic Literature Review (SLR) and the CUP Expert Panel discussion in June 2014. For further details please see the full Continuous Update Project Prostate Cancer SLR 2014 **(wcrf.org/sites/default/files/Prostate-Cancer-SLR-2014.pdf)**.

HOW TO CITE THIS REPORT

World Cancer Research Fund International/American Institute for Cancer Research Continuous Update Project Report:
Diet, Nutrition, Physical Activity, and Prostate Cancer. 2014. Available at:
www.wcrf.org/sites/default/files/Prostate-Cancer-2014-Report.pdf

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 ≥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

Strong evidence

- 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].

Limited evidence

- 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

1. To reduce the risk of developing advanced prostate cancer, we recommend maintaining a healthy weight.
2. Follow our Cancer Prevention Recommendations (available at wcrf.org), which include eating a healthy diet, being physically active and maintaining a healthy weight.
3. Better designed scientific research is needed to identify more clearly the tumours that are likely to progress to advanced prostate cancer (which will help when analysing the risk factors for the disease).

References

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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
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DIET, NUTRITION, PHYSICAL ACTIVITY AND PROSTATE CANCER

		DECREASES RISK	INCREASES RISK
STRONG EVIDENCE	Convincing		
	Probable		Body fatness (advanced prostate cancer)[1,2] Adult attained height[3]
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	Beta-carotene[4,5]	

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.

Continuous Update Project

1. Summary

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:

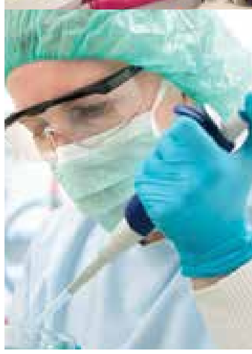
- **Greater body fatness (marked by BMI, waist circumference, and waist-hip ratio) is probably a cause of advanced prostate cancer.**
- **Developmental factors leading to greater linear growth (marked by adult attained height) are probably a cause of prostate cancer.**
- **Consuming beta-carotene in 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 6.

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 sections 3.3 and 3.5, and boxes 3.1, 3.2, 3.6 and 3.7 in the Second Expert Report.

'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 ≥ 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 **(www.wcrf.org/sites/default/files/Prostate-Cancer-SLR-2014)**.

6.1 Mechanistic evidence

Where relevant, mechanistic reviews previously conducted for the Second Expert Report are included in this report (more details can be found in chapters 2, 4 and 6 of the Second Expert Report). These reviews have not been updated, but will be updated as part of a systematic literature review of the mechanistic evidence for the CUP (see below). A brief summary of possible mechanisms for dairy products, diets high in calcium, low plasma alpha-tocopherol concentrations, low plasma selenium concentrations, body fatness (for advanced prostate cancer only) and adult attainted height are given. Where an exposure presented in this report was previously judged as ‘limited-no conclusion’ or was not discussed for the Second Expert Report there was no formal review of the mechanisms. Plausible mechanisms identified by CUP Panel members and published reviews are included in this report.

Work is under way to develop a method for systematically reviewing animal, human and other experimental studies, and will be used to conduct reviews of mechanisms for all cancer sites (see **www.wcrf.org** for further information). A full review of the mechanistic evidence for prostate cancer will form part of this larger review.

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^2	NO. STUDIES	NO. CASES
CUP 2014 Non-advanced	Per 400g/day	1.09 (1.00-1.18)	53%	8	16,749
CUP 2014 Advanced	Per 400g/day	0.97 (0.91-1.05)	0%	10	4,465
CUP 2014 Fatal	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^2	NO. STUDIES	NO. CASES
CUP 2014 Non-advanced	Per 200g/day	1.06 (1.00-1.13)	0%	4	4,092
CUP 2014 Advanced	Per 200g/day	0.98 (0.89-1.09)	0%	4	1,072
CUP 2014 Fatal	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^2 = 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

EXPOSURE	INCREMENT	RR (95% CI)	I^2	NO. STUDIES	NO. CASES
CUP 2014 Whole milk	Per 200g/day	0.98 (0.95-1.01)	0%	8	19,664
CUP 2014 Low-fat milk	Per 200g/day	1.06 (1.01-1.11)	67%	6	19,430
CUP 2014 Cheese	Per 50g/day	1.09 (1.02-1.18)	0%	11	22,950
CUP 2014 Yoghurt	Per 100g/day	1.08 (0.93-1.24)	82%	6	18,282

Mechanisms

Note: This is adapted from Chapter 2 and section 4.4 of the Second Expert Report. An updated review of mechanisms for this exposure will form part of a larger review of mechanisms (see section 6.1 in this report).

High calcium intake down regulates the formation of 1,25-dihydroxy vitamin D_3, thereby increasing cell proliferation in the prostate [27]. Prostate cancer tumours in rats treated with 1,25-dihydroxy vitamin D_3 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].

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^2	NO. STUDIES	NO. CASES
CUP 2014 Non-advanced	Per 400 mg/day	1.07 (1.03-1.12)	7%	8	9,048
CUP 2014 Advanced	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^2 = 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^2 = 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^2 = 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^2 = 72%) when comparing highest versus lowest intake categories.

Other calcium exposures

The Prostate Cancer SLR 2014 included a total of nine cohort studies in the CUP on calcium supplements. Dose-response meta-analysis of four studies on total, advanced, and non-advanced prostate cancer showed no significant association. Two studies were included in the dose-response meta-analysis on fatal prostate cancer and calcium supplements, which showed a significant positive effect. 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

Note: This is adapted from Chapter 2 and section 4.4 of the Second Expert Report. An updated review of mechanisms for this exposure will form part of a larger review of mechanisms (see section 6.1 in this report).

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_3, thereby increasing cell proliferation in the prostate. Prostate cancer tumours in rats treated with 1,25-dihydroxy vitamin D_3 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].

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

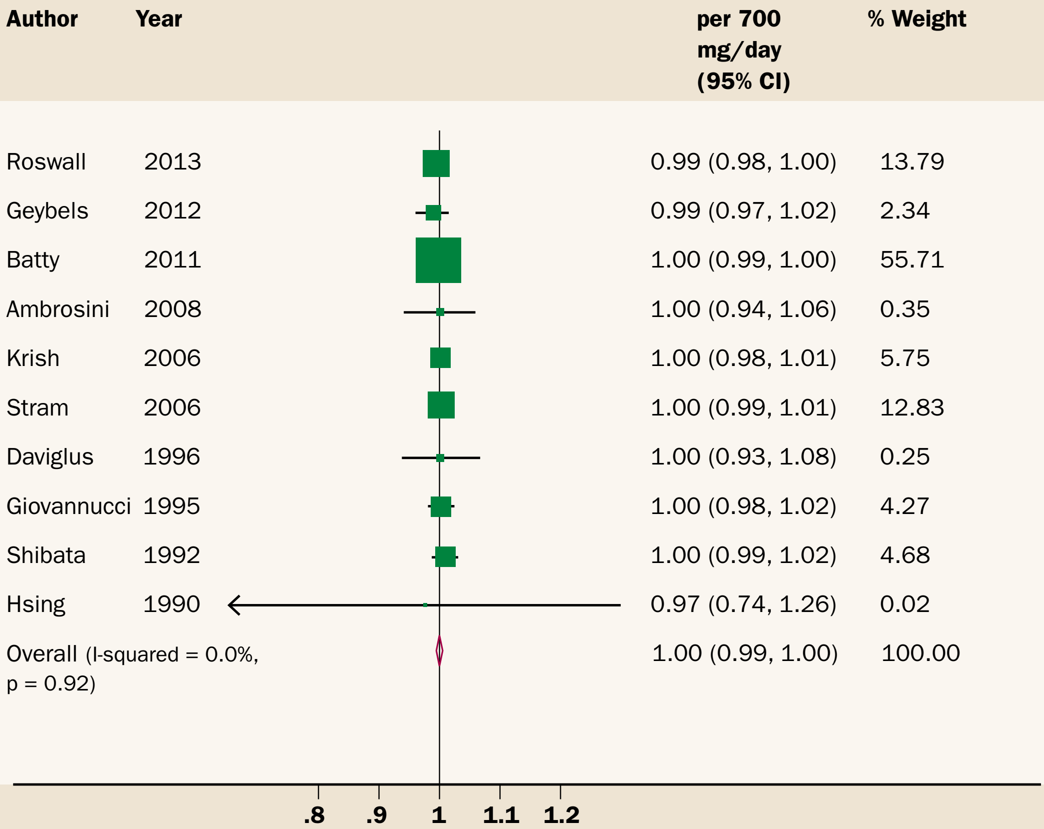
(Also see Prostate Cancer SLR 2014: Section 5.5.1.2)

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 association 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). All five studies 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)
Beta-carotene and Retinol Efficacy Trial (CARET) [46] [47]	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)
Physicians' Health Study (PHS) [48]	22,071	50 mg beta-carotene taken on alternate days	13 years		1.00 (0.90-1.10)
Alpha-Tocopherol Beta-Carotene Cancer Prevention (ATBC) Study (male smokers) [49] [50]	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 211). 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^2	NO. STUDIES	NO. CASES
CUP 2014 Dietary vitamin E	Per 10 mg/day	1.01 (0.96-1.06)	20%	5	11,112
CUP 2014 Serum gamma-tocopherol	Per 1 mg/L	0.97 (0.91-1.04)	52%	7	2,742
CUP 2014 Vitamin E supplements	Per 100 IU/day	1.00 (0.99-1.01)	0%	7	21,862

Mechanisms

Note: This is adapted from Chapter 2 and section 4.2 of the Second Expert Report. An updated review of mechanisms for this exposure will form part of a larger review of mechanisms (see section 6.1 in this report).

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.

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 µg/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 µg/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
CUP 2014 Non-advanced	Per 10 µg/L	0.99 (0.95-1.03)	0%	4	1,879
CUP 2014 Advanced	Per 10 µg/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 µg/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 µg/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 µg/L (RR 0.85 (95% CI 0.74-0.97)) and 170 µg/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 µg/L (RR 0.60 (95% CI 0.45-0.81)) and 170 µg/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 µg/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

Note: This is adapted from Chapter 2 and section 4.2 of the Second Expert Report. An updated review of mechanisms for this exposure will form part of a larger review of mechanisms (see section 6.1 in this report).

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.

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 anthropometrical measures are imperfect and cannot distinguish between lean mass and fat mass.

Body mass index (BMI)

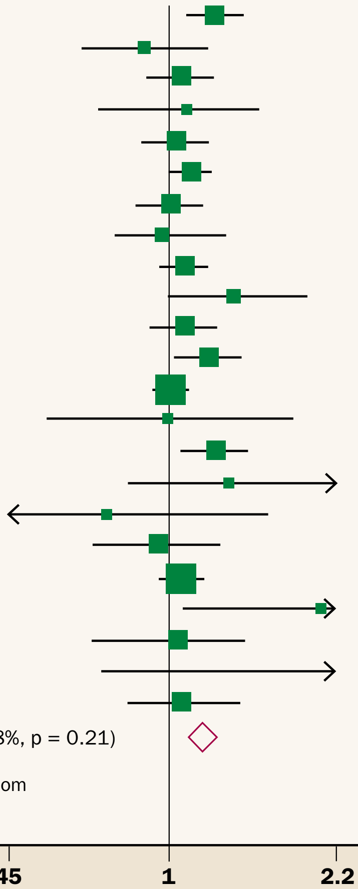
The CUP identified 18 new or updated studies (19 articles) [37, 56-73], giving a total of 24 studies (26 articles) on advanced prostate cancer in the CUP (see Prostate Cancer SLR 2014 table 257 for a full list of references). Of 15 studies (15 estimates) reporting on advanced prostate cancer incidence, 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^2 (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^2 (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/m²

Author	Year	per 5 kg/m² RR (95% CI)	% Weight
Advanced			
Bassett	2012	1.27 (1.08, 1.49)	5.10
Shafique	2012	0.91 (0.69, 1.21)	1.93
Batty	2011	1.07 (0.91, 1.26)	5.00
Dehal	2011	1.12 (0.75, 1.68)	0.97
Discacciati	2011	1.05 (0.89, 1.23)	5.13
Stocks	2010	1.11 (1.00, 1.22)	10.51
Hernandez	2009	1.00 (0.88, 1.13)	7.67
Martin	2009	0.97 (0.75, 1.26)	2.17
Pischon	2008	1.09 (0.96, 1.24)	7.25
Fujino	2007	1.40 (1.00, 1.96)	1.38
Littman	2007	1.07 (0.91, 1.26)	4.97
Rodriguez	2007	1.18 (1.02, 1.37)	5.97
Wright	2007	1.00 (0.94, 1.08)	15.04
Baillargeon	2006	0.99 (0.55, 1.79)	0.46
Gong	2006	1.20 (1.03, 1.41)	5.29
Kurahashi	2006	1.54 (0.85, 2.76)	0.47
Eichholzer	2005	0.77 (0.43, 1.40)	0.45
Gapstur	2001	0.98 (0.76, 1.25)	2.46
Rodriguez	2001	1.07 (0.99, 1.16)	12.57
Putnam	2000	2.08 (1.07, 4.03)	0.37
Schuurman	2000	1.03 (0.77, 1.36)	1.88
Cerhan	1997	2.43 (0.84, 7.05)	0.14
Giovannucci	1997	1.05 (0.83, 1.31)	2.83
Subtotal (I-squared = 18.8%, p = 0.21)		1.08 (1.04, 1.12)	100.00



NOTE: Weights are from random effects analysis

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^2 (RR 0.99 (95% CI 0.96-1.01); n = 633; I^2 = 0%), but the Prostate Cancer SLR 2014 included more studies and cases of advanced prostate cancer.

Published meta-analyses

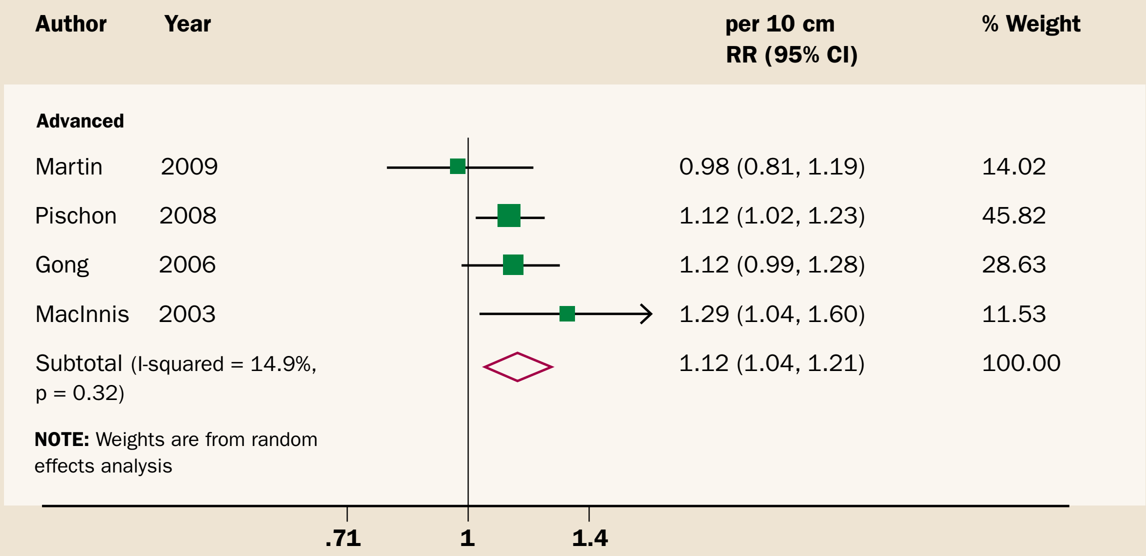
The results from two published meta-analyses on BMI and advanced prostate cancer were identified in the Prostate Cancer SLR 2014 [74, 75]. One meta-analysis included 13 studies and the other included six studies; both reported a statistically significant positive association per 5 kg/m^2 (RR 1.09 (95%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

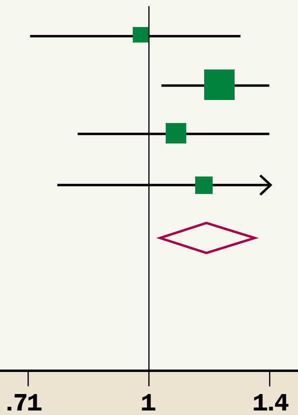
Waist-hip ratio

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

Author	Year	per 0.1 units RR (95% CI)	% Weight
Advanced			
Martin	2009	0.98 (0.73, 1.32)	13.81
Pischon	2008	1.21 (1.05, 1.40)	56.44
Gong	2006	1.09 (0.86, 1.39)	20.52
MacInnis	2003	1.17 (0.82, 1.67)	9.23
Subtotal (I-squared = 0.0%, p = 0.63)		1.15 (1.03, 1.28)	100.00



NOTE: Weights are from random effects analysis

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

Note: This is adapted from Chapter 2 and section 6.1 of the Second Expert Report. An updated review of mechanisms for this exposure will form part of a larger review of mechanisms (see section 6.1 in this report).

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].

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

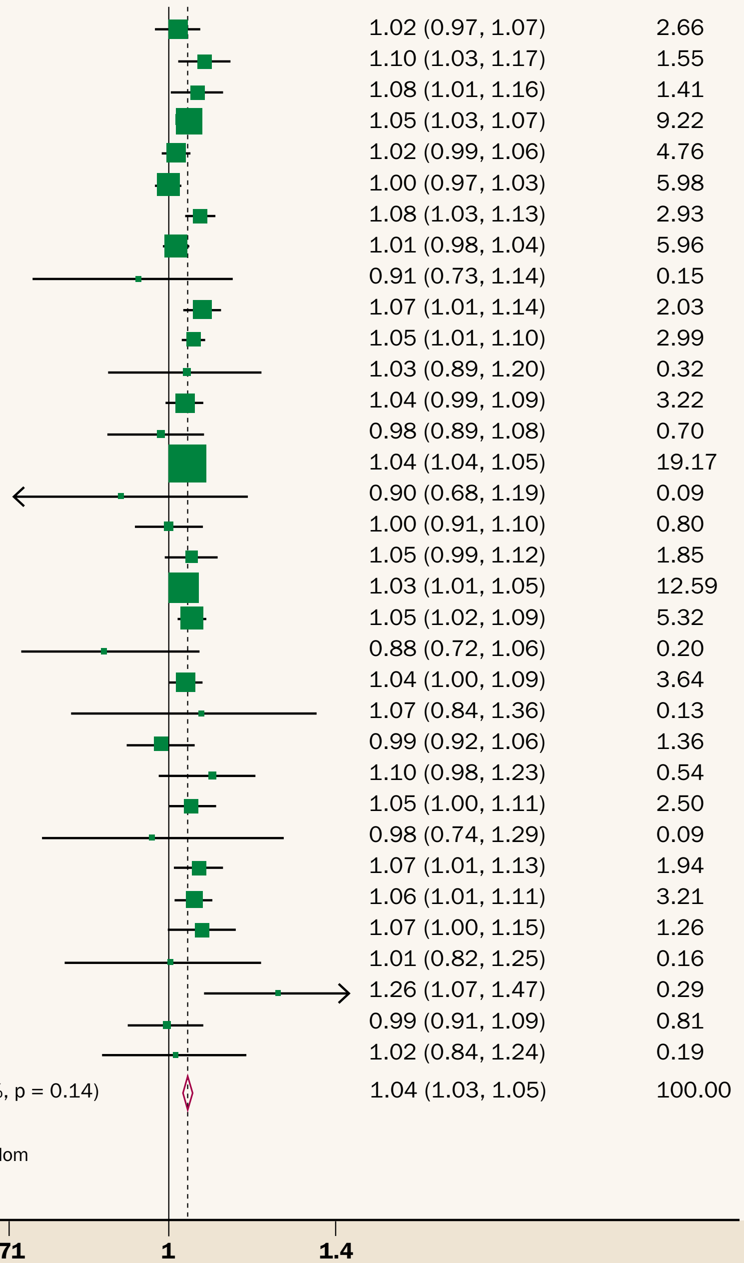
(Also see Prostate Cancer SLR 2014: Section 8.3.1)

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

Author	Year	per 5 cm RR (95% CI)	% Weight
Bassett	2012	1.02 (0.97, 1.07)	2.66
Shafique	2012	1.10 (1.03, 1.17)	1.55
Batty	2012	1.08 (1.01, 1.16)	1.41
Stocks	2010	1.05 (1.03, 1.07)	9.22
Ahn	2009	1.02 (0.99, 1.06)	4.76
Hernandez	2009	1.00 (0.97, 1.03)	5.98
Sung	2009	1.08 (1.03, 1.13)	2.93
Pischon	2008	1.01 (0.98, 1.04)	5.96
Fujino	2007	0.91 (0.73, 1.14)	0.15
Littman	2007	1.07 (1.01, 1.14)	2.03
Gong	2006	1.05 (1.01, 1.10)	2.99
Kurahashi	2006	1.03 (0.89, 1.20)	0.32
Sequoia	2006	1.04 (0.99, 1.09)	3.22
Tande	2006	0.98 (0.89, 1.08)	0.70
Engeland	2003	1.04 (1.04, 1.05)	19.17
Gunnell	2003	0.90 (0.68, 1.19)	0.09
Jonsson	2003	1.00 (0.91, 1.10)	0.80
Freeman	2001	1.05 (0.99, 1.12)	1.85
Rodriguez	2001	1.03 (1.01, 1.05)	12.59
Rodriguez	2001	1.05 (1.02, 1.09)	5.32
Davey Smith	2000	0.88 (0.72, 1.06)	0.20
Habel	2000	1.04 (1.00, 1.09)	3.64
Putnam	2000	1.07 (0.84, 1.36)	0.13
Schuurman	2000	0.99 (0.92, 1.06)	1.36
Lund Nilsen	1999	1.10 (0.98, 1.23)	0.54
Andersson	1997	1.05 (1.00, 1.11)	2.50
Cerhan	1997	0.98 (0.74, 1.29)	0.09
Giovannucci	1997	1.07 (1.01, 1.13)	1.94
Hebert	1997	1.06 (1.01, 1.11)	3.21
Tulinius	1997	1.07 (1.00, 1.15)	1.26
Veierod	1997	1.01 (0.82, 1.25)	0.16
Le Marchand	1994	1.26 (1.07, 1.47)	0.29
Thune	1994	0.99 (0.91, 1.09)	0.81
Albanes	1988	1.02 (0.84, 1.24)	0.19
Overall (I-squared = 21.0%, p = 0.14)		1.04 (1.03, 1.05)	100.00



NOTE: Weights are from random effects analysis

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^2	NO. STUDIES	NO. CASES
CUP 2014 Non-advanced	Per 5 cm	1.03 (1.01-1.05)	19%	10	16,749
CUP 2014 Advanced	Per 5 cm	1.04 (1.02-1.06)	47%	19	4,465
CUP 2014 Fatal	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^2	NO. STUDIES	NO. CASES	FACTORS ADJUSTED FOR
CUP Prostate Cancer SLR 2014	Per 5 cm	1.04 (1.03-1.05)	21%	34	79,387 incidence & mortality	
Emerging Risk Factor Collaboration [88]	Per 6.5 cm	1.07 (1.02-1.11)	9%	121	2,818 mortality	Age, sex, smoking, year of birth
Asia Pacific Cohort Studies Collaboration [87]	Per 6 cm	1.06 (0.95-1.18)	-	38	274 mortality	Age, study, year of birth

Mechanisms

Note: This is adapted from Chapter 2 and section 6.2 of the Second Expert Report. An updated review of mechanisms for this exposure will form part of a larger review of mechanisms (see section 6.1 in this report).

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].

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 6.

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 database is being continuously updated for all cancers. The Recommendations for Cancer Prevention will be reviewed in 2017 when the Panel has reviewed the conclusions for the other cancers.

The CUP Panel concluded:

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.

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Abbreviations

AICR American Institute for Cancer Research

ATBC Alpha-Tocopherol Beta-Carotene Cancer Prevention Study

BMI Body Mass Index

CARET Beta-carotene and Retinol Efficacy Trial

CI Confidence Interval

CUP Continuous Update Project

DNA Deoxyribonucleic Acid

IGF Insulin-like Growth Factor

IL Interleukin

n Number of Cases

PHS Physicians' Health Study

PSA Prostate-Specific Antigen

RCT Randomised Controlled Trial

RR Relative Risk

SLR Systematic Literature Review

TNF Tumour Necrosis Factor

WCRF 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 ($BMI = kg/m^2$). 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

(Taken from Chapter 3 of the Second Expert Report)

This appendix lists 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.

CONVINCING

These criteria are for evidence strong enough to support a judgement of a convincing causal relationship, which justifies goals and recommendations designed to reduce the incidence of cancer. A convincing relationship should be robust enough to be highly unlikely to be modified in the foreseeable future as new evidence accumulates.

All of the following were 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

These criteria are for evidence strong enough to support a judgement of a probable causal relationship, which would generally justify goals and recommendations designed to reduce the incidence of cancer.

All the following were 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

These criteria are for evidence that is too limited to permit a probable or convincing causal judgement, but where there is evidence suggestive of a direction of effect. The evidence may have methodological flaws, or be limited in amount, but shows a generally consistent direction of effect. This almost always does not justify recommendations designed to reduce the incidence of cancer. Any exceptions to this require special explicit justification.

All the following were 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 category 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 might be limited by the amount of evidence in terms of the number of studies available, by inconsistency of direction of effect, by poor quality of studies (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 (www.wcrf.org). However, such evidence is usually not included in the summaries.

SUBSTANTIAL EFFECT ON RISK UNLIKELY

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 were 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, either from human studies or relevant animal models, that typical human exposures lead to relevant cancer outcomes.

Factors that might misleadingly imply an absence of effect include imprecision of the exposure assessment, an insufficient range of exposure in the study population, and inadequate statistical power. Defects in these and 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 in 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. So an exposure that might be deemed a 'limited — suggestive' causal factor in the absence, say, of a biological gradient, might be upgraded to 'probable' in its presence. 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.

- 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 Recommendations for Cancer Prevention

Body fatness
Be as lean as possible without becoming underweight

Physical activity
Be physically active for at least 30 minutes every day

Foods and drink that promote weight gain
Limit consumption of energy-dense foods

Plant foods
Eat more of a variety of vegetables, fruits, wholegrains, & pulses such as beans

Animal foods
Limit consumption of red meats (such as beef, pork and lamb) and avoid processed meats

Alcoholic drinks
Limit alcoholic drinks

Preservation, processing, preparation
Limit consumption of salt & avoid mouldy grains and cereals

Dietary supplements
Don't use supplements to protect against cancer

Breastfeeding
It is best for mothers to breastfeed exclusively for up to 6 months and then add other liquids & foods

Cancer survivors
After treatment, cancer survivors should follow the recommendations for cancer prevention

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