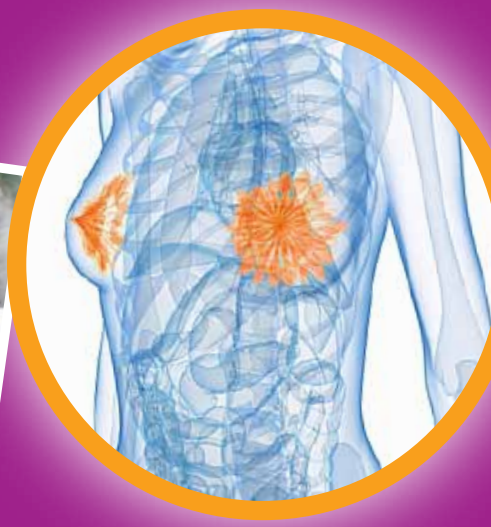
World Cancer Research Fund

American Institute for Cancer Research

Continuous Update Project

Keeping the science current



Breast Cancer 2010 Report

Food, Nutrition, Physical Activity, and the Prevention of Breast Cancer

Continuous Update Project

CUP

WORLD CANCER RESEARCH FUND GLOBAL NETWORK

OUR VISION

The World Cancer Research Fund global network helps people make choices that reduce their chances of developing cancer.

OUR HERITAGE

We were the first cancer charity:

- To create awareness of the relationship between diet and cancer risk
- To focus funding on research into diet and cancer prevention
- To consolidate and interpret global research to create a practical message on cancer prevention

OUR MISSION

Today the World Cancer Research Fund global network continues:

- Funding research on the relationship of nutrition, physical activity and weight management to cancer risk
- Interpreting the accumulated scientific literature in the field
- Educating people about choices they can make to reduce their chances of developing cancer

THE WCRF GLOBAL NETWORK

The World Cancer Research Fund (WCRF) global network comprises WCRF International, which operates as the umbrella association for the global network's four charitable organisations: The American Institute for Cancer Research (AICR); World Cancer Research Fund (WCRF UK); World Cancer Research Fund Netherlands (WCRF NL); World Cancer Research Fund Hong Kong (WCRF HK).

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This Report provides an updated version of section 7.10 Breast Cancer from the Second Expert Report: Food, Nutrition, Physical Activity and the Prevention of Cancer: a Global Perspective. This section has been updated with the latest information from the 2008 Continuous Update Project Breast Cancer SLR prepared by a team at Imperial College London, UK (see acknowledgements). For further details on the epidemiological evidence please see the full 2008 Continuous Update Project Breast Cancer SLR (Second Expert Report). For further details on mechanisms please see the Second Expert Report.

The First and Second Expert Reports represent the most extensive analysis of the existing science on the subject to date. To keep the evidence current and updated into the future, WCRF/AICR is undertaking the Continuous Update Project, in collaboration with Imperial College London. The Continuous Update Project builds upon the work conducted for the Second Expert Report and began by merging all the databases from the different cancer sites into an upgraded database.

The Continuous Update Project provides the scientific community with a comprehensive and up to date depiction of scientific developments on the relationship between diet, physical activity, obesity and cancer. It also provides an impartial analysis and interpretation of the data as a basis for reviewing and where necessary revising WCRF/AICR's cancer prevention recommendations based on the 2007 Expert Report.

In the same way that the Second Expert Report was informed by a process of systematic literature reviews (SLRs), the Continuous Update Project systematically reviews the science. WCRF/AICR has convened a panel of experts (the Continuous Update Project Panel (see acknowledgements) consisting of leading scientists in the field of diet, physical activity, obesity and cancer who consider the evidence produced by the systematic literature reviews and meta-analyses, and consider the results and draw conclusions before making recommendations.

The updates to the SLRs are being conducted by a team of scientists at Imperial College London in liaison with the SLR centres where possible.

Instead of periodically repeating the extensive task of conducting multiple systematic literature reviews that cover a long period of time, the continuous review process is based on a live system of scientific data that is updated on an ongoing basis from which, at any point in time, the most current review and meta-analysis of scientific data can be performed.

Periodically WCRF/AICR will produce reports which will outline the scientific developments in the field of diet, physical activity, obesity and cancer. The reports may also include updates to the WCRF/AICR recommendations.

The updated recommendations will be used by the WCRF/AICR education and media relation departments to inform the general public both of the benefits of a healthy lifestyle and of the developments in science that underpin these recommendations.

New information in this report

Section 1. Updated with recent mortality and survival data.

Section 2. Updated section on family history

Section 3. No update

Section 4. No update

Section 5. A new section briefly describing the methodology of the Continuous Update Project

Section 6. Evidence has been updated based on the 2008 Continuous Update Project Breast Cancer SLR and judgements from the Continuous Update Project Panel

Section 7. Provides a comparison with the Second Expert Report.

Since publication of this report in 2011, some changes have been made to the design and formatting, but no changes have been made to the content of the report or Panel conclusions. Please note, however, that the Second Expert Report matrix in this report has been replaced with the Continuous Update Project Matrix (on page 3).

FOOD, NUTRITION, PHYSICAL ACTIVITY AND BREAST CANCER (PREMENOPAUSE) 2010

	DECREASES RISK	INCREASES RISK
Convincing	Lactation	Alcoholic drinks
Probable	Body fatness	Adult attained height[1] Greater birth weight
Limited - suggestive	Physical activity[2]	
Limited - no conclusion	Dietary fibre; vegetables and fruits; soya and soya products; meat; fish; milk and dairy products; total fat; folate; vitamin D; calcium; glycaemic index; dietary patterns; adult weight gain; abdominal fatness	
Substantial effect on risk unlikely	None identified	

1 Adult attained height is unlikely directly to modify the risk of cancer. It is a marker for genetic, environmental, hormonal, and also nutritional factors affecting growth during the period from preconception to completion of linear growth (see chapter 6.2.13 – Second Expert Report).
2 Physical activity of all types: occupational, household, transport and recreational.

FOOD, NUTRITION, PHYSICAL ACTIVITY AND BREAST CANCER (POSTMENOPAUSE) 2010

	DECREASES RISK	INCREASES RISK
Convincing	Lactation	Alcoholic drinks Body fatness Adult attained height[1]
Probable	Physical activity[2]	Abdominal fatness Adult weight gain
Limited - suggestive		Total fat
Limited - no conclusion	Dietary fibre; vegetables and fruits; soya and soya products; meat; fish; milk and dairy products; folate; vitamin D; calcium; selenium; glycaemic index; dietary patterns; birth weight; energy intake	
Substantial effect on risk unlikely	None identified	

1 Adult attained height is unlikely directly to modify the risk of cancer. It is a marker for genetic, environmental, hormonal, and also nutritional factors affecting growth during the period from preconception to completion of linear growth (see chapter 6.2.13 – Second Expert Report).
2 Physical activity of all types: occupational, household, transport and recreational.

Cancer of the breast is the most common cancer in women worldwide. Around 1.1 million cases were recorded in 2004.

Observed rates of this cancer increase with industrialisation and urbanisation, and also with facilities for early detection. It remains much more common in high-income countries but is now increasing rapidly in middle- and low-income countries, including within Africa, much of Asia, and Latin America. Breast cancer is fatal in under half of all cases and is the leading cause of death from cancer in women (fifth for men and women combined), accounting for 16 per cent of all cancer deaths worldwide in 2004.

Breast cancer is hormone related, and the factors that modify risk of this cancer when diagnosed premenopausally and when diagnosed postmenopausally (much more common) are not the same.

The Continuous Update Project Panel judges as follows:
The evidence that lactation protects against breast cancer at all ages is convincing.

Physical activity probably protects against breast cancer postmenopause, and there is limited evidence suggesting that it protects against this cancer diagnosed premenopause. The evidence that alcoholic drinks are a cause of breast cancer at all ages is convincing. The evidence that the factors that lead to greater adult attained height, or its consequences, are a cause of postmenopausal breast cancer is convincing, and these are probably also a cause of breast cancer diagnosed premenopause.

The factors that lead to greater birth weight, or its consequences, are probably a cause of breast cancer diagnosed premenopause. Adult weight gain is probably a cause of postmenopausal breast cancer. The evidence that body fatness is a cause of postmenopausal breast cancer is convincing, and abdominal body fatness is probably also a cause. On the other hand, body fatness probably protects against breast cancer diagnosed premenopause. There is limited evidence suggesting that total dietary fat is a cause of postmenopausal breast cancer.

Life events that protect against breast cancer include late menarche, early pregnancy, bearing children, and early menopause, all of which have the effect of reducing the number of menstrual cycles, and therefore lifetime exposure to oestrogen. The reverse also applies.

See chapter 8 of the Second Expert Report for evidence and judgements on factors that modify risk of body fatness and abdominal fatness, including physical activity and sedentary ways of life, the energy density of foods and drinks, and breastfeeding.

In final summary, the strongest evidence, corresponding to judgements of "convincing" and "probable" show that lactation protects against breast cancer; that alcoholic drinks are a cause of this cancer; that the factors that lead to a greater adult attained height, or its consequences, are a cause of postmenopausal and probably also premenopausal breast cancer; that factors leading to greater birth weight, or its consequences, are

probably a cause of premenopausal breast cancer; and that abdominal body fatness and adult weight gain are probably a cause of postmenopausal breast cancer. Body fatness is a cause of postmenopausal breast cancer but probably protects against premenopausal breast cancer.

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.

Breast cancers are almost all carcinomas of the epithelial cells lining the ducts (the channels in the breast that carry milk to the nipple).[1] Premenopausal and postmenopausal breast cancers are considered separately in this Report. Although rare (less than 1 per cent of cases [2]), breast cancer can occur in men, but it is not included here.

1. Trends, incidence, and survival

Breast cancer is the most common cancer in women in high-, middle- and low-income countries.[3] Age-adjusted rates of breast cancer in women are increasing in most countries, particularly in areas where the incidence had previously been low, such as Japan, China and south-eastern and eastern Europe.[4, 5]

This is predominately a disease of high-income countries where overall rates are nearly three times higher than in middle- to low-income countries. Around the world, age-adjusted incidence rates range from 75-100 per 100 000 women in North America, northern Europe, and Australia, to less than 20 per 100 000 in parts of Africa and Asia.[6] In the USA, rates are higher among white women than those from other ethnic groups, although mortality is highest in black women.[7]

Overall risk doubles each decade until the menopause, when the increase slows down or remains stable. However, breast cancer is more common after the menopause. Studies of women who migrate from areas of low risk to areas of high risk assume the rate in the host country within one or two generations. This shows that environmental factors are important in the progression of the disease.[8]

Breast cancers can often be detected at a relatively early stage. In countries that provide or advocate screening, most of these cancers are diagnosed when the disease is still at a localised stage.[9] Survival rates range from 90 to less than 50 per cent, depending on the characteristics of the tumour, its size and spread, and the availability of treatment.[10] Average 5-year survival rates are more than 80% in North America, Sweden, Japan, Finland and Australia compared with less than 60 per cent in Brazil and Slovakia and less than 40 per cent in Algeria.[11] The low survival rate in middle- and low-income countries can be explained mainly by a lack of early detection programmes, resulting in a high proportion of women presenting with late-stage disease, as well as by a lack of adequate diagnosis and treatment facilities. Breast cancer accounts for nearly 23 per cent of all cancer incidence in women and 16 per cent of all cancer deaths (all sites except for skin (non-melanoma) and in women only). [3, 6] Breast cancer is the ninth most common cause of death in high income countries and around 69% of all breast cancer deaths occur in middle- and low-income countries.[3] Mortality rates have remained fairly stable between 1960 and 1990 in most of Europe and the Americas; and

have since showed a decline, which has reached 25-30% in northern Europe.[12] See box 1.

Box 1 cancer incidence and survival

The cancer incidence rates and figures given in this Report are those reported by cancer registries, now established in many countries. These registries record cases of cancer that have been diagnosed. However, many cases of cancer are not identified or recorded: some countries do not have cancer registries; regions of some countries have few or no records; records in countries suffering war or other disruption are bound to be incomplete; and some people with cancer do not consult a physician. Altogether, this means that the actual incidence of cancer is higher than the figures given here. The cancer survival rates given in this chapter and elsewhere are usually overall global averages. Survival rates are generally higher in high-income countries and other parts of the world where there are established services for screening and early detection of cancer and well established treatment facilities. Survival also is often a function of the stage at which a cancer is detected and diagnosed. The symptoms of some internal cancers are often evident only at a late stage, which accounts for relatively low survival rates. In this context, 'survival' means that the person with diagnosed cancer has not died 5 years after diagnosis.

2. Pathogenesis

Breast tissue, as well as hormones and hormone-receptor status, varies at different stages of life. It is therefore possible that individual risk factors will have different effects at different life stages (see 6. Evidence and Judgements). Early menarche, late menopause, not bearing children, and late (over 30) first pregnancy all increase breast cancer risk.[8, 13] The age when breasts develop, and menopause, are both influenced by nutrition, with overnutrition leading to early puberty and late menopause; undernutrition delays puberty and advances menopause (see chapter 6.2 Second Expert Report).

Hormones play an important role in breast cancer progression because they modulate the structure and growth of epithelial tumour cells.[10] Different cancers vary in hormone sensitivity. Many breast cancers also produce hormones, such as growth factors, that act locally, and these can both stimulate and inhibit the tumour's growth.[14, 15]

Family history of breast cancer is associated with a 2-3 fold higher risk of the disease. Some mutations, particularly in BRCA1, BRAC2 and p53 result in a very high risk of breast cancer. These mutations are rare and account for only 2 to 5 per cent of total cases.[16] In addition, growth factor receptor genes, as well as some oncogenes, are overexpressed in many breast cancers.[10] (Also see box 2.2. chapter 2, Second Expert Report).

3. Other established causes

3.1 General

This section lists factors outside the scope of this Report, identified as established causes of cancer by the World Health Organization International Agency for Research on Cancer, and other authoritative bodies. These factors are listed in Chapter 2.4 of the Second Expert Report: tobacco use; infectious agents; radiation; industrial chemicals; and some medications. Other diseases may also increase the risk of cancer. In the same way, life events that modify the risk of cancer – causative and protective – are also included.

'Established' effectively means 'beyond reasonable doubt' – roughly the equivalent of the judgement of 'convincing' used in this Report. Occasionally, authorative findings that perhaps fall short of 'established' are also included here.

Where possible, a note of interactive or multiplicative effects with food, nutrition, and the other factors covered by this Report is added, as is any indication of scale or relative importance. The factors here are almost all causative, whereas much of the evidence on food, nutrition, physical activity, and related factors shows or suggests protection against cancer.

3.2 Specific

Life events. Lifetime exposure to oestrogen, influenced by early menarche, late natural menopause, not bearing children, and late (over 30) first pregnancy all increase the risk of, and may be seen as causes of, breast cancer.[8, 13] The reverse also applies: late menarche, early menopause, bearing children, and early pregnancy all reduce the risk of, and may be seen as protective against breast cancer. Age of breast development and menopause are influenced by nutrition, with high-energy diets promoting earlier puberty and late menopause, and low-energy diets delaying puberty and advancing menopause.

Radiation. Ionising radiation exposure from medical treatment such as X-rays, particularly during puberty, increases risk, even at low doses.[17]

Medication. Hormone replacement therapy is a cause of breast cancer. The increased risk appears to disappear a few years after cessation.[18] Oral contraceptives containing both oestrogen and progesterone cause a small, transient, increased risk of breast cancer; the increased risk disappears after cessation.[19]

4. Interpretation of the evidence specific to breast cancer

4.1 General

For general considerations that may affect interpretation of the evidence, see chapters 3.3 and 3.5, and boxes 3.1, 3.2, 3.6 and 3.7 of the Second Expert Report.

'Relative risk' is used in this Report to denote ratio measures of effect, including 'risk ratios', 'rate ratios', 'hazard ratios', and 'odds ratios'.

4.2 Specific

Considerations specific to breast cancer include:

Patterns. The preponderance of data from high-income countries is a special issue with breast cancer. Breast cancer is hormone related, and factors that modify risk have different effects on cancers diagnosed pre- and postmenopause.

Classification. Because of the importance of menopause as an effect modifier, studies should stratify for menopause status. Many do not.

Confounding. Hormone replacement therapy is an important possible confounder in postmenopausal breast cancer. A few studies also reported results separately for different hormone receptor profiles within cancers. High-quality studies adjust for age, number of reproductive cycles, age at which children were born, and the taking of hormone-based medications.

Effect modification. There is growing evidence that the impact of dietary exposures on risk of breast cancer may differ according to the particular molecular subtypes of cancer.

5. Methodology

To ensure consistency with evidence collected and analysed for the Second Expert Report much of the methodology following for the Continuous Update Project remains unchanged from that used previously. Based upon the experience of conducting the systematic literature reviews for the Second Expert Report some modifications to the methodology were made. The literature search was restricted to Medline and included only randomised controlled trials, cohort and case-control studies. The 2008 Continuous Update Project Breast Cancer SLR included studies published up to December 2007. Publications in foreign languages were not included. Due to the large number of cohort studies, analysis and interpretation of case-control studies was not included in the Continuous Update Project SLR. Meta-analyses and forest plots of highest versus lowest categories were prepared for breast cancer incidence. Studies with mortality endpoints previously included in analyses were removed. Studies reporting mean difference as a measure of association are not included in the Continuous Update Project SLR as relative risks estimated from the mean differences are not adjusted for possible confounders, and thus not comparable to adjusted relative risks from other studies. (For more information on methodology see the full 2008 Continuous Update Project Breast Cancer SLR (Second Expert Report).

6. Evidence and judgements

The updated search identified 81 new articles, giving a total of 954 publications for breast cancer. The following sections include evidence from case-control studies considered as part of the Second Expert Report; however as mentioned in the previous section the evidence from case-control studies was not included in the 2008 Continuous Update Project Breast Cancer SLR. Fuller summaries of the experimental and mechanistic evidence can be found in chapters 4-6 of the Second Expert Report. For information on the criteria for grading the evidence see box 3.8 of the Second Expert Report. References to studies added in the Continuous Update Project have been included in the following sections; for details on references to other studies see Second Expert Report.

6.1 Alcoholic drinks

(Also see sections 3.7.1 Alcoholic drinks and 5.4 Alcohol (as ethanol) of the 2008 Continuous Update Project Breast Cancer SLR)

The Continuous Update Project identified 4 new cohort studies[20-23] that investigated alcoholic drinks and 2 new cohort studies[24, 25] and 3 recent publications from previously included cohort studies[26-28] that investigated ethanol intake. For premenopausal breast cancer a total of 4 cohort studies investigated alcoholic drinks and 6 cohort studies investigated ethanol intake. The respective numbers for postmenopausal breast cancer were 9 and 16. For all-age breast cancer a total of 13 cohort studies investigated alcoholic drinks and 11 cohort studies investigated ethanol intake. Most studies showed increased risk with increased intake. Meta-analysis of cohort studies for the Second Expert Report showed a 10 per cent increased risk for all-age breast cancer, a 9 per cent increased risk for premenopausal breast cancer and a 8 per cent increased risk for postmenopausal breast cancer per 10 g ethanol (Page 167 Second Expert Report). An updated meta-analysis for postmenopausal breast cancer

showed an 8 per cent increased risk per 10 g ethanol (Figure A1 2008 Continuous Update Project Breast Cancer SLR). The Second Expert Report included 31 case-control studies that investigated alcoholic drinks and 29 case-control studies that investigated ethanol intake and all-age breast cancer. Meta-analysis of case-control data showed a 5 per cent increased risk per 5 drinks/week, and a 6 per cent increased risk per 10 g ethanol/day (Pages 166-167 Second Expert Report). Menopausal status did not significantly alter the association.

Two pooled analyses also showed statistically significant increased risks of 9 and 7 per cent per 10 g ethanol/day. The first was based on 6 cohort studies with more than 320 000 participants, followed up for up to 11 years, with more than 4300 breast cancer cases. The other analysed 53 case-control studies, with more than 58 000 cases and more than 95 000 controls.[29, 30] A meta-analysis of 3 cohort and 7 case-control studies assessed the association between alcohol intake and the risk of ER-/PR-defined breast cancer. [31] The dose-response meta-analysis showed that an increase in alcohol consumption of 10 g of ethanol per day was associated with statistically significant increased risks for all ER+ (12 per cent), all ER- (7 per cent), ER+PR+ (11 per cent) and ER+PR- (15 per cent), but not ER-PR-. A statistically significant heterogeneity of the results across all ER+ *versus* ER-PR- was observed.

Reactive metabolites of alcohol, such as acetaldehyde, may be carcinogenic. Additionally, the effects of alcohol may be mediated through the production of prostaglandins, lipid peroxidation, and the generation of free radical oxygen species. Alcohol also acts as a solvent, enhancing penetration of carcinogens into cells. High consumers of alcohol may have diets deficient in essential nutrients, making tissues susceptible to carcinogenesis. In addition, most experimental studies in animals have shown that alcohol intake is associated with increased breast cancer risk. Alcohol interferes with oestrogen metabolism and action in multiple ways, influencing hormone levels and oestrogen receptors.

There is an interaction between folate and alcohol affecting breast cancer risk: increased folate status partially mitigates the risk from increased alcohol consumption.[32]

The evidence added for the Continuous Update Project is consistent with that from the Second Expert Report. There is ample and generally consistent evidence from cohort and case-control studies.

A dose-response relationship is apparent. There is robust evidence for mechanisms operating in humans. The conclusion reached for the Second Expert Report remains unchanged. The evidence that alcoholic drinks are a cause of premenopausal and postmenopausal breast cancer is convincing. No threshold was identified.

6.2 Lactation

(Also see section 1.6.1 Breastfeeding of the 2008 Continuous Update Project Breast Cancer SLR)

The Continuous Update Project identified 2 new cohort studies[33, 34] that investigated ever having breastfed as compared with never having breastfed and 3 new cohort studies[20, 21, 33] that investigated the total duration of lactation. For each of premenopausal and postmenopausal breast cancer a total of 2 cohort studies investigated ever having breastfed compared to never having breastfed and 2 cohort studies investigated total duration of lactation. For all-age breast cancer 3 studies investigated ever having breastfed and 6 studies investigated total duration of lactation. The Second Expert Report included 37 case-control studies that investigated ever having breastfed as compared with never having breastfed and 55 case-control studies that investigated the total duration of lactation. Most cohort and case-control studies reported decreased risk with ever having breastfed and with increasing duration of breastfeeding. Previous meta-analyses from the Second Expert Report for case-control data showed a 2 per cent decreased risk per 5 months of total breastfeeding; and for cohort data showed a non-significant decreased risk (Page 241 Second Expert Report). Pooled analysis from 47 epidemiological studies in 30 countries (more than 50 000 controls and nearly 97 000 breast cancer cases) showed a statistically significant decreased risk of breast cancer of 4.3 per cent for each 12 months of breastfeeding. Menopause status was not an effect modifier.[35] The relationship between breastfeeding and breast cancer according to hormone receptor status was investigated in a meta-analysis of 5 population-based case-control studies. A statistically significantly lower risk was found, both of ER+/PR+ breast cancers

(22 per cent) and for ER-/PR- cancers (26 per cent), for more than 6 months of breastfeeding compared with never breastfeeding. [36]

Lactation is associated with increased differentiation of breast cells and with lower exposure to endogenous sex hormones during amenorrhea accompanying lactation. In addition, the strong exfoliation of breast tissue during lactation, and the massive epithelial apoptosis at the end of lactation, could decrease risk by elimination of cells with potential DNA damage.

The evidence added for the Continuous Update Project is consistent with that from the Second Expert Report. There is abundant epidemiological evidence from both cohort and case-control studies, which is consistent and shows a dose-response relationship. There is robust evidence for plausible mechanisms that operate in humans. The conclusion reached for the Second Expert Report remains unchanged. The evidence that lactation protects against both premenopausal and postmenopausal breast cancer is convincing.

6.3 Physical activity

(Also see section 6. Physical Activity of the 2008 Continuous Update Project Breast Cancer SLR)

The Continuous Update Project identified 2 new cohort studies[37, 38] investigating total physical activity; 1 new cohort study investigating occupational activity[37]; 3 new cohort studies[37-39] and 1 recent publication from a previously included cohort study[40] investigating recreational activity; and 2 new cohort studies[37, 38] investigating household activity. For premenopausal breast cancer a total of 5 cohort studies investigated total physical activity and 4, 3 and 1 studies investigated occupational, recreational and household activities respectively. For postmenopausal breast cancer 2 studies investigated total activity and 5, 11 and 1 studies investigated occupational, recreational and household activities respectively. For all-age breast cancer 4 studies investigated total physical activity and 4, 5 and 1 studies investigated occupational, recreational and household activities respectively. The Second Expert Report included 8 case-control studies that investigated total physical activity, 7 case-control studies that investigated occupational activity and 11 case-control studies that investigated recreational activity.

Menopause age unspecified

Most studies showed decreased risk with increased physical activity. Meta-analysis of case-control studies for the Second Expert Report showed a 10 per cent decreased risk per 7 MET-hours recreational activity/ week (Page 204 Second Expert Report).

Premenopause

Data were inconsistent for cohort studies for physical activity; however most case-control studies reviewed for the Second Expert Report showed evidence of decreased risk (Page 204 Second Expert Report).

Postmenopause

Nearly all of the cohort studies showed decreased risk with increased physical activity. The meta-analyses from the Second Expert Report of cohort and case-

control data both showed a 3 per cent decreased risk per 7 MET-hours recreational activity/week (Page 205 Second Expert Report).

Sustained moderate physical activity raises the metabolic rate and increases maximal oxygen uptake. In the long term, regular periods of such activity increase the body's metabolic efficiency and capacity (the amount of work that it can perform), as well as reducing blood pressure and insulin resistance. In addition, it decreases levels of oestrogens and androgens in postmenopausal women. Some trials have also shown decreases in circulating oestrogens, increased menstrual cycle length, and decreased ovulation in premenopausal women with a high level of physical activity.

Premenopause: There is ample evidence from prospective studies, but it is inconsistent. There is evidence from case-control studies suggestive of a decreased risk with higher levels of physical activity. The conclusion reached for the Second Expert Report remains unchanged. There is limited evidence suggesting that physical activity protects against premenopausal breast cancer.

Postmenopause: The evidence added in the Continuous Update Project is consistent with that from the Second Expert Report. There is ample evidence from prospective studies showing lower risk of postmenopausal breast cancer with higher levels of physical activity, with a dose-response relationship, although there is some heterogeneity. There is little evidence on frequency, duration, or intensity of activity. The conclusion reached for the Second Expert Report remains unchanged. There is robust evidence for mechanisms operating in humans. Physical activity probably protects against postmenopausal breast cancer.

6.4 Body fatness

(Also see section 8.1.1 Body Mass Index of the 2008 Continuous Update Project Breast Cancer SLR)

The Continuous Update Project identified 10 new[34, 41-49] and 2 recent publications from previously included studies[39, 50] investigating body fatness, as measured by BMI for pre- and postmenopausal breast cancer. For premenopausal breast cancer there was a total of 22 studies and for postmenopausal breast cancer there were 28 studies. The Second Expert Report included more than 100 case-control studies that investigated body fatness. When grouped for all ages the Second Expert Report showed that the data were inconsistent in relationship to body fatness (Page 218 Second Expert Report) and this remained true for the Continuous Update Project. However, a consistent effect emerged when they were stratified according to menopausal status.

Premenopause

Most studies showed a decreased risk for premenopausal breast cancer. Meta-analyses for the Second Expert Report (Page 221 Second Expert Report) showed a 15 per cent decreased risk per 5kg/m^2 for cohort studies and an 8 per cent decreased risk per 5kg/m^2 for case-control studies; the updated meta-analysis for

cohort studies showed a 7 per cent decreased risk per 5kg/m^2 (Figure BMI4 2008 Continuous Update Project Breast Cancer SLR). A pooled analysis of four cohort studies with 723 cases of premenopausal breast cancer followed up for up to 11 years showed a 14 per cent decreased risk per 5kg/m^2.[51] A meta-analysis of 20 cohort studies reported an 8 per cent decreased risk per 5kg/m^2.[52]

Postmenopause

Most studies showed an increased risk for postmenopausal breast cancer with increased body fatness. Meta-analysis of cohort studies for the Second Expert Report (Page 219 Second Expert Report) showed an 8 per cent increased risk per 5kg/m^2 and a 13 per cent increased risk per 5kg/m^2; the updated meta-analysis of cohort studies showed a 13 per cent increased risk per 5kg/m^2 (Figure BMI7 2008 Continuous Update Project Breast Cancer SLR). A pooled analysis of seven cohort studies with 3208 cases of postmenopausal breast cancer followed up for up to 11 years showed a 9 per cent increased risk per 5kg/m^2.[51] A meta-analysis of 31 cohort studies reported a 12 per cent increased risk per 5kg/m^2.[52]

Body fatness directly affects levels of many circulating hormones, such as insulin, insulin-like growth factors, and oestrogens, creating an environment that encourages carcinogenesis and discourages apoptosis (programmed cell death). It also stimulates the body's inflammatory response, which may contribute to the initiation and progression of several cancers (see chapter 2.4.1.3 Second Expert Report). Adjusting for serum levels of oestradiol diminishes or destroys the association with BMI, suggesting that hormones are a predominant mechanism.[53]

There is no single well established mechanism though which body fatness could prevent premenopausal breast cancer. According to the oestrogen plus progesterone theory, overweight premenopausal women would be protected because they would be more frequently anovulatory, and therefore less likely to be exposed to endogenous progesterone. However, this theory is not well supported by recent studies, which suggest that natural progesterone could be protective.[54] Normal levels of natural progesterone are likely to be protective, and well nourished, or perhaps overnourished women, who may become slightly overweight in adulthood, may be protected by their natural fertile condition. Another possible mechanism is that the increased adipose tissue-derived oestrogen levels in overweight children could induce early breast differentiation and eliminate some targets for malignant transformation.[55] Anovulation and abnormal hormone profiles are commonly associated with obesity.[56] The age-specific pattern of association of breast cancer with BMI, therefore, is largely explained by its relationship with endogenous sex hormone levels.

Breast cancer diagnosed after the menopause is much more common. Therefore, throughout life, a decreased risk of premenopausal breast cancer would be outweighed by an increased risk of postmenopausal breast cancer.

Premenopause: The evidence added in the Continuous Update Project is consistent with that from the Second Expert Report. There is a substantial amount of consistent evidence epidemiological evidence with a dose-response relationship, but the mechanistic evidence is speculative. The conclusion reached for the Second Expert Report remains unchanged. Greater body fatness probably protects against premenopausal breast cancer.

Postmenopause: The evidence added in the Continuous Update Project is consistent with that from the Second Expert Report. There is abundant and consistent epidemiological evidence and a clear dose-response relationship with robust evidence for mechanisms operating in humans. The conclusion reached for the Second Expert Report remains unchanged. The evidence that greater body fatness is a cause of postmenopausal breast cancer is convincing.

6.5 Adult attained height

(Also see section 8.3.1 Height of the 2008 Continuous Update Project Breast Cancer SLR)

The Continuous Update Project identified 5 new cohort studies[34, 39, 41, 48, 57] that investigated adult attained height. The total number of cohort studies was 21 for all-age or age unspecified, 17 for premenopausal and 22 for postmenopausal breast cancer. The Second Expert Report included 29 case-control studies that investigated adult attained height and all-age breast cancer, 38 for premenopausal and 34 for postmenopausal breast cancer.

Menopausal age unspecified

Most of the studies showed increased risk. Meta-analysis for the Second Expert Report showed a 9 per cent increased risk per 5cm of height for cohort studies and a 3 per cent increased risk per 5cm of height for case-control studies (Page 233 Second Expert Report).

Premenopause

Most of the studies showed increased risk. Meta-analysis for the Second Expert Report showed a 9 per cent increased risk per 5cm of height for cohort studies and a 4 per cent increased risk per 5cm for case-control studies (Page 235 Second Expert Report). An updated meta-analysis of cohort studies also showed a 9 per increased risk per 5cm of height (Figure Ht1 2008 Continuous Update Project Breast Cancer SLR). A pooled analysis of four cohort studies with 723 cases of premenopausal breast cancer followed up for up to 11 years showed a non-significant increased risk with greater adult attained height.[51]

Postmenopause

Nearly all the cohort studies and most case-control studies showed increased risk, with no studies showing statistically significant contrary results. Meta-analyses for the Second Expert Report showed an 11 per cent increased risk per 5cm of height for cohort studies and a 2 per cent increased risk per 5cm for case-control studies (Page 234 Second Expert Report). An updated meta-analysis showed a 10 per increased risk per 5cm of height (Figure Ht4 2008 Continuous Update Project Breast Cancer SLR. A pooled analysis of seven cohort studies with

3208 cases of postmenopausal breast cancer followed up for up to 11 years showed a significantly significant 7 per cent increased risk per 5cm of height.[51]

The general mechanisms through which the factors that lead to greater adult attained height, or its consequences, could plausibly influence cancer risk are outlined in chapter 6.2.1.3 and box 2.4 of the Second Expert Report. Many of these, such as early-life nutrition, altered hormone profiles, and the rate of sexual maturation, could plausibly increase cancer risk.

Premenopause: There are fewer data for premenopausal than for postmenopausal breast cancer. The evidence added in the Continuous Update Project is consistent with that from the Second Expert Report. The epidemiological evidence is generally consistent, with a dose-response relationship and evidence for plausible mechanisms. The conclusion reached for the Second Expert Report remains unchanged. The factors that lead to greater adult height, or its consequences, are probably a cause of premenopausal breast cancer. The causal factor is unlikely to be tallness itself, but factors that promote linear growth in childhood.

Postmenopause: The evidence added in the Continuous Update Project is consistent with that from the Second Expert Report. There is abundant epidemiological evidence, which is generally consistent, with a clear dose-response relationship and evidence for plausible mechanisms operating in humans. The conclusion reached for the Second Expert Report remains unchanged. The evidence that the factors that lead to greater adult attained height, or its consequences, are a cause of postmenopausal breast cancer is convincing. The causal factor is unlikely to be tallness itself, but factors that promote linear growth in childhood.

6.6 Abdominal fatness (postmenopause)

(Also see sections 8.2.1 Waist Circumference and 8.2.3. and Waist to hip ratio of the 2008 Continuous Update Project Breast Cancer SLR)

The Continuous Update Project identified 3 new cohort studies[42, 47, 48] and 1 recent publication from a previously included cohort study[58] that investigated waist circumference and 3 cohort studies[42, 47, 48] and 2 recent publications from previously included cohort studies[28, 59] that investigated waist to hip ratio. In total 9 cohort studies investigated waist circumference and 13 waist to hip ratio. The Second Expert Report included 3 case-control studies that investigated waist circumference and 8 that investigated waist to hip ratio.

All of the waist circumference studies and most of those on waist to hip ratio showed increased risk with increased measures of abdominal fatness. Meta-analysis of cohort studies for the Second Expert Report showed a 5 per cent increased risk per 8 cm in waist circumference (Page 226 Second Expert Report). The updated meta-analyses were stratified by whether the study adjusted for BMI. Studies that did not adjust for BMI showed a 7 per cent increased risk per 8cm in waist circumference and those that did showed a 4 per cent increased risk (Figures W5 and W6 2008 Continuous Update Project Breast Cancer SLR).

Meta-analysis of cohort studies for the Second Expert Report showed a 19 per cent increased risk per 0.1 increment in waist to hip ratio (Page 226 Second Expert Report). The updated meta-analyses were stratified by whether the study adjusted for BMI. Studies that did not adjust for BMI showed a 9 per cent increased risk per 0.1 increment in waist to hip ratio and those that did showed a non-significant increased risk (Figures WHR6 and WHR7 2008 Continuous Update Project Breast Cancer SLR).

The general mechanisms through which abdominal fatness could plausibly cause cancer are outlined in chapter 6.1.3 9 and box 2.4 of the Second Expert Report. The hormonal and other biological effects of being overweight or obese are outlined in chapter 8 of the Second Expert Report. Many of these, such as increased levels of circulating oestrogens and decreased insulin sensitivity, are associated with abdominal fatness independently of overall body fatness.

The evidence added in the Continuous Update Project is consistent with that from the Second Expert Report. There is a substantial amount of epidemiological evidence but some inconsistency. There is robust evidence for mechanisms that operate in humans. The conclusion reached for the Second Expert Report remains unchanged. Abdominal fatness is a probable cause of postmenopausal breast cancer.

6.7 Adult weight gain (postmenopause)

(Also see section 8.1.6 Weight Change of the 2008 Continuous Update Project Breast Cancer SLR)

The Continuous Update Project identified 3 new cohort studies[42, 47, 48] and 1 recent publication from a previously included cohort study[60] that investigated adult weight change and postmenopausal breast cancer. In total 10 cohort studies investigated adult weight change. The Second Expert Report included 17 case-control studies that investigated adult weight change. Nearly all the studies showed increased risk with increased weight gain in adulthood. Meta-analyses for the Second Expert Report showed a 3 per cent increased risk per 5kg gained for the cohort studies and a 5 per cent increased risk per 5kg for case-control studies (Page 227 Second Expert Report). Heterogeneity may be explained by failure to separate postmenopausal women taking hormone replacement therapy.

Body fatness directly affects levels of many circulating hormones, such as insulin, insulin-like growth factors, and oestrogens, creating an environment that encourages carcinogenesis and discourages apoptosis (see chapter 2.7.1.3 Second Expert Report). It also stimulates the body's inflammatory response, which may contribute to the initiation and progression of several cancers.

The evidence added in the Continuous Update Project is consistent with that from the Second Expert Report. There is ample, consistent epidemiological evidence and a dose-response relationship was apparent. The conclusion reached for the Second Expert Report remains unchanged. Adult weight gain is a probable cause of postmenopausal breast cancer.

6.8 Greater birth weight (premenopause)

(Also see section 8.4.1 Birthweight of the 2008 Continuous Update Project Breast Cancer SLR)

The Continuous Update Project identified 1 new cohort study[61] that investigated birth weight and premenopausal breast cancer. In total 6 cohort and 4 case-control studies investigated birth weight. All cohort studies and most case-control studies showed increased risk with greater birth weight. Meta-analysis of cohort studies for the Second Expert Report showed an 8 per cent increased risk per kg (Page 238 Second Expert Report).

The general mechanisms through which the factors that lead to greater birth weight, or its consequences, could plausibly influence cancer risk are outline in chapter 6.2.11. of the Second Expert Report many of these, such as long-term programming of hormonal systems, could plausibly increase cancer risk. Greater birth weight raises circulating maternal oestrogen levels and may increase insulin-like growth factor (IGF)-1 activity; low birth weight raises fetal and maternal levels of IGF-1 binding protein. The action of both oestrogens and IGF-1 are thought to be important in fetal growth and mammary gland development, and play a central, synergistic role in the initiation and promotion of breast cancer.[62] Animal experiments also provide evidence that exposure to oestrogens during fetal and early postnatal development can increase the risk of mammary cancers.[63]

The evidence added in the Continuous Update Project is consistent with that from the Second Expert Report. There is general consistency amongst the relatively few epidemiological studies, with some evidence for a dose-response relationship. The mechanistic evidence is speculative. The conclusion reached for the Second Expert Report remains unchanged. The factors that lead to greater birth weight, or its consequences, are probably a cause of premenopausal breast cancer.

6.9 Total fat (postmenopause)

(Also see section 5.2 Total Fat of the 2008 Continuous Update Project Breast Cancer SLR)

The Continuous Update Project identified 1 new cohort study[64] and 1 recent publication from a previously included cohort study[65] that investigated total fat intake and 1 new cohort study[66] and 1 recent publication from a previously included cohort study[67] that investigated energy from fat and postmenopausal breast cancer. In total 9 cohort studies investigated total fat intake and 5 cohort studies investigated energy from fat and postmenopausal breast cancer. The Second Expert Report included 16 case-control studies that investigated total fat intake and postmenopausal breast cancer. For total fat most studies showed increased risk with increased intake. Meta-analyses for the Second Expert Report showed a non-significant increased risk for cohort studies and an 11 per cent increased risk per 20g/day for case-control studies (Page 138 Second Expert Report). A pooled analysis of cohort studies of more than 7300 cases of breast cancer showed an overall non-significant decreased risk with increased fat intake. Menopausal status did not significantly alter the result.[68] For energy from fat

most cohort studies reported decreased risk with increasing per cent energy from fat and one reported a statistically significant increased risk.

The Women's Health Initiative Dietary Modification Randomised Controlled Trial with 655 cases of postmenopausal breast cancer reported a relative risk of 0.91 (0.83-1.01) for intervention and comparison group after 8.1 years.[69] Adjusting for change in body weight had no effect on the relative risk. The trial was designed to reduce fat intake to 20% and increase servings of vegetables and fruit to 5 per day and increase servings of grains to at least 6 per day. However for women with at least 36.8% energy from fat at baseline a decrease was observed for intervention compared with control (RR- 0.78 (0.64-0.95)).

Higher endogenous oestrogen levels after menopause are a known cause of breast cancer.[53, 70] Dietary fat may also increase endogenous oestrogen production.[71]

The evidence added in the Continuous Update Project is consistent with that from the Second Expert Report. Evidence from prospective epidemiological studies of different types on the whole shows inconsistent effects, while case-control studies show a significant positive association. Mechanistic evidence is speculative. The conclusion reached for the Second Expert Report remains unchanged. Overall, there is limited evidence suggesting that consumption of total fat is a cause of postmenopausal breast cancer.

6.10 Other exposures

For pre- and postmenopausal breast cancer, other exposures were evaluated. However, the data were either of too low quality, too inconsistent, or the number of studies too few to allow conclusions to be reached. The list of exposures is shown in the matrices under limited – no conclusion. Additional meta-analyses of cohort studies on dietary fibre and highest versus lowest category forest plots for total, red and processed meat, fish, dietary folate and energy were also conducted as part of the Continuous Update Project (See 2008 Continuous Update Project Breast Cancer SLR for details).

There is considerable speculation around a biologically plausible interaction of soy and soya products with breast cancer development, due to their high phytoestrogen content. Data on pulses (legumes) were sparse and inconsistent.

A meta-analysis of 3 cohort and 6 case-control studies showed a statistically significant 25 per cent lower risk of breast cancer at any age for highest versus lowest intake of soy products. [72]

A meta-analysis of 6 cohort and 12 case-control studies reported a statistically significant 14 per cent lower risk of breast cancer at any age for highest versus lowest consumption of soy protein (estimated from intake of soy food and dietary isoflavones). [73] Another meta-analysis reported a statistically significant 12 per cent lower risk of breast cancer at any age for highest versus lowest intake of isoflavones.[74] In a subgroup analysis the association was statistically significant for Asian populations (29 per cent lower risk) but not for Western populations. [74] These meta-analyses are limited by the difficulty in the standardisation of

measure of soy intake. The quantity and type of soy consumed varied greatly across the studies, such that the contrasts in intake levels for the reported risk estimates differed widely. Although results of these meta-analyses suggest that soy intake is associated with a modest reduction in breast cancer risk, heterogeneity across studies limits the ability to interpret the findings.

7. Comparison with the Second Expert Report

Overall the evidence from the additional cohort studies identified in the Continuous Update Project was consistent with those reviewed as part of the Second Expert Report. Much of the new evidence related to body fatness, abdominal fatness and weight gain; there were also new studies reporting on alcohol consumption.

8. Conclusions

Since the new evidence that was found as part of the Continuous Update Project is consistent with the evidence presented in the Second Expert Report the conclusions are unchanged.

***The Continuous Update Project Panel concludes*:**

The evidence that lactation protects against breast cancer at all ages thereafter is convincing. Physical activity probably protects against postmenopausal breast cancer, and there is limited evidence suggesting that it protects against premenopausal breast cancer. The evidence that alcoholic drinks are a cause of breast cancer at all ages is convincing. The evidence that the factors that lead to greater attained adult height or its consequences are a cause of postmenopausal breast cancer is convincing; these are probably a cause of premenopausal breast cancer.

The factors that lead to greater birth weight or its consequences are probably a cause of breast cancer diagnosed premenopause. Adult weight gain is probably a cause of postmenopausal breast cancer. The evidence that body fatness is a cause of postmenopausal breast cancer is convincing, and abdominal body fatness is probably a cause of this cancer. On the other hand, body fatness probably protects against breast cancer diagnosed premenopause. There is limited evidence suggesting that total dietary fat is a cause of postmenopausal breast cancer.

Acknowledgements

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Appendix 1 Criteria for grading evidence

(Taken from Chapter 3 of the Second Expert Report)

This box lists the criteria finally agreed by the Panel that were necessary to support the judgements shown in the matrices. The grades shown here are 'convincing', 'probable', 'limited — suggestive', 'limited — no conclusion', and 'substantial effect on risk unlikely'. In effect, the criteria define these terms.

Convincing

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

All of the following were generally required:

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

Probable

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

All the following were generally required:

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

Limited — suggestive

These criteria are for evidence that is too limited to permit a probable or convincing causal judgement, but where there is evidence suggestive of a direction of effect. The

evidence may have methodological flaws, or be limited in amount, but shows a generally consistent direction of effect. This almost always does not justify recommendations designed to reduce the incidence of cancer. Any exceptions to this require special explicit justification.

All the following were generally required:

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

Limited — no conclusion

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

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

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

Substantial effect on risk unlikely

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

All of the following were generally required:

- Evidence from more than one study type.
- Evidence from at least two independent cohort studies.
- Summary estimate of effect close to 1.0 for comparison of high versus low exposure categories.
- No substantial unexplained heterogeneity within or between study types or in different populations.
- Good quality studies to exclude, with confidence, the possibility that the absence of an observed association results from random or systematic error,

including inadequate power, imprecision or error in exposure measurement, inadequate range of exposure, confounding, and selection bias.
- Absence of a demonstrable biological gradient ('dose response').
- Absence of strong and plausible experimental evidence, either from human studies or relevant animal models, that typical human exposures lead to relevant cancer outcomes.

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

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

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

Special upgrading factors

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

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

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World Cancer Research Fund International

www.wcrf.org

American Institute for Cancer Research

www.aicr.org

World Cancer Research Fund

www.wcrf-uk.org

Wereld Kanker Onderzoek Fonds

www.wcrf-nl.org

World Cancer Research Fund Hong Kong

www.wcrf-hk.org

www.dietandcancerreport.org

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