

# Lactation 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. [Lactation 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](http://dietandcancerreport.org)

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

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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 lactation affects the risk of developing cancer.<sup>1</sup> 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].

In this Third Expert Report, the term ‘lactation’ refers to the process by which the mother produces milk to breastfeed, whether directly or through expressing or pumping breastmilk. All the evidence about cancer risk presented in this part of the Third Expert Report relates to effects on the mother who is breastfeeding and not to effects on the child who is being breastfed.

Breastmilk provides a complete source of nourishment for newborns and young infants. The World Health Organization (WHO) recommends that babies should be exclusively breastfed (receive only breastmilk) for the first six months of life for the health of both mother and child, and that breastfeeding should continue for up to two years or beyond, alongside other appropriate foods and drinks when they are introduced.

A 2016 review of breastfeeding patterns around the world suggests that most mothers, regardless of income group, breastfeed their babies at some point after birth. However, even in *low-income countries*, where breastfeeding rates tend to be higher than in *high-income*

*countries*, only 47 per cent of infants are exclusively breastfed for the first six months of life. The global average is 36 per cent.

## How the research was conducted

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

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

### Findings

There is **strong evidence** that:

- **breastfeeding decreases** the risk of breast cancer in the mother.

The evidence shows that, in general, the greater the number of months that women continue breastfeeding their babies, the greater the protection these women have against breast cancer.

The Panel has used this strong evidence on breastfeeding when making Recommendations (see next page) designed to reduce the risk of developing cancer.

<sup>1</sup> 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.

There is also other evidence that is limited (either in amount or by methodological flaws) but is suggestive of a decreased risk of ovarian cancer in women who breastfeed. 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. The advice for mothers is to breastfeed your baby, if you can. 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. [wcrf.org/about-the-report](http://wcrf.org/about-the-report)

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.



# 1. Lactation and the risk of cancer: a summary matrix

LACTATION AND THE RISK OF CANCER					
WCRF/AICR GRADING		DECREASES RISK		INCREASES RISK	
		Exposure	Cancer site	Exposure	Cancer site
STRONG EVIDENCE	Convincing				
	Probable	Lactation <sup>1</sup>	Breast 2017 <sup>2</sup>		
LIMITED EVIDENCE	Limited – suggestive	Lactation <sup>1</sup>	Ovary 2014		
STRONG EVIDENCE	Substantial effect on risk unlikely	None identified			

**1** In this Third Expert Report, the term ‘lactation’ refers to the process by which the mother produces milk to breastfeed. Evidence about cancer risk presented here relates to effects on the mother who is breastfeeding and not to effects on the child who is being breastfed.

**2** The Panel’s conclusion for lactation and breast cancer relates to evidence for breast cancer overall, either pre or postmenopause (which was not always specified in studies). The CUP uses the term ‘breast cancer (unspecified)’ in this case. The separate evidence for lactation and pre or postmenopausal breast cancer was less conclusive but consistent with the overall finding.

**‘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 lactation to the risk of development of particular cancer types. Each conclusion on the likely causal relationship between lactation and a cancer forms a part of the overall body of evidence that is considered during the process of making Cancer Prevention Recommendations. Any single conclusion does not represent a recommendation in its own right. The Cancer Prevention Recommendations are based on a synthesis of all these separate conclusions, as well as other relevant evidence, and can be found at the end of this Third Expert Report.

### The CUP Panel concluded:

#### STRONG EVIDENCE

##### Probable

- **Decreased risk**
  - Lactation<sup>1</sup> probably protects against breast cancer.<sup>2</sup>

The evidence shows that, in general, the greater the number of months that women continue breastfeeding their babies, the greater the protection these women have against breast cancer.<sup>3</sup>

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

#### LIMITED EVIDENCE

##### Limited – suggestive

- **Decreased risk**
  - The evidence suggesting that lactation<sup>1</sup> decreases the risk of ovarian cancer is limited.

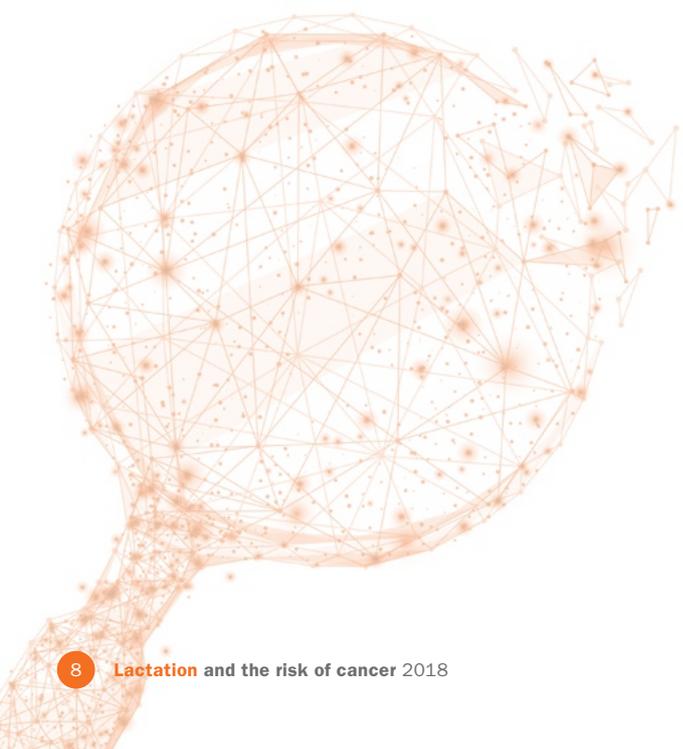
The Panel did not use the limited evidence when making Recommendations designed to reduce the risk of developing cancer. Further research is required into these possible effects on the risk of cancer.

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

<sup>1</sup> In this Third Expert Report, the term 'lactation' refers to the process by which the mother produces milk to breastfeed. Evidence about cancer risk presented here relates to effects on the mother who is breastfeeding and not to effects on the child who is being breastfed.

<sup>2</sup> The Panel's conclusion for lactation and breast cancer relates to evidence for breast cancer overall, either pre or postmenopause (which was not always specified in studies). The CUP uses the term 'breast cancer (unspecified)' in this case. The separate evidence for lactation and pre or postmenopausal breast cancer was less conclusive but consistent with the overall finding.

<sup>3</sup> Throughout this report, when discussing the length of time that women breastfeed, the CUP is referring to the number of days, weeks, months or years that women carry on breastfeeding their babies after birth. The CUP is not referring to the length of time that babies spend suckling at the breast either during an individual feed or during their lifetime.



## 3. Definitions and patterns

### 3.1 Lactation

In this Third Expert Report, the term ‘lactation’ refers to the process by which the mother produces milk to breastfeed, whether directly or through expressing or pumping breastmilk.

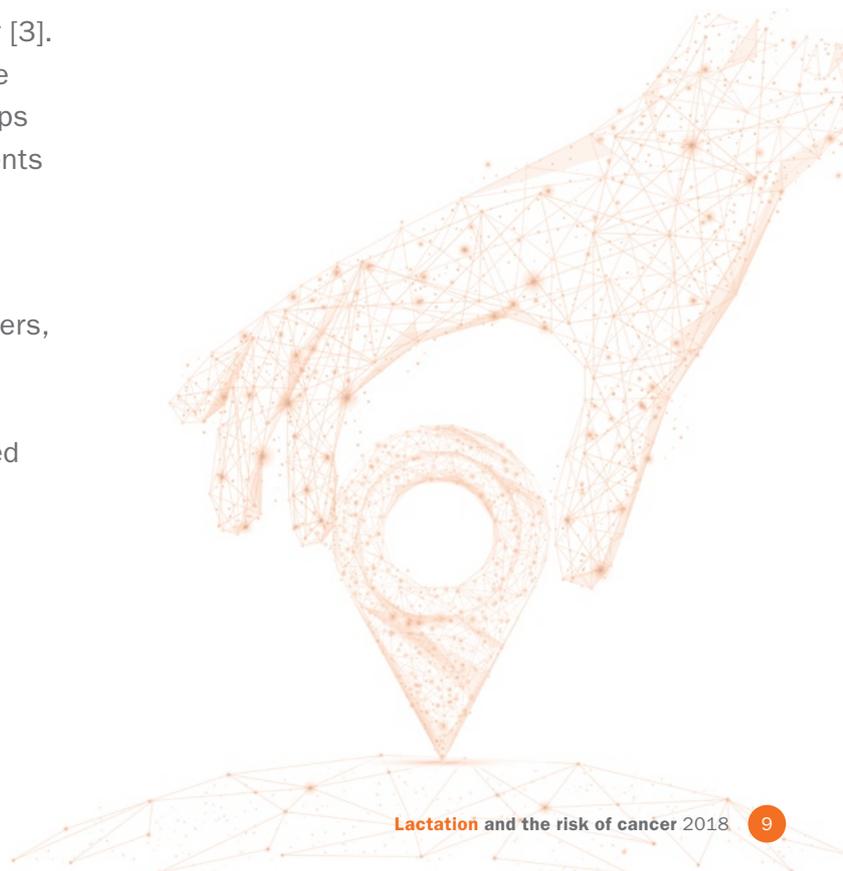
Breastmilk provides a complete source of nourishment for newborns and young infants, as well as bioactive factors that augment the infant’s immature immune system, providing protection against infection, and other factors that help the infant’s digestion and *absorption of nutrients* [2]. The WHO’s ‘Global Strategy for Infant and Young Child Feeding’ recommends that babies should be exclusively breastfed (receive only breastmilk) for the first six months of life for the health of both mother and child, and that breastfeeding should continue for up to two years or beyond, alongside other appropriate foods and drinks when they are introduced [2, 3].

‘Exclusive breastfeeding’ is defined as giving a baby only breastmilk (including feeding directly from the breast or feeding with breastmilk that has been expressed) and nothing else – no other liquids or solid foods, not even water [3]. It does, however, allow the infant to receive oral rehydration solution and drops or syrups consisting of vitamins, minerals, supplements or medicines [3].

A 2016 review of breastfeeding patterns around the world suggests that most mothers, regardless of income group, breastfeed their babies at some point after birth. The proportion of babies who have ever received

breastmilk is higher in *low- and middle-income countries* than in *high-income countries* and is 80 per cent or higher in all countries apart from France, Spain and the USA [4]. Despite these figures, rates of exclusive breastfeeding fall short of WHO recommendations even in low-income countries, as only 47 per cent of infants who are less than six months old are exclusively breastfed [5]. The global average is 36 per cent [6].

The duration of breastfeeding also tends to be shorter in high-income countries than in low- and middle-income countries [4]. Breastfeeding of babies who are 12 months old is widespread in low-income and lower-middle-income settings but less common elsewhere [4]. Globally, the proportion of babies who are breastfed at 12 months is highest in sub-Saharan Africa, south Asia and parts of Latin America. In most high-income countries, less than 20 per cent of babies are breastfed at 12 months, although there are some notable differences between countries – for example, between the UK (less than one per cent) and the USA (27 per cent), and between Norway (35 per cent) and Sweden (16 per cent) [4].



## 4. Interpretation of the evidence

### 4.1 General

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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

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

#### 4.2.1 Lactation

**Definitions.** In this Third Expert Report, the term 'lactation' refers to the process by which the mother produces milk to breastfeed, whether directly or through expressing or pumping breastmilk. All the evidence about cancer risk presented in this part of the Third Expert Report relates to effects on the mother who is breastfeeding and not to effects on the child who is being breastfed.

Many studies did not report results separately for pre and postmenopausal breast cancer. Analyses were therefore conducted for breast cancer overall – which could include data on either pre or postmenopausal cancer and for which the CUP uses the term 'breast cancer (unspecified)' – as well as for pre and postmenopausal breast cancer separately.

**Measurement.** Studies measure breastfeeding in different ways. Some studies have

simply distinguished between those who have ever been breastfed at any time and those who have never been breastfed. This means that there is no agreed way of classifying the duration of breastfeeding, and results from minimal amounts of breastfeeding are combined with results from extended durations of breastfeeding.

Initiation and duration of breastfeeding was usually self-reported by the women who took part in the studies when completing questionnaires at the time of enrolment. In some areas and cultures, there is the possibility of over-reporting if women are knowledgeable about the benefits of breastfeeding.

**Patterns and ranges of duration.** Most studies have been carried out in *high-income countries* where, since the second half of the twentieth century, the duration of breastfeeding — exclusive or not — has usually been up to six months. Therefore, the findings of these studies may be of limited relevance to areas of the world where breastfeeding practices differ.

#### 4.2.2 Cancers

##### 4.2.2.1 Breast

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

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

Breast cancers are classified by their receptor type; 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 – identified outside the CUP by the International Agency for Research on Cancer (IARC) [7] unless a different reference is given – 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 [8–10]. The reverse also applies: late menarche, early menopause, bearing children and pregnancy before the age of 30 all reduce the risk of breast cancer [8, 9].

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 postmenopausal 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 [11, 12].



### Medication

*Menopausal hormone therapy* (MHT; containing oestrogen or progesterone) increases the risk of breast cancer [13]. 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 [14].



### Family history

Some inherited *mutations*, particularly in *BRCA1*, *BRCA2* and *p53*, result in a very high risk of breast cancer. However, germline mutations in these genes are infrequent and account for only two to five per cent of all cases of breast cancer [15].

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.

**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 on lactation, see Evidence and judgements (**Section 5.1.1**).

#### 4.2.2.2 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* [16].

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 – identified outside the CUP by the IARC [7] unless a different reference is given – include the following:



### Life events

The risk of ovarian cancer is affected by the number of menstrual cycles during a woman's lifetime [17–19]. 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 [20–22]. The reverse also applies: bearing children, late menarche and early menopause all reduce the risk of ovarian cancer [20–22]. Tubal ligation (sterilisation) also decreases the risk of ovarian cancer [23].



### Medication

Oral contraceptives protect against ovarian cancer [24]. Use of MHT therapy has been shown to increase risk.



### Smoking tobacco

Smoking tobacco increases the risk of *mucinous ovarian cancer* [25]. It is estimated that 17 per cent of mucinous ovarian cancer cases are due to smoking tobacco [26].



### Family history

Most ovarian cancers occur spontaneously, although five to 10 per cent of cases develop due to a genetic predisposition [27]. The latter, involving dysfunctional *BRCA1* or *BRCA2* genes produces high-grade carcinomas, with poorer prognosis [28].

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.

**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.

**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 [29].

## 5. Evidence and judgements

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

Full [systematic literature reviews](#) (SLRs) for each cancer are available online. For most cancer sites considered in the CUP<sup>1</sup>, there is also a CUP cancer report. [CUP cancer reports](#) summarise findings from the SLRs, again focusing on a specific cancer site. The section also presents findings from the SLRs, but from a different perspective: it brings together all of the key findings on lactation 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 Lactation

All the evidence about cancer risk presented in this part of the Third Expert Report relates to effects on the mother who is breastfeeding and not to effects on the child who is being breastfed.

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

Evidence for endometrial cancer was discussed in the CUP but was too limited to draw a conclusion<sup>2</sup>.

**Table 5.1: Summary of CUP dose-response meta-analyses of lactation<sup>1</sup> and the risk of cancer**

Cancer	Total no. of studies	No. of studies in meta-analysis	No. of cases	Risk estimate (95% confidence interval [CI])	Increment/contrast	I <sup>2</sup> (%)	Conclusion <sup>2</sup>	Date of CUP cancer report <sup>3</sup>
Breast <sup>4</sup>	18	13	11,610	0.98 (0.97–0.99)	5 months of breastfeeding	0	Probable: Decreases risk	2017
Ovary <sup>5</sup>	3	3	817	0.90 (0.75–1.08)	Ever vs never	–	Limited – suggestive: Decreases risk	2014

- 1 In this Third Expert Report, the term 'lactation' refers to the process by which the mother produces milk to breastfeed. Evidence about cancer risk presented here relates to effects on the mother who is breastfeeding and not to effects on the child who is being breastfed.
- 2 See Definitions of WCRF/AICR grading criteria (**Section 1**: Lactation and the risk of cancer: a summary matrix) for explanations of what the Panel means by 'probable' and 'limited – suggestive'.
- 3 Throughout this Third Expert Report, the year given for each cancer site is the year the CUP cancer report was published, apart from for nasopharynx, cervix and skin, where the year given is the year the SLR was last reviewed. Updated CUP cancer reports for nasopharynx and skin will be published in the future.
- 4 The Panel's conclusion for lactation and breast cancer relates to evidence for breast cancer overall, either pre or postmenopause (which was not always specified in studies). The CUP uses the term 'breast cancer (unspecified)' in this case. The separate evidence for lactation and pre or postmenopausal breast cancer was less conclusive but consistent with the overall finding.
- 5 A dose-response meta-analysis of cohort studies could not be conducted in the CUP. Evidence is from a CUP highest versus lowest meta-analysis as studies did not report information on the duration of breastfeeding.

<sup>1</sup> 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.

<sup>2</sup> **'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.

The strong evidence on the effects of lactation on the risk of cancer is described in the following subsection. 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 lactation and the risk of cancer that was graded by the Panel as ‘limited – suggestive’ and suggests a direction of effect, see the following CUP document:

- [CUP ovarian cancer report 2014](#): Section 7.1 and [CUP ovarian cancer SLR 2013](#): Section 1.6.

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 subsection and in [Appendix 2](#) supersedes that in CUP cancer reports published before this Third Expert Report.

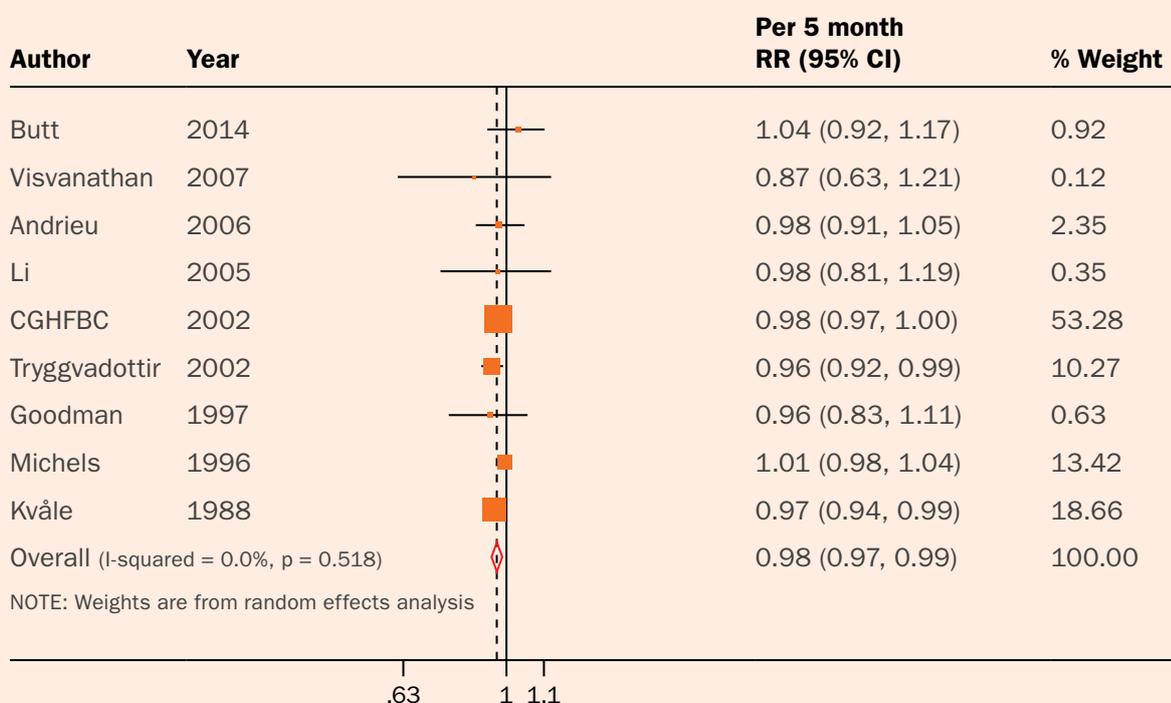
### 5.1.1 Breast

(Also see [CUP breast cancer report 2017](#): Section 7.13 and [CUP breast cancer SLR 2017](#): Section 1.6.1)

#### 5.1.1.1 CUP dose–response meta-analyses

Thirteen of 18 identified studies (including one *pooled analysis*) were included in the dose–response meta-analysis, which showed a statistically significant two per cent decreased risk of breast cancer per five months increase in breastfeeding (RR 0.98 [95% CI 0.97–0.99]; n = 11,610 cases) (see [Figure 5.1](#)). No *heterogeneity* was observed, and there was no evidence of small study bias with *Egger’s test* (p = 0.90).

**Figure 5.1: CUP dose–response meta-analysis<sup>1,2</sup> for the risk of breast cancer per five months increase in breastfeeding duration**



**Source:** Butt, 2014 [30]; Visvanathan, 2007 [31]; Andrieu, 2006 [32]; Li, 2005 [33]; Collaborative Group on Hormonal Factors in Breast Cancer (CGHFBC), 2002 [34]; Tryggvadottir, 2002 [35]; Goodman, 1997 [36]; Michels, 1996 [37]; Kvåle, 1988 [38].

<sup>1</sup> Five studies could not be included in the dose–response meta-analysis; three reported on specific subtypes only and two did not provide sufficient information. For further details, see CUP breast cancer SLR 2017, Table 16.

<sup>2</sup> The CUP dose–response meta-analysis included one pooled analysis (Collaborative Group on Hormonal Factors in Breast Cancer (CGHFBC), 2002 [34]), which included five of the identified studies.

Four studies were included in a separate dose–response meta-analysis that showed no statistically significant association between the risk of premenopausal breast cancer and lactation (RR 0.95 [95% CI 0.89–1.01], per five months increase in breastfeeding duration; n = 1,321 cases). High heterogeneity was observed ( $I^2 = 63\%$ ) (see [CUP breast cancer SLR 2017](#), Figure 22).

Five studies were included in another dose–response meta-analysis that showed no statistically significant association between the risk of postmenopausal breast cancer and lactation (RR 1.00 [95% CI 0.99–1.02], per five months increase in breastfeeding duration; n = 7,359 cases). Low heterogeneity was observed ( $I^2 = 5\%$ ) (see [CUP breast cancer SLR 2017](#), Figure 25).

Apart from one study [31], all studies included in the main dose–response meta-analysis on lactation and breast cancer adjusted for parity, which is one of the main protective factors against breast cancer [34, 39, 40]. For information on the *adjustments* made in individual studies, see [CUP breast cancer SLR 2017](#), Table 15.

#### 5.1.1.2 Published pooled analyses and meta-analyses

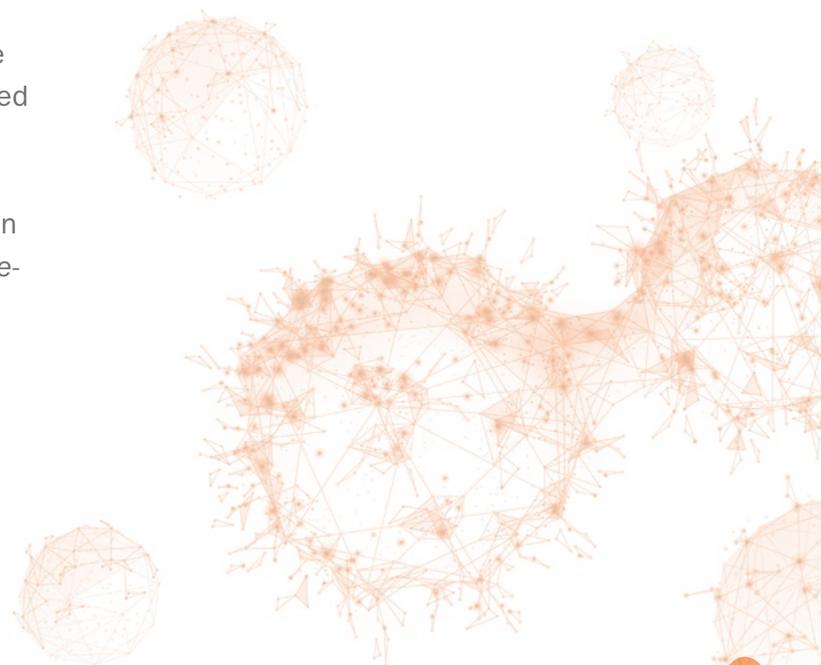
One published *pooled analysis* and two other published meta-analyses on lactation and the risk of breast cancer were identified. The published pooled analysis, which was included in the CUP dose–response meta-analysis, reported a statistically significant decreased risk of breast cancer with breastfeeding when including evidence from both *cohort* and *case-control studies*; however, when restricted to cohort studies this was not significant [34].

One of the published meta-analyses of cohort studies reported a statistically significant decreased risk for joint oestrogen receptor-negative and progesterone receptor-negative breast cancer (ER-negative/PR-negative, RR 0.84 [95% CI 0.72–0.97]) and ER-negative/PR-negative/human epidermal growth factor-negative (HER2-negative or HER2–) breast cancer (also known as triple negative breast cancer, RR 0.73 [95% CI 0.62–0.87]) when comparing women who had breastfed with those who had never breastfed [41]. The other published meta-analysis of cohort studies reported no significant association when comparing the highest with the lowest level of lactation duration [42]. All cohort studies from these two meta-analyses were included in the CUP.

#### 5.1.1.3 Mechanisms

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

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



The principal mechanism through which lactation or breastfeeding could plausibly influence breast cancer risk is through the hormonal influence of the associated period of *amenorrhea* and infertility. This decreases lifetime exposure to menstrual cycles and therefore alters cumulative exposures to specific hormones, particularly *androgens*, which can influence cancer risk (see [The cancer process](#)). Increased levels of sex steroids are strongly associated with the risk of postmenopausal breast cancer [21]. In addition, the sustained exfoliation of breast tissue during lactation and the pronounced *epithelial apoptosis* at the end of lactation could decrease breast cancer risk through the elimination of cells with DNA damage and *mutations*.

#### 5.1.1.4 CUP Panel's conclusion

The evidence for lactation was generally consistent. The CUP dose–response meta-analysis, which included one pooled analysis, showed a significant decreased risk of breast cancer with increasing duration of breastfeeding in studies that included pre and postmenopausal breast cancers. No heterogeneity was observed. No significant association was observed in CUP dose–response meta-analyses of the limited number of studies on pre or postmenopausal breast cancers.

Two other published meta-analyses were identified, one of which reported significant increased risk for joint ER-negative and PR-negative and joint ER-negative, PR-negative and HER2-negative (triple negative) breast cancer. There is robust evidence for mechanisms operating in humans.

Because of the strong evidence for breast cancer overall and the limited information about risk according to menopausal status, the Panel decided to make one conclusion for breast cancer rather than separate conclusions for pre and postmenopausal breast cancers.

#### The CUP Panel concluded:

- **Lactation probably protects against breast cancer.**

## 6. Comparison with the 2007 Second Expert Report

Judgements made about lactation and the risk of breast and ovarian cancers have not changed since 2007, but they are based on evidence from a larger number of studies.



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## Abbreviations

<b>AICR</b>	American Institute for Cancer Research
<b>CI</b>	Confidence interval
<b>CUP</b>	Continuous Update Project
<b>ER-negative</b>	Oestrogen-receptor-negative
<b>ER-positive</b>	Oestrogen-receptor-positive
<b>hEGF</b>	Human epidermal growth factor
<b>MHT</b>	Menopausal hormone therapy
<b>PR-negative</b>	Progesterone-receptor-negative
<b>PR-positive</b>	Progesterone-receptor-positive
<b>RR</b>	Relative risk
<b>SLR</b>	Systematic literature review
<b>WCRF</b>	World Cancer Research Fund

# Glossary

## **Absorption**

The movement of nutrients and other food constituents from the gut into the blood.

## **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.

## **Adjustment**

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

## **Amenorrhoea**

The absence of menstruation

## **Androgen**

Any masculinising sex hormone, such as testosterone.

## **Apoptosis**

The death of cells that occurs as a normal and controlled part of the cell cycle.

## **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.

## **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.

## **Confidence interval (CI)**

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

**Confounder/confounding factors**

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

**Diet, nutrition and physical activity**

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

**Dose–response**

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

**Effect modification**

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

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

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

**Exposure**

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

**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.

**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.

**Lactation**

The production and secretion of milk by the mammary glands.

**Low- and middle-income countries**

As defined by the World Bank, low-income countries are countries with an average annual gross national income per capita of US\$1,005 or less in 2016. Middle-income countries, are countries with an average annual gross national income per capita of between US\$1,006 and US\$12,235 in 2016. These terms are more precise than and used in preference to 'economically developing countries'.

**Menarche**

The start of menstruation.

**Menopausal hormone therapy (MHT)**

Treatment with oestrogens and progestones 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.

**Metastasis/metastatic spread**

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

**Mucinous carcinoma**

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

**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/m<sup>2</sup> or more. Different cut-off points have been proposed for specific populations.

**Odds ratio**

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

**Oestrogen**

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

**Oophorectomy**

The surgical removal of one or both ovaries.

**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.

**Selection bias**

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

**Statistical power**

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

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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](http://dietandcancerreport.org)). However, such evidence is usually not included in the summaries.

### **SUBSTANTIAL EFFECT ON RISK UNLIKELY (STRONG EVIDENCE)**

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

All of the following are generally required:

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

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

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

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

### **SPECIAL UPGRADING FACTORS**

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

Factors may include the following:

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

## 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.

### Lactation

#### Breast cancer

The principal mechanism through which lactation or breastfeeding could plausibly influence breast cancer risk is through the hormonal influence of the associated period of *amenorrhea* and infertility. This decreases lifetime exposure to menstrual cycles and therefore alters cumulative exposures to specific hormones, particularly *androgens*, which can influence cancer risk (see [The cancer process](#)). Increased levels of sex steroids are strongly associated with risk of postmenopausal breast cancer [21]. In addition, the sustained exfoliation of breast tissue during lactation and the pronounced *epithelial apoptosis* at the end of lactation could decrease breast cancer risk through the elimination of cells with DNA damage and mutations.

#### Ovarian cancer

The mechanisms underlying a lower risk of ovarian cancer among women who have breastfed are not well elucidated. One prevailing hypothesis is that breastfeeding is associated with longer periods of *amenorrhea* and therefore longer suppression of ovulation and decrease in gonadotropin levels and thus lower lifetime exposure to plasma oestradiol [43, 44].

# 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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