

Height and birthweight and the risk of cancer

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

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

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Key

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

References to other parts of the Third Expert Report are highlighted in [purple](#).

Executive summary

Background and context

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

A baby’s size and shape at birth depends on how well they grow in the womb. Within the usual range, heavier (and longer) babies tend to become taller children and adults.

Adult attained height is linked to genetics, birthweight, rate of growth and age of puberty, as well as environmental factors that include nutrition. Periods of peak growth (such as in infancy and adolescence) are especially important in determining height, because growth is particularly sensitive to nutritional supply during these times. Growth is also especially dependent on the action of growth hormones and growth factors.

A baby’s birthweight and an adult’s height therefore both reflect a complex interplay of genetic, nutritional and other environmental factors that affect growth within the womb and during childhood and adolescence. Birthweight and height are markers of these factors. Neither birthweight nor height is likely to affect the risk of cancer directly.

How the research was conducted

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

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

Findings

There is **strong evidence** that:

- **developmental factors leading to greater growth in length in childhood (marked by adult attained height) increase** the risk of cancers of the following types: pancreas, colorectum, breast (pre and postmenopause), ovary, endometrium, prostate, kidney and skin (malignant *melanoma*).
- **factors that lead to a greater birthweight, or its consequences, increase** the risk of premenopausal breast cancer.

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

The evidence shows that, in general, the taller people are during adulthood and the more people weighed at birth, the higher their risk of some cancers.

The Panel uses such strong evidence, where possible, when making Recommendations (see below) designed to reduce the risk of developing cancer. Although adult attained height and birthweight are public health issues, as adults, people cannot modify these factors. It is therefore inappropriate to make a global recommendation on height and birthweight (see [Recommendations and public health and policy implications](#), Section 3: Issues of public health significance – Height and birthweight). A better understanding of the developmental factors that underpin the associations between greater growth and cancer risk is needed.

There is also other evidence on developmental factors leading to greater growth in length in childhood (marked by adult attained height) that is limited (either in amount or by methodological flaws) but is suggestive of an increased risk of skin cancer (*basal cell carcinoma*). In addition, there is evidence on factors that lead to a greater birthweight, or its consequences, that is limited but is suggestive of an increased risk of skin cancer (*malignant melanoma*). Further research is required, and the Panel has not used this evidence to make recommendations.

Recommendations

Our Cancer Prevention Recommendations – for preventing cancer in general – include maintaining a healthy weight, being physically active and eating a healthy diet. As birthweight and adult attained height are public health issues and people cannot necessarily influence these themselves, there are no global recommendations for these factors. The Recommendations are listed on the inside back cover.

References

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



1. Height and birthweight and the risk of cancer: a summary matrix

HEIGHT AND BIRTHWEIGHT AND THE RISK OF CANCER					
WCRF/AICR GRADING		DECREASES RISK		INCREASES RISK	
		Exposure	Cancer site	Exposure	Cancer site
STRONG EVIDENCE	Convincing			Adult attained height ^{1,2}	Colorectum 2017 Breast (premenopause) 2017 Breast (postmenopause) 2017 Ovary 2014
	Probable			Adult attained height ^{1,2}	Pancreas 2012 Endometrium 2013 Prostate 2014 Kidney 2015 Skin (malignant melanoma) 2017
				Birthweight ^{2,3}	Breast (premenopause) 2017
LIMITED EVIDENCE	Limited – suggestive			Adult attained height ^{1,2}	Skin (basal cell carcinoma) 2017
				Birthweight ^{2,3}	Skin (malignant melanoma) 2017
STRONG EVIDENCE	Substantial effect on risk unlikely	None identified			
<div><div>1</div><div>Adult attained height is unlikely to directly influence the risk of cancer. It is a marker for genetic, environmental, hormonal and nutritional factors affecting growth during the period from preconception to completion of growth in length.</div></div> <div><div>2</div><div>The evidence shows that, in general, the taller people are during adulthood and the more people weighed at birth, the higher their risk of some cancers. A better understanding of the developmental factors that underpin the associations between greater growth and cancer risk is needed.</div></div> <div><div>3</div><div>Birthweight is a marker for prenatal growth, reflecting a combination of factors including fetal nutrition, and is also a predictor of later growth and maturation – for example, age at menarche – which are themselves determinants of breast cancer risk.</div></div>					

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

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

‘Strong evidence’: Evidence is strong enough to support a judgement of a

convincing or probable causal (or protective) relationship and generally justify making public health recommendations.

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

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

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

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

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

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

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

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



2. Summary of Panel judgements

The conclusions drawn by the CUP Panel are based on the evidence from both epidemiological and mechanistic studies relating height and birthweight to the risk of development of particular cancer types. Each conclusion on the likely causal relationship between height and birthweight and a cancer forms a part of the overall body of evidence that is considered during the process of making Cancer Prevention Recommendations. Although birthweight and adult attained height are linked to cancer risk, in adulthood there is no way to modify these factors. Any single conclusion does not represent a recommendation in its own right. The Cancer Prevention Recommendations are based on a synthesis of all these separate conclusions, as well as other relevant evidence, and can be found at the end of this Third Expert Report.

The CUP Panel concluded:

STRONG EVIDENCE

Convincing

- **Increased risk**
 - **Adult attained height:**^{1,2} Developmental factors leading to greater growth in length in childhood (marked by adult attained height) are a convincing cause of cancers of the colorectum, breast (pre and postmenopause) and ovary.

Probable

- **Increased risk**
 - **Adult attained height:**^{1,2} Developmental factors leading to greater growth in length in childhood (marked by adult attained height) are probably a cause of cancers of the pancreas, endometrium, prostate, kidney and skin (malignant *melanoma*).
 - **Birthweight:**^{2,3} The factors that lead to a greater birthweight, or its consequences, are probably a cause of premenopausal breast cancer.

The evidence shows that, in general, the taller people are during adulthood, and the more people weighed at birth, the higher their risk of some cancers.

The Panel uses such strong evidence, where possible, when making Recommendations (see [Recommendations and public health and policy implications](#), Section 2: Recommendations for Cancer Prevention) designed to reduce the risk of developing cancer. Although adult attained height and birthweight are public health issues, as adults, people cannot modify these factors. It is therefore inappropriate to make a global recommendation on height and birthweight (see [Recommendations and public health and policy implications](#), Section 3: Issues of public health significance – Height and birthweight).

The Panel considers height and birthweight to be markers of genetic, environmental, hormonal and nutritional factors that affect growth during the period from preconception to completion of growth in length and that these factors affect the risk of cancer. A better understanding of the developmental factors that underpin the associations between greater growth and cancer risk is needed.

See page 10 for footnotes.

The association between height and birthweight and cancer is different from the association between these factors and some other non-communicable diseases, such as cardiovascular disease. Thus, a greater birthweight and being taller in adulthood predict a decreased risk of cardiovascular disease [2] in contrast to the increased risk of several cancers based on the evidence presented in this part of the Third Expert Report. To date, growth standards have not taken into account the lifelong risk of non-communicable diseases, including cancer, as policies and programmes have focused on the need to provide adequate nutrition to prevent retarded growth [3]. This remains an issue for some parts of the world.

LIMITED EVIDENCE

Limited – suggestive

- **Increased risk**
 - **Adult attained height:**^{1,2} The evidence suggesting that developmental factors leading to greater growth in length in childhood (marked by adult attained height) increase the risk of skin cancer (*basal cell carcinoma*) is limited.
 - **Birthweight:**^{2,3} The evidence suggesting that the factors that lead to a greater birthweight, or its consequences, increase the risk of skin cancer (*malignant melanoma*) is limited.

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

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



¹ Adult attained height is unlikely to directly influence the risk of cancer. It is a marker for genetic, environmental, hormonal and nutritional factors affecting growth during the period from preconception to completion of growth in length.

² The evidence shows that, in general, the taller people are during adulthood, and the more people weighed at birth, the higher their risk of some cancers. A better understanding of the developmental factors that underpin the associations between greater growth and cancer risk is needed.

³ Birthweight is a marker for prenatal growth, reflecting a combination of factors including fetal nutrition, and is also a predictor of later growth and maturation – for example, age at menarche – which are themselves determinants of breast cancer risk.

3. Definitions and patterns

3.1 Adult attained height

Adult attained height is linked to genetics, birthweight, rate of growth and age of puberty, as well as environmental factors, all of which affect growth during the period from preconception to completion of linear growth (see **Box 1** and **Box 2**).

The influence of environmental versus genetic factors can be seen when genetic factors are controlled for; for example, when looking at variations in height between generations of the same family, in studies of children who are adopted, or in children who migrate from an area where their nutrition is poor or limited to an area of high or even over-nutrition [4].

Adult attained height increases as populations become less vulnerable to undernutrition and infection and as food supplies become more secure; it continues to increase when food is abundant [5]. Increases in height have plateaued in Northern and Eastern Europe and in the USA, but are still increasing in Southern Europe and Latin America [5].

Increases in adult attained height between generations are generally due to increased leg, rather than spine, length. Leg length is linked to pre-pubertal growth, particularly before the age of 5; after this, trunk growth becomes more prominent [6, 7]. Periods of peak growth (such as in infancy and adolescence) are especially important in determining height, because growth is particularly sensitive to nutritional supply during these times.

Together, growth hormones, *insulin-like growth factors (IGFs)* and sex hormones are the dominant signalling molecules that influence growth, sexual maturation, height, fat storage and many other processes relevant to cancer at different stages of development. Blood

concentrations of the binding proteins of these molecules are important in determining their biological activity (see [The cancer process](#)).

3.1.1 Height and other diseases

In this Third Expert Report we analyse global research on how height affects the risk of developing cancer. There is a complex relationship between height and non-communicable diseases. Greater height in adulthood predicts a higher risk of cancer, as discussed in this Third Expert Report; however, it also predicts a lower risk of dying from cardiovascular diseases, stroke, heart failure and diabetes [10]. Although adult attained height is related to disease risk it is unlikely to modulate these diseases directly. For further details on the proposed mechanisms by which adult attained height may be associated with the risk of cancer, see **Appendix 2**.

3.2 Birthweight

A baby's size and shape at birth are an indication of the extent and quality of intra-uterine growth and development (see **Box 1** and **Box 2**). Birthweight can be measured simply and reliably, whereas head circumference, which marks growth of the brain, and head-to-foot length, which marks linear growth, are more difficult to measure reliably. Within the usual range, heavier (and longer) babies tend to become taller children and adults.



Box 1: Surrogate markers

When considering evidence on cancer risk and either adult attained height or birthweight, it is important to be aware that both of these measures are imperfect markers of internal physiological processes that are the actual determinants of cancer development (see [The cancer process](#)) [8]. The precise links between these processes and cancer are yet to be characterised. For further details on the proposed mechanisms by which adult attained height may be associated with the risk of cancer, see [Appendix 2](#).

Box 2: Growth

Growth increases metabolic capacity and the ability to cope with environmental challenges.

From a single cell at conception, human growth progresses through embryogenesis and fetal development. Cells multiply and differentiate in both structure and function. The timing and order of these processes are determined by the selective expression of genes, which is both innate and modifiable by the wider environment, including the availability of oxygen, *energy* and *nutrients*. Nutrients also act by regulating the expression, release and activity of *hormones*, growth factors, binding proteins and receptors. Well before the time of birth, the body's tissues and organs are highly organised and regulated.

For every tissue or organ, adverse environmental influences, such as limited energy or nutrients, during critical periods of development can restrict development and future capacity for function. The timing, severity and duration of any adverse *exposure* will determine the extent and pattern of any restriction in capacity. For instance, restriction of early growth, reflected in relatively low birthweight, is linked to a greater tendency to store fat in later life, in particular abdominally.

Growth can be divided into three phases: fetal–infant, childhood and puberty [9]. During the first period, growth is most sensitive to the availability of energy and nutrients. Brain growth is protected more effectively than growth in stature, which is protected more effectively than weight. The timing of an adverse influence on growth tends to be reflected in a person's body shape, both as a child and as an adult. For instance, for lean tissue to be deposited efficiently and effectively, the appropriate pattern of nutrients must be available at the relevant times.

Birthweight can predict the risk of death and of various diseases in infancy and later in life. Very low birthweight – less than 2.5 kilograms (5.5 pounds) for boys and 2.4 kilograms (5.3 pounds) for girls – increases the risk of perinatal death and disease, or death in infancy and young childhood, usually because of increased vulnerability to infection.

It is well established, at least in *high-income countries*, that there is a graded relationship, throughout the normal range, between size at birth, and at one year of age, and risk of *chronic* disease such as cardiovascular disease

and type 2 diabetes during adult life, such that lower weight predicts higher risk [11].

Very high birthweight may also be associated with increased risk of certain diseases – for instance, maternal diabetes or poor glucose homeostasis can cause higher birthweight as well as increased risk of diabetes in the infant [12]. These findings have been shown to be independent of smoking tobacco or *socioeconomic status*, although they may be accentuated in the presence of these additional factors [13].

4. Interpretation of the evidence

4.1 General

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

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

4.2 Specific

Specific factors that the Panel bears in mind when interpreting evidence on whether height and birthweight increase or decrease the risk of developing cancer are described in the following subsections. Factors that are relevant to specific cancers are presented here too.

4.2.1 Exposures

4.2.1.1 Adult attained height

Definitions. The CUP interpreted height reported in studies as adult attained height. Adult attained height is unlikely to directly influence the risk of cancer. It is a marker for genetic, environmental, hormonal and nutritional factors affecting growth during the period from preconception to completion of linear growth.

Confounding. The association between *adiposity*, growth and maturational events is complex. Single *anthropometric measures* do not capture maturational events, including the presence of critical windows of susceptibility for cancer risk (for example, age of *menarche*).

Measurement. Epidemiologic studies often rely on self-reported height. People from some cultures or geographic areas may report that

they are taller than they actually are, and others may not know their height [8]. However, studies have shown a strong correlation (> 0.9) between self-reported and measured height [8]. Furthermore, the impact of such systematic measurement error on relative risk estimates in epidemiologic studies is generally small [8].

Other measures of skeletal size may be used in some studies, including leg length, sitting height, or a ratio of these two; however, only measures of height were available for CUP analyses.

4.2.1.2 Birthweight

Definition. A baby’s size and shape at birth are an indication of the extent and quality of intra-uterine growth and development.

Measurement. Birthweight is usually self-reported by people who took part in the studies. Weight at birth is usually recalled accurately by parents. Fair-to-moderate agreement in adults between their reported and actual birthweights has been reported [14, 15].

4.2.2 Cancers

The information provided here on ‘Other established causes’ of cancer is based on judgements made by the International Agency for Research on Cancer (IARC) [16], unless a different reference is given. For more information on findings from the CUP on diet, nutrition, physical activity and the risk of cancer, see other parts of this Third Expert Report.

4.2.2.1 Pancreas

Definitions. The pancreas is an elongated gland located behind the stomach. It contains two types of tissue, *exocrine* and *endocrine*. The exocrine pancreas produces digestive enzymes that are secreted into the small intestine. Cells in the endocrine pancreas

produce *hormones* including *insulin* and *glucagon*, which influence glucose metabolism.

Classification. Over 95 per cent of pancreatic cancers are *adenocarcinomas* of the exocrine pancreas, the type included in the CUP.

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



Smoking tobacco, chewing tobacco and snuff

Smoking tobacco (or use of smokeless tobacco, sometimes called ‘chewing tobacco’ or ‘snuff’) is an established cause of pancreatic cancer, and approximately 22 per cent of deaths from pancreatic cancer are attributable to smoking tobacco [17].



Family history

More than 90 per cent of pancreatic cancer cases are sporadic (due to spontaneous rather than inherited *mutations*), although a family history increases risk, particularly where more than one family member is involved [18].

Confounding. Smoking tobacco is a possible *confounder*.

For more detailed information on *adjustments* made in CUP analyses on adult attained height, see Evidence and judgements (**Section 5.1.5**).

Measurement. Owing to very low survival rates, both incidence and mortality can be assessed.

4.2.2.2 Colon and rectum

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

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

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



Other diseases

Inflammatory bowel disease (Crohn’s disease and ulcerative colitis) increases the risk of, and so may be seen as a cause of, colon cancer [19].



Smoking tobacco

There is an increased risk of colorectal cancer in people who smoke tobacco. It has been estimated that 12 per cent of cases of colorectal cancer are attributable to smoking cigarettes [20].



Family history

Based on twin studies, up to 45 per cent of colorectal cancer cases may involve a heritable component [21]. Between 5 and 10 per cent of colorectal cancers are consequences of recognised hereditary conditions [22]. The two major ones are *familial* adenomatous polyposis (FAP) and hereditary non-polyposis colorectal cancer (HNPCC, also known as Lynch syndrome). A further 20 per cent of cases occur in people who have a family history of colorectal cancer.

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

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

4.2.2.3 Breast

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

Classification. Breast cancers are almost all *carcinomas* of the *epithelial cells* lining the breast ducts (the channels in the breast that carry milk to the nipple). Fifteen per cent of breast cancers are lobular carcinoma (from lobes); most of the rest are ductal carcinoma. Although breast cancer can occur in men, it is rare (less than 1 per cent of cases) and thus is not included in the CUP.

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

Most data come from *high-income countries*. Breast cancer is hormone related, and factors that modify risk may have different effects on cancers diagnosed in the pre and postmenopausal periods.

Due to the importance of menopausal status as an *effect modifier*, studies should stratify for *menopause* status, but many do not. Breast cancer is now recognised as a heterogeneous disease, with several subtypes according to *hormone receptor status* or molecular intrinsic markers. Although there is growing evidence that these subtypes have different causes, most studies have limited *statistical power* to evaluate effects by subtype.

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

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



Life events

Early *menarche* (before the age of 12), late natural *menopause* (after the age of 55), not bearing children and first pregnancy over the age of 30 all increase lifetime exposure to oestrogen and progesterone and the risk of breast cancer [23–25]. The reverse also applies: late menarche, early menopause, bearing children and pregnancy before the age of 30 all reduce the risk of breast cancer [23, 24].

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



Radiation

Exposure to ionising radiation from medical treatment such as X-rays, particularly during puberty, increases the risk of breast cancer [26, 27].



Medication

MHT (containing oestrogen or progesterone) increases the risk of breast cancer [28]. Oral contraceptives containing both oestrogen and progesterone also cause a small increased risk of breast cancer in young women, among current and recent users only [29].



Family history

Some inherited *mutations*, particularly in BRCA1, BRCA2 and *p53*, result in a very high risk of breast cancer. However, germline mutations in these genes are infrequent and account for only 2 to 5 per cent of all cases of breast cancer [30].

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

For more detailed information on *adjustments* made in CUP analyses, see Evidence and judgements on adult-attained height (**Sections 5.1.2** and **5.1.3** for pre and postmenopausal breast cancer, respectively) and greater birthweight (**Section 5.2.1** for premenopausal breast cancer).

4.2.2.4 Ovary

Definition. The ovaries are the sites of ovum (egg) production in women. They are also the main source of the *hormones* oestrogen and progesterone in premenopausal women.

Classification. Cancers may arise from three types of ovarian tissue: *epithelial* cells, which cover the ovary; stromal cells, which produce hormones; and *germ cells*, which become ova (eggs). About 85 to 90 per cent of ovarian cancers are epithelial *carcinomas* [31]. Because ovarian cancer is hormone related, factors that modify risk might have different effects at different times of life.

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



Life events

The risk of ovarian cancer is affected by the number of menstrual cycles during a woman's lifetime [32–34]. Not bearing children, early *menarche* (before the age of 12) and late natural *menopause* (after the age of 55) all increase the risk of ovarian cancer [45–47]. The reverse also applies: bearing children, late menarche and early menopause all reduce the risk of ovarian cancer [45–47]. Tubal ligation (sterilisation) also decreases the risk of ovarian cancer [35].



Medication

Oral contraceptives protect against ovarian cancer [36]. Use of menopausal oestrogen hormone therapy has been shown to increase risk.



Smoking tobacco

Smoking tobacco increases the risk of *mucinous ovarian cancer* [37]. It is estimated that 17 per cent of mucinous ovarian cancer cases are due to smoking tobacco [38].



Family history

Most ovarian cancers occur spontaneously, although 5 to 10 per cent of cases develop due to a genetic predisposition [39]. The latter, involving dysfunctional *BRCA1* or *BRCA2* genes produces high-grade carcinomas, with poorer prognosis [40].

Confounding. Including data on women who were at high risk of ovarian cancer who have had oophorectomies may have influenced the results of some studies.

For more detailed information on *adjustments* made in CUP analyses on adult attained height, see Evidence and judgements (**Section 5.1.4**).

Tumour heterogeneity. There is growing evidence that different histologic subtypes of ovarian cancer have different aetiologies and clinical courses. However, most studies lack the *statistical power* to evaluate associations by histologic subtype [41].

4.2.2.5 Endometrium

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

Classification. The majority of cancers that occur in the body of the uterus are endometrial cancers, mostly *adenocarcinomas* [31]. Because endometrial cancer is *hormone* related, factors that modify risk might have different effects at different times of life.

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



Life events

Not bearing children and late natural *menopause* (after the age of 55) both increase the risk of endometrial cancer [42]. The reverse also applies: bearing children and early menopause both reduce the risk of endometrial cancer [36, 43–46].



Medication

Oral contraceptives, which contain either a combination of *oestrogen* and *progesterone*, or progesterone only, protect against endometrial cancer [46, 47]. Menopausal oestrogen hormone therapy unaccompanied by progesterone is a cause of this cancer. Menopausal oestrogen-only hormone therapy is normally prescribed only to women who have had a hysterectomy [46, 47]. Tamoxifen, a hormonal therapy used for breast cancer, can also increase the risk of endometrial cancer.



Family history

Women with a family history of endometrial or colorectal cancer have a higher risk of endometrial cancer [48]. Lifetime risk of endometrial cancer in women with Lynch syndrome *mutations* *MLH1* or *MSH2* is approximately 40 per cent, with a median age of 49. Women with *MSH6* mutations have a similar risk of endometrial cancer but a later age of diagnosis [49].

Confounding. Including data on women who were at high risk of endometrial cancer who have had hysterectomies may have influenced the results. MHT is an *effect modifier*; in women who have never used MHT there is a stronger association between body mass index (BMI) and endometrial cancer than in women who have ever used it [50].

For more detailed information on *adjustments* made in CUP analyses on adult attained height, see Evidence and judgements (**Section 5.1.6**).

4.2.2.6 Prostate

Definition. 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.

Classification. Almost all cases of prostate cancer are *adenocarcinoma*, a glandular *malignancy*. The clinical course and natural history of diagnosed prostate cancer vary 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. The term ‘advanced’ prostate cancer is sometimes employed in epidemiologic studies and is variably defined as higher grade, later stage, presence of metastatic disease or death. Further research is needed to better define the biological potential of newly diagnosed prostate cancer.

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

- stage 3–4 in 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

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



Family history and ethnicity

Approximately 9 per cent of all prostate cancers may result from heritable susceptible genes [51]. Genetic susceptibility has been linked to African heritage and *familial* disease [52]. In the USA, 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 [53].

Confounding. Screening for prostate cancer is a potential *confounder* or *effect modifier*.

For more detailed information on *adjustments* made in CUP analyses on adult attained height, see Evidence and judgements (**Section 5.1.7**).

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*. Furthermore, when only modestly raised, PSA alone cannot be used to distinguish between early-stage or indolent tumours (which may never be of clinical significance) and more aggressive or later-stage cancers.

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 in the USA, PSA screening is widely used. However, in other populations, such as in 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 on the grade or stage of cancer detected.

4.2.2.7 Kidney

Definition. The kidneys are a pair of organs located at the back of the abdomen outside the peritoneal cavity. They filter waste products and water from the blood, producing urine, which empties into the bladder through the ureters.

Classification. Different subtypes of kidney cancer likely have different aetiologies, yet some epidemiologic studies do not distinguish the *clear cell subtype*, the predominant parenchymal renal cancer, from *papillary* or other subtypes. Cancers of the renal pelvis are typically *transitional cell carcinomas*, which probably share aetiological risk factors such as smoking tobacco with other transitional cell carcinomas of the ureter and bladder.

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



Smoking tobacco

Smoking tobacco is a cause of kidney cancer. People who smoke have a 52 per cent increased risk of kidney cancer, and people who used to smoke have a 25 per cent increased risk, compared with those who have never smoked [54].



Medication

Painkillers containing phenacetin are known to cause cancer of the renal pelvis. Phenacetin is no longer used as an ingredient in painkillers [55].



Kidney disease

Polycystic kidney disease predisposes people to developing kidney cancer [56].



Hypertension

High blood pressure is associated with a higher risk of kidney cancer [57].



Family history

Inherited genetic predisposition accounts for only a minority of kidney cancers [58]. Von Hippel-Lindau syndrome is the most common, with up to 40 per cent of those inheriting the mutated gene developing kidney cancer [59].

Confounding. Smoking tobacco is a possible *confounder*.

For more detailed information on *adjustments* made in CUP analyses on adult attained height, see Evidence and judgements (**Section 5.1.8**).

4.2.2.8 Skin

Definition. The skin is the outer covering of the body and is one of the largest organs in terms of surface area and weight. Its primary function is to act as a barrier between the body and the environment.

Classification. There are two main types of skin cancer: *melanoma* and non-melanoma. The most common non-melanoma tumours are *basal cell carcinoma* and *squamous cell carcinoma*, which together account for 90 per cent of skin cancers. Melanoma accounts for 4 per cent of skin cancers¹.

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



Radiation

Over-exposure to ultraviolet radiation (mainly from sunlight, but also from ultraviolet-emitting tanning devices) is the chief cause of melanoma and non-melanoma skin cancers [60, 61].

¹ Kufe D, Pollock R, Weichselbaum R, et al. *Holland Frei Cancer Medicine*. 6 ed. Hamilton, Ontario: BC Decker, 2003.



Medication

Immune suppression following organ transplantation is associated with an increased risk of skin cancers, especially squamous cell carcinoma [62].



Infection and infestation

Human papillomavirus can cause squamous cell carcinomas of the skin, especially in immune-compromised people [62]. Patients with AIDS, who are immunocompromised, are also at increased risk of squamous cell carcinoma, but development of Kaposi's sarcoma, which is otherwise rare, is a characteristic complication.



Occupational exposure

Exposure to polychlorinated biphenyls (chemicals used in the plastic and chemical industries) has also been strongly associated with an elevated risk for this cancer.



Genetics and family history

There are some rare, high-penetrance genetic mutations known to cause melanoma, such as mutations in the CDKN2A gene, but these do not make a large contribution to the total number of melanoma cases¹. People who have a family history of melanoma are predisposed to this cancer [63]^{2,3}.



Skin pigmentation

There is an inverse relationship between risk of skin cancer and skin pigmentation, with highest risks observed in populations with the fairest skin. This is likely due to lower production of the protective skin pigment melanin [60].

Confounding. Sun exposure is an important *confounder*.

For more detailed information on *adjustments* made in CUP analyses on adult attained height, see Evidence and judgements (**Section 5.1.9** for malignant melanoma).

5. Evidence and judgements

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

Full [systematic literature reviews \(SLRs\)](#) for each cancer are available online. For most cancer sites considered in the CUP⁴, there is also a [CUP cancer report](#). CUP cancer reports summarise findings from the SLRs, again focusing on a specific cancer site. The following section also presents findings from the SLRs, but from a different perspective: it brings together all of the key findings on height and birthweight and the risk of cancer.

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

5.1 Adult attained height

Table 5.1 summarises the main findings from the CUP *dose-response meta-analyses* of *cohort studies* on height and the risk of cancer.

Evidence for cancers of the following types was discussed in the CUP but was too limited to draw a conclusion⁵: mouth, pharynx and larynx (2018), oesophagus (adenocarcinoma and squamous cell carcinoma, 2016), lung (2017), stomach (2016), gallbladder (2015), cervix (2017) and bladder (2015).

¹ Berwick M *et al.* *Cancer Epidemiol Biomarkers Prev* 2006; 15: 1520–5

² Ward SV *et al.* *Cancer Epidemiol* 2015; 39: 346–5

³ Chen T *et al.* *Eur J Cancer* 2014; 50: 2659–67

⁴ Cancers at the following sites are reviewed in the CUP: mouth, pharynx and larynx; nasopharynx; oesophagus; lung; stomach; pancreas; gallbladder; liver; colorectum; breast; ovary; endometrium; cervix; prostate; kidney; bladder; and skin. CUP cancer reports are not currently available for nasopharynx, cervix and skin.

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

Table 5.1: Summary of CUP dose–response meta-analyses of height^{1,2} and the risk of cancer

Cancer	Total no. of studies	No. of studies in meta-analysis	No. of cases	Risk estimate (95% CI)	Increment	I ² (%)	Conclusion ³	Date of CUP cancer report ⁴
Colorectum	20	13	65,880	1.05 (1.02–1.07)	5 cm	90	Convincing: Increases risk	2017
Breast (pre-menopause)	29	26	6,479	1.06 (1.02–1.11)	5 cm	46	Convincing: Increases risk	2017
Breast (post-menopause)	41	33	24,975	1.09 (1.07–1.11)	5 cm	33	Convincing: Increases risk	2017
Ovary	18	14	17,312	1.08 (1.05–1.10)	5 cm	35	Convincing: Increases risk	2014
Pancreas	14	10	6,147	1.07 (1.03–1.12)	5 cm	57	Probable: Increases risk	2012
Endometrium	13	10	17,732	1.07 (1.03–1.11)	5 cm	69	Probable: Increases risk	2013
Prostate	42	34	79,387	1.04 (1.03–1.05)	5 cm	21	Probable: Increases risk	2014
Kidney	11	10	9,874	1.10 (1.08–1.12)	5 cm	0	Probable: Increases risk	2015
Skin (malignant melanoma)	18	15	13,020	1.12 (1.09–1.16)	5 cm	64	Probable: Increases risk	2017
Skin (basal cell carcinoma)⁵	2	0	–	Statistically significant increased risk in 2 studies	–	–	Limited – suggestive: Increases risk	2017

- 1 Adult attained height is unlikely to directly influence the risk of cancer. It is a marker for genetic, environmental, hormonal and nutritional factors affecting growth during the period from preconception to completion of growth in length.
- 2 The evidence shows that, in general, the taller people are during adulthood, and the more people weighed at birth, the higher their risk of some cancers. A better understanding of the developmental factors that underpin the associations between greater growth and cancer risk is needed.
- 3 See Definitions of WCRF/AICR grading criteria (**Section 1:** Height and birthweight and the risk of cancer: a summary matrix) for explanations of what the Panel means by ‘convincing’, ‘probable’ and ‘limited – suggestive’.
- 4 Throughout this Third Expert Report, the year given for each cancer site is the year the CUP cancer report was published, apart from for nasopharynx, cervix and skin, where the year given is the year the SLR was last reviewed. Updated CUP cancer reports for nasopharynx and skin will be published in the future.
- 5 A dose–response meta-analysis of cohort studies could not be conducted in the CUP for height and the risk of basal cell carcinoma. A statistically significant increased risk was observed in two highest versus lowest analyses; one study reported a significant increased risk in men and women combined (RR 1.28 [95% CI 1.01–1.62]), but not for men and women analysed separately [64], and the other study reported a significant increased risk in women (RR 1.64 [95% CI 1.40–1.93]), but not in men [65].

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

For more information on the evidence for adult attained height and the risk of cancer that was graded by the Panel as ‘limited – suggestive’ and suggests a direction of effect, see the CUP document listed:

- CUP skin cancer SLR 2017: Section 8.3.1

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

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

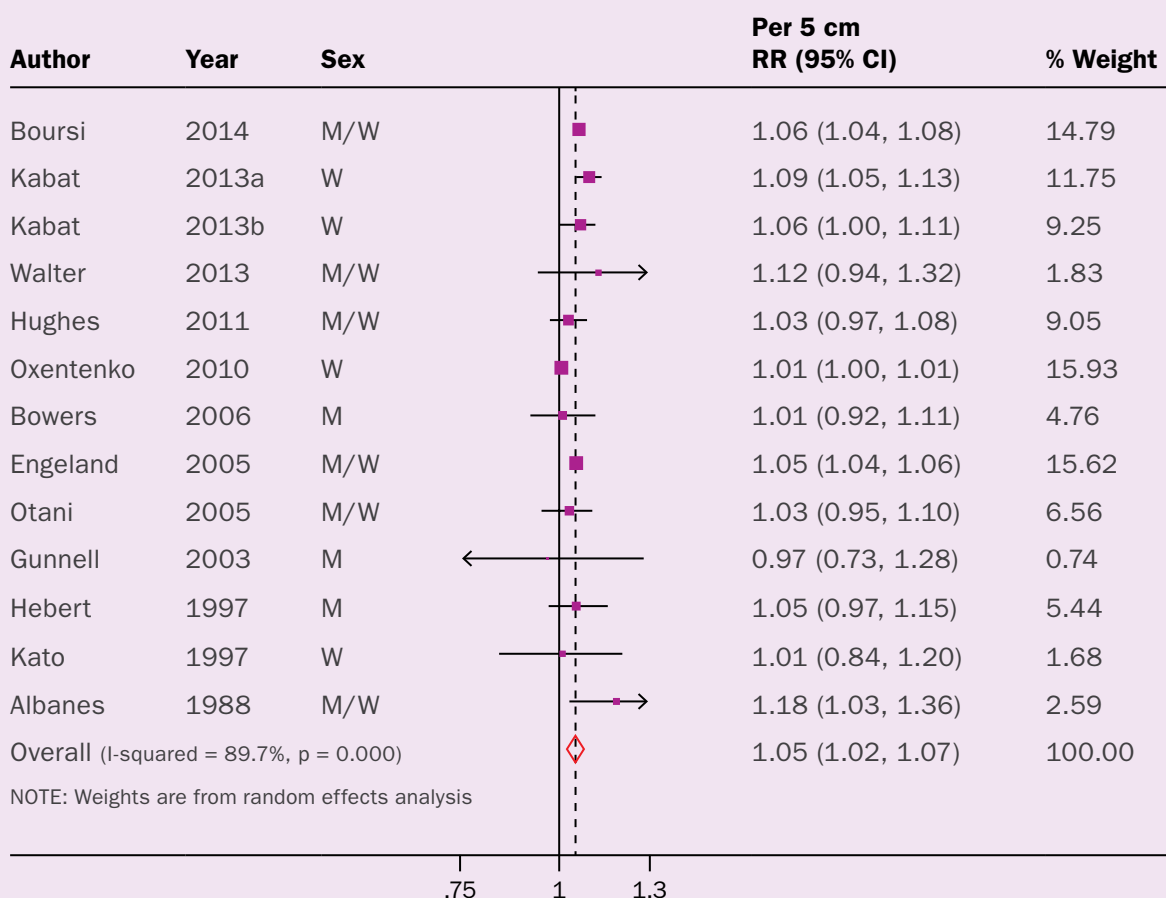
5.1.1 Colorectum

(Also see CUP colorectal cancer report 2017: Section 7.15 and CUP colorectal cancer SLR 2016: Sections 8.3.1)

5.1.1.1 CUP dose-response meta-analyses

Thirteen of 20 identified studies were included in the dose-response meta-analysis, which showed a statistically significant 5 per cent increased risk of colorectal cancer per 5 centimetres increase in height (RR 1.05 [95% CI 1.02–1.07]; n = 65,880 cases) (see **Figure 5.1**).

Figure 5.1: CUP dose-response meta-analysis¹ for the risk of colorectal cancer, per 5 centimetres increase in height



Source: Boursi, 2014 [67]; Kabat, 2013a [68]; Kabat, 2013b [69]; Walter, 2013 [70]; Hughes, 2011 [71]; Oxentenko, 2010 [72]; Bowers, 2006 [73]; Engeland, 2005 [74]; Otani, 2005 [75]; Gunnell, 2003 [66]; Hebert, 1997 [76]; Kato, 1997 [77]; Albanes, 1988 [78].

¹ Seven studies could not be included in the dose-response meta-analysis, one reported on gene-interactions and four did not provide sufficient information. For further details, see CUP colorectal cancer SLR 2016, Table 345.

High *heterogeneity* was observed ($I^2 = 90\%$). In stratified analyses, high heterogeneity was observed for women and studies in North America and appeared largely to be related to the size of the effect. There was evidence of small study bias with *Egger’s test* ($p < 0.001$) with one small study [66] reporting a decreased risk (although not statistically significant) rather than an increased risk (see [CUP colorectal cancer SLR 2016](#), Figure 576).

Stratified analyses for the risk of colorectal cancer per 5 centimetres increase in height were conducted for sex, geographic location and cancer type.

When stratified by sex, a statistically significant increased risk was observed for men (RR 1.04 [95% CI 1.03–1.05]) and women (RR 1.06 [95% CI (1.02–1.09; see [CUP colorectal cancer report 2017](#), Table 41 and [CUP colorectal cancer SLR 2016](#), Figure 577). When stratified by geographic location, a significant increased risk was observed in Europe (RR 1.05 [95% CI 1.04–1.06]) and North America (RR 1.06 [95% CI 1.01–1.11]), but not in Asia (see [CUP colorectal cancer SLR 2016](#), Figure 578). When stratified by cancer type, a significant increased risk was observed for colon (RR 1.05 [95% CI 1.04–1.07]) and rectal cancer (RR 1.03 [95% CI 1.01–1.06]; see [CUP colorectal cancer report 2017](#), Table 41 and [CUP colorectal cancer SLR 2016](#), Figures 582 and 589).

There was no evidence of a non-linear dose–response relationship ($p = 0.12$).

Most studies included in the dose–response meta-analysis *adjusted* for alcohol and tobacco smoking, and some studies adjusted for MHT use. For information on the adjustments made in individual studies see [CUP colorectal cancer SLR 2016](#), Table 344.

5.1.1.2 Published pooled analyses and meta-analyses

One published *pooled analysis* (see **Table 5.2**) on height and the risk of colorectal cancer was identified. No other published meta-analyses have been identified. The pooled analysis reported a statistically significant increased risk of death from colorectal cancer per 6.5 centimetres increase in height [79].

5.1.1.3 Mechanisms

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

Table 5.2: Summary of published pooled analysis of height and the risk of colorectal cancer

Publication	Increment	RR (95% CI)	I^2 (%)	No. of studies (cohort)	No. of cases (deaths)
Emerging risk factors collaboration [79]	6.5 cm	1.07 (1.03–1.11)	12	121	4,855

For further information on general processes involved in the development of cancer, see [The cancer process](#).

The proposed mechanisms by which adult attained height is linked to risk of colorectal cancer include greater exposure to growth factors such as growth hormone and *insulin-like growth factors (IGFs)* in childhood and early adulthood [6, 80], and excess calorie consumption in early life. Taller people have more cells and thus there is greater opportunity for *mutations* leading to cancer development [81]. In addition, taller adults also have longer intestines; therefore, there may be greater potential for DNA damage resulting from exposure to mutagenic or cancer-promoting agents. Overall there are moderate mechanistic data supporting greater adult height as a risk factor for colorectal cancer.

5.1.1.4 CUP Panel's conclusion

The evidence was consistent, and the CUP dose–response meta-analysis showed a statistically significant increased risk of colorectal cancer with increasing height. There was evidence of high *heterogeneity*, particularly for women and studies in North America; but it was mainly due to the size of the effect. The significant increased risk remained when the data were stratified by sex, geographic location and cancer type. There was no evidence of a non-linear dose–response relationship. One published *pooled analysis* also reported a statistically significant increased risk for colorectal cancer mortality. There is robust evidence for mechanisms operating in humans.

The CUP Panel concluded:

- **Developmental factors leading to greater growth in length in childhood (marked by adult attained height) are a convincing cause of colorectal cancer.**

5.1.2 Breast (premenopause)

(Also see [CUP breast cancer report 2017](#): Section 7.11 and [CUP breast cancer SLR 2017](#): Section 8.3.1.)

5.1.2.1 CUP dose–response meta-analyses

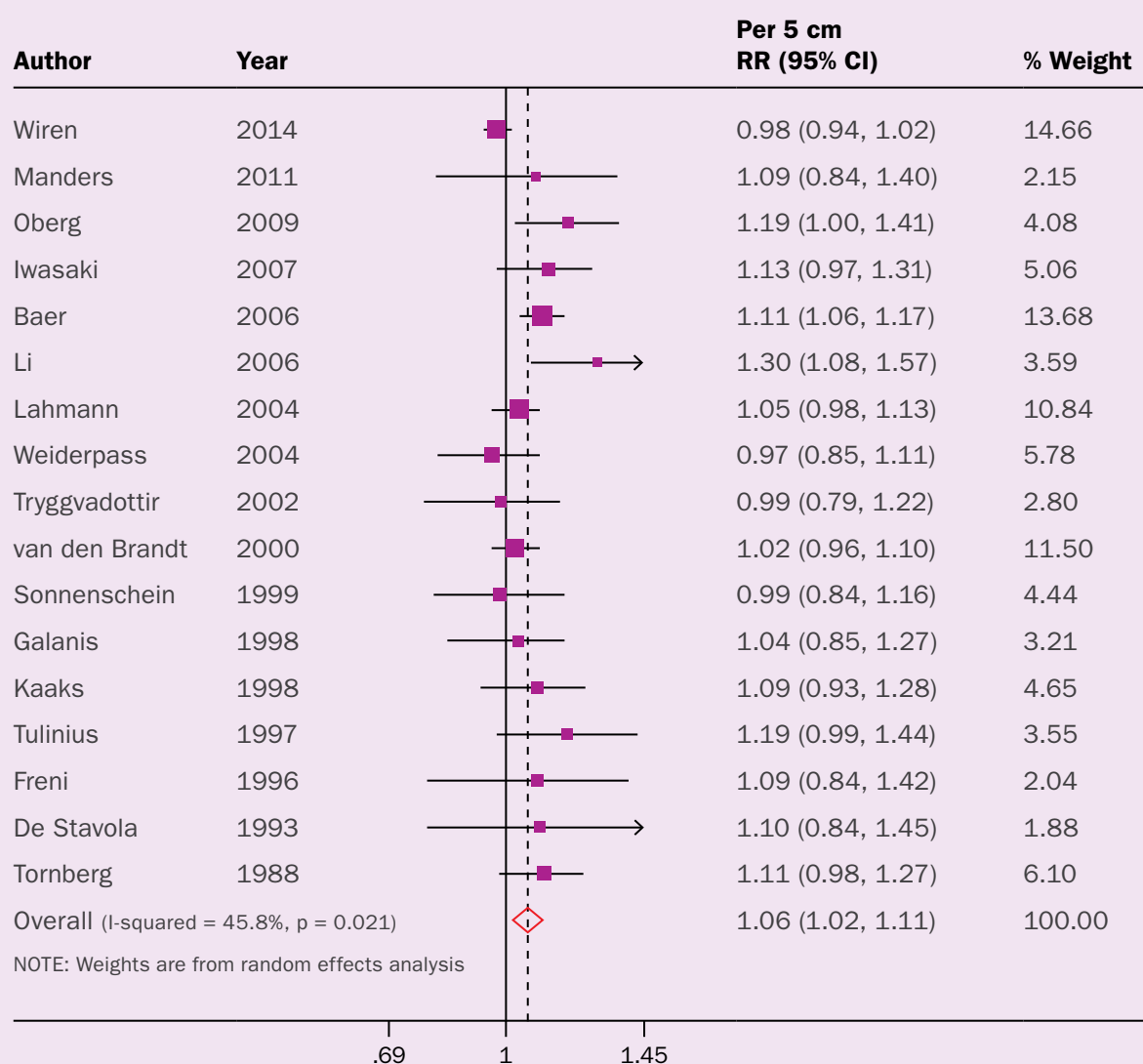
Twenty-six of 29 identified studies (including two *pooled analyses*) were included in the dose–response meta-analysis, which showed a statistically significant 6 per cent increased risk of premenopausal breast cancer per 5 centimetres increase in height (RR 1.06 [95% CI 1.02–1.11]; $n = 6,479$ cases) (see **Figure 5.2**). Moderate *heterogeneity* was observed ($I^2 = 46\%$) and there was no evidence of small study bias with *Egger's test* ($p = 0.11$).

Stratified analyses for the risk of premenopausal breast cancer per 5 centimetres increase in height were conducted for geographic location and for simultaneous *adjustment* for age, alcohol intake and reproductive factors. Please see [CUP breast cancer SLR 2017](#), Section 8.3.1, for details of other stratified analyses that have been conducted.

When stratified by geographic location, a statistically significant increased risk was observed in North America (RR 1.08 [95% CI 1.03–1.12]) and Asia (RR 1.20 [95% CI 1.04–1.37]), but not in Europe (see [CUP breast cancer report 2017](#), Table 24 and [CUP breast cancer SLR 2017](#), Figure 638). When stratified by simultaneous adjustment for *confounding factors*, the significant increased risk remained in studies that adjusted for age, alcohol intake and reproductive factors (RR 1.07 [95% CI 1.03–1.12]), but not in studies that did not adjust for those confounding factors, see [CUP breast cancer SLR 2017](#), Table 601.

Most studies included in the dose–response meta-analysis did not simultaneously adjust for age, alcohol intake and reproductive factors. For information on the adjustments made in individual studies, see [CUP breast cancer SLR 2017](#), Table 603.

Figure 5.2: CUP dose–response meta-analysis¹ for the risk of premenopausal breast cancer, per 5 centimetres increase in height



Source: Wiren, 2014 [82]; Manders, 2011 [83]; Oberg, 2009 [84]; Iwasaki, 2007 [85]; Baer, 2006 [86]; Li, 2006 [87]; Lahmann, 2004 [88]; Weiderpass, 2004 [89]; Tryggvadottir, 2002 [90]; van den Brandt, 2000 [91]; Sonnenschein, 1999 [92]; Galanis, 1998 [93]; Kaaks, 1998 [94]; Tulinius, 1997 [95]; Freni, 1996 [96]; De Stavola, 1993 [97]; Tornberg, 1988 [98].

5.1.2.2 Published pooled analyses and meta-analyses

Two published *pooled analyses* and one other published meta-analysis on height and the risk of premenopausal breast cancer were identified. Both pooled analyses were included in the CUP dose–response meta-analysis, and neither reported a statistically significant increase or decrease in risk [82, 91]. The published meta-analysis included *cohort* and *case-control studies* and reported a significant increased risk of premenopausal breast cancer

per 10 centimetres increase in height (RR 1.03 [95% CI 1.02–1.05]) [99].

5.1.2.3 Mechanisms

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

¹ The CUP dose–response meta-analysis included two pooled analyses, van den Brandt, 2000 [91] and Wiren, 2014 [82], which included 10 of the identified studies and one publication reported on two studies [85].

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

[The cancer process](#).

Adult height is directly related to the rate of growth during fetal life and childhood [100, 101]. The number of cell divisions in fetal life and childhood and the age of sexual maturity are all determined by the hormonal microenvironment (circulating plasma levels of growth factors and oestrogens and their respective binding proteins), which is influenced by nutritional status.

Many of these mechanisms, such as early-life nutrition affecting body composition and altered circulating and *hormone* profiles, can modulate the rate of tissue growth and sexual maturation. It is therefore plausible that nutritional factors during childhood and adolescence that affect height could also influence cancer risk. Specific tissues in taller people are exposed to higher levels of *insulin*, pituitary-derived growth hormone and IGFs, and thus may have undergone more cell divisions. This increased number of cell divisions may contribute to greater potential for error during DNA replication, resulting in an increased risk of developing cancer [81, 102]. Therefore, adult attained height may be a marker of inherited factors as well as fetal and childhood experience and is also a surrogate for important nutritional exposures, which affect several hormonal and metabolic axes and which may influence breast cancer risk.

5.1.2.4 CUP Panel's conclusion

The evidence was consistent, and the CUP dose–response meta-analysis showed a statistically significant increased risk of premenopausal breast cancer with increasing height. There was evidence of moderate *heterogeneity*. The significant increased risk remained when the data were stratified by geographic location, except in Europe. There is also robust evidence for mechanisms operating in humans.

The CUP Panel concluded:

- Developmental factors leading to greater growth in length in childhood (marked by adult attained height) are a convincing cause of premenopausal breast cancer.

5.1.3 Breast (postmenopause)

(Also see [CUP breast cancer report 2017](#): Section 7.11 and [CUP breast cancer SLR 2017](#): Section 8.3.1.)

5.1.3.1 CUP dose–response meta-analyses

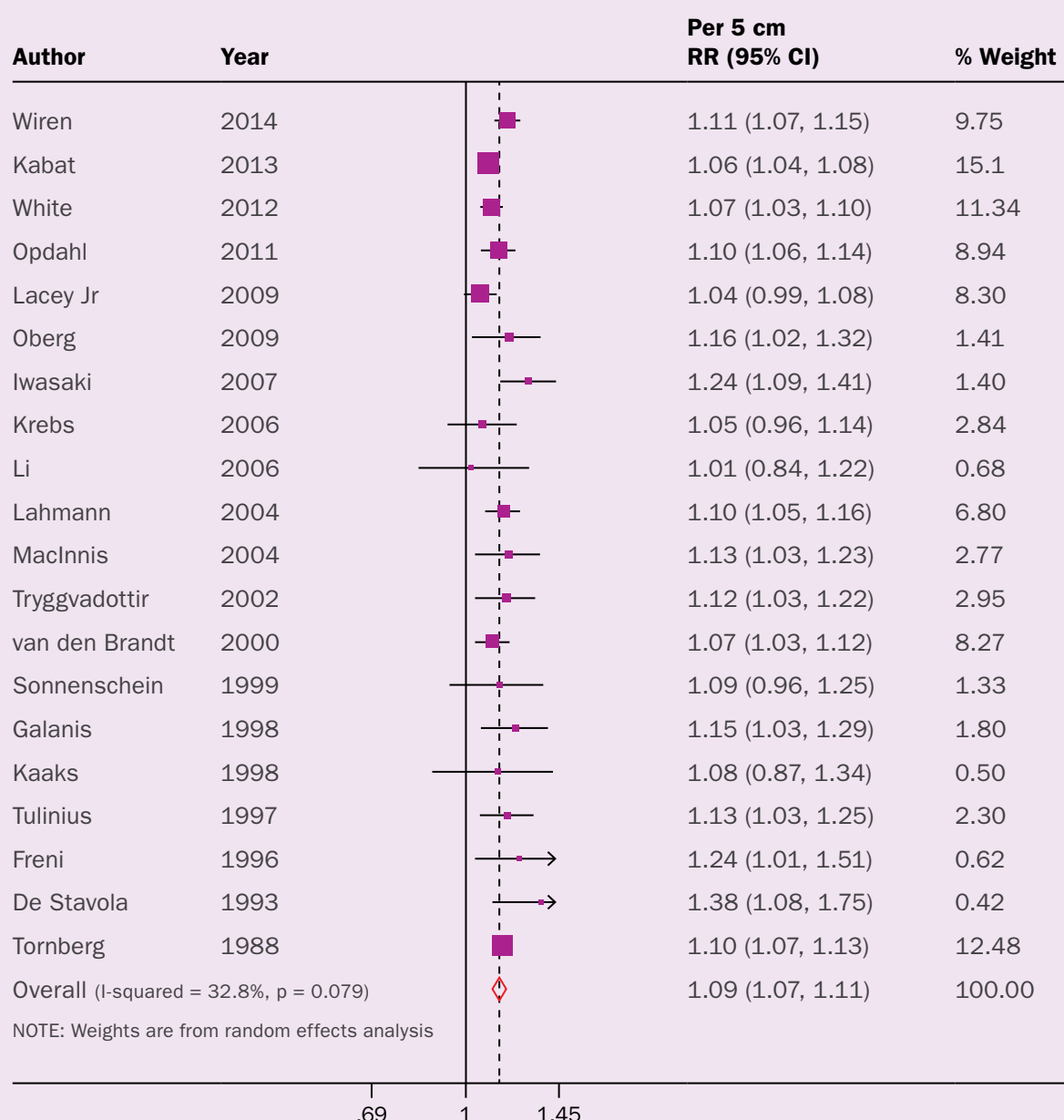
Thirty-three of 41 identified studies (including two *pooled analyses*) were included in the dose–response meta-analysis, which showed a statistically significant 9 per cent increased risk of postmenopausal breast cancer per 5 centimetres increase in height (RR 1.09 [95% CI 1.07–1.11]; $n = 24,975$ cases) (see **Figure 5.3**).

Moderate *heterogeneity* was observed ($I^2 = 33\%$). There was evidence of small study bias with *Egger's test* ($p = 0.02$). Inspection of the funnel plot showed that more smaller studies reported an increased risk (see [CUP breast cancer SLR 2017](#), Figure 643).

Stratified analyses for the risk of postmenopausal breast cancer per 5 centimetres increase in height were conducted for geographic location and for simultaneous *adjustment* for age, alcohol intake and reproductive factors. Please see [CUP breast cancer SLR 2017](#), Section 8.3.1, for details of other stratified analyses that have been conducted.

When stratified by geographic location, a statistically significant increased risk was observed in North America (RR 1.06 [95% CI 1.04–1.08]) and Europe (RR 1.10 [95% CI 1.08–1.12]), but not in Asia (see [CUP breast cancer report 2017](#), Table 25 and [CUP breast cancer SLR 2017](#), Figure 644).

Figure 5.3: CUP dose–response meta-analysis¹ for the risk of postmenopausal breast cancer, per 5 centimetres increase in height



Source: Wiren, 2014 [82]; Kabat, 2013a [68]; White, 2012 [103]; Opdahl, 2011 [104]; Lacey, 2009 [105]; Oberg, 2009 [84]; Iwasaki, 2007 [85]; Krebs, 2006 [106]; Li, 2006 [87]; Lahmann, 2004 [88]; MacInnis, 2004 [107]; Tryggvadottir, 2002 [90]; van den Brandt, 2000 [91]; Sonnenschein, 1999 [92]; Galanis, 1998 [93]; Kaaks, 1998 [94]; Tulinius, 1997 [95]; Freni, 1996 [96]; De Stavola, 1993 [97]; Tornberg, 1988 [98].

When stratified by simultaneous adjustment for *confounding factors*, a significant increased risk was observed in studies that adjusted for age, alcohol intake and reproductive factors (RR 1.08 [95% CI 1.06–1.10]) and in studies that did not adjust for those *confounding factors* (RR 1.10 [95% CI 1.07–1.12]) (see [CUP breast cancer SLR](#), Table 606).

In a separate CUP dose–response meta-analysis of seven studies (including one pooled analysis) on postmenopausal breast cancer mortality, a statistically significant 8 per cent increased risk per 5 centimetres increase in height was observed (RR 1.08 [95% CI 1.05–1.11], n = 3,181 cases, I² = 0%; see [CUP breast cancer SLR 2017](#), Figure 646).

¹ The CUP dose–response meta-analysis included two pooled analyses Van den Brandt, 2000 [91] and Wiren, 2014 [82], which included 13 of the identified studies and two publications reported on two studies [68, 85]



Fewer than half of the studies included in the main dose–response meta-analysis simultaneously adjusted for age, alcohol intake and reproductive factors. For information on the adjustments made in individual studies, see [CUP breast cancer SLR 2017](#), Table 607.

5.1.3.2 Published pooled analyses and meta-analyses

Two published *pooled analyses* on height and the risk of postmenopausal breast cancer were identified. No other published meta-analyses have been identified. Both pooled analyses [82, 91] were included in the CUP dose–response meta-analysis, and both reported a statistically significant increased risk of postmenopausal breast cancer incidence per 5 centimetres increase in height.

5.1.3.3 Mechanisms

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

For further information on general processes involved in the development of cancer, see [The cancer process](#).

Adult height is directly related to the rate of growth during fetal life and childhood [100, 101]. The number of cell divisions in fetal life and childhood and age of sexual maturity are all determined by the hormonal

microenvironment (circulating plasma levels of growth factors and *oestrogens* and their respective binding proteins), which is influenced by nutritional status.

Many of these mechanisms, such as early-life nutrition affecting body composition and altered circulating and *hormone* profiles, can modulate the rate of tissue growth and sexual maturation. It is therefore plausible that nutritional factors during childhood and adolescence that affect height could also influence cancer risk. Specific tissues in taller people are exposed to higher levels of *insulin*, pituitary-derived growth hormone and IGFs, and thus may have undergone more cell divisions. This increased number of cell divisions may contribute to greater potential for error during DNA replication, resulting in an increased risk of developing cancer [81, 102]. Therefore, adult attained height may be a marker of inherited factors as well as fetal and childhood experience and is also a surrogate for important nutritional exposures, which affect several hormonal and metabolic axes and which may influence breast cancer risk.

5.1.3.4 CUP Panel's conclusion

The evidence was consistent, and the CUP dose–response meta-analysis showed a statistically significant increased risk of postmenopausal breast cancer with increasing height. There was evidence of moderate *heterogeneity*. The significant increased remained when stratified by geographic location, except for in Asia. There is robust evidence for mechanisms operating in humans.

The CUP Panel concluded:

- **Developmental factors leading to greater growth in length in childhood (marked by adult attained height) are a convincing cause of postmenopausal breast cancer.**

5.1.4 Ovary

(Also see [CUP ovarian cancer report 2014](#): Section 7.3 and [CUP ovarian cancer SLR 2013](#): Section 8.3.1.)

5.1.4.1 CUP dose-response meta-analysis

Fourteen of 18 identified studies were included in the dose-response meta-analysis, which showed a statistically significant 8 per cent increased risk of ovarian cancer per 5 centimetres increase in height (RR 1.08 [95% CI 1.05–1.10]; $n = 17,312$ cases) (see **Figure 5.4**). Moderate *heterogeneity* was observed ($I^2 = 35\%$), which was related to the size of the effect. There was no evidence of small study bias with *Egger's test* ($p = 0.29$).

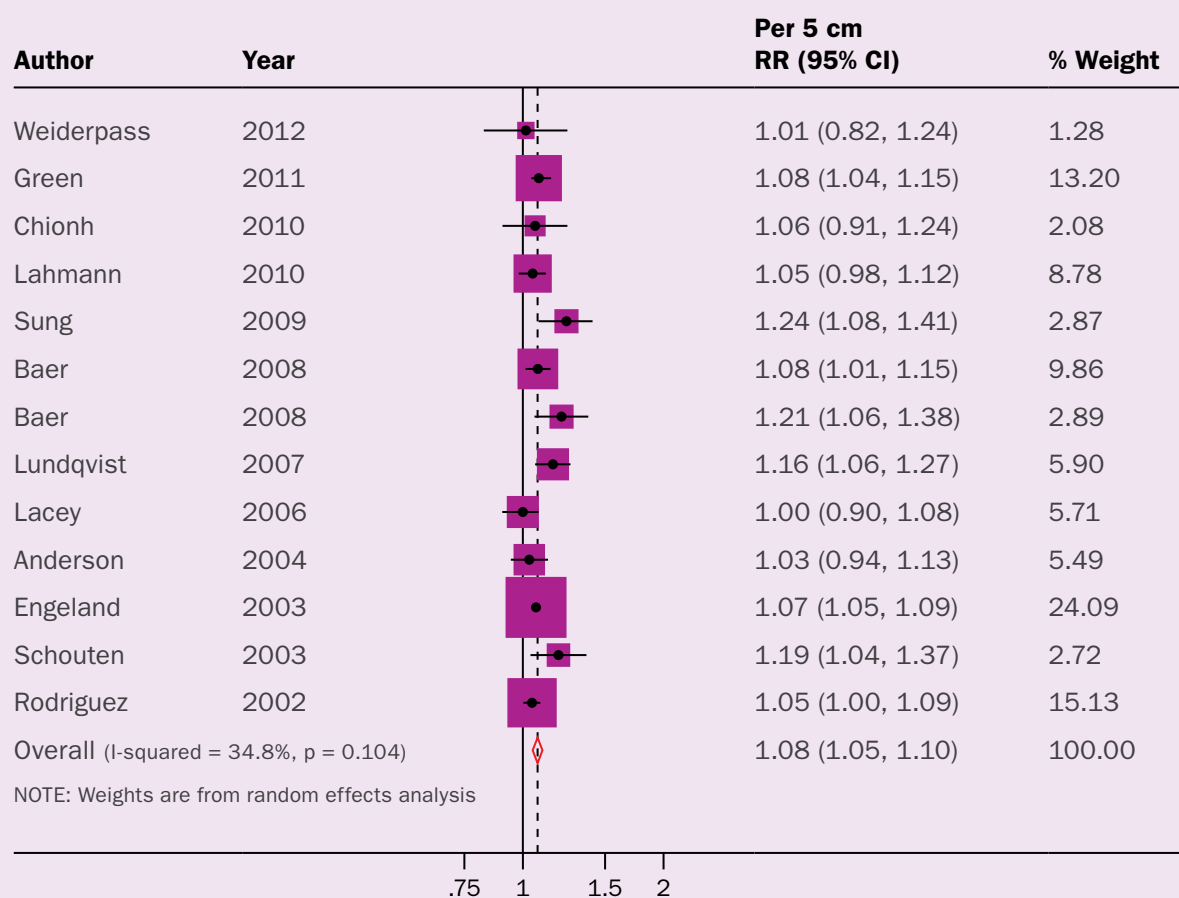
There was no evidence of a non-linear dose-response relationship ($p = 0.9$).

All studies included in the dose-response meta-analysis *adjusted* for age, most studies adjusted for reproductive factors, and some studies adjusted for tobacco smoking, physical activity and/or HRT use.

5.1.4.2 Published pooled analyses and meta-analyses

Three published *pooled analyses* (see **Table 5.3**) on height and the risk of ovarian cancer were identified. No other published meta-analyses have been identified. The pooled analyses all reported a statistically significant increased risk [79, 120, 121].

Figure 5.4: CUP dose-response meta-analysis¹ for the risk of ovarian cancer, per 5 centimetres increase in height



Source: Weiderpass, 2012 [108]; Green, 2011 [109]; Chionh, 2010 [110]; Lahmann, 2010 [111]; Sung, 2009 [112]; Baer, 2008 [113]; Lundqvist, 2007 [114]; Lacey, 2006 [115]; Anderson, 2004 [116]; Engeland, 2003 [117]; Schouten, 2003 [118]; Rodriguez, 2002 [119].

¹ The CUP dose-response meta-analysis included 14 studies. Thirteen risk estimates were included in the analysis as one publication reported a risk estimate for two studies combined (Lundqvist, 2007 [114]). Another publication included two separate risk estimates for two studies (Baer, 2008 [113]).

Table 5.3: Summary of published pooled analyses on height and the risk of ovarian cancer

Publication	Increment	RR (95% CI)	I ² (%)	No. of studies (cohort)	No. of cases
Collaborative Group on Epidemiological Studies of Ovarian Cancer, 2012 [121]	5 cm	1.08 (1.06–1.10)	–	17	10,858 diagnoses
The Emerging Risk Factors Collaboration, 2012 [79]	6.5 cm	1.07 (1.01–1.14)	0	–	1,353 deaths
Pooling Project of Prospective Studies of Diet and Cancer [120]	5 cm	1.10 (1.05–1.15)	–	12	2,036 diagnoses

An additional CUP analysis of 24 studies (n = 16,062) from the Pooling Project of Prospective Studies of Diet and Cancer [120] and the non-overlapping studies from the CUP [74, 108, 109, 111, 112, 114] showed a statistically significant eight per cent increased risk of ovarian cancer per 5 centimetres increase in height (RR 1.08 [95% CI 1.06–1.11]).

5.1.4.3 Mechanisms

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

For further information on general processes involved in the development of cancer, see [The cancer process](#).

Adult height is determined by inherited genetic factors and specific exposures, such as nutrition and infections in utero as well as throughout childhood and adolescence [6]. These factors may also affect ovarian cancer risk later in life through alterations in hormonal pathways, in particular the IGF-I pathway. However, results from epidemiological studies on circulating IGF-I levels and ovarian cancer risk have been inconclusive [122].

5.1.4.4 CUP Panel's conclusion

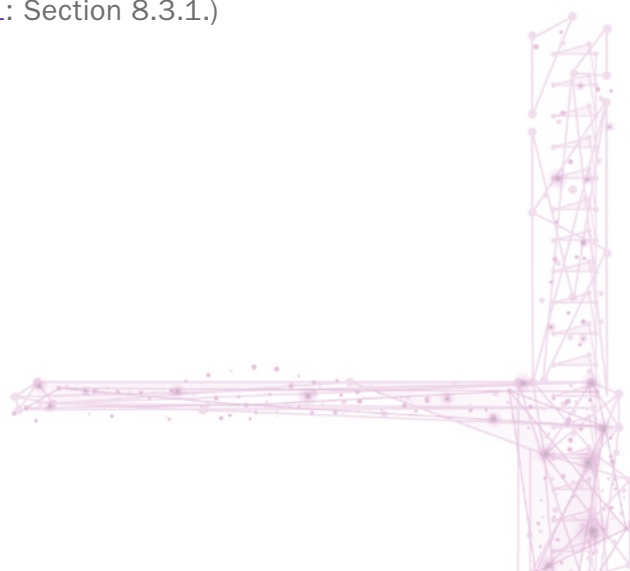
The evidence was consistent and the CUP dose–response meta-analysis showed a statistically significant increased risk of ovarian cancer with increasing height. There was evidence of moderate *heterogeneity*. There was no evidence of a non-linear dose–response relationship. The results of three published *pooled analyses* showed a significant increased risk. There is evidence of plausible mechanisms operating in humans.

The CUP Panel concluded:

- **Developmental factors leading to greater growth in length in childhood (marked by adult attained height) are a convincing cause of ovarian cancer.**

5.1.5 Pancreas

(Also see [CUP pancreatic cancer report 2012: Section 7.8](#) and [CUP pancreatic cancer SLR 2011: Section 8.3.1.](#))



5.1.5.1 CUP dose-response meta-analyses

Ten of 14 identified studies were included in the dose-response meta-analysis, which showed a statistically significant 7 per cent increased risk of pancreatic cancer per 5 centimetres increase in height (RR 1.07 [95% CI 1.03–1.12]; $n = 6,147$ cases) (see **Figure 5.5**). High *heterogeneity* was observed ($I^2 = 57\%$), which may be due to one study reporting a decreased risk rather than an increased risk [123]. There was no evidence of small study bias with *Egger's test* ($p = 0.15$), but there was some evidence of asymmetry in the funnel plot (see [CUP pancreatic cancer SLR 2011](#), Figure 217).

Stratified analyses for the risk of pancreatic cancer per 5 centimetres increase in height were conducted for sex; a statistically significant increased risk was observed

in men (RR 1.07 [95% CI 1.01–1.14]), but not women (RR 1.07 [95% CI 0.99–1.15]; see [CUP pancreatic cancer SLR 2011](#), Figure 219).

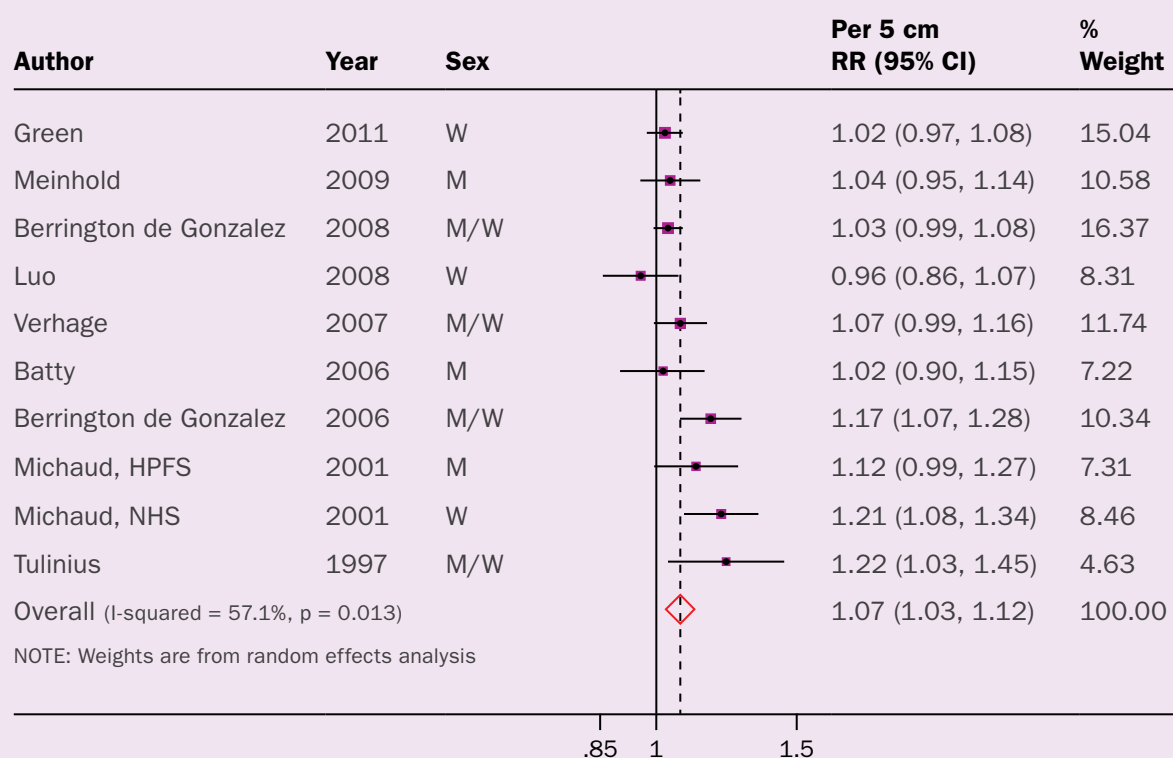
There was no evidence of a non-linear dose-response relationship ($p = 0.14$).

All studies included in the dose-response meta-analysis *adjusted* for age, sex and tobacco smoking.

5.1.5.2 Published pooled analyses and meta-analyses

Three published *pooled analyses* on height and the risk of pancreatic cancer were identified (see **Table 5.4**). No other published meta-analyses have been identified. All of the pooled analyses reported no statistically significant increase or decrease in risk [130–132].

Figure 5.5: CUP dose-response meta-analysis^{1,2} for the risk of pancreatic cancer, per 5 centimetres increase in height



Source: Green, 2011 [109]; Meinhold, 2009 [124]; Berrington de Gonzalez, 2008 [125]; Luo, 2008 [123]; Verhage, 2007 [126]; Batty, 2006 [127]; Berrington de Gonzalez, 2006 [128]; Michaud, 2001 [129]; Tulinius, 1997 [95].

¹ Four studies could not be included in the dose-response meta-analysis as they did not provide sufficient information. For further details, see [CUP pancreatic cancer SLR 2011](#), Table 192.

² One publication included two separate risk estimates for two studies (Michaud, 2001 [129]).

Table 5.4: Summary of published pooled analyses of height and the risk of pancreatic cancer

Publication	Increment/contrast	Sex	RR (95% CI)	I ² (%)	No. of studies	No. of cases
Pooling Project of Prospective Studies on Diet and Cancer [130]	≥ 180 vs. < 170 cm	Men	1.18 (0.93–1.49)	11	14 cohort	1,019 diagnoses
	≥ 170 vs. < 160 cm	Women	1.03 (0.84–1.25)	0		1,115 diagnoses
Pancreatic Cancer Cohort Consortium (PanScan) [132]	Highest vs. lowest	–	0.99 (0.83–1.18)	–	12 cohort and 1 case-control	2,095 diagnoses
Asia-Pacific Cohort Studies Collaboration [131]	6 cm	Men	1.08 (0.94–1.24)	–	38 cohort	294 deaths
	6 cm	Women	0.99 (0.82–1.21)	–		

5.1.5.3 Mechanisms

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

For further information on general processes involved in the development of cancer, see [The cancer process](#).

Specific mechanisms that link greater adult height with an increased risk of pancreatic cancer have not been clearly identified but may include those that have been proposed for other height-related cancers. Greater adult height may be related to increased exposure to *endocrine* and metabolic patterns, such as IGFs, in childhood and early adulthood, which have been associated with organ growth, greater cell division, and thus risk of cancer-initiating *mutations* [6, 80]. In addition, taller people have more cells and thus there is greater opportunity for mutations to arise and lead to cancer development [81].

5.1.5.4 CUP Panel's conclusion

The evidence was generally consistent, and the CUP dose–response meta-analysis showed a statistically significant increased risk of pancreatic cancer with increasing height. High *heterogeneity* was observed, which seemed to be due to one study reporting a decreased rather than an increased risk. When stratified by sex, the statistically significant increase in risk remained for men, but not women. There was no evidence of a non-linear dose–response relationship. Three published *pooled analyses* reported no significant increase or decrease in risk. There is also evidence of plausible mechanisms operating in humans.

The CUP Panel concluded:

- **Developmental factors that lead to greater growth in length in childhood (marked by adult attained height) are a probable cause of pancreatic cancer.**

5.1.6 Endometrium

(Also see [CUP endometrial cancer report 2013: Section 7.6](#) and [CUP endometrial cancer SLR 2012: Section 8.3.1.](#))

5.1.6.1 CUP dose–response meta-analysis

Ten of 13 identified studies were included in the dose–response meta-analysis, which showed a statistically significant 7 per cent increased risk of endometrial cancer per 5 centimetres increase in height (RR 1.07 [95% CI 1.03–1.11]; $n = 17,732$ cases) (see **Figure 5.6**). High *heterogeneity* was observed ($I^2 = 69\%$), which appeared to be due to one study reporting a larger increased risk with a narrow 95 per cent confidence interval [69].

There was no evidence of a non-linear dose–response relationship ($p = 0.39$).

All studies included in the dose–response meta-analysis *adjusted* for age, most studies adjusted for tobacco smoking and some adjusted for reproductive factors and/or physical activity.

5.1.6.2 Published pooled analyses and meta-analyses

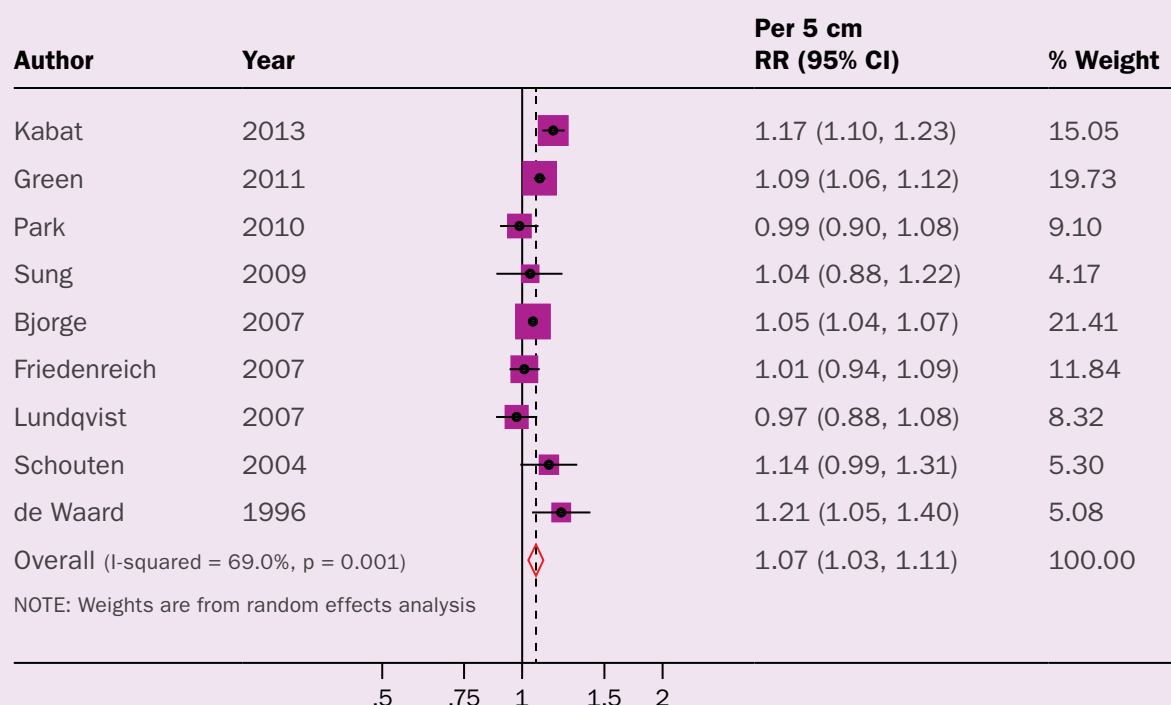
No published pooled analyses and no other published meta-analyses on height and the risk of endometrial cancer were identified.

5.1.6.3 Mechanisms

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

For further information on general processes involved in the development of cancer, see [The cancer process](#).

Figure 5.6: CUP dose–response meta-analysis¹ for the risk of endometrial cancer, per 5 centimetres increase in height



Source: Kabat, 2013b [69]; Green, 2011 [109]; Park, 2010 [133]; Sung, 2009 [112]; Bjorge, 2007 [134]; Friedenreich, 2007 [135]; Lundqvist, 2007 [114]; Schouten, 2004 [136]; de Waard, 1996 [137].

¹ The CUP dose–response meta-analysis included ten studies. Nine risk estimates were included in the analysis as one publication reported a risk estimate for two studies combined (Lundqvist, 2007 [114]).

Adult height is directly related to the rate of growth during fetal life and childhood [100, 101]. The number of cell divisions in fetal life and childhood, health and nutrition status in childhood, and age of sexual maturity are all determined by the hormonal microenvironment (plasma levels of growth factors and *oestrogens* and their respective binding proteins), which is influenced by nutritional status. Many of these mechanisms, such as early-life nutrition affecting body composition and altered circulating and free *hormone* profiles, can modulate the rate of tissue growth and sexual maturation. It is therefore plausible that nutritional factors that affect height could also influence cancer risk. Specific tissues in taller people are exposed to higher levels of *insulin*, pituitary-derived growth hormone and IGFs, and thus may have undergone more cell divisions. This increased number of cell divisions may contribute to greater potential for error during DNA replication, resulting in an increased risk of developing cancer [81, 102]. Therefore, adult attained height is a marker of inherited factors as well as fetal and childhood experience and is also a surrogate for important nutritional exposures, which affect several hormonal and metabolic axes and which may influence endometrial cancer risk.

5.1.6.4 CUP Panel's conclusion

The evidence was generally consistent, and the CUP dose–response meta-analysis showed a statistically significant increased risk of endometrial cancer with increasing height. There was evidence of high *heterogeneity*, which appeared to be due to one study reporting a larger increase in risk. There was no evidence of a non-linear dose–response relationship. There is also evidence of plausible mechanisms operating in humans.

The CUP Panel concluded:

- Developmental factors leading to greater growth in length in childhood (marked by adult attained height) are probably a cause of endometrial cancer.

5.1.7 Prostate

(Also see CUP prostate cancer report 2014: Section 7.7 and CUP prostate cancer SLR 2014: Section 8.3.1.)

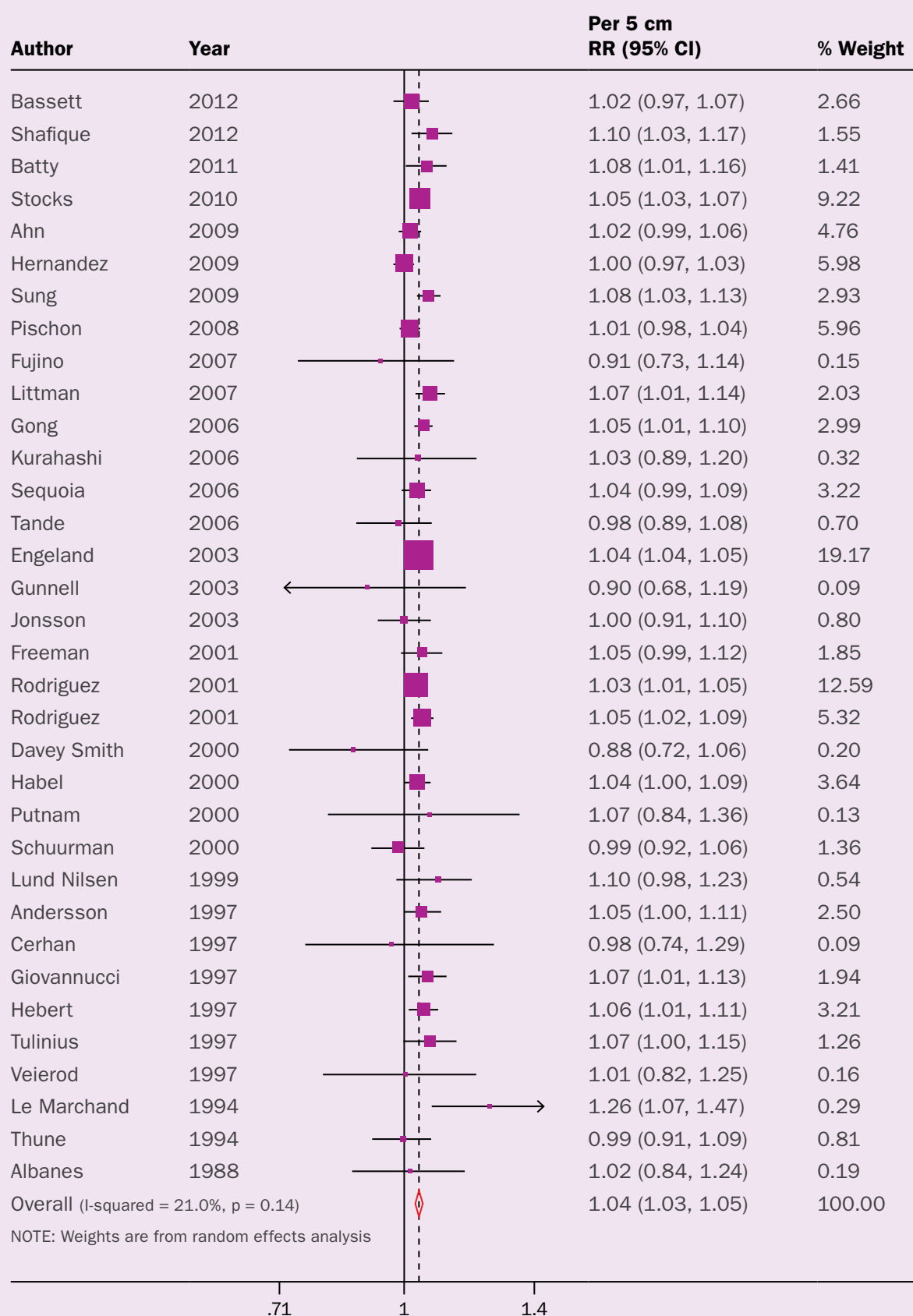
5.1.7.1 CUP dose–response meta-analyses

Thirty-four of 42 identified studies were included in the dose–response meta-analysis, which showed a statistically significant 4 per cent increased risk of prostate cancer (type of prostate cancer not specified) per 5 centimetres increase in height (RR 1.04 [95% CI 1.03–1.05]; $n = 79,387$ cases) (see **Figure 5.7**). Low *heterogeneity* was observed ($I^2 = 21\%$), and there was no evidence of small study bias with Egger's test ($p = 0.79$).

Stratified analyses for the risk of prostate cancer per 5 centimetres increase in height were conducted for cancer outcome; a statistically significant increased risk was observed for advanced (RR 1.04 [95% CI 1.02–1.06]), fatal (RR 1.04 [95% CI 1.01–1.06]) and non-advanced (RR 1.03 [95% CI 1.01–1.05]) prostate cancer (see CUP prostate cancer SLR 2014, Figures 318 and 320).



Figure 5.7: CUP dose-response meta-analysis for the risk of prostate cancer, per 5 centimetres increase in height



Source: Bassett, 2012 [138]; Shafique, 2012 [139]; Batty, 2011 [140]; Stocks, 2010 [141]; Ahn, 2009 [142]; Hernandez, 2009 [143]; Sung, 2009 [112]; Pischon, 2008 [144]; Fujino, 2007 [145]; Littman, 2007 [146]; Gong, 2006 [147]; Kurahashi, 2006 [148]; Sequoia, 2006 [149]; Tande, 2006 [150]; Engeland, 2003 [151]; Gunnell, 2003 [66]; Jonsson, 2003 [152]; Freeman, 2001 [153]; Rodriguez, 2001 [154]; Davey-Smith, 2000 [155]; Habel, 2000 [156]; Putnam, 2000 [157]; Schuurman, 2000 [158]; Lund Nilsen, 1999 [159]; Andersson, 1997 [160]; Cerhan, 1997 [161]; Giovannucci, 1997 [162]; Hebert, 1997 [76]; Tulinius, 1997 [95]; Veierod, 1997 [163]; Le Marchand, 1994 [164]; Thune, 1994 [165]; Albanes, 1988 [78].

All studies included in the dose–response meta-analysis *adjusted* for age; some adjusted for tobacco smoking, physical activity and/or BMI.

There was evidence of a non-linear dose–response relationship in analyses on prostate cancer as well as for the subtype of advanced prostate cancer ($p = 0.01$ and $p < 0.01$, respectively) (see **Figure 5.8** and **Figure 5.9** and **CUP prostate cancer SLR 2014**, Tables 281 and 282). For 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.

5.1.7.2 Published pooled analyses and meta-analyses

Two published *pooled analyses* and one other published meta-analysis on height and the risk of prostate cancer incidence or mortality were identified (see **Table 5.5** for results of pooled analyses). One pooled analysis showed a statistically significant increased risk of death from prostate cancer with increasing height, and the other reported no significant increase or decrease in the risk of death. The published meta-analysis reported a significant increased risk of prostate cancer per 10 centimetres increase in height (RR 1.09 [95% CI 1.06–1.12]) [166].

5.1.7.3 Mechanisms

The information on mechanisms is based on both human and animal studies, with a preference for human studies whenever

possible. This section covers the primary hypotheses that currently prevail and is not based on a systematic or exhaustive search of the literature.

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

Greater adult attained height is associated with higher risk of prostate cancer; however, specific mechanisms that link greater adult height with higher risk of prostate cancer have not been identified. Adult height may be viewed as a marker of factors affecting linear growth including nutritional and genetic factors as well as cumulative exposure to *endogenous hormones* such as growth hormone and IGFs. The IGF axis plays a major role in the regulation of cell growth and survival, and experimental studies demonstrate that increased signalling through the IGF system can exert a pro-tumorigenic effect. Recently, a large-scale collaborative meta-analysis of studies examining the relation between circulating IGF-I and the incidence of prostate cancer reported a robust, positive association between IGF-I levels and prostate cancer risk [167]. Therefore, the IGF axis may represent a plausible mechanism linking height to prostate cancer development. An additional proposed mechanism relates to taller people having more cells and thus there is greater opportunity for *mutations* to arise and lead to cancer development [81].

Table 5.5: Summary of published pooled analyses of height and the risk of prostate cancer

Publication	Increment	RR (95% CI)	I ² (%)	No. of studies (cohort)	No. of cases (deaths)
Emerging Risk Factor Collaboration [79]	6.5 cm	1.07 (1.02–1.11)	9	121	2,818
Asia Pacific Cohort Studies Collaboration [131]	6 cm	1.06 (0.95–1.18)	–	38	274

Figure 5.8: CUP non-linear dose-response association of height and the risk of prostate cancer

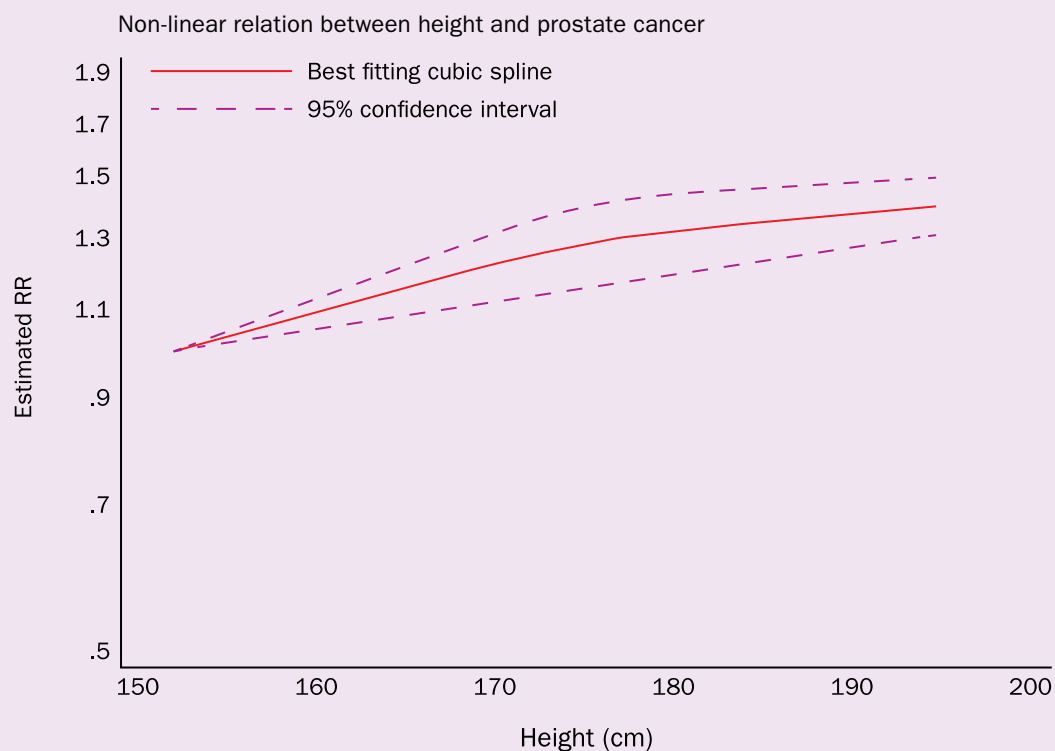
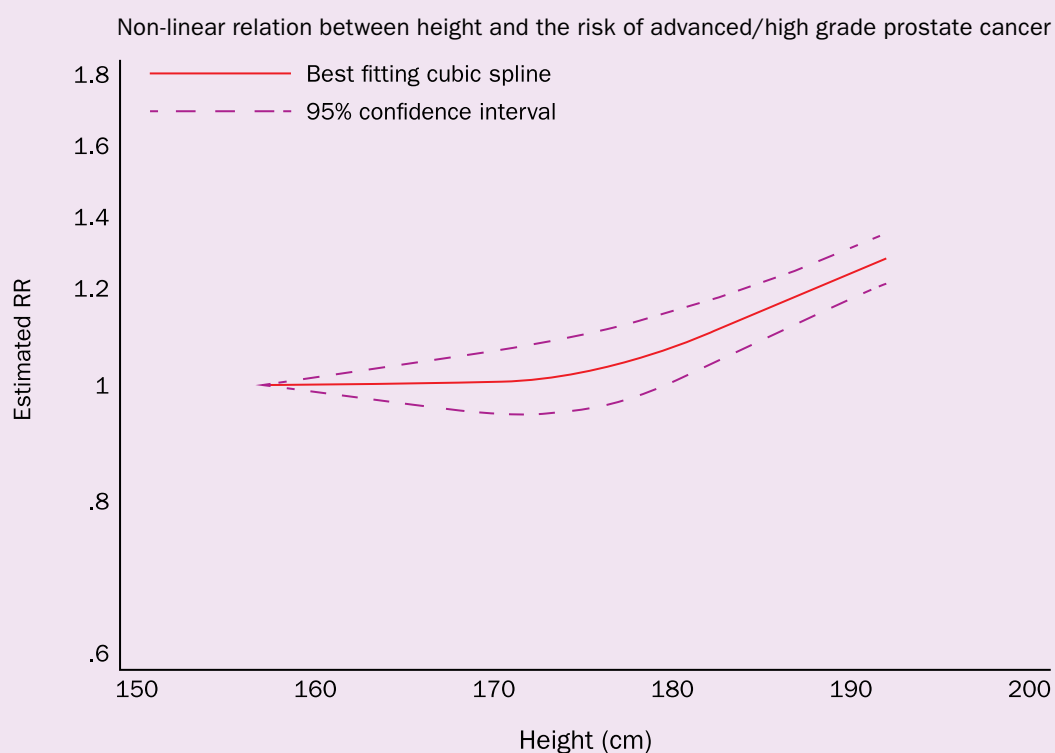


Figure 5.9: CUP non-linear dose-response association of height and the risk of advanced prostate cancer



5.1.7.4 CUP Panel's conclusion

The evidence was generally consistent and the CUP dose–response meta-analysis showed a statistically significant increased risk of prostate cancer with increasing height. Low *heterogeneity* was observed. The significant increased risk remained for both advanced and non-advanced cancers. There was evidence of a non-linear dose–response relationship in analyses on prostate cancer (where type of prostate cancer was not specified) and advanced prostate cancer. One of two published *pooled analyses* showed a statistically significant increased risk of death from prostate cancer. There is also evidence of plausible mechanisms operating in humans.

The CUP Panel concluded:

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

5.1.8 Kidney

(Also see CUP kidney cancer report 2015: Section 7.4 and CUP kidney cancer SLR 2015: Section 8.3.1.)

5.1.8.1 CUP dose–response meta-analyses

Ten of 11 identified studies were included in the dose–response meta-analysis, which showed a statistically significant 10 per cent increased risk of kidney cancer per 5 centimetres increase in height (RR 1.10 [95% CI 1.08–1.12]; $n = 9,874$) (see **Figure 5.10**). No *heterogeneity* was observed, and there was no evidence of small study bias with Egger's test ($p = 0.54$).

Stratified analyses for the risk of kidney cancer per 5 centimetres increase in height were conducted for sex. A statistically significant increased risk was observed in men (RR 1.10 [95% CI 1.06–1.13]) and women (RR 1.10 [95% CI 1.07–1.14]; see CUP kidney cancer report 2015, Table 6 and CUP kidney cancer SLR 2015, Figure 139).

There was no evidence of a non-linear dose–response relationship ($p = 0.62$).

All studies included in the dose–response meta-analysis *adjusted* for age and sex, and most studies adjusted for tobacco smoking.

5.1.8.2 Published pooled analyses and meta-analyses

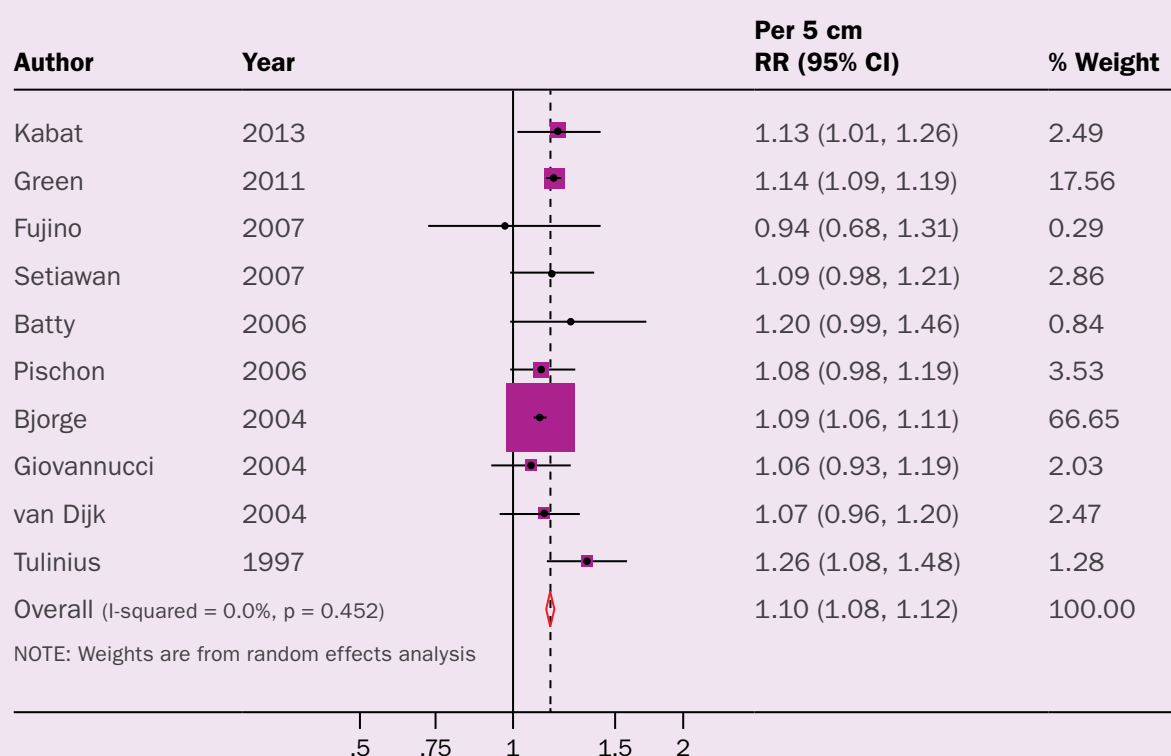
One published *pooled analysis* on height and the risk of kidney cancer mortality was identified (see **Table 5.6**). No other published meta-analyses have been identified. The pooled analysis contained very few cases of kidney cancer and reported no significant increase or decrease in risk in men or women [131].

5.1.8.3 Mechanisms

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



Figure 5.10: CUP dose–response meta-analysis for the risk of kidney cancer, per 5 centimetres increase in height



Source: Kabat, 2013b [69]; Green, 2011 [109]; Fujino, 2007 [145]; Setiawan, 2007 [168]; Batty, 2006 [127]; Pischon, 2006 [169]; Bjorge, 2004 [170]; Giovannucci, 2004 [171]; van Dijk, 2004 [172]; Tulinius, 1997 [95].

Table 5.6: Summary of published pooled analyses of height and the risk of kidney cancer

Publication	Increment	Sex	RR (95% CI)	No. of studies (cohort)	No. of cases (deaths)
Asia-Pacific Cohort Studies Collaboration [131]	6 cm	Men	1.04 (0.83–1.31)	38	67
	6 cm	Women	1.21 (0.81–1.83)		23

For further information on general processes involved in the development of cancer, see [The cancer process](#).

Specific mechanisms that link greater adult height with an increased risk of kidney cancer have not been clearly identified but may include those that have been proposed for other height-related cancers. Greater adult height may be related to increased exposure to *endocrine* and metabolic patterns, such as IGFs, in childhood and early adulthood, which have been associated with organ growth, greater cell division, and thus risk of cancer-

initiating *mutations* [6]. In addition, taller people have more cells and thus there is greater opportunity for mutations to arise and lead to cancer development [81].

5.1.8.4 CUP Panel's conclusion

The evidence was generally consistent, and the CUP dose–response meta-analysis showed a statistically significant increased risk of kidney cancer with increasing height. No *heterogeneity* was observed. The significant increased risk remained for men and women. There was no evidence of a non-linear

dose–response relationship. The results of the published *pooled analysis*, with few cases, showed no statistically significant increase or decrease in risk. There is evidence of plausible mechanisms operating in humans.

The CUP Panel concluded:

- **Developmental factors leading to greater growth in length in childhood (marked by adult attained height) are probably a cause of kidney cancer.**

5.1.9 Skin (malignant melanoma)

(Also see [CUP skin cancer SLR 2017](#): Section 8.3.1.)

The evidence for malignant *melanoma* is presented in the following subsections.

For information on studies on any form of skin cancer, non-melanoma skin cancer, *basal cell*

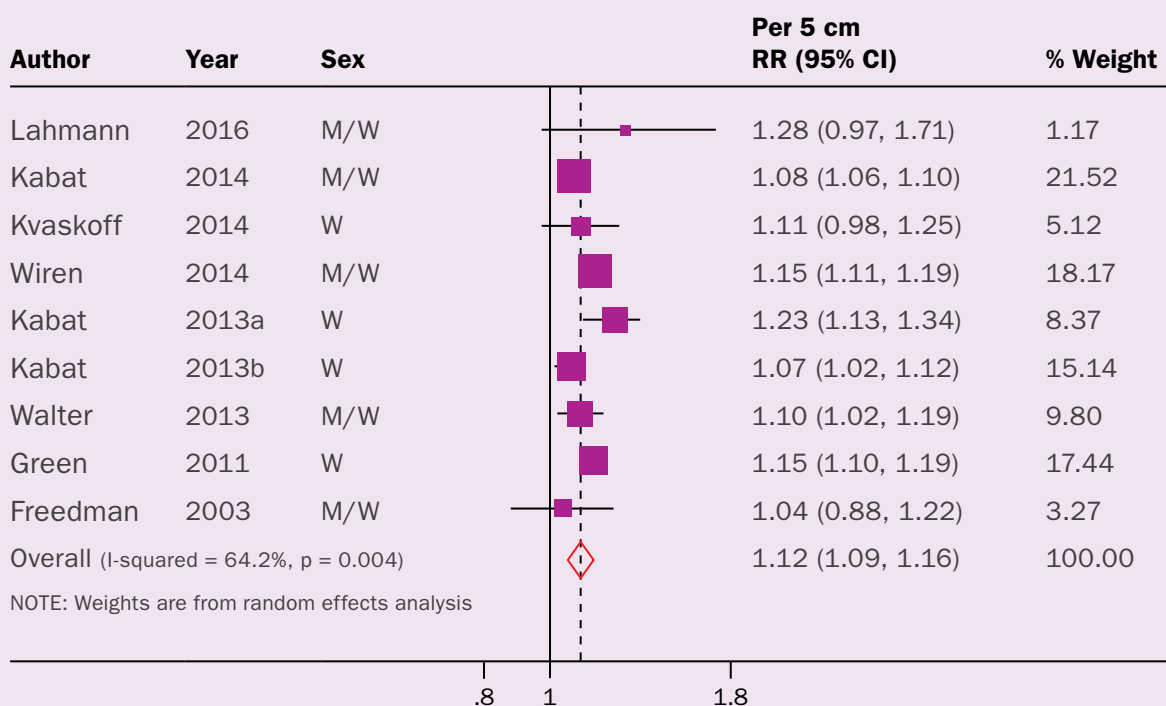
carcinoma and *squamous cell carcinoma*, see [CUP skin cancer SLR 2017](#): Section 8.3.1.

5.1.9.1 CUP dose–response meta-analyses

Fifteen of 18 identified studies were included in the dose-response meta-analysis, which showed a statistically significant 12 per cent increased risk of malignant melanoma per 5 centimetres increase in height (RR 1.12 [95% CI 1.09-1.16]; $n = 13,020$) (see **Figure 5.11**). High *heterogeneity* was observed ($I^2 = 64\%$), which was due to the size of effect rather than the direction of effect. There was no evidence of small study bias with *Egger's test* ($p = 0.31$). However, the funnel plot showed asymmetry that was driven by a higher than expected increased risk in a small Norwegian study (28 cases; see [CUP skin cancer SLR 2017](#), Figure 69) [64].

Stratified analyses for the risk of malignant melanoma per 5 centimetres increase in

Figure 5.11: CUP dose–response meta-analysis for the risk of malignant melanoma, per 5 centimetres increase in height



Source: Lahmann, 2016 [64]; Kabat, 2014 [173]; Kvaskoff, 2014 [174]; Wiren, 2014 [82]; Kabat, 2013a [69]; Kabat, 2013b [68]; Walter, 2013 [70]; Green, 2011 [109]; Freedman, 2003¹.

¹ Freedman DM et al. *Cancer, causes & control* 2003; 14: 847-57a.

height were conducted for sex and geographic location. Please see [CUP skin cancer SLR 2017](#), Section 8.3.1, for details of other stratified analyses that have been conducted.

When stratified by sex, a statistically significant increased risk was observed in men (RR 1.10 [95% CI 1.05-1.15]) and women (RR 1.12 [95% CI 1.08-1.17]); see [CUP skin cancer SLR 2017](#), Table 57 and Figure 70. When stratified by geographic location, a significant increased risk was observed in Europe (RR 1.15 [95% CI 1.12–1.18]) and North America (RR 1.10 [95% CI 1.06–1.14]), but not Australia; see [CUP skin cancer SLR 2017](#), Table 57 and Figure 71.

All studies included in the dose–response meta-analysis adjusted for age, most conducted analyses stratified by sex and some adjusted for an indicator of skin colour and/or sun exposure. For information on the *adjustments* made in individual studies, see [CUP skin cancer SLR 2017](#), Table 59.

5.1.9.2 Published pooled analyses and meta-analyses

One published pooled analysis on height and the risk of malignant melanoma incidence was identified [82]; this was included in the CUP dose–response meta-analysis. Results

from three published pooled analyses [79, 82, 131] on height and malignant melanoma mortality are shown in Table 5.7 (also see [CUP skin cancer SLR 2017](#), Table 58). No other published meta-analyses were identified.

5.1.9.3 Mechanisms

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

For further information on general processes involved in the development of cancer, see [The cancer process](#).

The mechanisms by which higher adult attained height is linked to elevated risks of malignant melanoma and *basal cell carcinoma* are unclear. Taller people have more skin cells, and thus there is greater opportunity for *mutations* leading to cancer development [81]. In addition, early life and early adulthood exposures may play a role, such as greater exposure to growth factors including growth hormone and IGFs and excess calorie consumption in early life [6, 80].

Table 5.7: Summary of published pooled analyses of height and malignant melanoma mortality

Publication	Increment	Sex	RR (95% CI)	I ² (%)	No. of studies (cohort)	No. of cases (deaths)
Emerging Risk Factors Collaboration ¹ [79]	6.5 cm	Men and Women	1.26 (1.12–1.42)	43	121	679
Asia-Pacific Cohort Studies Collaboration ¹ [131]	6 cm	Men	1.44 (1.15–1.79)	–	44	63
		Women	1.04 (0.71–1.52)	–		25
The Metabolic Syndrome and Cancer Project (Me-Can) ¹ [82]	5 cm	Men	1.10 (0.99–1.21)	–	7	246
		Women	1.09 (0.92–1.29)	–		102

Specific adjustments for skin sensitivity or sun exposure

1 In this meta-analysis, the authors did not add confounding variables relating to skin sensitivity or sun exposure to the multivariate model used. For details of adjustments made please see original studies.

5.1.9.4 CUP Panel's conclusion

The evidence was generally consistent and the CUP dose–response meta-analysis showed a statistically significant increased risk of skin cancer with increasing height. There was high *heterogeneity*, which was due to the size of effect rather than the direction of effect. The significant increased risk remained when stratified by sex and by geographic location for Europe and North America, but not Australia. Two published *pooled analyses*, not included in the CUP analyses, mainly reported a statistically significant increased risk. There is evidence of plausible mechanisms operating in humans.

The CUP Panel concluded:

- **Developmental factors leading to greater growth in length in childhood (marked by adult attained height) are probably a cause of malignant melanoma.**

5.2 Birthweight

Table 5.8 summarises the main findings from the CUP *dose–response meta-analyses* of *cohort studies* on birthweight and the risk of cancer. Birthweight refers to the weight at birth of the people taking part in the studies.

Evidence for cancers of the following types was discussed in the CUP but was too limited to draw a conclusion¹: breast (postmenopause; 2017), prostate (2014) and kidney (2015).

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

Table 5.8: Summary of CUP dose–response meta-analyses of birthweight^{1,2} and the risk of cancer

Cancer	Total no. of studies	No. of studies in meta-analysis	No. of cases	Risk estimate (95% CI)	Increment	I ² (%)	Conclusion ³	Date of CUP cancer report ⁴
Breast (premenopause)	25	16	>3,135	1.05 (1.02–1.09)	500 g birthweight	0	Probable: Increases risk	2017
Skin (malignant melanoma)	6	5	3,561	1.06 (1.02–1.10)	500 g birthweight	0	Limited – suggestive: Increases risk	2017

- 1 Birthweight is a marker for prenatal growth, reflecting a combination of factors including fetal nutrition, and is also a predictor of later growth and maturation – for example, age at menarche – which are themselves determinants of breast cancer risk.
- 2 The evidence shows that, in general, the taller people are during adulthood, and the more people weighed at birth, the higher their risk of some cancers. A better understanding of the developmental factors that underpin the associations between greater growth and cancer risk is needed.
- 3 See Definitions of WCRF/AICR grading criteria (**Section 1**: Height and birthweight and the risk of cancer: a summary matrix) for explanations of what the Panel means by ‘convincing’, ‘probable’ and ‘limited – suggestive’.
- 4 Throughout this Third Expert Report, the year given for each cancer site is the year the CUP cancer report was published, apart from for nasopharynx, cervix and skin, where the year given is the year the SLR was last reviewed. Updated CUP cancer reports for nasopharynx and skin will be published in the future.

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

For more information on the evidence for birthweight and the risk of cancer that was graded by the Panel as ‘limited – suggestive’ and suggests a direction of effect, see the CUP document listed:

- CUP skin cancer SLR 2017: Section 8.4.1.

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

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

5.2.1 Breast (premenopause)

(Also see CUP breast cancer report 2017: Section 7.12 and CUP breast cancer SLR 2017: Section 8.4.1.)

The evidence for premenopausal breast cancer is presented in the following subsections. For information on postmenopausal breast cancer, see CUP breast cancer SLR 2017, Section 8.4.1.

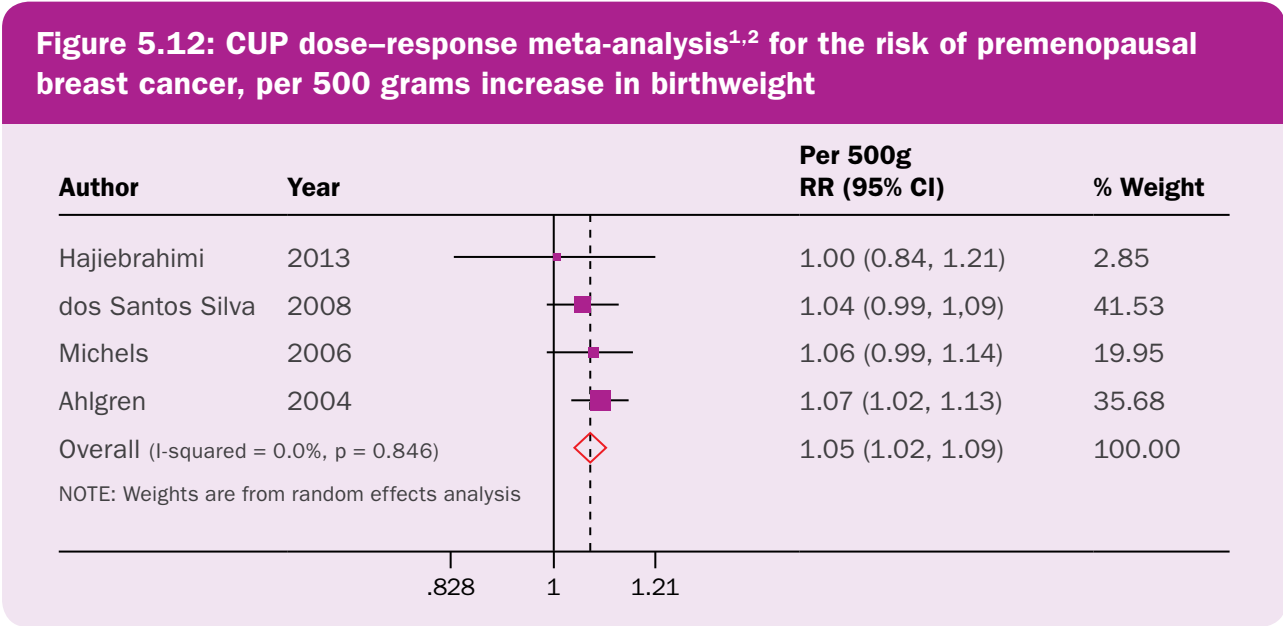
5.2.1.1 CUP dose–response meta-analysis

Sixteen of 25 identified studies (including one *pooled analysis*) were included in the dose–response meta-analysis, which showed a statistically significant 5 per cent increased risk of premenopausal breast cancer per 500 grams increase in birthweight (RR 1.05 [95% CI 1.02–1.09]; n > 3,135) (see **Figure 5.12**). No *heterogeneity* was observed.

All studies included in the dose–response meta-analysis *adjusted* for age; some also adjusted for reproductive factors and adult BMI. For information on the adjustments made in individual studies, see CUP breast cancer SLR 2017, Table 618.

5.2.1.2 Published pooled analyses and meta-analyses

One published *pooled analysis* and one other published meta-analysis on birthweight and the risk of premenopausal breast cancer was identified. The published pooled analysis reported no statistically significant increase or decrease in risk overall and was included in the CUP dose–response meta-analysis [176].



Source: Hajiebrahimi, 2013 [175]; dos Santos Silva, 2008 [176]; Michels, 2006 [177]; Ahlgren, 2004 [178].

¹ Nine studies could not be included in the dose–response meta-analysis, seven were excluded from the pooled analysis [176] due to methodological issues, one from another pooled analysis [179] due to one of the studies being included in dos Santos Silva 2008 [176] and one did not provide sufficient information. For further details, see CUP breast cancer SLR 2017, page 2095.
² The CUP dose-response meta-analysis included one pooled analysis (dos Santos Silva, 2008 [176]), which included 13 (8 cohort and 5 case-control studies) of the identified studies.

The published meta-analysis included *cohort* and *case-control* studies and reported no significant increase or decrease in risk when comparing the highest with the lowest birthweight [180].

5.2.1.3 Mechanisms

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

For further information on general processes involved in the development of cancer, see [The cancer process](#).

There are many general mechanisms, such as long-term programming of hormonal systems, which could possibly increase cancer risk and can be marked by variation in birthweight. Greater birthweight is associated with higher circulating maternal *oestrogen* levels and may increase IGF-I activity; low birthweight raises fetal and maternal levels of IGF-I binding protein [181]. The action of both *oestrogens* and IGF-I are thought to be important in fetal growth and very early fetal mammary gland development and play a role in the initiation and promotion of breast cancer [182]. Animal experiments also provide evidence that exposure to *oestrogens* during fetal and early postnatal development can increase the risk of mammary cancers [183].

5.2.1.4 CUP Panel's conclusion

The evidence was generally consistent and the CUP dose–response meta-analysis showed a statistically significant increased risk of premenopausal breast cancer with increasing birthweight. No *heterogeneity* was observed. There is robust evidence for mechanisms operating in humans.

The CUP Panel concluded:

- **The factors that lead to a greater birthweight, or its consequences, are probably a cause of premenopausal breast cancer.**

6. Comparison with the 2007 Second Expert Report

In 2007, there was strong evidence that developmental factors leading to greater growth in length in childhood (marked by adult attained height) increase the risk of four cancers (pancreas, colorectum, breast and ovary). The evidence for all of those cancers has remained strong. There is new strong evidence that the risk is also increased for four other cancers (endometrium, prostate, kidney and malignant *melanoma*), bringing the total to eight cancers.

As in 2007, there is strong evidence that factors that lead to a greater birthweight, or its consequences, increase the risk of premenopausal breast cancer.

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Abbreviations

AICR	American Institute for Cancer Research
BMI	Body mass index
CI	Confidence interval
CUP	Continuous Update Project
DNA	Deoxyribonucleic acid
hEGF	Human epidermal growth factor
IARC	International Agency for Research on Cancer
IGFs	Insulin-like growth factors
MHT	Menopausal hormone therapy
PSA	Prostate-specific antigen
RR	Relative risk
SLR	Systematic literature review
WCRF	World Cancer Research Fund

Glossary

Adenocarcinoma

Cancer of glandular epithelial cells.

Adipose tissue

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

Adiposity

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

Adjustment

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

Anthropometric measures

Measures of body dimensions.

Basal cell carcinoma

A type of cancer of the basal cells at the bottom of the epidermis. The most common form of skin cancer. Basal cell carcinomas are usually found on areas of the body exposed to the sun. They rarely metastasise (spread) to other parts of the body.

Body mass index (BMI)

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

Caecum

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

Carcinogen

Any substance or agent capable of causing cancer.

Carcinoma

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

Case-control study

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

Chronic

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

Clear cell renal cell carcinoma (CCRCC)

The most common type of kidney cancer in adults, characterised by malignant epithelial cells with clear cytoplasm.

Cohort study

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

Colon

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

Confidence interval (CI)

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

Confounder/confounding factors

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

Diet, nutrition and physical activity

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

Deoxyribonucleic acid (DNA)

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

Dose–response

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

Effect modification

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

Egger's test

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

Endocrine

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

Endogenous

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

Energy

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

Epithelial (see **epithelium**)**Epithelium**

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

Exocrine

Relating to or denoting glands that secrete their products through ducts opening on to an epithelium rather than directly into the blood.

Exposure

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

Familial

Relating to or occurring in a family or its members.

Germ cells

The cells that develop into eggs and sperm, through which genetic information is passed from generation to generation.

Heterogeneity

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

High-income countries

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

Hormone

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

Hormone receptor status

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

Hyperplasia

An increase in the number of cells in a tissue.

Insulin

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

Insulin-like growth factor (IGF)

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

Lactation

The production and secretion of milk by the mammary glands.

Malignancy

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

Melanoma

Malignant tumour of the skin derived from the pigment-producing cells (melanocytes).

Menarche

The start of menstruation.

Menopausal hormone therapy (MHT)

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

Menopause

The cessation of menstruation.

Meta-analysis

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

Mucinous carcinoma

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

Mutation

A permanent change in the nucleotide sequence of the genome (an organism's complete set of DNA).

Non-communicable diseases (NCDs)

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

Non-linear analysis

A non-linear dose–response meta-analysis does not assume a linear dose–response relationship between exposure and outcome. It is useful for identifying whether there is a threshold or plateau.

Nutrient

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

Obesity

Excess body fat to a degree that increases the risk of various diseases. Conventionally defined as a BMI of 30 kg/m² or more. Different cut-off points have been proposed for specific populations.

Odds ratio

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

Oestrogen

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

p53

A protein central to regulation of cell growth. The mutations of the p53 gene are important causes of cancer.

Papillary renal cell carcinoma

A type of cancer that forms inside the lining of the kidney tubules.

Polymorphisms

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

Pooled analysis

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

Progesterone

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

Relative risk (RR)

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

Socioeconomic status

A combined product of social and economic status reflecting education level, personal wealth, class and associated factors.

Squamous cell carcinoma

A malignant cancer derived from squamous epithelial cells.

Statistical power

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

Systematic literature review (SLR)

A means of compiling and assessing published evidence that addresses a scientific question with a predefined protocol and transparent methods.

Transitional cell carcinomas

Cancer that develops in the lining of the renal pelvis, ureter or bladder.

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Appendix 1: Criteria for grading evidence for cancer prevention

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

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

CONVINCING (STRONG EVIDENCE)

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

All of the following are generally required:

- Evidence from more than one study type.
- Evidence from at least two independent *cohort studies*.
- No substantial unexplained *heterogeneity* within or between study types or in different populations relating to the presence or absence of an association, or direction of effect.
- Good-quality studies to exclude with confidence the possibility that the observed association results from random or systematic error, including *confounding*, measurement error and *selection bias*.
- Presence of a plausible biological gradient ('*dose-response*') in the association. Such a gradient need not be linear or even in the same direction across the different levels of *exposure*, so long as this can be explained plausibly.
- Strong and plausible experimental evidence, either from human studies or relevant animal models, that typical human exposures can lead to relevant cancer outcomes.

PROBABLE (STRONG EVIDENCE)

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

All of the following are generally required:

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

LIMITED – SUGGESTIVE

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

All of the following are generally required:

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

LIMITED – NO CONCLUSION

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

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

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

SUBSTANTIAL EFFECT ON RISK UNLIKELY (STRONG EVIDENCE)

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

All of the following are generally required:

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

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

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

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

SPECIAL UPGRADING FACTORS

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

Factors may include the following:

- Presence of a plausible biological gradient ('dose-response') in the association. Such a gradient need not be linear or even in the same direction across the different levels of exposure, so long as this can be explained plausibly.
- A particularly large summary effect size (an odds ratio or relative risk of 2.0 or more, depending on the unit of exposure) after appropriate control for *confounders*.
- Evidence from randomised trials in humans.
- Evidence from appropriately controlled experiments demonstrating one or more plausible and specific mechanisms actually operating in humans.
- Robust and reproducible evidence from experimental studies in appropriate animal models showing that typical human exposures can lead to relevant cancer outcomes.

Appendix 2: Mechanisms

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

Adult attained height

Colorectum

The proposed mechanisms by which adult attained height is linked to risk of colorectal cancer include greater exposure to growth factors such as growth hormone and *insulin-like growth factors* (IGFs) in childhood and early adulthood [6, 80] and excess calorie consumption in early life. Taller people have more cells and thus there is greater opportunity for *mutations* leading to cancer development [81]. In addition, taller adults also have longer intestines; therefore, there may be greater potential for DNA damage resulting from exposure to mutagenic or cancer-promoting agents. Overall there are moderate mechanistic data supporting greater adult height as a risk factor for colorectal cancer.

Breast (pre and postmenopause)

Adult height is directly related to the rate of growth during fetal life and childhood [100, 101]. The number of cell divisions in fetal life and childhood and age of sexual maturity are all determined by the hormonal microenvironment (circulating plasma levels of growth factors and *oestrogens* and their respective binding proteins), which is influenced by nutritional status.

Many of these mechanisms, such as early-life nutrition affecting body composition and altered circulating and *hormone* profiles, can modulate the rate of tissue growth and sexual maturation. It is therefore plausible that nutritional factors during childhood and adolescence that affect height could also influence cancer risk. Specific tissues in taller people are exposed to higher levels of *insulin*, pituitary-derived growth hormone and IGFs, and thus may have undergone more cell divisions. This increased number of cell divisions may contribute to greater potential for error during DNA replication, resulting in an increased risk of developing cancer [81, 102]. Therefore, adult attained height may be a marker of inherited factors as well as fetal and childhood experience and is also a surrogate for important nutritional exposures, which affect several hormonal and metabolic axes and which may influence breast cancer risk.

Ovary

Adult height is determined by inherited genetic factors as well as through specific exposures, such as nutrition and infections in utero, as well as throughout childhood and adolescence [6]. These factors may also affect ovarian cancer risk later in life through alterations in hormonal pathways, in particular the IGF-I pathway. However, results from epidemiological studies on circulating IGF-I levels and ovarian cancer risk have been inconclusive [122].

Pancreas

Specific mechanisms that link greater adult height with an increased risk of pancreatic cancer have not been clearly identified but may include those that have been proposed for other height-related cancers. Greater adult height may be related to increased exposure to *endocrine* and

metabolic patterns, such as IGFs, in childhood and early adulthood, which have been associated with organ growth, greater cell division, and thus the risk of cancer-initiating *mutations* [6, 80]. In addition, taller people have more cells and thus there is greater opportunity for mutations to arise and lead to cancer development [81].

Endometrium

Adult height is directly related to the rate of growth during fetal life and childhood [100, 101]. The number of cell divisions in fetal life and childhood, health and nutrition status in childhood, and age of sexual maturity are all determined by the hormonal microenvironment (plasma levels of growth factors and *oestrogens* and their respective binding protein), which is influenced by nutritional status. Many of these mechanisms, such as early-life nutrition affecting body composition and altered circulating and free *hormone* profiles, can modulate the rate of tissue growth and sexual maturation. It is therefore plausible that nutritional factors that affect height could also influence cancer risk. Specific tissues in taller people are exposed to higher levels of *insulin*, pituitary-derived growth hormone and IGFs, and thus may have undergone more cell divisions. This increased number of cell divisions may contribute to greater potential for error during DNA replication, resulting in an increased risk of developing cancer [81, 102]. Therefore, adult attained height is a marker of inherited factors as well as fetal and childhood experience and is also a surrogate for important nutritional exposures, which affect several hormonal and metabolic axes and which may influence endometrial cancer risk.

Prostate

Greater adult attained height is associated with higher risk of prostate cancer; however, specific mechanisms that link greater adult height with higher risk of prostate cancer have not been identified. Adult height may be viewed as a marker of factors affecting linear growth, including nutritional and genetic factors as well as cumulative exposure to *endogenous hormones* such as growth hormone and IGFs. The IGF axis plays a major role in the regulation of cell growth and survival, and experimental studies demonstrate that increased signalling through the IGF system can exert a pro-tumorigenic effect. Recently, a large-scale collaborative meta-analysis of studies examining the relation between circulating IGF-I and the incidence of prostate cancer reported a robust, positive association between IGF-I levels and prostate cancer risk [167]. Therefore, the IGF axis may represent a plausible mechanism linking height to prostate cancer development. An additional proposed mechanism relates to taller people having more cells and thus there is greater opportunity for *mutations* to arise and lead to cancer development [81].

Kidney

Specific mechanisms that link greater adult height with an increased risk of kidney cancer have not been clearly identified but may include those that have been proposed for other height-related cancers. Greater adult height may be related to increased exposure to *endocrine* and metabolic patterns, such as IGFs, in childhood and early adulthood, which have been associated with organ growth and greater cell division, and thus the risk of cancer-initiating *mutations* [6]. In addition, taller people have more cells and thus there is greater opportunity for mutations to arise and lead to cancer development [81].

Skin (malignant melanoma and basal cell carcinoma)

The mechanisms by which higher adult attained height is linked to elevated risks of malignant *melanoma* and *basal cell carcinoma* are unclear. Taller people have more skin cells, and thus there is greater opportunity for *mutations* leading to cancer development [81]. In addition, early life and early adulthood exposures may play a role, such as greater exposure to growth factors, including growth hormone and IGFs, and excess calorie consumption in early life [6, 80].

Greater birthweight

Breast (premenopause)

There are many general mechanisms, such as long-term programming of hormonal systems, which could possibly increase cancer risk and can be marked by variation in birthweight. Greater birthweight is associated with higher circulating maternal *oestrogen* levels and may increase IGF-I activity; low birthweight raises fetal and maternal levels of IGF-I binding protein [181]. The action of both oestrogens and IGF-I are thought to be important in fetal growth and very early fetal mammary gland development and play a role in the initiation and promotion of breast cancer [182]. Animal experiments also provide evidence that exposure to oestrogens during fetal and early postnatal development can increase the risk of mammary cancers [183].

Skin (malignant melanoma)

Birthweight is a marker of certain aspects of the general fetal growth environment that may influence the development of cancer at later life, through largely uncharacterised biological pathways. Proposed mechanisms include larger infants having a greater number of susceptible cells and in utero programming of IGFs such as IGF-I, which may lead to greater postnatal cellular proliferation [184].

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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