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## **Alcoholic beverages, obesity, physical activity and other nutritional factors, and cancer risk: A review of the evidence**

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### ► To cite this version:

Paule Latino-Martel, Vanessa Cottet, Nathalie Druesne-Pecollo, Fabrice H.F. Pierre, Marina Touillaud, et al.. Alcoholic beverages, obesity, physical activity and other nutritional factors, and cancer risk: A review of the evidence. *Critical Reviews in Oncology/Hematology*, 2016, 99, pp.308 - 323. 10.1016/j.critrevonc.2016.01.002 . hal-01440350

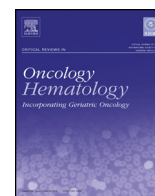
**HAL Id: hal-01440350**

**<https://hal.science/hal-01440350v1>**

Submitted on 28 May 2020

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## Review

## Alcoholic beverages, obesity, physical activity and other nutritional factors, and cancer risk: A review of the evidence



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## ARTICLE INFO

## Article history:

Received 30 October 2015

Received in revised form

18 December 2015

Accepted 7 January 2016

## Keywords:

Cancer

Diet

Beta-carotene supplements

Obesity

Alcohol

Physical activity

Breastfeeding

Prevention

## ABSTRACT

**Purpose:** Prevention is a priority in the fight against cancers, especially nutritional prevention. To update the levels of evidence of relationships between 10 nutritional factors and cancer risk, the scientific literature published from 2006 to 2014 was reviewed by an expert group.

**Methods:** Data from 133 meta-analyses, pooled analyses or intervention trials were examined. Nearly 150 relationships between nutritional factors and cancer at various sites were evaluated.

**Results:** According to the evidence graded as convincing or probable, these factors were divided in two groups. Factors which increase the risk of cancer are alcoholic beverages, overweight and obesity, red meat and processed meat, salt and salted foods and beta-carotene supplements. Factors which decrease the risk of cancer are physical activity, fruits and vegetables, dietary fiber, dairy products and breastfeeding.

**Conclusion:** Three main nutritional objectives should be attained to improve cancer prevention: to reduce alcoholic beverages consumption, to have a balanced and diversified diet and to be physically active.

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## 1. Introduction

The worldwide burden of cancer has been estimated to 14 million new cases for the year 2012, the most common cancers diagnosed globally being those of the lung, breast, and large bowel. This figure is expected to rise to 22 million per year within the next two decades (Ferlay et al., 2013). This alarming situation emphasizes the need for urgent prevention measures to win the battle against cancer (IARC, 2014a).

Prevention strategies must be based on a better evidence-based knowledge of factors able to either increase or decrease cancer risk. Cancer is a multifactorial disease involving genetic, environmental and behavioral factors, the latter including nutritional factors that comprise diet, alcohol consumption, body fatness and physical activity. For more than two decades, the World Cancer Research Fund (WCRF) and the American Institute for Cancer Research (AICR) have joined their efforts to summarize, assess and judge the evidence on nutritional factors and the risk of various cancers. Since their report published in 2007 (WCRF/AICR, 2007), the WCRF/AICR expert panel keep updating the evidence for individual cancer sites, according to the Continuous Update Project (CUP), in collaboration with a team of the Imperial College of London (ICL) in charge of systematic reviews and meta-analyses of epidemiological data, independently of the expert panel's judgement of the evidence.

In 2013, within the framework of the third Cancer Plan (2014–2019), the French National Institute of Cancer (INCa) decided to review the most recent scientific literature and update the levels of evidence for the relationships between risk of cancers and nutritional factors. Ten nutritional factors were considered: alcoholic beverages, overweight and obesity, red meat and processed meat, salt and salted foods, beta-carotene supplements, physical activity, fruits and vegetables, dietary fiber, dairy products, breastfeeding. They were selected on the basis of the following criteria: (i) relevant in terms of modifiable exposure for the French population and more generally for developed countries and (ii) level of evidence qualified as convincing or probable in the 2007 WCRF/AICR report (WCRF/AICR, 2007) for at least one cancer site. For these factors, the levels of evidence have been evaluated by WCRF/AICR in the 2007 main report (WCRF/AICR, 2007), and 2010–2014 CUP reports on breast, colorectal, pancreatic, endometrial and ovarian cancers (WCRF/AICR, 2010, 2011, 2012, 2013, 2014a). However, many epidemiological studies have been published since then, requiring a reassessment of the levels of evidence.

## 2. Methods

### 2.1. Evaluation process

From April 2013 to March 2015, INCa gathered an expert group bringing together scientists from the French network on Nutrition And Cancer Research (NACRe network), who have expertise in the field of nutrition and cancer. The modalities for the systematic literature review and evaluation of the evidence have been discussed and adopted by the expert group. Notably, the nutritional factors and types of studies to consider, the search strategies, and the selection criteria for publications have been defined. The bibliographic review was divided among experts according to their respective competences. The method of bibliography analysis, the nature of data to extract from articles and the criteria for evaluating the levels of evidence for the relationships between nutritional factors and risk of cancers have been defined by the expert group. They are summarized in the next section.

### 2.2. Search strategy and selection criteria

Searches were conducted in PubMed database from January 2006 to February 2014, restricted to English language, by combining medical subject headings (MeSH) and/or entry terms. Study types were limited to meta-analyses, pooled analyses and intervention trials. Search strategies for each of the 10 selected nutritional factors are detailed in Appendix A, Part 1. For each nutritional factor, the title and abstract of all references provided by the search were examined by one expert to select potential relevant full-text articles, any uncertainties being resolved by discussion within the expert group. Studies were selected if they met the following inclusion criteria: meta-analysis, pooled analysis or intervention trial, association between one of the 10 selected nutritional factors and cancer risk in adults, report of hazard ratio (HR), relative risk (RR) or odds ratio (OR) and of their 95% confidence interval (CI). Studies on a specific cancer site were selected if their publication date was subsequent to the more recent WCRF/AICR report (2007 main report or CUP report on this cancer site) (WCRF/AICR, 2007, 2010, 2011, 2012, 2013, 2014a); publications from the ICL team were considered as new meta-analyses if they provided updated or additional results as compared to those presented in the “systematic literature review” reports associated to the main WCRF/AICR or CUP reports (WCRF/AICR, 2007, 2010, 2011, 2012, 2013, 2014a). The outcome

should be first primary cancers, excluding preneoplastic lesions or biomarkers, and mortality. Populations at high risk of cancer (e.g., with Lynch syndrome, polycystic ovary syndrome or diabetes) were excluded.

### 2.3. Data extraction

Using a standardized data collection form, each expert extracted the following information from the full-text selected articles: for all studies, first author's last name, publication year, type of study, populations' characteristics (sample size, mean age, gender), cancer site, number of cases, groups' comparison or dose-response relationship and corresponding HRs, RRs or ORs, and 95% CIs, heterogeneity, adjustment factors and bias; for meta-analyses or pooled analyses: inclusion/exclusion criteria, number and type of studies included, mean follow-up for included cohort studies, countries in which the included studies were conducted, exposure, adjustment for covariates and stratification; for meta-analyses: sensitivity analyses; for intervention trials: name of the trial, country in which the trial was conducted, randomization, blindness, intervention (type, duration), follow-up duration and number of subjects lost to follow-up. For each nutritional factor, a second expert independently double checked the extraction of primary data from every study. Discrepancies were solved through discussion. All extracted data are available in French language on the INCa website (INCa, 2015a).

### 2.4. Updating the evidence

The summary of extracted data and the updated level of evidence proposed by each expert were reviewed independently by a second expert and discussed by the overall expert group until a consensus was found. Finally, the levels of evidence were qualified as convincing, probable, suggestive or not conclusive, according to the criteria that were defined (Table 1).

## 3. Results

Fig. 1 shows the flow chart of the study selection process. From the 1959 abstracts provided by searches in Medline database, 262 potentially full text articles were identified and examined. Finally, 133 articles meeting the inclusion criteria and reporting usable information were analyzed by the expert group. They include 108 meta-analyses, 20 pooled analyses, 4 intervention trials and one post-intervention study which relate to 26 cancer sites overall. Generally, in the studies included in meta-analyses or pooled analyses, age, gender and the main known confounding factors for the studied cancer site have been controlled for. In Tables 1–10 of Appendix A, Part 2, the main results from these studies and the updated levels of evidence are reported for the associations between the ten nutritional factors and cancer sites. In the following sections the definition and indicators of each nutritional factor and the new studies identified are presented. Then, the results and conclusions of the evaluation process by the expert group are summarized: for cancers sites for which a convincing or probable level of evidence is established, followed by those for which it is suggestive or not conclusive, and finally plausible mechanisms when available.

### 3.1. Alcoholic beverages

Alcoholic beverages include wines, beers, spirits, ciders and various other alcoholic drinks that may be locally important. They contain ethanol which results from the process of fermentation. In epidemiological studies, the exposure to alcoholic beverages is examined by different measures: drinking or not, number of drinks/glasses or units of 10 g alcohol per day or per week.

The associations between alcohol drinking and the risk of various cancers have been evaluated by WCRF/AICR in 2007 and 2010–2014 CUP reports (WCRF/AICR, 2007, 2010, 2011, 2012, 2013, 2014a). Since the publication of these reports, 25 meta-analyses (Islami et al., 2010; Turati et al., 2010; Tramacere et al., 2010; Turati et al., 2013a; Petti et al., 2013; Islami et al., 2011; Tramacere et al., 2012a; Seitz et al., 2012; Song et al., 2012; Rota et al., 2012; Mao et al., 2010; Pelucchi et al., 2012; Tramacere et al., 2012b,c,d; Li et al., 2011a; Zhuo et al., 2012; Fang et al., 2011; Yang et al., 2010; Zhang et al., 2010; Liu et al., 2011a; Liu et al., 2012a; Chao, 2007; Boccia et al., 2009; Guo et al., 2012) and 12 pooled analyses were identified (Hashibe et al., 2007; Hashibe et al., 2009; Purdue et al., 2009; Freedman et al., 2011; Lubin et al., 2012; Lucenteforte et al., 2012; Lee et al., 2007a; Kelemen et al., 2013; Boffetta et al., 2012; Kitahara et al., 2012; Langevin et al., 2009; Shimazu et al., 2012) (Appendix A, Part 2: Table 1). The association between alcohol drinking and the incidence of 19 different cancer sites was investigated. Among the 37 new studies identified, 25 provided results on total alcohol drinking and cancer risk (Islami et al., 2010; Turati et al., 2010; Tramacere et al., 2010; Turati et al., 2013a; Petti et al., 2013; Islami et al., 2011; Tramacere et al., 2012a; Seitz et al., 2012; Song et al., 2012; Rota et al., 2012; Mao et al., 2010; Pelucchi et al., 2012; Tramacere et al., 2012b,c,d; Hashibe et al., 2007; Hashibe et al., 2009; Purdue et al., 2009; Freedman et al., 2011; Lubin et al., 2012; Lucenteforte et al., 2012; Lee et al., 2007a; Kelemen et al., 2013; Boffetta et al., 2012; Kitahara et al., 2012) and 12 focused on certain genetic polymorphisms (Zhuo et al., 2012; Fang et al., 2011; Yang et al., 2010; Zhang et al., 2010; Liu et al., 2011a; Liu et al., 2012a; Boccia et al., 2009; Guo et al., 2012; Langevin et al., 2009), Asian populations (Li et al., 2011a; Shimazu et al., 2012) or specific alcoholic beverages (Chao, 2007).

Overall, the associations between alcohol drinking and increased risk of several cancers, previously evaluated and considered as “convincing” in the WCRF/AICR previous reports, are strengthened by the results of recent publications. For the cancers of the mouth, pharynx and larynx combined, the results of 6 recent meta-analyses (Islami et al., 2010; Turati et al., 2010; Tramacere et al., 2010; Turati et al., 2013a; Li et al., 2011a; Zhuo et al., 2012) and 3 pooled analyses (Hashibe et al., 2007; Hashibe et al., 2009; Purdue et al., 2009) of observational studies confirmed the association. The increased risk of oesophageal cancer was observed in 2 recent pooled analyses of observational studies (Freedman et al., 2011; Lubin et al., 2012) and 2 meta-analyses, one including observational studies (Li et al., 2011a) and one exclusively cohorts (Islami et al., 2010). For breast cancer, the WCRF/AICR conclusion (WCRF/AICR, 2010) was reinforced by a new meta-analysis of cohort studies (Seitz et al., 2012). Concerning colorectal cancer associations considered as “convincing” in men and “probable” in women, the level of evidence was not changed since the only new meta-analysis including exclusively 10 case-control studies conducted on Chinese men and women combined showed no significant results (Li et al., 2011a). The association with liver cancer, considered as “probable” in the 2007 WCRF/AICR report (WCRF/AICR, 2007), was also confirmed by 2 meta-analyses (Li et al., 2011a; Liu et al., 2011a) and one pooled analysis (Shimazu et al., 2012) of observational studies.

The increased risk of pancreatic cancer associated with consumption of 3 drinks per day or more is confirmed by the results of a recent pooled analysis of 10 case-control studies (Lucenteforte et al., 2012) though a non-significant increased risk was observed in the meta-analysis conducted on Chinese populations (Li et al., 2011a). Thus, the corresponding level of evidence previously judged as “suggestive” is unchanged.

The new results available for other cancer sites—kidney (Song et al., 2012; Lee et al., 2007a), lung (Li et al., 2011a; Chao, 2007), prostate (Rota et al., 2012; Li et al., 2011a), bladder (Mao et al., 2010; Pelucchi et al., 2012; Li et al., 2011a), stomach (Tramacere et al.,

**Table 1**  
Criteria used by the INCa expert group to confirm or update the evidence.

Grade	Criteria required	Lacks or limits
Convincing	Meta-analysis or pooled analysis of prospective studies with: –Statistically significant association –Dose-response analysis –High number of studies or cases –No high and unexplained heterogeneity* –Robustness of results in sensitivity analyses –Intervention trial if possible –Plausible mechanisms	
Probable	Meta-analysis or pooled analysis with: –Statistically significant association –High number of studies or cases –No high and unexplained heterogeneity* –Plausible mechanisms	–Neither meta-analysis nor pooled analysis of prospective studies OR –No dose-response analysis
Suggestive	Meta-analysis or pooled analysis with: –Statistically significant association –Plausible mechanisms	–Neither meta-analysis nor pooled analysis of prospective studies AND no dose-response OR –High unexplained or unspecified heterogeneity
Not conclusive	–Neither meta-analysis nor pooled analysis OR –No statistically significant association from meta-analysis or pooled analysis OR –Inconsistency between meta-analyses or pooled analyses OR –No plausible mechanisms	
Improbable	Meta-analysis or pooled analysis of prospective studies with: –No statistically significant association –Dose-response that is not statistically significant –High number of studies or cases –No high and unexplained heterogeneity* –Robustness of results in sensitivity analyses –Intervention trial if possible –No plausible mechanisms	

\* High heterogeneity:  $I^2 \geq 75\%$  (WCRF/AICR, 2007).

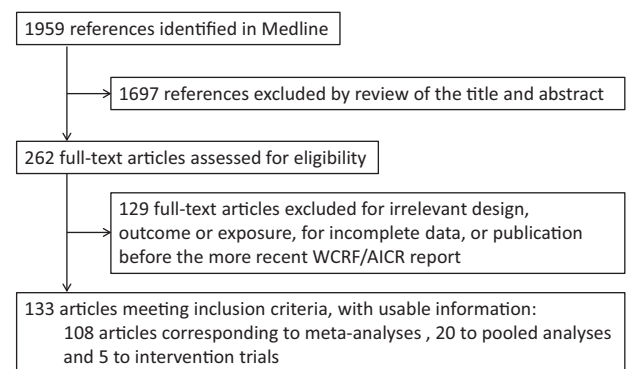
2012b; Li et al., 2011a) and ovary (Kelemen et al., 2013)—confirm the “not conclusive” level of evidence of the WCRF/AICR reports (WCRF/AICR, 2007, 2014a). Recent publications concerning cancer sites which were not previously evaluated by WCRF/AICR—small intestine (Boffetta et al., 2012), Hodgkin and non-Hodgkin lymphoma (Tramacere et al., 2012c, 2012d), Ampulla of Vater (Li et al., 2011a) and thyroid (Kitahara et al., 2012)—do not suggest any association between the risk of these cancers and alcohol drinking. In the absence of new data, the “not conclusive” level of evidence for endometrial cancer remains unchanged.

The mechanisms of alcoholic beverages-mediated carcinogenesis mainly involve the pro-carcinogenic effects of acetaldehyde, the main metabolite of ethanol. Several other molecular and physiopathological effects have been identified: redox changes, formation of radicals, liver injury, elevation of sex hormones levels, folate deficiency, interaction with tobacco smoking etc (IARC, 2012).

### 3.2. Overweight and obesity

Body fatness which includes overweight and obesity is generally estimated by the body mass index (IMC) calculated by the ratio weight (kg)/height<sup>2</sup> (m<sup>2</sup>). Abdominal fatness, estimated by the waist measurement or the waist-to-hips ratio, is another indicator used to characterize corpulence.

The associations between overweight/obesity and the risk of various cancers have been evaluated by WCRF/AICR in 2007 and 2010–2014 CUP reports (WCRF/AICR, 2007, 2010, 2011, 2012, 2013, 2014a). Since the publication of the 2007 report, 24 new meta-analyses (Turati et al., 2013b; Aune et al., 2012a; Ma et al., 2013; Cheraghi et al., 2012; Amadou et al., 2013; Ildaphonse et al., 2009;



**Fig. 1.** Flow chart of study selection.

Mathew et al., 2009; Chen et al., 2012a; Rui et al., 2012; Wang et al., 2012; Discacciati et al., 2012; Willett et al., 2008; Larsson and Wolk, 2011, 2008; Castillo et al., 2012; Wallin and Larsson, 2011; Yang et al., 2009; Chen et al., 2013; Zhao et al., 2012; Lerro et al., 2010; Olsen et al., 2008; Sergentanis et al., 2013; Yang et al., 2013a; Gaudet et al., 2010) and one pooled analysis were identified (Hoyo et al., 2012) (Appendix A, Part 2: Table 2). They cover a total of 17 different cancer sites.

The association between body fatness and the increased risk of oesophagus adenocarcinoma, previously judged as “convincing” (WCRF/AICR, 2007), is confirmed by recent results of both a pooled analysis (Hoyo et al., 2012) and a meta-analysis (Turati et al., 2013b) of observational studies. Since the WCRF/AICR 2012 report (WCRF/AICR, 2012), one recent meta-analysis of the ICL team (Aune et al., 2012a) confirms the increase of pancreas

cancer risk associated with both body and abdominal fatness, and the corresponding level of evidence judged as “convincing”. Consistent with previous evaluations (WCRF/AICR, 2011), the associations between body/abdominal fatness and colorectal/colon/rectum cancer with a level of evidence judged as “convincing”, are confirmed by one new meta-analysis of prospective studies (Ma et al., 2013). For breast cancer, 2007 and 2010 WCRF/AICR reports (WCRF/AICR, 2007, 2010) emphasized the need for stratification according to the menopausal status. The increase of postmenopausal breast cancer risk with body fatness which was judged as “convincing”, is confirmed by one new meta-analysis of observational studies (Cheraghi et al., 2012). In addition, the decrease of premenopausal breast cancer risk with body fatness which was judged as “probable” considering the speculative mechanisms and the divergent data, is confirmed by two new meta-analyses of observational (Cheraghi et al., 2012) and prospective (Amadou et al., 2013) studies. The “convincing” level of evidence established in the 2013 WCRF/AICR report (WCRF/AICR, 2013) for the increase of endometrial cancer risk associated with body fatness, weight gain in the adulthood and abdominal fatness, is unchanged, since no new study was identified. For kidney cancer, the level of evidence of the increased risk associated with body fatness which was judged as “convincing” (WCRF/AICR, 2007) is confirmed by two meta-analyses of observational studies (Ildaphonse et al., 2009; Mathew et al., 2009).

In the absence of new data, the level of evidence judged as “probable” for an increased risk of gallbladder and ovary cancer associated with body fatness (WCRF/AICR, 2007) remains unchanged. The evidence of the association between body fatness and the risk of liver cancer judged as “suggestive” (WCRF/AICR, 2007), in the light of three new meta-analyses of prospective studies (Chen et al., 2012a; Rui et al., 2012; Wang et al., 2012), is thereafter considered as “probable”. For prostate cancer, the level of evidence of the association between body fatness and the increased risk was judged as “not conclusive” considering the heterogeneity of data (WCRF/AICR, 2007). In the light of one new meta-analysis of 13 prospective studies (Discacciati et al., 2012), the link between body/abdominal fatness and advanced prostate cancer risk is strengthened and the level of evidence is defined as “probable”. For the localised prostate cancer, the “not conclusive” level of evidence remains unchanged in the absence of plausible mechanisms. Concerning lymphoid and haemopoietic system which were not previously evaluated by WCRF/AICR, recent meta-analyses on non-Hodgkin (Willett et al., 2008; Larsson and Wolk, 2011) and Hodgkin (Larsson and Wolk, 2011) lymphoma, leukemia (Larsson and Wolk, 2008; Castillo et al., 2012), and multiple myeloma (Wallin and Larsson, 2011) suggest an increased risk associated with body fatness (IMC) with a level of evidence judged as “probable”.

For stomach, since the WCRF/AICR 2007 report (WCRF/AICR, 2007), three new meta-analyses (Turati et al., 2013b; Yang et al., 2009; Chen et al., 2013) are in favor of an increased risk of proximal (cardia) gastric cancer in relation with body fatness. So the level of evidence is thereafter defined as “suggestive”. For distal (not cardia) gastric cancer the “not conclusive” level of evidence remains unchanged. In the light of results of one new meta-analysis of 7 prospective studies (Zhao et al., 2012), the level of evidence of the association between body fatness and the increased risk of thyroid cancer is judged as “suggestive”. The new results available for testis (Lerro et al., 2010) and skin (melanoma) (Olsen et al., 2008; Sergentanis et al., 2013) cancers do not suggest any association with body fatness. The levels of evidence of a decreased risk of lung (Yang et al., 2013a) and mouth, pharynx, larynx cancers (Gaudet et al., 2010) associated with body fatness, are judged as “not conclusive”, considering the lack of mechanistic justification and the existence of confounding factors not taken into account.

Some mechanisms seem common to all cancer sites: the excess of intra-abdominal adipose tissue favors tissue insulin resistance, chronic hyperinsulinemia, increased production and activity of the mitogenic factor insulin growth factor 1 (IGF-1), estrogen production via the aromatase activity, chronic low-grade inflammation resulting from the production of pro-inflammatory factors i.e., tumor-necrosis factor- $\alpha$  (TNF $\alpha$ ), interleukin (IL-6), and adipokins, and oxidative stress due to lipid peroxidation production (Calle and Kaaks, 2004). Other mechanisms are specific to certain cancer sites: for oesophagus, gastro-oesophageal reflux favoring lesions of the oesophageal epithelium and cardia; for postmenopausal breast and endometrial cancer, increased proliferation-effect of estrogens via their estrogen receptor expression; for kidney, development of a high blood pressure leading to an increase of the glomerular filtration and thus the risk of renal damage, and alterations of the cholesterol metabolism; for gallbladder, increased formation of gallstones, probably by an over-saturation of the bile in cholesterol; for liver: development of a steatosis with a local inflammation through an oxidative stress and a greater risk of fibrosis and carcinogenesis; for prostate, a reduced production of testosterone, an important factor in the differentiation of the prostatic epithelium; for haemopoietic system, local inflammation of the bone marrow microenvironment activating T cells and macrophages (Askmyr et al., 2011; Meijer et al., 2011).

### 3.3. Red and processed meat

Red meat comprises all flesh from domesticated animals that have more red than white muscle fibers. In epidemiological studies, it refers to beef, pork, lamb and goat. Processed meat refers to meats preserved by smoking, curing or salting or addition of chemical preservatives.

The associations between the intakes of red and processed meat and the risk of various cancers have been evaluated by WCRF/AICR in 2007 and 2010–2014 CUP reports (WCRF/AICR, 2007, 2010, 2011, 2012, 2013, 2014a). Since the publication of these reports, 15 new meta-analyses (Chan et al., 2011; Alexander et al., 2011; Larsson and Wolk, 2012; Paluszkiwicz et al., 2012; D'Elia et al., 2012; Yang et al., 2012; Choi et al., 2013; Huang et al., 2013; Salehi et al., 2013; Wang and Jiang, 2012; Taylor et al., 2009; Alexander et al., 2010a; Alexander and Cushing, 2009; Faramawi et al., 2007; Alexander et al., 2010b) and one pooled analysis (Lee et al., 2008) were identified (Appendix A, Part 2: Table 3). They cover a total of 9 different cancer sites. Twelve studies concern both red and processed meat (Chan et al., 2011; Alexander et al., 2011; Larsson and Wolk, 2012; Yang et al., 2012; Choi et al., 2013; Huang et al., 2013; Salehi et al., 2013; Wang and Jiang, 2012; Alexander et al., 2010a; Faramawi et al., 2007; Alexander et al., 2010b; Lee et al., 2008), three focus on red meat (Alexander et al., 2011; Paluszkiwicz et al., 2012; Taylor et al., 2009) and one on processed meat (D'Elia et al., 2012).

The “convincing” level of evidence of the association between red and processed meat and the increase of colorectal cancer risk established in the 2011 WCRF/AICR report (WCRF/AICR, 2011), is confirmed by results of recent meta-analyses of cohort studies (Chan et al., 2011; Alexander et al., 2011).

Based on results of two recent meta-analyses (Larsson and Wolk, 2012; Paluszkiwicz et al., 2012), the level of evidence previously judged as “suggestive” (WCRF/AICR, 2007) for increased risk of pancreas cancer associated with red and processed meat remains unchanged. The level of evidence also previously judged as “suggestive” for the increased risk of stomach cancer with processed meat and for the increased risk of lung cancer with red meat is confirmed by the recent results of respectively one meta-analysis including seven cohorts (D'Elia et al., 2012) and one meta-analysis of 18 observational studies (Yang et al., 2012).

In the light of results of three new meta-analyses (Choi et al., 2013; Huang et al., 2013; Salehi et al., 2013), the level of evidence of the association between the risk of oesophagus cancer and red and processed meat previously judged as “suggestive” (WCRF/AICR, 2007) is thereafter considered as “not conclusive”. The association between the increase of lung and prostate cancers with processed meat previously judged as “suggestive” (WCRF/AICR, 2007) is not confirmed respectively by a new meta-analysis of 10 observational studies (Yang et al., 2012) and by a new meta-analysis of 15 prospective studies (Alexander et al., 2010b). Therefore, the level of evidence is judged as “not conclusive”.

Recent publications investigated the associations between red and processed meat and bladder, breast and kidney cancers and between red meat and prostate cancer, which were not previously evaluated by WCRF/AICR. The new results available for bladder (Wang and Jiang, 2012) and breast (Taylor et al., 2009; Alexander et al., 2010a) suggest an association between the increased risk of these cancers and the consumption of red meat, and the level of evidence is judged as “suggestive”. Considering the heterogeneity of results between meta-analyses or the limited number of studies, the level of evidence is considered “not conclusive” for kidney cancer and red and processed meat (Alexander and Cushing, 2009; Faramawi et al., 2007; Lee et al., 2008), and for bladder (Wang and Jiang, 2012) and breast (Alexander et al., 2010a) cancers and processed meat, and for prostate cancer and red meat (Alexander et al., 2010b). In addition, the evidence for endometrial (WCRF/AICR, 2013) and ovarian (WCRF/AICR, 2014a) cancers for which no new study was identified, remains “not conclusive”.

The mechanisms explaining the association of red and processed meat consumption with an increased risk of cancer in several sites are not clearly defined. The effect on cancers may be linked to mutagenic compounds such as neofomed products generated in red meats and processed meat: heterocyclic amines (HCA), polycyclic aromatic hydrocarbons (PAHs) and N-nitroso compounds (NOC) (Abid et al., 2014). For colon cancer, in addition to those assumptions, excess of heme iron has been proposed to play a central role. For processed meats, nitrates and nitrites used during process may represent an important part of the carcinogenic effect via facilitation of NOC formation (Bastide et al., 2011).

#### 3.4. Salt and salted foods

According to epidemiological studies, the general term “salt” comprises total salt consumption, including salt added during cooking and at table but also salt from processed foods, including salty and salted foods.

Since the evaluation of the association between the intake of salt and the risk of stomach cancer by WCRF/AICR in 2007 (WCRF/AICR, 2007), only one new meta-analysis of 7 cohort studies was identified (D’Elia et al., 2012) (Appendix A, Part 2: Table 4). The “probable” level of evidence of the increased risk of stomach cancer proposed is thus confirmed.

Several mechanisms involved in the tumor promoting effect of salt on stomach cancer risk have been proposed. High dietary salt intake may (i) facilitate the colonization of *H. pylori*, a risk factor for stomach cancer, (ii) change the mucous viscosity and thus aggravate exposure to N-nitroso compounds, known as carcinogens, and (iii) cause inflammatory responses of the gastric epithelium, with an increased epithelial cell proliferation and so an increased risk of endogenous mutations (Wang and Jiang, 2012).

#### 3.5. Beta-carotene supplements

Beta-carotene is a pigment from the carotenoid family and a precursor to vitamin A. It enters in the composition of many food supplements, as defined by the European Directive 2002/46/CE.

The associations between the intake of beta-carotene supplements and the risk of various cancers have been evaluated by WCRF/AICR in 2007 and 2010–2014 CUP reports (WCRF/AICR, 2007, 2010, 2011, 2012, 2014a). Since the publication of these reports, 17 new studies were identified: 11 meta-analyses (Aune et al., 2012e; Jeon et al., 2011; Papaioannou et al., 2011; Stratton and Godwin, 2011; Cooper et al., 2010; Druesne-Pecollo et al., 2010; Jiang et al., 2010; Bardia et al., 2008; Gallicchio et al., 2008; Tanvetyanon and Bepler, 2008; Bjelakovic et al., 2008), one pooled analysis (Li et al., 2012), 4 intervention trials (Lin et al., 2009; Neuhouser et al., 2009; Herberg et al., 2007; Wright et al., 2007) and one post-intervention study (Ezzedine et al., 2010) (Appendix A, Part 2, Table 5). They cover a total of 15 different cancer sites.

The evidence of the association between the intake of beta-carotene supplements (high doses:  $\geq 20$  mg/d) and increased lung cancer risk in smokers and subjects exposed to asbestos was previously evaluated in the 2007 WCRF/AICR report as “convincing” (WCRF/AICR, 2007). This direct association is confirmed by three recent meta-analyses of intervention trials, especially in smokers and subjects exposed to asbestos (Druesne-Pecollo et al., 2010; Bardia et al., 2008; Tanvetyanon and Bepler, 2008). Two other meta-analyses of intervention trials in the general population (Jeon et al., 2011; Gallicchio et al., 2008) observed no association. No level of evidence was provided in the 2007 WCRF/AICR report (WCRF/AICR, 2007) regarding the association between the intake of beta-carotene supplements and stomach cancer risk. Based on a meta-analysis of 7 intervention trials observing an increased risk in all subjects for doses  $\geq 20$  mg/d and in smokers and subjects exposed to asbestos (Druesne-Pecollo et al., 2010), the increased risk at high doses ( $\geq 20$  mg/d), especially for smokers and subjects exposed to asbestos, is thus considered as “probable”.

The new results (meta-analyses and intervention trials) available for other cancer sites (detailed in Appendix A, Part 2: Table 5)—breast (Aune et al., 2012e; Druesne-Pecollo et al., 2010), prostate (Stratton and Godwin, 2011; Druesne-Pecollo et al., 2010; Jiang et al., 2010; Neuhouser et al., 2009), skin (melanoma and non-melanoma) (Druesne-Pecollo et al., 2010; Herberg et al., 2007; Ezzedine et al., 2010), pancreas (Druesne-Pecollo et al., 2010; Bjelakovic et al., 2008), colon and rectum (Papaioannou et al., 2011; Cooper et al., 2010; Druesne-Pecollo et al., 2010; Bjelakovic et al., 2008), bladder (Bardia et al., 2008), oesophagus (Bjelakovic et al., 2008; Wright et al., 2007), ovary (Lin et al., 2009), mouth/pharynx (Wright et al., 2007), larynx (Wright et al., 2007), uterus (Lin et al., 2009), non-Hodgkin lymphoma (Lin et al., 2009) and head and neck (Li et al., 2012)—were not sufficient to draw conclusions regarding their association with beta-carotene supplement use, thus, the evidence remains “not conclusive”. Similarly, the evidence for kidney cancer, for which no new study was identified, remains “not conclusive”.

Some mechanisms may be suggested to explain the adverse effect of beta-carotene supplementation on cancer risk, especially in interaction with cigarette smoking. Direct contact of cigarette smoke with tissues of some organs such as lung or stomach may explain why these two cancer sites may be more susceptible to beta-carotene effect. For instance, high doses of beta-carotene may exert a pro-oxidative effect: increased activation of carcinogenic molecules released during smoking (activation of phase I enzymes of the xenobiotic metabolism, such as cytochromes P450) resulting in the release of free radicals (Paolini et al., 2003) which, when combined to the ones produced by cigarette smoking, may lead to their cleavage into unstable compounds that could intervene in the oxidative process. Next, experimental models also suggest that low doses of beta-carotene may be protective against the alteration of the tumor suppressive gene P53 caused by cigarette smoking, whereas high doses may promote these alterations. Besides, when combined to cigarette smoke condensate, beta-carotene may

contribute to reduce the expression of a response protein to cellular stress (heme oxygenase 1), thereby decreasing the production of anti-proliferation agents (Brambilla et al., 2008).

### 3.6. Physical activity

Physical activity is defined as any bodily movement produced by skeletal muscle contraction resulting in increased energy expenditure above the resting energy expenditure. Physical activity in the broad sense includes all movements performed in daily life and cannot be reduced only to sport, whether recreational or competitive (WHO, 2010). It is generally expressed by its intensity in metabolic equivalent of task (MET), given that one MET refers by convention to the energy expenditure of an individual at rest, sitting (estimated at about one kcal per kg of body weight per hour). The intensity of a person's physical activity expressed in MET corresponds to the ratio of their working metabolic rate (i.e., rate of energy consumption) to their resting metabolic rate. Thus, different intensities of physical activity are defined (Norton et al., 2010): very light intensity (or sedentary): 1–1.5 METs; light intensity: 1.6 to less than 3 METs; moderate intensity: 3 to less than 6 METs; vigorous intensity: 6 METs or more. In epidemiological studies, physical activity is computed by combining intensity, duration and frequency of different types of physical activity. Corresponding total energy expenditure is frequently expressed in MET.h/week. According to their physical activity profile, subjects are classified into three levels of physical activity, “low”, “moderate” or “high”. Physical activity is conventionally divided into four types: occupational, transport, recreational and household settings. Studies present “total physical activity, calculated overall as the sum of the four types, or any of the four types that are presented as all-type physical activity. Thus, a major barrier to conducting meta-analyses is the disparity between physical activity measures.

The associations between physical activity and the risk of various cancers have been evaluated by WCRF/AICR in 2007 and in 2010–2014 CUP reports (WCRF/AICR, 2007, 2010, 2011, 2012, 2013, 2014a). Since their publication, seven new meta-analyses (Boyle et al., 2012; Wu et al., 2013a; Sun et al., 2012; Liu et al., 2011b; Behrens and Leitzmann, 2013; Schmid et al., 2013; Vermaete et al., 2013) and one new pooled analysis (Nicolotti et al., 2011) were identified that cover a total of eight different cancer sites: head and neck, colon, lymphoma, lung, prostate, kidney, breast and thyroid (Appendix A, Part 2: Table 6).

The association between physical activity and the decrease of colon cancer risk, previously evaluated in the CUP WCRF/AICR 2011 report with a level of evidence judged as ‘convincing’ (WCRF/AICR, 2011), is confirmed by results of a recent meta-analysis of prospective studies evaluating all-type physical activity (Boyle et al., 2012); the protective effect was similar for proximal and distal colon cancer, and was stronger for men than for women. The association with the risk of postmenopausal breast cancer, previously evaluated in the CUP WCRF/AICR 2010 report with a level of evidence judged as “probable” (WCRF/AICR, 2010), is confirmed by results of a recent meta-analysis of prospective studies evaluating all-type physical activity (Wu et al., 2013a). The decreased risk of premenopausal breast cancer associated with physical activity, judged as “suggested” by the WCRF/AICR 2007 report (WCRF/AICR, 2007), is confirmed by a recent meta-analysis of prospective studies (Wu et al., 2013a) and the evidence is now considered as “probable”. Since the CUP WCRF/AICR 2013 report where the decrease in endometrial cancer risk associated with physical activity was judged as “probable” (WCRF/AICR, 2013), no new study was identified. The decreased risk of lung cancer associated with physical activity, judged as “suggested” by the WCRF/AICR 2007 report, was confirmed by a recent meta-analysis of prospective studies (Sun et al., 2012). The risk reduction was even stronger for the highest

than for moderate physical activity level, compared to the lowest level, with a level of evidence now judged as “probable”.

New results available since the publication of WCRF/AICR reports for the risk of cancers of the prostate (Liu et al., 2011b), kidney (Behrens and Leitzmann, 2013), head and neck (Nicolotti et al., 2011) and thyroid (Schmid et al., 2013) and the risk of lymphoma (Vermaete et al., 2013) suggest a level of evidence qualified as “not conclusive”. No recent result was available to reassess the level of evidence judged as “not conclusive” in the WCRF/AICR reports for the association between physical activity and the risk of rectal, ovarian and pancreatic cancers (WCRF/AICR, 2007, 2013, 2014a).

The main mechanisms that could explain the beneficial effect of physical activity on cancer risk are related to its direct effects on circulating levels of various hormones and growth factors, including decreased plasma levels of estrogens, insulin and IGF-1 that increase with overweight and obesity and promote cell proliferation (McTiernan, 2008). Physical activity may also lower cancer risk by improving sensitivity to insulin, by stimulating immunity and by decreasing adipokine levels, oxidative stress and inflammatory markers (Wu et al., 2013a). Physical activity also indirectly contributes to cancer risk reduction by decreasing the risk of overweight or obesity, limiting fat and promoting lean body mass. Physical activity may specifically lower the risk of colon cancer through the acceleration of gut transit, reducing the exposure time of the digestive mucosa to foodborne carcinogens. It may also lower lung cancer risk by reducing the concentrations and interactions of carcinogens with lung tissue through improved lung function (Tardon et al., 2005; Buffart et al., 2014).

### 3.7. Fruits and vegetables

Fruits and vegetables comprise fresh, frozen, canned, raw and cooked fruits and vegetables, excluding nuts, seeds, dried fruits, potatoes and pulses (WCRF/AICR, 2007). According to epidemiological studies, the general term “vegetables” may cover different categories: total vegetables (non-starchy vegetables and starchy vegetables), non-starchy vegetables, fresh vegetables (as opposed to preserved vegetables) and raw vegetables (excluding cooked vegetables).

The associations between the intakes of fruits and (non-starchy) vegetables and the risk of various cancers have been evaluated by WCRF/AICR in 2007 and 2010–2014 CUP reports (WCRF/AICR, 2007, 2010, 2011, 2012, 2013, 2014a). Since the publication of these reports, 17 studies were identified: 14 meta-analyses (Soerjomataram et al., 2010; Liu et al., 2013a; Kim et al., 2010; Zhou et al., 2011; Aune et al., 2012b; Wu et al., 2013c, 2013b; Liu and Lv, 2013; Liu et al., 2013c; Chen et al., 2012b; Liu et al., 2012b; Liu et al., 2013b; Wu et al., 2013d; Yang et al., 2013b) and 3 pooled analyses (Jung et al., 2013; Koushik et al., 2012; Lee et al., 2009) (Appendix A, Part 2: Table 7). They cover a total of 10 different cancer sites. Seven meta-analyses focus on fruits and vegetables alone or in combination (Soerjomataram et al., 2010; Liu et al., 2013a; Kim et al., 2010; Aune et al., 2012b; Jung et al., 2013; Koushik et al., 2012; Lee et al., 2009) and others study more specifically certain subgroups of vegetables: cruciferous vegetables (Wu et al., 2013c,b; Liu and Lv, 2013; Liu et al., 2013c, 2012b, 2013b; Wu et al., 2013d), tomatoes (Chen et al., 2012b; Yang et al., 2013b), and allium vegetables (Zhou et al., 2011).

The associations between fruits and (non-starchy) vegetables and the decrease of the risk of cancers of the mouth, pharynx and larynx combined, previously evaluated in the 2007 WCRF/AICR report (WCRF/AICR, 2007), are confirmed by results of a recent meta-analysis of observational studies (Soerjomataram et al., 2010). Consistent with previous evaluations (WCRF/AICR, 2007), the association between fruits and vegetables and oesophagus cancer is confirmed by two new meta-analyses of observational studies



(Soerjomataram et al., 2010; Liu et al., 2013a). The association with stomach cancer is confirmed for fruits by one meta-analysis (Soerjomataram et al., 2010), for vegetables by two meta-analyses (Soerjomataram et al., 2010; Kim et al., 2010) and for allium vegetables by one meta-analysis (Zhou et al., 2011). The decrease of lung cancer associated with fruits is confirmed by one meta-analysis (Soerjomataram et al., 2010). Since the 2011 WCRF/AICR report (WCRF/AICR, 2011), where the decrease of colorectal cancer risk associated with garlic was judged as “probable”, no new study was identified. For breast cancer, whereas a recent meta-analysis showed no significant association between total breast cancer risk and vegetables (Aune et al., 2012b), consistent with the 2010 WCRF/AICR report evaluation (WCRF/AICR, 2010), a recent pooled analysis including 20 cohort studies showed a reduction of the risk of estrogen receptor-negative (ER-) breast cancer associated with non-starchy vegetables (Jung et al., 2013). Overall, with a level of evidence judged as “probable”, these results confirm the decrease of risks of cancers of the mouth, pharynx, larynx, oesophagus, and stomach associated with the consumption of fruits and vegetables, the decrease in lung cancer risk associated with the consumption of fruits and the decrease in colorectal cancer risk associated with the consumption of garlic; they indicate a decreased risk of (ER-) breast cancer associated with the consumption of vegetables.

With a level of evidence judged as “suggestive”, other new studies confirm a decrease in lung cancer risk associated with consumption of vegetables (Soerjomataram et al., 2010); they indicate a decreased risk of lung (Wu et al., 2013c), colorectal (Wu et al., 2013b) and breast (Liu and Lv, 2013) cancer associated with the consumption of cruciferous vegetables. In the absence of new data, the “suggestive” level of evidence for decreased risk of colorectal and nasopharynx cancer associated with the consumption of fruits and vegetables remains unchanged.

The new results available for other cancer sites—pancreas (Koushik et al., 2012), kidney (Liu et al., 2013c; Lee et al., 2009), prostate (Chen et al., 2012b; Liu et al., 2012b), bladder (Liu et al., 2013b) and ER+ breast for non-starchy vegetables (Aune et al., 2012b; Jung et al., 2013)—do not suggest any association between the risk of these cancers and the consumption of fruits and vegetables. In addition, the evidence for cervical, endometrial, ovarian, and total breast cancers, for which no new studies were identified, remains “not conclusive”.

Fruits and vegetables contain a great diversity of components which can exert protective properties against various cancers. Their microconstituents like polyphenols, carotenoids and sulfur compounds have antioxidant and antiproliferative activities, and they modulate xenobiotic and hormonal metabolism, and immunity (Liu, 2013a; Liu, 2013b). Fruits and vegetables are an important source of micronutrients, notably folates (vitamin B9) which play an important role in DNA synthesis and methylation and in the expression of genes involved in carcinogenesis (Cridler et al., 2012). They also contain fibers that may exert various protective effects (see next paragraph). More specifically, concerning ER- breast cancer, oestrogen-independent mechanisms have been proposed: reduction of proliferative factors like IGF-1 and cyclin E, and of nuclear transcription factor NF-kappaB involved in the immune response (Jung et al., 2013).

### 3.8. Dietary fiber

Dietary fiber refers to carbohydrate polymers (degree of polymerization: DP  $\geq$  3) of plant origin that may or may not be associated in the plant to lignin or other non-carbohydrate compounds (polyphenols, waxes, saponins, cutin, phytates, phytosterols...), and to modified (physically, enzymatically or chemically) or synthetic carbohydrate polymers.

The associations between dietary fiber intake and the risk of various cancers have been evaluated by WCRF/AICR in 2007 and 2010–2014 CUP reports (WCRF/AICR, 2007, 2010, 2011, 2012, 2013, 2014a). Since the publication of these reports, 3 new meta-analyses were identified (Aune et al., 2012c; Coleman et al., 2013; Zhang et al., 2013) (Appendix A, Part 2: Table 8). They cover 3 different cancer sites. Two meta-analyses (Aune et al., 2012c; Zhang et al., 2013) considered different types (soluble and insoluble) and sources (fruits, vegetables and cereals) of dietary fiber.

Since the 2011 WCRF/AICR report (WCRF/AICR, 2011), where the decrease of colorectal cancer risk associated with dietary fiber intake was judged as “convincing”, no new study was identified. The association between breast cancer risk and dietary fiber intake previously judged as “not conclusive” in the 2010 WCRF/AICR report (WCRF/AICR, 2010) was strengthened by one new meta-analysis of 16 prospective studies (Aune et al., 2012c) showing a decreased risk, especially observed for soluble fiber intake, and for total dietary fiber intake  $\geq$  25 g/d. These new results were considered as sufficient to increase the level of evidence to a “probable” decreased risk of breast cancer associated with dietary fiber intake.

One new meta-analysis (8 case-control studies) confirms a decrease in oesophagus cancer risk associated with dietary fiber intake (Coleman et al., 2013), with a level of evidence judged as “suggestive”. A new meta-analysis (2 cohorts and 19 case-control studies) (Zhang et al., 2013) suggested a decreased stomach cancer risk associated with dietary fiber intake (insoluble and soluble and from fruits, vegetables or cereals). However, since the results from the two included prospective studies were non-significant, the level of evidence remains “not conclusive”. In addition, the evidence for endometrium, ovary, pancreas, mouth, larynx, pharynx, lung and prostate cancers, for which no new study was identified, remains “not conclusive”.

Dietary fibers are not digested or absorbed in the small intestine. They show at least one of the following physiological properties: increased stool bulk, increased fermentation by colonic microbiota, reduced fasting blood cholesterol, reduced post-prandial blood glucose and/or insulin. Dietary fibers may exert a protective effect in the development of several cancers through prevention of insulin-resistance, decrease in IGF-1 activity, decrease in systemic inflammation via the production of short-chain fatty acids (SCFA) by gut microbiota, and optimization of the colonic microbiota reinforcing the intestinal barrier (Probst-Hensch et al., 2003; Canani et al., 2011; Kaczmarczyk et al., 2012). Dietary fiber may also have a specific protective role against hormone-dependent cancer (i.e., breast cancer) through the reduction of circulating steroid hormones concentration (Moore et al., 1998; Longcope et al., 2000). Finally, the decreased colorectal cancer risk is supported by a local action of dietary fibers in the colon: increased stool bulk and dilution of carcinogens through water binding, decreased intestinal transit time, binding to carcinogens and secondary biliary acids and production of SCFA with anti-proliferative and pro-apoptosis properties (Moore et al., 1998).

### 3.9. Dairy products

Dairy products generally comprise milk (whole or skim milk), cheese (fresh, cottage and hard cheese), and yoghurt. Some rare studies also include butter or ice cream (Huncharek et al., 2008).

The associations between dairy products consumption and the risk of various cancers have been evaluated by WCRF/AICR in 2007 and 2010–2014 CUP reports (WCRF/AICR, 2007, 2010, 2011, 2012, 2013, 2014a). Since the publication of these reports, 7 new meta-analyses were identified (Huncharek et al., 2008; Aune et al., 2012d; Qin et al., 2007; Li et al., 2011b; Mao et al., 2011; Dong et al., 2011; Lee et al., 2007b) (Appendix A, Part 2: Table 9). They cover 5 different cancer sites. Most of these studies considered total dairy

**Table 2**  
Nutritional factors either increasing or reducing the risk of cancer with a convincing or probable level of evidence, as updated by the INCa expert group.

Nutritional factors increasing cancer risk	Cancer sites	Nutritional factors reducing cancer risk	Cancer sites
Alcoholic beverages	Mouth Pharynx Larynx Oesophagus Colon and rectum Liver Breast	Physical activity	Colon Lung Breast Endometrium
Overweight and obesity	Oesophagus Pancreas Colon and rectum Breast ( <i>postmenopause</i> ) Kidney Gallbladder Endometrium Ovary Liver Prostate ( <i>advanced cancer</i> ) Hematological malignancies	Fruits and vegetables	Mouth Pharynx Larynx Oesophagus Stomach Lung ( <i>fruits</i> )
Red meat and processed meat	Colon and rectum	Dietary fiber	Colon and rectum Breast
Salt and salted foods	Stomach	Dairy products	Colon and rectum
Beta-carotene supplements*	Lung Stomach	Breastfeeding	Breast

\* Notably for smokers or asbestos-exposed subjects, and a dose >20 mg/d of beta-carotene.

products (including milk) and 6 studies detailed results for milk or cheese separately (Huncharek et al., 2008; Aune et al., 2012d; Qin et al., 2007; Li et al., 2011b; Mao et al., 2011; Lee et al., 2007b).

The association between colorectal cancer risk and milk intake previously judged as “probable” in the 2011 WCRF/AICR CUP report (WCRF/AICR, 2011) was confirmed by one new meta-analysis of 9 prospective studies (Aune et al., 2012d) showing a decreased risk. The association with total dairy products, not evaluated in the 2011 WCRF/AICR CUP report (WCRF/AICR, 2011), is also considered as “probable” since the meta-analysis based on 10 prospective studies (Aune et al., 2012d) also showed a decreased risk of colorectal cancer. On the opposite, the meta-analysis of 7 prospective studies found no association between cheese intake and risk of colorectal cancer, justifying to requalify the level of evidence from “suggestive” to “not conclusive”.

The level of evidence previously judged as “suggestive” for increased risk of prostate cancer associated with total dairy products intake is confirmed by the new meta-analyses of 11 prospective studies (Huncharek et al., 2008) and 13 prospective studies (Qin et al., 2007), respectively. The decreased risk of bladder cancer with the consumption of milk was previously evaluated as “suggestive”. The association is confirmed by one meta-analysis (6 prospective and 13 case-control studies combined or analyzed separately) (Mao et al., 2011) but not by the other meta-analysis (5 prospective and 9 case-control studies) (Li et al., 2011b).

The decreased risk of breast cancer associated with total dairy products intake observed in a new meta-analysis of 8 prospective studies (Dong et al., 2011) was considered as sufficient to increase the level of evidence from “not conclusive” (WCRF/AICR, 2010) to “suggestive”. The evidence for the association between kidney cancer and total dairy products intake, for which no new study was identified, remains “not conclusive”.

Concerning cancer sites or subcategories of dairy products which were not previously evaluated by WCRF/AICR, the new results available did not allow to conclude. It concerned associations between the risk of bladder cancer and total dairy products intake (Li et al., 2011b) and between kidney (Lee et al., 2007b) or prostate cancers (Huncharek et al., 2008; Qin et al., 2007) and milk consumption. Finally, there was no new published study

concerning ovary, endometrium, pancreas, oesophagus, mouth, larynx, pharynx, lung, stomach, testis, lymphoma and skin cancers. The level of evidence remains “not conclusive”.

Dairy products have the specificity to contain a variety of bioactive compounds that could be related to positive or negative effects on carcinogenesis in the same time. The main hypothesis underlying a possible protective effect of dairy products against cancer risk relates to their calcium content and to a lesser extent vitamin D, lactoferrin and fermentation products (Lamprecht and Lipkin, 2001; Norat and Riboli, 2003; Tsuda et al., 2010). A recent review of the literature highlighted the ability of dairy products to modulate inflammatory processes (Bordoni et al., 2015). Milk is a source of cholesterol and saturated fatty acids that might increase cancer risk; but it also contains conjugated linoleic acid, sphingolipids and butyric acid, which may have hypolipidaemic and antioxidant properties (Hague and Paraskeva, 1995; Parodi, 1997; Kelley et al., 2007). Independently of its composition in carbohydrates and lipids, milk consumed in high quantities increases blood levels of IGF-1 which has been associated with an increased risk of breast (EHBC Collaborative Group et al., 2010) and prostate cancer (Chan et al., 1998). Although the level of evidence of an increased risk of prostate cancer is “suggestive” for total dairy products and “not conclusive” for milk, suggested hypotheses concern a role of high consumption of milk, via increased levels of androgens and oestrogens (Fleshner et al., 2004), presence of phytanic acid (Wright et al., 2012) and high intake of proteins (Allen et al., 2008).

### 3.10. Breastfeeding

Epidemiological studies reporting on breastfeeding by the mother and her risk of cancer either simply distinguish between “ever”, exclusive or not, and “never”, or they measure lifetime duration of lactation.

The associations between breastfeeding and the risk of various cancers have been evaluated by WCRF/AICR in 2007 and 2010–2014 CUP reports (WCRF/AICR, 2007, 2010, 2014a). Since the publication of these reports, two new meta-analyses (Anothaisintawee et al., 2013; Luan et al., 2013) and one pooled analysis (Cronin-Fenton et al., 2010) were identified (Appendix A, Part 2: Table 10). The

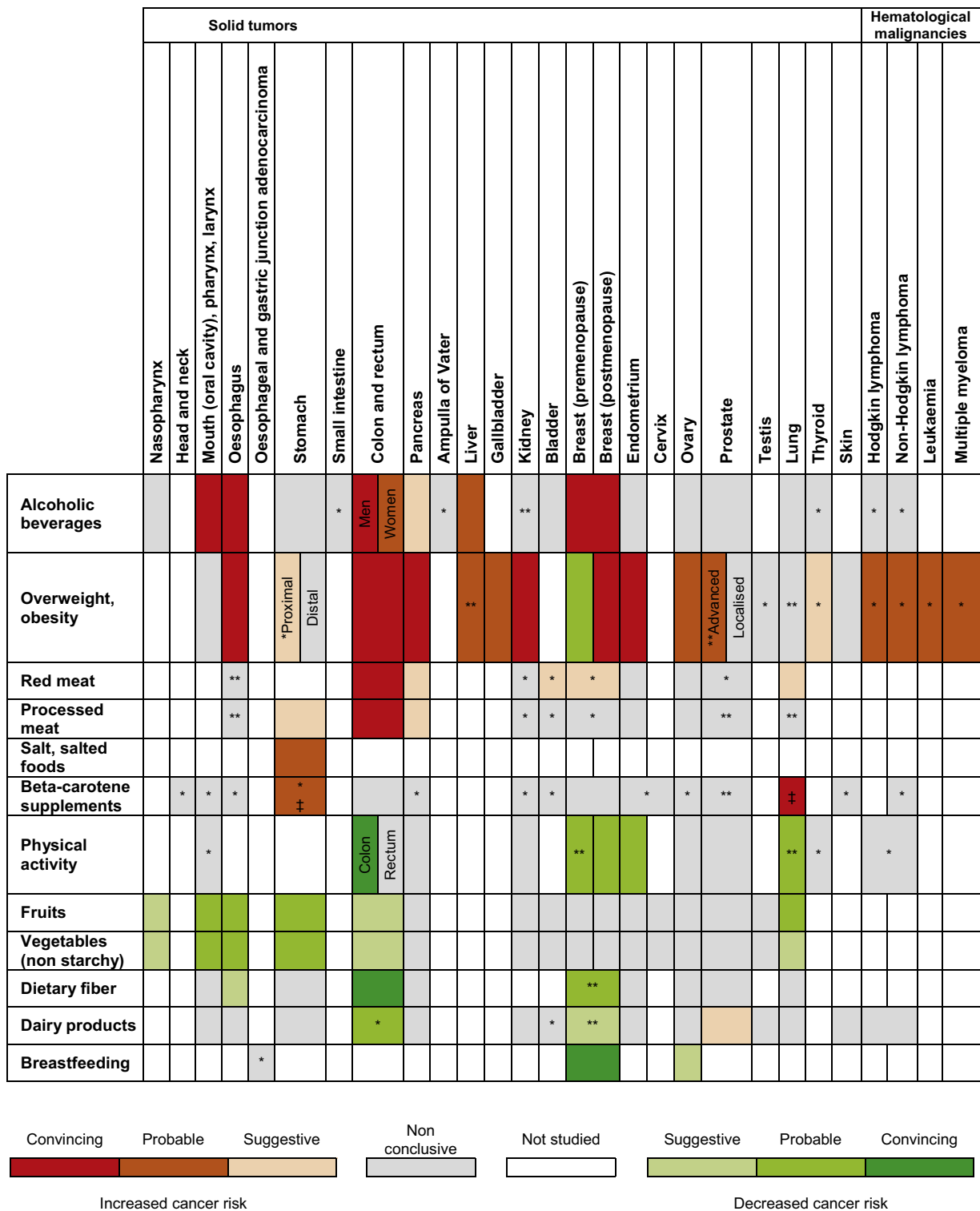


Fig. 2. Summary Table for levels of evidence between alcoholic beverages, obesity, physical activity and other nutritional factors and cancer risk.

\*Level of evidence was newly studied since 2007 or 2010–2014 CUP WCRF/AICR reports.

\*Level of evidence has been changed since 2007 or 2010–2014 CUP WCRF/AICR reports.

‡Supplements containing high doses of beta-carotene, notably for smokers and asbestos-exposed subjects.

associations between breastfeeding and cancer of the breast, ovary, and adenocarcinoma of the oesophageal and gastric junction were investigated.

The “convincing” level of evidence of the association between breastfeeding and decreased risk of breast cancer in the WCRF/AICR previous report (WCRF/AICR, 2010), is strengthened by the results

of a recent meta-analysis including 69 observational studies (Anohaisintawee et al., 2013).

The level of evidence previously judged as “suggestive” for decreased risk of ovarian cancer associated with breastfeeding, is confirmed by the recent results of a meta-analysis including 3 cohorts (Luan et al., 2013). A recent pooled analysis (Cronin-Fenton

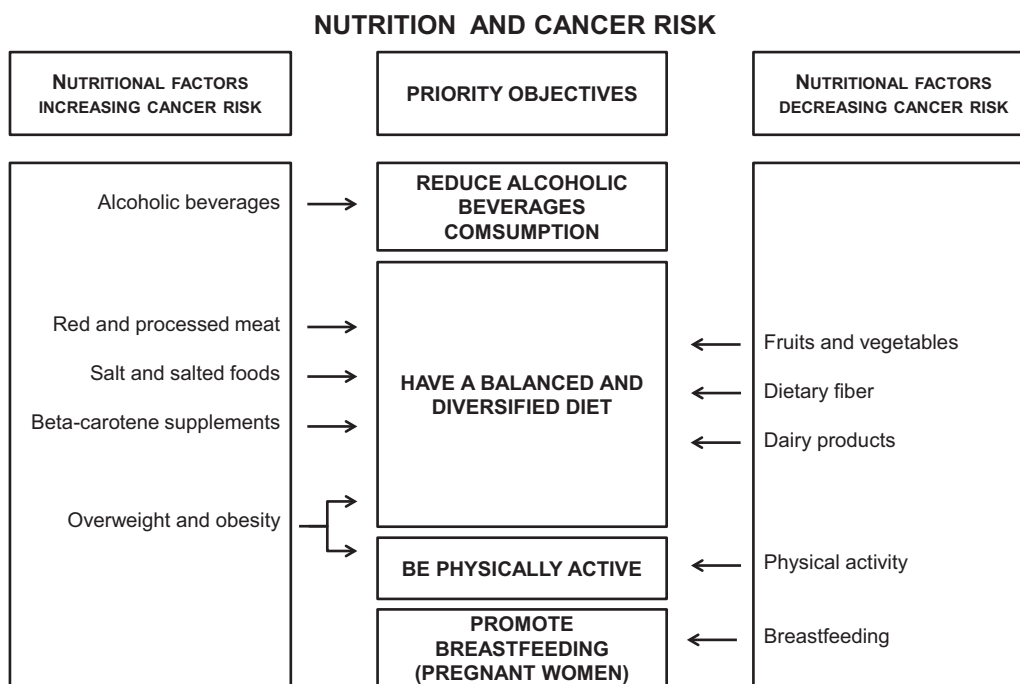


Fig. 3. From nutritional factors to priority objectives.

et al., 2010) investigating the associations between breastfeeding and oesophageal and gastric junction adenocarcinoma cancers, which were not previously evaluated by WCRF/AICR (WCRF/AICR, 2007), observed significant decreased risks. Considering the limited number of cases included, the level of evidence is considered “not conclusive”.

Several plausible mechanisms involved in lactation-induced protective effects have been identified: increased differentiation of breast cells and lower exposure to sex hormones during amenorrhea, elimination of cells with DNA damage through strong exfoliation of breast tissue and massive epithelial apoptosis during or at the end of lactation (WCRF/AICR, 2010).

### 3.11. Summary of the updated evidence

Fig. 2 gives an overview of all the levels of evidence updated through the evaluation process. Based on this state of knowledge, and the evidence graded as convincing or probable, the ten nutritional factors can be divided in two groups (Table 2): factors that increase the risk of cancer—alcoholic beverages, overweight and obesity, red and processed meat, salt and salted foods, and beta-carotene supplements—and factors that decrease the risk of cancer—physical activity, fruits and vegetables, dietary fiber, dairy products, and breastfeeding. Although, no quantitative risk assessment has been conducted, this information can be translated into three priority nutritional objectives for cancer prevention in the general population (Fig. 3) (i) to reduce alcoholic beverages consumption, (ii) to have a balanced and diversified diet, (iii) to be physically active; and one objective directed to pregnant women: to promote breastfeeding. Indeed, all objectives related to food factors that increase cancer risk (red meat and processed meat, salt and salted foods, and beta-carotene supplements) or to those that decrease cancer risk (fruits and vegetables, dietary fiber, dairy products) can be aggregated in only one objective which is “to have a balanced and diversified diet”. In addition, the reduction of overweight and obesity can be divided in two objectives “to have a balanced and diversified diet” and “to be physically active”.

## 4. Discussion

Overall, in this evaluation nearly 150 relationships between the alcoholic beverages, obesity, physical activity and the other nutritional factors considered and the risk of cancer at various sites were examined by the expert group. This work reinforces previous evidence and also provides new information. Firstly, it establishes for the first time a level of evidence for cancer sites that were not mentioned before, notably the evidence of the increased risk of hematologic malignancies associated with overweight and obesity, graded as “probable”. Secondly, it modifies the level of evidence for several associations, for instance the evidence of breast cancer risk associated with dietary fiber, judged as “probable”. This evaluation also highlights, for levels of evidence qualified as suggestive or not conclusive which represent two thirds of all associations examined, that epidemiological and mechanistic research is still needed to strengthen or refute them.

This updated state of knowledge enables to classify the nutritional factors considered as either risk factors or protective factors and to identify three priority objectives for nutritional cancer prevention in the general population: to reduce alcoholic beverages consumption, to have a balanced and diversified diet and to be physically active. These priority objectives are pertinent in France like in other developed countries (IARC, 2014b; Stein and Colditz, 2004). The report of the INCa expert group has been published in French language in June 2015 (INCa, 2015b) and its main content is now delivered to the general public, via the Internet and a leaflet, in the framework of the French Cancer plan and National nutrition and health program.

Since this evaluation, four WCRF/AICR CUP reports have been published (WCRF/AICR, 2014b, 2015a,b,c). They focused on prostate, liver, gallbladder and kidney cancers. Overall, their conclusions are in agreement with those of the INCa expert group, for the associations between body fatness and increased risk of cancer of the prostate (advanced cancer only), liver, gallbladder and kidney. Regarding alcoholic beverages and liver cancer, the judgment of the evidence in the CUP report is “convincing” whereas that of the INCa expert group is “probable”. This discrepancy can be explained

by some differences in the criteria that were met in each evaluation. In addition, the CUP report on kidney cancer concluded that less than 30 g/d alcohol consumption is associated with a decreased risk of kidney cancer with an evidence judged as “probable”, and that beyond 30 g/d the level of evidence is insufficient. However, the mechanisms that might explain a decreased risk of kidney cancer associated with alcohol remain unclear. This is the reason why the INCa expert group considered the evidence as “not conclusive”. Furthermore, it must be recalled the importance of considering that alcohol consumption is associated with increased risk of several other cancer sites with a convincing or probable level of evidence, such as the cancers of the mouth, pharynx, larynx, oesophagus, liver, colon and rectum, and breast.

The International Agency for Research on Cancer (IARC) evaluates the carcinogenicity of various factors among which some lifestyle factors. In a monography published in 2012, alcoholic beverages, ethanol in alcoholic beverages and acetaldehyde associated with consumption of alcoholic beverages have been classified as carcinogens to humans (Group 1) (IARC, 2012). In October 2015, another IARC monograph working group concluded that processed meat is carcinogenic to humans (Group 1) and that red meat is probably carcinogenic to humans (Group 2A) (Bouvard et al., 2015). These conclusions are consistent with our evaluations.

Recently, the fourth edition of the European code against cancer has been published (Schuz et al., 2015). This initiative of the European Commission aims to inform people about actions that may help them to reduce their risk of cancer. This edition, which has been coordinated by the IARC, consists of twelve recommendations including nutritional recommendations. Recommendation 4 is “Be physically active in everyday life. Limit the time you spend sitting.” Recommendation 5 is “Have a healthy diet: eat plenty of whole grains, pulses, vegetables and fruits. Limit high-calorie foods (foods high in sugar or fat) and avoid sugary drinks. Avoid processed meat; limit red meat and foods high in salt”. Recommendation 6 is “If you drink alcohol of any type, limit your intake. Not drinking alcohol is better for cancer prevention.” Recommendation 10a for women is “Breastfeeding reduces the mother’s cancer risk. If you can, breastfeed your baby”. Although the methods to evaluate the literature for alcohol drinking, diet, obesity/body fatness, physical activity and breastfeeding in association with cancer, slightly differed according to factors (Scoccianti et al., 2015a; Norat et al., 2015; Anderson et al., 2015; Leitzmann et al., 2015; Scoccianti et al., 2015b) and with the method of the INCa expert group, the general nutritional recommendations of the European code are consistent with the conclusions and priority objectives that the INCa expert group has identified.

Finally, the overall impact of modifications of exposures to nutritional factors on cancer incidence has been estimated: addressing these priority objectives based on nutritional factors might help populations of developed countries to reduce the burden of cancer and avoid about 30% of the most frequent cancers (WCRF/AICR, 2009; WCRF, 2015).

## 5. Conclusions

This comprehensive review and evaluation of the current evidence on 10 nutritional factors and the risk of more than 25 cancer sites emphasizes three main objectives addressing alcohol consumption, diet and physical activity that should be attained to improve cancer prevention at the population and individual levels. In the meantime, research effort must be maintained on numerous associations whose evidence is still considered as “suggestive” or not “conclusive”.

## Conflict of interest

The authors have no conflict of interest associated with this publication.

## Funding

Vanessa Cottet was partially supported by a French Government grant managed by the French National Research Agency under the program “Investissements d’Avenir”, reference ANR-11-LABX-0021.

Mélanie Deschasaux was funded by a PhD grant from the Cancéropole Ile-de-France (public funding from the Paris region).

## Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at <http://dx.doi.org/10.1016/j.critrevonc.2016.01.002>.

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