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Nutrition and cancer: the current epidemiological evidence

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We have examined the current scientific evidence on the relationship between nutrition and the most frequent tumours in the Spanish population: lung, colorectal, prostate, breast and stomach. Consumption of fruit is negatively associated with cancer of the lung and stomach, possibly with colorectal cancer, but probably not with prostate cancer and breast cancer. Consumption of vegetables probably reduces the risk of colorectal and stomach cancer, but probably is not associated with cancer of the lung, prostate and breast. Consumption of red and processed meat is positively associated with colorectal cancer and probably with stomach cancer. Animal fat is possibly associated with colorectal cancer and probably with prostate and breast cancer. High alcohol intake increases the risk of colorectal and breast cancer, while dairy products and calcium seem to decrease the risk of colorectal cancer. Obesity is a recognised risk factor of colorectal cancer and breast cancer in postmenopausal women, while foods with a high glycaemic index and glycaemic load possibly increase the risk of colorectal and prostate cancer. The relevance of nutrition on the cancer process is evident. Nevertheless important issues remain to be solved and further studies are needed. This accumulative knowledge should be used by public health authorities to develop recommendations and activities to reduce overweight and obesity and to promote healthy dietary habits.

Nutrition and cancer: Epidemiological evidence

It is widely accepted that nutrition has an important role in cancer occurrence, being the most important cause of cancer after smoking. In 1997, an important report from an international expert committee (World Cancer Research Fund/American Institute for Cancer Research, 1997; hereafter referred to as the WCRF/AICR report) summarised the scientific evidence on the effect of food and nutrients up to the middle of the last decade. It was estimated that between 30 and 40 % of cancer incidence worldwide was preventable by healthy eating, weight control and appropriate physical activity. However, at the time of publication of this report, the evidence was considered convincing in a limited number of associations: a high intake of vegetables and fruit decrease the risk of oropharynx, oesophagus, lung, stomach and colorectal cancer; physical activity is associated with colon cancer; use of refrigeration decreases stomach cancer; and alcohol consumption is causally associated with cancer of the oropharynx, larynx, oesophagus and liver.

Further evidence has been published in the last 8 years. In the present article, we describe the most recent findings related to the most frequent cancers in our society: lung, colon and rectum, prostate, breast and gastric. Fibre as a protective factor in colorectal cancer is described in an accompanying article.

Food, nutrition and lung cancer

Lung cancer is the most frequent tumour in males (22·2 % of cancer incidence) and the seventh in females (3·5 % of cancer incidence) in the Spanish population. Up to 1997 (WCRF/AICR report), it was considered that there was convincing evidence that diets high in vegetables and fruit (particularly green vegetables and carrots) protect against lung cancer. This conclusion was based on seven cohort studies and seventeen case–control studies. On the other hand, it was considered that probably carotenoid intake and possibly vitamin C, vitamin E and Se intake protect against lung cancer, while animal fat possibly increases the risk.

Thereafter, a pooled analysis of eight cohort studies (Smith-Warner *et al.* 2003) was published in which a protective effect of fruit (relative risk (RR) = 0·77; 95 % CI 0·67, 0·87) was observed with a dose–response relationship ($P<0·001$), but the effect was weaker for vegetables (RR = 0·88; 95 % CI 0·78, 1·0) and without dose–response. The authors concluded that there was a modest reduction in the lung cancer risk, mostly attributable to fruit, but not to vegetable intake. A recent meta-analysis (Riboli & Norat, 2003) found a significant but slight protective effect of fruit and vegetables in case–control studies; however, in cohort studies the protective effect was observed to be associated with fruit intake (odds ratio (OR) = 0·86; 95 % CI 0·78, 0·94), but not associated with vegetable intake. Other pooled analysis focused on nutrients (Mannisto *et al.* 2004) observed a protective effect only of β-cryptoxanthin (RR = 0·76; 95% CI 0·67, 0·86), but not in relation to other carotenoids. Citrus fruits are the most important sources of β-cryptoxanthin. Finally, the results from European Prospective

Abbreviations: AICR, American Institute for Cancer Research; EPIC, European Prospective Investigation into Cancer and Nutrition; OR, odds ratio; RR, relative risk; WCRF, World Cancer Research Fund.

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Investigation into Cancer and Nutrition (EPIC; Miller *et al.* 2004), the largest cohort study in the world, showed a significant inverse association between fruit consumption and lung cancer (RR for the highest quintile of consumption relative to the lowest = 0·60; 95 % CI 0·46, 0·78). However, there was no association between vegetable or vegetable subtype consumption and lung cancer. Overall, in relation to nutrition and lung cancer this recent evidence confirms the protective effect of fruit but not of vegetables (Table 1).

Regarding the intake of animal fat and the possible increase of risk of lung cancer, a recently published pooled analysis of eight cohort studies (Smith-Warner *et al.* 2002) did not support an association between fat or cholesterol intake and lung cancer risk.

Food, nutrition and colorectal cancer

Colorectal cancer is the second most frequent tumour in males and females in the Spanish population, representing 14·1 and 17·2 % of the total cancer incidence, respectively. Up to 1997 it was stated (WCRF/AICR report) that there was convincing evidence that a high intake of vegetables and regular physical activity decrease the risk of colorectal cancer; that probably alcohol and red meat increase the risk, that possibly a high intake of fibre decreases the risk and that obesity increases the risk. It was also concluded that possibly Ca intake has no relationship with colorectal cancer.

Over the last year, further evidence has confirmed that high intake of red and processed meat is positively associated with the risk of colorectal cancer. A pooled analysis on thirteen cohort studies on meat consumption and colorectal cancer (Sandhu *et al.* 2001) has shown a 12–17 % increase risk of colorectal cancer for each daily increase of 100 g red meat, and a 49 % increase of risk for each daily increase of 25 g processed meat. Furthermore, a comprehensive review of all epidemiological studies published between 1973 and 1999 (Norat *et al.* 2002) concluded that for each daily increase of 120 g red meat intake the risk of colorectal cancer increased 24 %, and the risk is increased 36 % for each daily increase of 30 g in consumption of processed meat.

A recent publication has also confirmed the positive association between alcohol intake and colorectal cancer. A pooled analysis of eight cohort studies (Cho *et al.* 2004) has shown that an alcohol intake greater than 45 g/d (approximately more than three drinks a day) is associated with a 41 % increase of colorectal cancer risk (RR = 1·41; 95 % CI 1·16, 1·72).

However, in relation to fruit and vegetables, a recent meta-analysis (Riboli & Norat, 2003) showed a significant but slight protective effect of vegetable intake (OR = 0·87; 95 % CI 0·80, 0·95) and fruit intake (OR = 0·93; 95 % CI 0·87, 0·99) in case–control studies, but no association in cohort studies.

Recent epidemiological studies have given rise to new hypotheses about the potential role of elevated level of insulin-like growth factors and other related factors in the pathogenesis of colorectal cancer. This is part of a complex metabolic syndrome, characterised by general obesity and intra-abdominal body fat, physical inactivity, hyperinsulinaemia and alteration in the metabolism of endogenous hormones (oestrogens, androgens, insulin-like growth factors and their binding proteins) that could be associated with the risk of colorectal cancer but also to prostate, pancreas and breast cancer (Kaaks & Lukanova, 2001). A diet with a high content of glycaemic index and glycaemic load could be an important component of this metabolic syndrome.

With regard to dairy products, most recent evidence showed a moderate protective effect of total dairy products, milk and Ca on the risk of colorectal cancer. A recent review (Riboli & Norat, 2003) concluded there was a moderate protective effect for total dairy products and milk in cohort studies, although this was not observed in case–control studies. A pooled analysis of ten cohort studies (Cho *et al.* 2004) showed that milk consumption of more than 250 g/d in comparison with less than 10 g/d is associated with a 15 % reduction of the risk of colorectal cancer. The highest *v.* the lowest dietary intake of Ca was associated with a 14 % reduction of risk. A 22 % of reduction was observed when dietary and supplement intake were considered simultaneously. A Cochrane review has been published (Weingarten *et al.* 2004) about the effect of Ca supplementation. A moderate protection in two randomised controlled trials on the development of adenomatous polyps of the colon was observed. However, it was concluded that there was insufficient evidence to recommend the general use of Ca supplementation for the prevention of colorectal cancer.

Food, nutrition and prostate cancer

Prostate cancer is the third most frequent cancer in men in Spain. About 12·7 % of cancer cases in the male Spanish population are

Table 1. Groups of foods associated with selected cancers according to current epidemiological evidence*

Foods	Lung	Colorectal	Prostate	Stomach	Breast
Total fruit	(−) S/Pr	(−) Ps	(NA) Pr	(−) S/Pr	(NA) Pr
Total vegetables	(NA) Ps	(−) Pr	(NA) Pr	(−) Pr/Ps	(NA) Pr
Red and processed meat		(+) S/Pr		(+) Pr/Ps	(+) Ps
Animal fat	(NA) Ps	(+) Ps	(+) Pr		(+) Pr
Salted food				(+) S	
Alcohol	(NA) Pr	(+) S/Pr	(NA) S	(NA) S/Pr	(+) S/Pr
Food with high glycaemic load		(+) Ps	(+) Ps		
Dairy products		(−) Pr			
Obesity		(+) S	(NA) Ps		(+) S

Association: −, negative; +, positive; NA, no association. Level of evidence: S, sufficient; Pr, probable; Ps, possible.
*According to the evaluation of the current epidemiological evidence done by the author.

prostate cancer. The 1997 WCRF/AICR report concluded that there was no evidence of a convincing or probable causal relationship with diet. It was stated that vegetable intake may decrease the risk of prostate cancer and that animal fat, animal protein and red meat may increase the risk. Since then, results from the EPIC cohort study on prostate cancer incidence and the consumption of vegetables and fruit have been published (Key *et al.* 2004). No significant association between total vegetables, cruciferous vegetables, total fruit, and total fruit and total vegetables combined was observed. The finding of a possible protective effect of lycopene remains to be confirmed. On the other hand, a published epidemiological review supports the association between fat, meat and prostate cancer (Kolonel, 2001). Of the twenty-two studies reviewed (eight cohort and fourteen case–control), a positive association was observed in sixteen. Of the twenty studies (four cohort and sixteen case–control) that have examined the relationship between animal or saturated fat, fourteen found a positive association.

Food, nutrition and breast cancer

Breast cancer is the most frequent cancer in women in Spain. More than 28 % of cancer cases in women are breast cancer. The 1997 WCRF/AICR report concluded that a high consumption of vegetables and fruit probably decreases the risk of breast cancer, while probably alcohol and possibly saturated and animal fat increase the risk. In contrast, a recent pooled analysis of eight cohort studies showed no evidence of a protective effect of fruits and vegetables (Smith-Warner *et al.* 2001). Another meta-analysis (Riboli & Norat, 2003) found a slight protective effect in fifteen case–control studies, but found no relationship in the analysis of ten cohort studies. Finally, the EPIC study did not show any relationship with vegetable and fruit intake (van Gils *et al.* 2005).

Recent publication of a collaborative reanalysis of fifty-three epidemiological studies (Hamajima *et al.* 2002) has confirmed that alcohol is causally associated with breast cancer. An increase of 10 g alcohol per day is associated with an increase of 7 % of the risk of breast cancer, alcohol being the cause of about 4 % of breast tumours in women from developed countries. The association between saturated and animal fat and breast cancer has become very controversial over the last decade. The most recent solid evidence comes from a meta-analysis of fourteen cohort studies and thirty-four case–control studies which showed an increase of 19 % in the risk of breast cancer for the highest level of consumption of saturated fat (Boyd *et al.* 2003).

Food, nutrition and gastric cancer

Gastric cancer is the fifth most frequent cancer in the Spanish population. About 6·1 % of cancer incidence in men and 5·5 % of cancer incidence in women are gastric cancers. In 1997, the WCRF/AICR report concluded that there was convincing evidence that use of refrigeration and a diet high in vegetables and fruit protect against stomach cancer. It was considered that probably vitamin C and possibly carotenoids, allium vegetables and whole grains decrease the risk of stomach cancer. On the other hand, it was stated that probably a high intake of salt-preserved food and possibly consumption of grilled and barbecued meat increase the risk.

Since 1997, little further important evidence has been added. According to a meta-anlysis (Riboli & Norat, 2003) taking into account results from case–control studies, a significant protective effect was found for a daily increase of 100 g fruit (OR = 0·69; 95 % CI 0·62, 0·77) or vegetables (OR = 0·78; 95 % CI 0·71, 0·86). However, the meta-analysis of cohort studies showed a weaker and no significant protective effect for fruit (OR = 0·89; 95% CI 0·73, 1·09) or vegetables (OR = 0·89; 95% CI 0·75, 1·05). It seems that the protective effect of fruit is higher than that of vegetables, particularly in Asian studies. There is also new evidence available about the effect of nutrient supplements against stomach cancer provided by community trials. A chemoprevention trial on gastric dysplasia in a high-risk area of Colombia (Correa *et al.* 2000) observed a similar rate of regression in precursor lesions of gastric cancer in patient treated with β-carotene (30 mg/d), ascorbic acid (2 g/d) or eradication therapy against *Helicobacter pylori* infection. However, a recent systematic review and meta-analysis on antioxidant supplements (Bjelakovic *et al.* 2004) for the prevention of gastric and other gastrointestinal cancer (including oesophagus, colorectal, pancreatic and liver cancers) showed no significant beneficial effects with the exception of Se. However, seven trials considered to be of high quality showed that antioxidants significantly increased mortality. The use of antioxidant supplements is not recommended for the prevention of cancer.

Obesity and cancer

Over the last years, obesity has become a serious public health problem in most developed countries and the large cities of some developing countries. Such an increase in weight gain in many populations has probably been caused by reduced levels of physical activity and by changes in the patterns of food intake. In Spain in 2004, 53 % of the population between 25 and 65 years was classified as overweight or obese (Dorica, study). The prevalence of obesity was twice that of 1990. The current epidemiological evidence shows that obesity is an important risk factor of cancer occurrence. It is considered (International Agency for Research on Cancer, 2002) that there is convincing evidence about the causal relationship between obesity and colorectal cancer, breast cancer in postmenopausal women, kidney cancer, endometrial cancer and adenocarcinoma of the oesophagus. It is estimated that 11 % of colorectal cancer and 9 % of breast cancer in postmenopausal women are associated with obesity. Between a quarter and a third of tumours of the kidney, endometrium and oesophagus are associated with obesity.

Conclusion

We have examined the cumulative scientific evidence on the relationship between nutrition and the most frequent cancers. The relevance of nutrition on the cancer process is evident. Even so, despite the large number of epidemiological studies carried out up to the present, the evidence about the effect of some important foods and groups of food is limited and some results are still inconsistent. Important issues remain to be solved and further studies are needed. However, the relationship between nutrition and cancer is more complex than it was previously considered to be. In order for scientific knowledge to

be improved, it is necessary to study results from large prospective studies, carried out in populations with heterogeneous dietary habits, reducing the level of measurement errors and using multidisciplinary approaches including biochemical markers, molecular biology and genetic markers.

Finally, this cumulative knowledge should be used by public health authorities to promote nutritional recommendations for better and healthier nutrition. In Spain, it is imperative to develop public health measures to reduce overweight and obesity and to promote healthy dietary habits.

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