

| Wholegrains, Vegetables and Fruit and the Risk of Cancer  |  |  |   |   |                              |                           |
|---|--|--|---|---|------------------------------|---------------------------|
| WCRF/AICR Grading   |  | Decreases Risk   |   | Increases Risk  |                              |                           |
|   |  | Exposure   | Cancer site   | Exposure  | Cancer site                  |                           |
| STRONG EVIDENCE   | Convincing   |  |   | Aflatoxins  | Liver 2015 <sup>1</sup>      |                           |
|   | Probable   | Wholegrains  | Colorectum 2017   | Foods preserved by salting (including preserved non-starchy vegetables) | Stomach 2016 <sup>2</sup>    |                           |
|   |  | Foods containing dietary fibre                         | Colorectum 2017 <sup>3</sup>  |   |                              |                           |
|   |  | Non-starchy vegetables and fruit (aggregated)          | Aerodigestive cancer and some other cancers (aggregated) <sup>4</sup> |   |                              |                           |
| LIMITED EVIDENCE  | Limited – suggestive   | Non-starchy vegetables                                 | Mouth, pharynx and larynx 2018  | Non-starchy vegetables (low intake)                                     | Colorectum 2017 <sup>5</sup> |                           |
|   |  |  | Nasopharynx 2017  | Preserved non-starchy vegetables  | Nasopharynx 2017             |                           |
|   |  |  | Oesophagus (adenocarcinoma) 2016                                      |   |                              |                           |
|   |  |  | Oesophagus (squamous cell carcinoma) 2016                             |   |                              |                           |
|   |  |  | Lung (people who smoke or used to smoke tobacco) 2017                 |   |                              |                           |
|   |  | Breast (oestrogen receptor-negative) <sup>8</sup> 2017 |   |   |                              |                           |
|   |  | Fruit  | Oesophagus (squamous cell carcinoma) 2016                             | Fruit (low intake)  | Stomach 2016 <sup>6</sup>    |                           |
|   |  | Lung (people who smoke or used to smoke tobacco) 2017  | Colorectum 2017 <sup>7</sup>  |   |                              |                           |
|   |  | Citrus fruit   |   |   |                              | Stomach (cardia) 2016     |
|   |  | Non-starchy vegetables and fruit                       |   |   |                              | Bladder 2015 <sup>9</sup> |
|   |  | Foods containing carotenoids                           |   |   |                              | Lung 2017 <sup>10</sup>   |
|   | Breast 2017 <sup>11</sup>                                      |  |   |   |                              |                           |
| Foods containing beta-carotene  | Lung 2017 <sup>12</sup>  |  |   |   |                              |                           |
| Foods containing vitamin C  | Lung (people who smoke tobacco) 2017 <sup>13</sup>             |  |   |   |                              |                           |
|   | Colorectum (colon) 2017 <sup>14</sup>                          |  |   |   |                              |                           |
| Foods containing isoflavones  | Lung (people who have never smoked tobacco) 2017 <sup>15</sup> |  |   |   |                              |                           |
| STRONG EVIDENCE   | Substantial effect on risk unlikely                            | Beta-carotene:<br>Prostate 2014 <sup>16</sup>          |   |   |                              |                           |
| <p><b>1</b> The evidence for aflatoxins and liver cancer relates to foods that may be contaminated with aflatoxins and includes cereals (grains) as well as pulses (legumes), seeds, nuts and some vegetables and fruit. The studies reported on elevated levels of biomarkers of aflatoxin exposure.</p> <p><b>2</b> For preserved non-starchy vegetables and stomach cancer, there is no separate conclusion. The evidence was included in ‘foods preserved by salting’, which assessed the evidence for salt-preserved vegetables, salt-preserved fish and salt-preserved foods. The term ‘foods preserved by salting’ refers mainly to high-salt foods and salt-preserved foods, including pickled vegetables and salted or dried fish, as traditionally prepared in East Asia.</p> <p><b>3</b> The evidence for foods containing dietary fibre and colorectal cancer includes both foods that naturally contain fibre and foods that have had fibre added.</p> <p><b>4</b> The Panel notes that while the evidence for links between individual cancers and non-starchy vegetables or fruit is limited, the pattern of association is consistent and in the same direction, and overall the evidence is more persuasive of a protective effect: greater consumption of non-starchy vegetables or fruit probably protects against a number of aerodigestive cancers.</p> <p><b>5</b> Although the dose–response meta-analysis for colorectal cancer showed a statistically significant decreased risk with increased consumption of non-starchy vegetables, a non-linear relationship was apparent, which showed a significant increased risk at intakes of 100 grams or less per day when compared with an intake of 200 grams per day. For information on the evidence that led to the Panel’s conclusion, see <b>Section 5.4.8</b>.</p> <p><b>6</b> An increased risk of stomach cancer was not apparent when the data for fruit were analysed assuming a linear response but became apparent when conducting a non-linear analysis, which showed a significant increased risk at intakes below 45 grams per day when compared with an intake of about 100 grams per day. For information on the evidence supporting the conclusion, see <b>Section 5.6.4</b>.</p> <p><b>7</b> Although the dose–response meta-analysis for colorectal cancer showed a statistically significant decreased risk with increased consumption of fruit, a non-linear relationship was apparent, which showed a significant increased risk at intakes of 100 grams or less per day when compared with an intake of 200 grams per day. For information on the evidence that led to the conclusion, see <b>Section 5.6.5</b>.</p> <p><b>8</b> The Panel’s conclusion for non-starchy vegetables and breast cancer relates to evidence for breast cancer overall (menopausal status not specified). The observed association was in oestrogen receptor-negative (ER-negative or ER–) breast cancer only.</p> <p><b>9</b> The evidence for non-starchy vegetables and fruit and bladder cancer relates to combined consumption of vegetables and fruit.</p> <p><b>10</b> The evidence for foods containing carotenoids and lung cancer is derived from studies on dietary intake and serum levels.</p> <p><b>11</b> The Panel’s conclusion for foods containing carotenoids and breast cancer relates to the evidence for breast cancer overall (menopausal status not specified). The evidence is derived from studies on dietary intake and serum or plasma levels and includes both foods that naturally contain carotenoids and foods that have had carotenoids added.</p> <p><b>12</b> The evidence for foods containing beta-carotene and lung cancer is derived from studies on dietary intake and serum levels.</p> <p><b>13</b> The evidence for foods containing vitamin C and lung cancer in people who smoke tobacco is derived from studies on dietary intake.</p> <p><b>14</b> The Panel’s conclusion is for foods containing vitamin C and colon cancer. No conclusion was drawn for foods containing vitamin C and rectal cancer.</p> <p><b>15</b> The evidence for foods containing isoflavones and lung cancer in people who have never smoked tobacco is derived from studies on dietary intake.</p> <p><b>16</b> The evidence for beta-carotene and prostate cancer is derived from studies on dietary intake and serum or plasma levels, as well as studies on supplement use (20, 30 and 50 milligrams per day).</p> |  |  |   |   |                              |                           |

# CUP dose–response meta-analysis for consumption of wholegrains and the risk of colorectal cancer

| Cancer     | Total no. of studies | No. of studies in meta-analysis | No. of cases | Risk estimate (95% CI) | Increment | I <sup>2</sup> (%) | Conclusion <sup>1</sup>  | Date of CUP cancer report <sup>2</sup> |
|------------|----------------------|---------------------------------|--------------|------------------------|-----------|--------------------|--------------------------|--|
| Colorectum | 6                    | 6                               | 8,320        | 0.83 (0.78–0.89)       | 90 g/day  | 18                 | Probable: Decreases risk | 2017                                   |

- 1 See Definitions of WCRF/AICR grading criteria (**Section 1:** Wholegrains, vegetables and fruit and the risk of cancer: a summary matrix) for explanations of what the Panel means by ‘probable’.
- 2 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.

Summary of published pooled analyses for consumption of wholegrains and the risk of colorectal cancer

| Publication          | Contrast          | RR (95% CI)      | No. of studies (cohort) | No. of cases |
|----------------------|-------------------|------------------|-------------------------|--------------|
| Pooling Project [90] | Highest vs lowest | 0.92 (0.84–1.00) | 13                      | 8,081        |

# CUP dose–response meta-analysis for consumption of foods containing dietary fibre and the risk of colorectal cancer

| Cancer                  | Total no. of studies | No. of studies in meta-analysis | No. of cases | Risk estimate (95% CI) | Increment | I <sup>2</sup> (%) | Conclusion <sup>1</sup>  | Date of CUP cancer report <sup>2</sup> |
|-------------------------|----------------------|---------------------------------|--------------|------------------------|-----------|--------------------|--------------------------|--|
| Colorectum <sup>3</sup> | 23                   | 21                              | 16,562       | 0.93 (0.87–1.00)       | 10 g/day  | 72                 | Probable: Decreases risk | 2017                                   |

- 1 See Definitions of WCRF/AICR grading criteria (**Section 1:** Wholegrains, vegetables and fruit and the risk of cancer: a summary matrix) for explanations of what the Panel means by ‘probable’.
- 2 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.
- 3 The evidence for foods containing dietary fibre and colorectal cancer includes both foods that naturally contain fibre and foods that have had fibre added.

# Summary of published pooled analyses for consumption of foods containing dietary fibre and the risk of colorectal cancer

| Publication  | Contrast          | Source of fibre   | RR (95% CI)      | No. of studies (cohort) | No. of cases |
|--|-------------------|---|------------------|-------------------------|--------------|
| Pooling Project of Prospective Studies on Diet and Cancer [90] | Highest vs lowest | Cereal fibre (g/day)  | 0.94 (0.86–1.03) | 13                      | 8,081        |
|  |                   | Vegetable fibre (g/day)   | 1.00 (0.93–1.08) |                         |              |
|  |                   | Fruit fibre (g/day)   | 0.96 (0.89–1.04) |                         |              |
| UK Dietary Cohort Consortium [106]                             | Highest vs lowest | Dietary fibre intake density (g/MJ) assessed by food diaries                  | 0.66 (0.45–0.96) | 7                       | 579          |
|  |                   | Dietary fibre intake density (g/MJ) assessed by food frequency questionnaires | 0.88 (0.57–1.36) |                         |              |

# Summary of published cohort and nested case-control studies on consumption of foods contaminated by aflatoxins and the risk of liver cancer

| Cancer             | Total no. of studies | No. of analyses | No. of cases (No. of controls) | No. of analyses reporting a statistically significant increased risk | Increment  | Conclusion <sup>1</sup>    | Date of CUP cancer report <sup>2</sup> |
|--------------------|----------------------|-----------------|--------------------------------|--|--|----------------------------|--|
| Liver <sup>3</sup> | 4                    | 11              | 350 (1,541)                    | 8  | Biomarkers of exposure above mean vs below mean or Biomarkers of exposure detectable vs undetectable | Convincing: Increases risk | 2015                                   |

- 1 See Definitions of WCRF/AICR grading criteria (**Section 1:** Wholegrains, vegetables and fruit and the risk of cancer: a summary matrix) for explanations of what the Panel means by ‘convincing’.
- 2 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.
- 3 The evidence for aflatoxins and liver cancer relates to foods that may be contaminated with aflatoxins and includes cereals (grains) as well as pulses (legumes), seeds, nuts and some vegetables and fruit. The studies reported on elevated levels of biomarkers of aflatoxin exposure.

# Summary of published nested case-control and cohort studies for aflatoxins (as measured by any biomarker of exposure) and the risk of liver (hepatocellular) cancer

| Study description                               | Publication     | No. of cases/controls                      | RR (95% CI)      | Contrast   |
|---|-----------------|--|------------------|--|
| Community-based Cancer Screening Cohort, Taiwan | Wu 2009 [109]   | 241 cases<br>1,052 controls                | 1.54 (1.01–2.36) | AFB <sub>1</sub> -albumin adducts above vs below mean (59.8 fmol/mg)                     |
|   |                 |  | 1.76 (1.18–2.58) | Urinary AFB <sub>1</sub> above vs below mean (55.2 fmol/ml)                              |
|   | Sun 2001 [110]  | HBsAg carriers<br>75 cases<br>140 controls | 2.0 (1.1–3.7)    | AFB <sub>1</sub> -albumin adducts detectable vs non-detectable                           |
|   | Wang 1996 [111] | 56 cases<br>220 controls                   | 1.6 (0.4–5.5)    | Serum level aflatoxin albumin detectable vs non-detectable                               |
|   |                 |  | 3.8 (1.1–12.8)   | Urinary levels of aflatoxin high vs low  |
| Shanghai Cohort Study, China                    | Yuan 2006 [112] | 50 cases<br>265 controls                   | 3.25 (1.63–6.48) | Urinary aflatoxin biomarker positive vs negative   |
|   | Qian 1994 [113] | 55 cases<br>267 controls                   | 5.0 (2.1–11.8)   | Any urinary aflatoxin biomarker vs none  |
|   | Ross 1992 [114] | 22 cases<br>110 controls                   | 2.4 (1.0–5.9)    | Any urinary aflatoxin biomarker vs none  |
| Qidong Cohort, China                            | Sun 1999 [115]  | 22 cases<br>149 controls                   | 3.3 (1.2–8.7)    | Urinary AFM <sub>1</sub> detectable (above 3.6 ng/l) vs non-detectable                   |
| Cohort Government Clinics, Taiwan               | Yu 1997 [116]   | HBsAg carriers<br>21 cases<br>63 controls  | 12.0 (1.2–117.4) | Both markers (urinary AFM <sub>1</sub> and AFB <sub>1</sub> -N7-guanine adducts) vs none |
|   | Chen 1996 [117] | HBsAg carriers<br>32 cases<br>73 controls  | 3.8 (1.0–14.5)   | AFB <sub>1</sub> -albumin adducts high vs undetectable                                   |

Summary of CUP dose–response meta-analyses of vegetable intake and the risk of cancer

| Cancer   | Type                          | Total no. of studies | No. of studies in meta-analysis | No. of cases | Risk estimate (95% CI)   | Increment  | I <sup>2</sup> (%) | Conclusion <sup>1</sup>                                   | Date of CUP cancer report <sup>2</sup> |
|--|-------------------------------|----------------------|---------------------------------|--------------|--|--|--------------------|---|--|
| Mouth, pharynx and larynx <sup>3</sup>               | Vegetables                    | 3                    | 0                               | –            | Statistically significant decreased risk in 1 study <sup>3</sup>         | –  | –                  | Limited – suggestive: Decreases risk                      | 2018                                   |
| Nasopharynx <sup>4</sup>                             | Vegetables                    | 2 meta-analyses      | –                               | –            | Statistically significant decreased risk in 2 meta-analyses <sup>4</sup> | –  | –                  | Limited – suggestive: Decreases risk                      | 2017                                   |
| Oesophagus (adenocarcinoma)                          | Vegetables                    | 3                    | 3                               | 415          | 0.89 (0.80–0.99)   | 100 g/day  | 0                  | Limited – suggestive: Decreases risk                      | 2016                                   |
| Oesophagus (squamous cell carcinoma)                 | Vegetables                    | 4                    | 4                               | 2,273        | 0.91 (0.81–1.03)   | 100 g/day  | 31                 | Limited – suggestive: Decreases risk                      | 2016                                   |
| Lung (people who smoke tobacco) <sup>5</sup>         | Vegetables                    | 9                    | 6                               | 6,520        | 0.88 (0.79–0.99)   | 100 g/day  | 81                 | Limited – suggestive: Decreases risk <sup>5</sup>         | 2017                                   |
| Lung (people who used to smoke tobacco) <sup>5</sup> |                               | 6                    | 4                               | 3,771        | 0.97 (0.91–1.05)   |  | 25                 |   |  |
| Breast (oestrogen receptor-negative) <sup>6</sup>    | Vegetables                    | 3                    | 3                               | 1,346        | 0.79 (0.63–0.98)   | 200 g/day  | 37                 | Limited – suggestive: Decreases risk                      | 2017                                   |
| Bladder <sup>7</sup>                                 | Vegetables and fruit combined | 9                    | 8                               | 2,508        | 0.97 (0.95–0.99)   | 80 g/day   | 0                  | Limited – suggestive: Decreases risk                      | 2015                                   |
| Colorectum <sup>8</sup>                              | Vegetables                    | 23                   | 9                               | –            | 1.08 (1.06–1.10)   | Non-linear dose–response analysis 100 vs 200 g/day | 0                  | Limited – suggestive: Increases risk with low consumption | 2017                                   |

**1** See Definitions of WCRF/AICR grading criteria (**Section 1:** Wholegrains, vegetables and fruit and the risk of cancer: a summary matrix) for explanations of what the Panel means by ‘limited – suggestive’.

**2** 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.

**3** A dose–response meta-analysis on vegetables and cancers of the mouth, pharynx and larynx could not be conducted in the CUP. One of three identified published studies reported a statistically significant decreased risk of oral cavity cancer (RR 0.84 [95% CI 0.73–0.95], per serving/1,000 kcal, n = 319), and of head and neck cancer (RR 0.89 [95% CI 0.82–0.97], per serving/1,000 kcal, n = 787), with increased consumption of vegetables in dose–response meta-analyses [124].

**4** A dose–response meta-analysis on vegetables and nasopharyngeal cancer could not be conducted in the CUP. Two published meta-analyses of case-control studies on vegetable intake and nasopharyngeal cancer were identified, both of which showed a statistically significant decreased risk of nasopharyngeal cancer when comparing the highest with the lowest level of vegetables consumed (RR 0.60 [95% CI 0.47–0.76] [27] and RR 0.64 [95% CI 0.48–0.85] [28]).

**5** A separate dose–response meta-analysis on green leafy vegetables and lung cancer also showed a significant decreased risk. For more information on the evidence that led to the conclusion, see **Section 5.4.5**.

**6** The Panel’s conclusion for non-starchy vegetables (greater intake) and breast cancer relates to evidence for breast cancer overall (menopausal status not specified). The observed association was in oestrogen receptor-negative (ER-negative or ER–) breast cancer only.

**7** The evidence for vegetables and fruit and bladder cancer relates to combined consumption of vegetables and fruit and is summarised in **Section 5.4.7** and **Table 5.15**.

**8** Although the dose–response meta-analysis for colorectal cancer showed a statistically significant decreased risk with increased consumption of vegetables, a non-linear relationship was apparent, which showed a significant increased risk at intakes of 100 grams or less per day when compared with an intake of 200 grams per day. For information on the evidence that led to the Panel’s conclusion, see **Section 5.4.8**.



# Summary of published dose–response analyses from individual cohort studies on consumption of vegetables and the risk of cancers of the mouth, pharynx and larynx

| Cancer site                      | Study  | Increment          | No. of cases | RR (95% CI)      |
|----------------------------------|--|--------------------|--------------|------------------|
| Oral cavity                      | Netherlands cohort study [125]                                     | 25 g/day           | 131          | 0.95 (0.89–1.02) |
|                                  | NIH-AARP [124]   | serving/1,000 kcal | 319          | 0.84 (0.73–0.95) |
| Oro- and hypopharyngeal combined | Netherlands cohort study [125]                                     | 25 g/day           | 88           | 0.94 (0.85–1.04) |
|                                  | NIH-AARP [124]   | serving/1,000 kcal | 142          | 0.90 (0.74–1.09) |
| Laryngeal                        | Netherlands cohort study [125]                                     | 25 g/day           | 193          | 0.98 (0.92–1.04) |
|                                  | NIH-AARP [124]   | serving/1,000 kcal | 279          | 0.91 (0.79–1.05) |
| Head and neck                    | Netherlands cohort study [125]                                     | 25 g/day           | 415          | 0.96 (0.92–1.01) |
|                                  | NIH-AARP [124]   | serving/1,000 kcal | 787          | 0.89 (0.82–0.97) |
| Upper aerodigestive tract        | European Prospective Investigation into Cancer and Nutrition [126] | 40 g/day           | 352          | 0.89 (0.78–1.02) |

Summary of published pooled analyses of vegetable intake and the risk of head and neck cancer

| Publication        | Contrast          | RR (95% CI)      | No. of studies (case control) | No. of cases |
|--------------------|-------------------|------------------|-------------------------------|--------------|
| Chuang, 2012 [127] | Highest vs lowest | 0.66 (0.49–0.90) | 22                            | 12,968       |

# Summary of published highest versus lowest meta-analyses for consumption of vegetables and the risk of nasopharyngeal cancer

| Publication           | Contrast  | RR (95% CI)      | P value | No. of studies (case control) | No. of cases |
|-----------------------|---|------------------|---------|-------------------------------|--------------|
| Jin, 2014 [27]        | Highest vs lowest total or fresh vegetable intake | 0.60 (0.47–0.76) | 0.03    | 11 (all studies)              | 3,749        |
|                       |   | 0.47 (0.38–0.58) | 0.18    | 4 (hospital-based studies)    |              |
|                       |   | 0.80 (0.65–0.99) | 0.84    | 7 (population-based studies)  |              |
| Gallicchio, 2006 [28] | Highest vs lowest non-preserved vegetable intake  | 0.64 (0.48–0.85) | 0.09    | 5 (all studies)               | 1,695        |

## Summary of published pooled analyses of vegetable intake and the risk of lung cancer

| Publication  | Contrast                 | Subgroup                     | RR (95% CI)      | No. of studies (cohort) | No. of cases |
|--|--------------------------|------------------------------|------------------|-------------------------|--------------|
| <b>Pooling Project of Prospective Studies on Diet and Cancer [145]</b> | Quintile 4 vs Quintile 1 | People who smoke             | 0.86 (0.74–1.00) | 5                       | 1,915        |
|  |                          | People who used to smoke     | 0.97 (0.76–1.24) |                         | 981          |
|  |                          | People who have never smoked | 0.90 (0.58–1.40) |                         | 259          |

# Summary of published pooled analyses of vegetable intake and the risk of oestrogen receptor-negative breast cancer

| Publication  | Increment/contrast       | RR (95% CI)      | No. of studies (cohort) | No. of cases |
|--|--------------------------|------------------|-------------------------|--------------|
| Pooling Project of Prospective Studies on Diet and Cancer 2013 [149] | Quintile 5 vs Quintile 1 | 0.82 (0.74–0.90) | 20                      | 4,820        |
|  | Per 300 g/day            | 0.88 (0.81–0.95) |                         |              |

**CUP non-linear dose–response  
estimates of vegetable intake  
and the risk of colorectal cancer**

| Vegetable intake<br>(grams per day) | RR (95% CI)      |
|-------------------------------------|------------------|
| 22                                  | 1.16 (1.11–1.21) |
| 100                                 | 1.08 (1.06–1.10) |
| 200                                 | 1.00             |
| 300                                 | 0.96 (0.95–0.97) |
| 400                                 | 0.95 (0.95–0.96) |
| 500                                 | 0.96 (0.96–0.96) |

## Summary of CUP dose–response meta-analyses of preserved vegetable intake and the risk of cancer

| Cancer                          | Type                               | Total no. of studies | No. of studies in meta-analysis | No. of cases | Risk estimate (95% CI) | Increment /contrast | I <sup>2</sup> (%) | Conclusion <sup>1</sup>                     | Date of CUP cancer report <sup>2</sup> |
|---------------------------------|------------------------------------|----------------------|---------------------------------|--------------|------------------------|---------------------|--------------------|---|--|
| <b>Stomach<sup>3</sup></b>      | Salt-pre-served vegetables         | 14                   | 9                               | 3,932        | 1.09 (1.05–1.13)       | 20 g/day            | 0                  | <b>Probable: Increases risk</b>             | 2016                                   |
|                                 | Salt-pre-served foods <sup>4</sup> | 6                    | 5                               | 635          | 1.70 (1.18–2.45)       | Highest vs lowest   | –                  |   |  |
| <b>Naso-pharynx<sup>5</sup></b> | Preserved vegetables               | 14                   | 5                               | 3,924        | 1.42 (1.04–1.93)       | once/week           | 76                 | <b>Limited – suggestive: Increases risk</b> | 2017                                   |

- 1 See Definitions of WCRF/AICR grading criteria (**Section 1**: Wholegrains, vegetables and fruit and the risk of cancer: a summary matrix) for explanations of what the Panel means by ‘probable’ and ‘limited – suggestive’.
- 2 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.
- 3 For preserved non-starchy vegetables and stomach cancer, there is no separate conclusion. The evidence was included in ‘foods preserved by salting’, which assessed the evidence for salt-preserved vegetables, salt-preserved fish and salt-preserved foods. The term ‘foods preserved by salting’ refers mainly to high-salt foods and salt-preserved foods, including pickled vegetables and salted or dried fish, as traditionally prepared in East Asia. There was no significant association for salt-preserved fish in the CUP dose–response meta-analysis. See Exposures: Preservation and the processing of foods.
- 4 A dose–response meta-analysis on salt-preserved foods and stomach cancer could not be conducted in the CUP as there were too few studies. Evidence is from a CUP highest versus lowest meta-analysis.
- 5 A dose–response meta-analysis of cohort studies could not be conducted in the CUP. Evidence is from a CUP dose–response meta-analysis of case-control studies on preserved vegetable intake and nasopharyngeal cancer.

## Summary of CUP dose–response meta-analyses of fruit intake and the risk of cancer

| Cancer   | Type                          | Total no. of studies | No. of studies in meta-analysis | No. of cases | Risk estimate (95% CI) | Increment  | I <sup>2</sup> (%) | Conclusion <sup>1</sup>  | Date of CUP cancer report <sup>2</sup> |
|--|-------------------------------|----------------------|---------------------------------|--------------|------------------------|--|--------------------|--|--|
| <b>Oesophagus (squamous cell carcinoma)</b>    | Fruit                         | 4                    | 3                               | 320          | 0.84 (0.75–0.94)       | 100 g/day  | 0                  | Limited – suggestive: Decreases risk                             | 2016                                   |
| <b>Lung (people who smoke tobacco)</b>         | Fruit                         | 11                   | 9                               | 7,141        | 0.91 (0.85–0.98)       | 100 g/day  | 57                 | Limited – suggestive: Decreases risk                             | 2017                                   |
| <b>Lung (people who used to smoke tobacco)</b> |                               | 7                    | 5                               | 3,828        | 0.97 (0.92–1.02)       | 100 g/day  | 0                  |  |  |
| <b>Stomach (cardia)</b>                        | Citrus fruit                  | 3                    | 3                               | 555          | 0.76 (0.58–0.99)       | 100 g/day  | 53                 | Limited – suggestive: Decreases risk                             | 2016                                   |
| <b>Bladder<sup>3</sup></b>                     | Vegetables and fruit combined | 9                    | 8                               | 2,508        | 0.97 (0.95–0.99)       | 80 g/day   | 0                  | Limited – suggestive: Decreases risk                             | 2015                                   |
| <b>Stomach<sup>4</sup></b>                     | Fruit                         | 24                   | 7                               | –            | 1.08 (1.05–1.11)       | Non-linear dose–response analysis 43 vs 86 g/day   | –                  | Limited – suggestive: Increases risk <b>with low consumption</b> | 2016                                   |
| <b>Colorectum<sup>5</sup></b>                  | Fruit                         | 21                   | 9                               | –            | 1.07 (1.05–1.09)       | Non-linear dose–response analysis 100 vs 200 g/day | –                  | Limited – suggestive: Increases risk <b>with low consumption</b> | 2017                                   |

- 1 See Definitions of WCRF/AICR grading criteria (**Section 1**: Wholegrains, vegetables and fruit and the risk of cancer: a summary matrix) for explanations of what the Panel means by ‘limited – suggestive’.
- 2 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.
- 3 The evidence for non-starchy vegetables and fruit and bladder cancer relates to combined consumption of vegetables and fruit and is included in **Section 5.4.7**.
- 4 An increased risk of stomach cancer was not apparent when the data for fruit were analysed assuming a linear response, but became apparent when conducting a non-linear analysis. The Panel’s conclusion for fruit (low intake) and stomach cancer relates to intakes below 45 grams per day when compared with an intake of about 100 grams per day. For information on the evidence supporting the conclusion, see **Section 5.6.4**.
- 5 No statistically significant association was observed between consumption of fruit and the risk of colorectal cancer when the data were analysed assuming a linear response. A significant increased risk became apparent when a non-linear analysis was conducted. The Panel’s conclusion for fruit (low intake) and colorectal cancer relates to intakes of 100 grams or less per day when compared with an intake of 200 grams per day. For information on the evidence that led to the conclusion, see **Section 5.6.5**.



# Summary of published pooled analyses of fruit intake and the risk of lung cancer

| Publication   | Contrast                 | Subgroup                     | RR (95% CI)      | No. of studies (cohort) | No. of cases |
|---|--------------------------|------------------------------|------------------|-------------------------|--------------|
| Pooling Project of Prospective Studies on Diet and Cancer [145] | Quintile 4 vs Quintile 1 | People who smoke             | 0.82 (0.68–0.99) | 5                       | 1,915        |
|   |                          | People who used to smoke     | 0.85 (0.69–1.05) |                         | 981          |
|   |                          | People who have never smoked | 0.59 (0.34–1.04) |                         | 259          |

**CUP non-linear dose–response  
estimates of fruit intake and the  
risk of stomach cancer**

| Fruit intake<br>(grams per day) | RR (95% CI)      |
|---------------------------------|------------------|
| 0                               | 1.18 (1.11–1.26) |
| 43                              | 1.08 (1.05–1.11) |
| 86                              | 1.00             |
| 137                             | 0.95 (0.93–0.97) |
| 196                             | 0.94 (0.92–0.97) |
| 236                             | 0.95 (0.92–0.98) |

**CUP non-linear dose–response  
estimates of fruit intake and the  
risk of colorectal cancer**

| Fruit intake<br>(grams per day) | RR (95% CI)      |
|---------------------------------|------------------|
| 2                               | 1.21 (1.15–1.26) |
| 100                             | 1.07 (1.05–1.09) |
| 200                             | 1.00             |
| 300                             | 0.99 (0.98–0.99) |
| 400                             | 0.99 (0.98–0.99) |
| 500                             | 0.99 (0.98–1.00) |

# Summary of CUP dose–response meta-analyses for consumption of foods containing carotenoids and the risk of cancer

| Cancer                | Type                               | Total no. of studies | No. of studies in meta-analysis | No. of cases | Risk estimate (95% CI) | Increment         | I <sup>2</sup> (%) | Conclusion <sup>1</sup>              | Date of CUP cancer report <sup>2</sup> |
|-----------------------|------------------------------------|----------------------|---------------------------------|--------------|------------------------|-------------------|--------------------|--------------------------------------|--|
| Lung <sup>3</sup>     | Dietary carotenoids                | 9                    | 7                               | 4,491        | 0.98 (0.97–0.99)       | 1,000 µg/day      | 37                 | Limited – suggestive: Decreases risk | 2017                                   |
|                       | Serum carotenoids <sup>4</sup>     | 5                    | 5                               | 724          | 0.64 (0.44–0.93)       | Highest vs lowest | –                  |                                      |  |
| Breast <sup>5,6</sup> | Serum/ plasma carotenoids          | 9                    | 9                               | 3,407        | 0.82 (0.71–0.96)       | 100 µg/ 100 ml    | 0                  | Limited – suggestive: Decreases risk | 2017                                   |
|                       | Dietary beta-carotene <sup>7</sup> | 24                   | 18                              | 3,055        | 1.00 (0.98–1.02)       | 5000 µg/day       | 0                  |                                      |  |
|                       | Serum/ plasma beta-carotene        | 13                   | 11                              | 3,558        | 0.78 (0.66–0.92)       | 50 µg/ 100 ml     | 0                  |                                      |  |

- 1 See Definitions of WCRF/AICR grading criteria (**Section 1:** Wholegrains, vegetables and fruit and the risk of cancer: a summary matrix) for explanations of what the Panel means by ‘limited – suggestive’.
- 2 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.
- 3 The evidence for foods containing carotenoids and lung cancer is derived from studies on dietary intake and serum levels.
- 4 A dose–response meta-analysis for serum carotenoids and lung cancer could not be conducted in the CUP as there were not enough studies. Evidence is from a CUP highest versus lowest meta-analysis.
- 5 The Panel’s conclusion for foods containing carotenoids and breast cancer relates to the evidence for breast cancer overall (menopausal status not specified). The evidence is derived from studies on dietary intake and serum/plasma levels and includes both foods that naturally contain carotenoids and foods that have had carotenoids added.
- 6 For additional information on breast cancer and other carotenoids, such as alpha-carotene, lutein, beta-cryptoxanthin and lycopene, see **Section 5.7.2.4**.
- 7 A dose–response meta-analysis was not conducted in the CUP for dietary beta-carotene and breast cancer, as all identified studies were superseded by a published pooled analysis. Evidence is from the published pooled analysis of 18 cohort studies [188].

## Summary of CUP dose–response meta-analyses for other carotenoid exposures and the risk of breast cancer

| Serum/<br>plasma levels   | Total no.<br>of studies <sup>1</sup> | No. studies on<br>meta-analysis | RR (95% CI)      | Increment    | I <sup>2</sup> (%) | No. of<br>cases |
|---------------------------|--------------------------------------|---------------------------------|------------------|--------------|--------------------|-----------------|
| <b>Alpha-carotene</b>     | 11                                   | 10                              | 0.90 (0.77–1.05) | 10 µg/100 ml | 0                  | 3,506           |
| <b>Lutein</b>             | 7                                    | 7                               | 0.72 (0.55–0.93) | 25 µg/100 ml | 0                  | 1,296           |
| <b>Beta-cryptoxanthin</b> | 11                                   | 10                              | 0.87 (0.68–1.11) | 15 µg/100 ml | 59                 | 3,517           |
| <b>Lycopene</b>           | 11                                   | 10                              | 0.90 (0.70–1.16) | 25 µg/100 ml | 39                 | 3,506           |

# Summary of published pooled analyses for any carotenoid and the risk of breast cancer stratified by hormone receptor status

| Exposure/publication                                   | Increment/contrast       | ER status | RR (95% CI)      | No. of studies (cohort) | No. of cases |
|--|--------------------------|-----------|------------------|-------------------------|--------------|
| Serum/plasma carotenoids<br>Eliassen 2012 [211]        | Quintile 5 vs Quintile 1 | ER–       | 0.81 (0.56–1.16) | 8                       | 417          |
|  | Quintile 5 vs Quintile 1 | ER+       | 0.86 (0.69–1.07) |                         | 1,481        |
| Dietary beta-carotene<br>Zhang 2012 [188]              | 5,000 µg/day             | ER–       | 0.93 (0.88–0.99) | 18                      | 4,463        |
|  | 5,000 µg/day             | ER+       | 1.02 (0.99–1.05) |                         | 19,282       |
| Serum/plasma beta-carotene<br>Eliassen 2012 [211]      | Quintile 5 vs Quintile 1 | ER–       | 0.52 (0.36–0.77) | 8                       | 417          |
|  | Quintile 5 vs Quintile 1 | ER+       | 0.83 (0.66–1.04) |                         | 1,481        |
| Dietary alpha-carotene<br>Zhang 2012 [188]             | 5,000 µg/day             | ER–       | 0.95 (0.90–1.01) | 18                      | 4,463        |
|  | 5,000 µg/day             | ER+       | 1.01 (0.99–1.03) |                         | 19,282       |
| Serum/plasma alpha-carotene<br>Eliassen 2012 [211]     | Quintile 5 vs Quintile 1 | ER–       | 0.61 (0.40–0.93) | 8                       | 417          |
|  | Quintile 5 vs Quintile 1 | ER+       | 0.85 (0.65–1.12) |                         | 1,481        |
| Dietary beta-cryptoxanthin<br>Zhang 2012 [188]         | 5,000 µg/day             | ER–       | 0.97 (0.93–1.00) | 18                      | 4,463        |
|  | 5,000 µg/day             | ER+       | 0.99 (0.97–1.00) |                         | 19,282       |
| Serum/plasma beta-cryptoxanthin<br>Eliassen 2012 [211] | Quintile 5 vs Quintile 1 | ER–       | 1.03 (0.69–1.53) | 8                       | 417          |
|  | Quintile 5 vs Quintile 1 | ER+       | 1.09 (0.86–1.39) |                         | 1,481        |
| Dietary lycopene<br>Zhang 2012 [188]                   | 5,000 µg/day             | ER–       | 0.98 (0.93–1.03) | 18                      | 4,463        |
|  | 5,000 µg/day             | ER+       | 1.01 (0.99–1.03) |                         | 19,282       |
| Serum/plasma lycopene<br>Eliassen 2012 [211]           | Quintile 5 vs Quintile 1 | ER–       | 0.72 (0.44–1.17) | 8                       | 417          |
|  | Quintile 5 vs Quintile 1 | ER+       | 0.83 (0.60–1.15) |                         | 1,481        |

# Summary of CUP dose–response meta-analyses for consumption of foods containing beta-carotene and the risk of cancer

| Cancer                | Type         | Total no. of studies | No. of studies in meta-analysis | No. of cases | Risk estimate (95% CI)                                | Increment    | I <sup>2</sup> (%) | Conclusion <sup>1</sup>              | Date of CUP cancer report <sup>2</sup> |
|-----------------------|--------------|----------------------|---------------------------------|--------------|---|--------------|--------------------|--------------------------------------|--|
| Lung <sup>3</sup>     | Dietary      | 15                   | 13                              | 7,560        | 0.99 (0.98–1.00)                                      | 700 µg/day   | 5                  | Limited – suggestive: Decreases risk | 2017                                   |
|                       | Serum        | 17                   | 9                               | 2,958        | 0.92 (0.87–0.97)                                      | 10 µg/100 ml | 40                 |                                      |  |
| Prostate <sup>4</sup> | Dietary      | 11                   | 10                              | 12,219       | 1.00 (0.99–1.00)                                      | 700 µg/day   | 0                  | Substantial effect on risk unlikely  | 2014                                   |
|                       | Serum/plasma | 14                   | 9                               | 3,449        | 0.99 (0.95–1.04)                                      | 10 µg/100 ml | 38                 |                                      |  |
|                       | Supplements  | 8                    | 0                               | –            | No statistically significant association in 8 studies | –            | –                  |                                      |  |

- 1 See Definitions of WCRF/AICR grading criteria (**Section 1**: Wholegrains, vegetables and fruit and the risk of cancer: a summary matrix) for explanations of what the Panel means by ‘substantial effect on risk unlikely’ and ‘limited – suggestive’.
- 2 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.
- 3 The Panel made two separate conclusions on lung cancer and beta-carotene: one on ‘foods containing beta-carotene’, which is based on evidence on dietary intake and serum levels, and another on ‘high-dose beta-carotene supplements’. The evidence for foods containing beta-carotene is presented here. For information on high-dose beta-carotene supplements, see Exposures: Other dietary exposures, Section 5.10.
- 4 The Panel made one conclusion for prostate cancer and beta-carotene, which is based on evidence derived from studies on dietary intake and serum levels, as well as studies on high-dose supplement use (20, 30 and 50 mg/day). A dose–response meta-analysis could not be conducted in the CUP for prostate cancer and beta-carotene supplements. Evidence is from five cohort studies and three randomised controlled trials which all reported no statistically significant association.

Summary of published pooled analyses of dietary beta-carotene intake and the risk of lung cancer

| Publication         | Contrast                 | RR (95% CI)      | No. of studies (cohort) | No. of cases |
|---------------------|--------------------------|------------------|-------------------------|--------------|
| Männistö 2004 [228] | Quintile 5 vs Quintile 1 | 0.98 (0.87–1.11) | 7                       | 3,155        |



# Summary of published randomised controlled trials for consumption of beta-carotene supplements and the risk of prostate cancer

| Trial name  | No. of participants                           | Intervention   | Intervention length (years) | Follow-up (years) | RR (95% CI)   |
|---|---|--|-----------------------------|-------------------|---|
| <b>Beta-Carotene and Retinol Efficacy Trial (CARET) [255, 256]</b>                                      | 18,314 at high risk of developing lung cancer | 30 mg beta-carotene and 25,000 IU retinyl palmitate                  | 4 (trial ended early)       | 5                 | 1.01 (0.80–1.27)                                    |
| <b>Physicians' Health Study (PHS) [257]</b>   | 22,071  | 50 mg beta-carotene taken on alternate days                          | 13                          |                   | 1.00 (0.90–1.10)                                    |
| <b>Alpha-Tocopherol Beta-Carotene Cancer Prevention (ATBC) Study (men who smoke tobacco) [258, 259]</b> | 29,133  | 20 mg of beta-carotene only or with 50 mg of <i>alpha-tocopherol</i> | 5–8                         | 6–8               | 1.26 (0.98–1.62) for the 1985–1993 follow-up period |

# Summary of CUP dose–response meta-analyses for consumption of foods containing vitamin C and the risk of cancer

| Cancer                                       | Total no. of studies | No. of studies in meta-analysis | No. of cases | Risk estimate (95% CI) | Increment | I <sup>2</sup> (%) | Conclusion <sup>1</sup>                 | Date of CUP cancer report <sup>2</sup> |
|--|----------------------|---------------------------------|--------------|------------------------|-----------|--------------------|---|--|
| Lung (people who smoke tobacco) <sup>3</sup> | 5                    | 4                               | 1,664        | 0.87 (0.79–0.96)       | 40 mg/day | 62                 | Limited – suggestive:<br>Decreases risk | 2017                                   |
| Colorectum (colon) <sup>4</sup>              | 18                   | 6                               | 4,391        | 0.94 (0.89–0.99)       | 40 mg/day | 50                 | Limited – suggestive:<br>Decreases risk | 2017                                   |

- 1 See Definitions of WCRF/AICR grading criteria (**Section 1:** Wholegrains, vegetables and fruit and the risk of cancer: a summary matrix) for explanations of what the Panel means by ‘limited – suggestive’.
- 2 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.
- 3 The evidence for foods containing vitamin C and lung cancer in people who smoke tobacco is derived from studies on dietary intake.
- 4 The Panel’s conclusion is for foods containing vitamin C and colon cancer. No conclusion was drawn for foods containing vitamin C and rectal cancer.

# Summary of published pooled analyses of vitamin C intake and the risk of lung cancer

| Publication  | Contrast          | RR (95% CI)      | No. of studies (cohort) | No. of cases |
|--|-------------------|------------------|-------------------------|--------------|
| Pooling Project of Prospective Studies on Diet and Cancer (people who smoke) [262] | Highest vs lowest | 0.85 (0.70–1.02) | 8                       | 1,915        |

# Summary of published pooled analyses of dietary vitamin C intake and the risk of colon cancer

| Publication   | Contrast          | RR (95% CI)      | No. of studies (cohort) | No. of cases |
|---|-------------------|------------------|-------------------------|--------------|
| Pooling Project of Prospective Studies on Diet and Cancer [269] | Highest vs lowest | 1.06 (0.95–1.18) | 13                      | 5,454        |

# CUP highest versus lowest meta-analysis for consumption of foods containing isoflavones and the risk of lung cancer

| Cancer   | Total no. of studies | No. of studies in meta-analysis | No. of cases | Risk estimate (95% CI) | Conclusion <sup>1</sup>                 | Date of CUP cancer report <sup>2</sup> |
|--|----------------------|---------------------------------|--------------|------------------------|---|--|
| Lung (people who have never smoked tobacco) <sup>3</sup> | 4                    | 3                               | 714          | 0.66 (0.51–0.84)       | Limited – suggestive:<br>Decreases risk | 2017                                   |

- 1 See Definitions of WCRF/AICR grading criteria (**Section 1:** Wholegrains, vegetables and fruit and the risk of cancer: a summary matrix) for explanations of what the Panel means by ‘limited – suggestive’.
- 2 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.
- 3 The evidence for foods containing isoflavones and lung cancer in people who have never smoked tobacco is derived from studies on dietary intake.