

The potential of nuts in the prevention of cancer

Carlos A. González¹* and Jordi Salas-Salvadó²

¹*Department of Epidemiology and Cancer Registry, Catalan Institute of Oncology, Barcelona, Spain*

²*Human Nutrition Unit, Faculty of Medicine and Health Sciences, Rovira i Virgili University, Reus, Spain*

Cancer is a disease that is characterized by the loss of genetic control over cell growth and proliferation, mainly as a result of the exposure to environmental factors. Cessation of smoking and a high consumption of fruits and vegetables are the most important means of reducing the risk of cancer in our society. Like fruits and vegetables, nuts are a source of vegetable protein, monounsaturated fatty acids, vitamin E, phenolic compounds, selenium, vegetable fibre, folic acid and phytoestrogens. There are numerous mechanisms of action by which these components can intervene in the prevention of cancer, although they have not been fully elucidated. There are very few epidemiological studies analyzing the relationship between nuts consumption and risk of cancer. One of the greatest difficulties in interpreting the results is that the consumption of nuts, seeds and legumes are often presented together. The most commonly studied location is the colon/rectum, an organ in which the effect of nuts is biologically plausible. Although the results are not conclusive, a protective effect on colon and rectum cancer is possible. Likewise, some studies show a possible protective effect on prostate cancer, but there is insufficient data on other tumour locations. New epidemiological studies are required to clarify the possible effects of nuts on cancer, particularly prospective studies that make reliable and complete estimations of their consumption and which make it possible to analyse their effects independently of the consumption of legumes and seeds.

Nuts: Cancer: Prevention: Diet: Epidemiology: Disease

Cancer is the second most important cause of death in Europe, in both men and women. In the year 2000 in Europe, 1 741 398 people died as a result of a malignant tumour, which is approximately 19 % of the overall mortality in both sexes (21 % in men and 17 % in women) (WHO, 2004). Approximately one out of every three men and one out of every four women in Europe will be diagnosed as having a cancer at some point in their lives.

Cancer is a disease that is principally characterized by the loss of genetic control over cell growth and proliferation. In this sense it is a genetic disease. Tumours of hereditary origin, however, are in a vast minority and the factors that cause the process of tumoural genesis are mainly environmental, largely related to lifestyle. The consumption of tobacco and diet are the main recognized causes of cancer in our society.

At the end of 1990, two reports by panels of leading international experts were published, summarizing the scientific evidence on the relation between diet and cancer (WCRF & AICR, 1997; COMA, 1998). From the exhaustive evaluation of the impact of food and nutrients, it was concluded that between 29.3 and 40.6 % of malignant tumours could be prevented by making beneficial modifications to the consumption of food and nutrients, the consumption of alcohol, body weight and physical activity (WCRF & AICR, 1997).

This article reviews the data in the literature that analyze the possible relation between the consumption of nuts and cancer.

Consumption of food plants and their effect on the risk of cancer

The potential effects on cancer of five groups of food plants have been investigated: cereals, tubers, legumes, fruit and vegetables and nuts. Cereals, particularly whole grains, are a source of dietary fibres, which probably have a protective effect on cancer of the colon and rectum (WCRF & AICR, 1997; COMA, 1998). The data concerning the effect of legumes and tubers is too limited and insufficient to draw any conclusions (WCRF & AICR, 1997; COMA, 1998). Below, we will describe in greater detail the evidence on fruit and vegetables and nuts.

Fruit and vegetables

The high consumption of fruit and vegetables is one of the most important means of reducing the risk of cancer, particularly of malignant epithelial tumours, and it is probably one of the main bases of the healthy effects of the Mediterranean diet (Kushi *et al.* 1995). The considerable amount of scientific evidence from epidemiological and experimental studies on the relationship between fruit and vegetable consumption and cancer has been evaluated by various committees of experts. Using the results of thirty-seven cohort studies, 196 case-control studies and fourteen ecological studies, the World Cancer Research Fund and the American Institute for Cancer Research (WCRF & AICR, 1997) concluded that there was convincing evidence that a high

* Corresponding author: Carlos A. González Svatetz, fax +34 93 2607787, email cagonzalez@ico.scs.es

consumption of fruit and vegetables reduces the risk of cancer of the oral cavity and pharynx, oesophagus, lung and stomach, and that a high consumption of vegetables reduces the risk of cancer of the colon and rectum. The same committee considered that a high consumption of fruit and vegetables would probably reduce the risk of cancer of the larynx, pancreas, breast and urinary bladder, and possibly protect against cancer of the cervix, ovary, endometrium and thyroid gland. Likewise, a high consumption of vegetables would protect against cancer of the prostate, liver and kidney. However, a more recently published review (Key *et al.* 2002) makes a less optimistic evaluation and considers that the protective effects of the high consumption of fruit and vegetables on cancer of the colon and rectum, stomach and oesophagus are probable, but that the evidence regarding the effect on breast cancer is insufficient.

Fruit and vegetables are the source of a wide variety of chemical compounds (vitamins, carotenoids, minerals, fibre, etc) that can protect from cancer. Various population trials have been carried out (Greenwald *et al.* 2001) to determine how effective the vitamin supplements and compounds contained in fruits and vegetables (beta-carotene, vitamins C and E, retinol, selenium, etc.) are at preventing cancer. The results have been contradictory. Some of them proved to be effective on gastric dysplasia (Correa *et al.* 2000), but others were shown as not useful to prevent colorectal adenomas (Greenberg *et al.* 1994), and could even increase the risk of lung cancer (Omenn, 2000). Population trials on prostate cancer, however, have observed a protective effect of alpha-tocopherol (Heinonen *et al.* 1998) and selenium (Clark *et al.* 1998), although these studies need to be confirmed since prostate cancer was not their primary objective. In general, these trials show that the protective effect of isolated compounds contained in fruit and vegetables is not equivalent to the protective effect of the fruit and vegetables themselves. Two explanations have been given for this. On the one hand, there are hundreds of compounds contained in fruit and vegetables whose effects have not been elucidated and the ones used in the trials may not be those which are responsible for their biological effects. On the other hand, the biological effects may be achieved by the combined

action of numerous compounds, not by the administration of just one.

Nuts

Very few published studies have evaluated the effect of the consumption of nuts and the risk of cancer. We will describe the results below. The panel of experts of the World Cancer Research Fund and the American Institute of Cancer Research (WCRF & AICR, 1997) concluded that: 'Although there are theoretical reasons to believe that a diet rich in nuts and seeds can protect against some cancers, the present evidence is insufficient.' This panel of experts finally recommended that the effects of consuming nuts and seeds on health should be studied and investigated separately.

Potential mechanisms by which the compounds in nuts can prevent cancer

The diet consists of a very wide range of components that interact with one another and with other environmental and genetic factors that can potentially favour or reduce the formation of tumours. In terms of absolute risk in the population, the most important effect of the diet on the incidence of cancer may be due to the capability of numerous components from vegetable sources to inhibit or reduce the process of carcinogenesis.

Nuts are generally a source of vegetable proteins, unsaturated fatty acids, vitamin E, phenolic compounds and selenium, vegetable fibre, folic acid and phytosterols, although the concentrations can vary among the different sorts of nuts (Dreher *et al.* 1996). The potential mechanisms of action of these components of nuts and food vegetable plants that may intervene in the prevention of cancer have not been totally elucidated. Some of them are related with antioxidant activity, the regulation of cell differentiation and proliferation, the reduction of tumour initiation or promotion, the repair of DNA damage, the regulation of immunological activity and inflammatory response, the induction or inhibition of metabolic enzymes and hormonal mechanisms, and the supply of fibre and monounsaturated fatty acids (Greenwald *et al.* 2001; Kris-Etherton *et al.* 2002) (Table 1)

Table 1. Potential mechanisms of action for reducing the risk of cancer of compounds in nuts

Mechanisms	Compounds	Greatest concentration in
1. Antioxidants	Vitamin E Selenium	Almonds, hazelnuts Brazil nuts, walnuts, cashew nuts, pecans
2. Regulation of cell differentiation and proliferation	Flavonoids (quercetin) Resveratrol	Pine nuts
3. Inhibition of chemically induced carcinogenesis	Vitamin E	Almonds, hazelnuts
4. Reduction of DNA damage	Flavonoids (quercetin) Resveratrol	Almonds pine nuts
5. Regulation of inflammatory response and immunological activity	Polyphenols (ellagic acid)	Walnuts and pecans
6. Induction of phase 2 metabolic enzymes	Folic acid	Pine nuts, almonds, hazelnuts
7. Regulation of hormonal mechanisms (phytoestrogens)	Flavonoids (quercetin) Resveratrol	Pine nuts
8. Supply of dietary fibre	Flavonoids Resveratrol	Pine nuts
9. Supply of monounsaturated fatty acids	Isoflavonoids (deidzein, genistein)	Hazelnuts, Brazil nuts
	Lignans	
	Dietary fibre	Almonds, walnuts, pistachio
	Oleic acid	Hazelnuts, macadamia

Antioxidant compounds

Of the antioxidant compounds contained in nuts, one of the most important is vitamin E. Another is selenium, which is not directly an antioxidant nutrient but an important component of antioxidant enzymes. Selenium is found particularly in Brazil nuts, in greater concentrations in those with shells, and in lower concentrations in walnuts, cashew nuts and pecans (Kannamkumarath *et al.* 2002). Likewise, the presence of some phenolic compounds, such as quercetin (which belongs to the flavonoid group) and resveratrol (which belongs to the groups of the stilbenes,) has been described, particularly in pine nuts, which are also considered to be antioxidants (Yang *et al.* 2001).

There is extensive scientific evidence from studies of cell cultures, from experimental studies carried out in animals and observational epidemiological studies which indicate that antioxidants can prevent the development of cancer (WCRF & AICR, 1997). However, controlled population trials that administer supplements of antioxidant vitamins have not shown any consistent results (Greenwald *et al.* 2001), and it seems that natural foods have a greater effect than supplements, perhaps because they combine the action of hundreds of compounds.

Nutritional factors which act by regulating cell differentiation and proliferation

Nuts contain vitamin E. There is evidence from numerous experimental studies in animals and cultures of cell lines to show that alpha-tocopherol can inhibit cell proliferation (Greenwald *et al.* 2001) and therefore influence the reduction of carcinogenesis. Numerous observational epidemiological studies in humans have shown that a high consumption of vitamin E can protect against various tumour locations (WCRF & AICR, 1997).

Nutritional factors which can inhibit or reduce carcinogenesis by affecting molecular events during the initiation or promotion of cell tumours

Among these factors are phenolic compounds (polyphenols), particularly flavonoids such as quercetin and stilbenes such as resveratrol. Likewise, walnuts, pecans and perhaps other sorts of nuts contain ellagic acid (Stoner & Mukhtar, 1995), a polyphenol with similar abilities. *In vitro* studies have suggested that these polyphenols may be able to reduce chemically-induced carcinogenesis, and also inhibit proliferation and trigger apoptosis of cancerous cells (Yang *et al.* 2001). Some observational epidemiological studies also show that a high consumption of flavonoids is negatively associated with some tumours (WCRF & AICR, 1997).

Factors that can reduce DNA damage and/or induce DNA repair

Nuts contain folic acid, which is implicated in the metabolism and synthesis of DNA. Folic acid acts as a coenzyme in the synthesis of nucleic acids and the metabolism of aminoacids. Therefore, it is fundamental to the processes of DNA synthesis, methylation and repair. A folate deficiency may

favour chromosome rupture and genetic instability. Although the ruptures can be repaired, the chromosomes become fragile and the risk of cancer increases.

Scientific evidence from observational epidemiological studies (WCRF & AICR, 1997; Greenwald *et al.* 2001) shows that a diet low in folate can increase the risk of colorectal cancer and possibly cervical cancer.

Compounds that regulate immunological activity and inflammatory response

Among these compounds are such phenolics as quercetin and resveratrol. According to Stoner & Mukhtar (1995) and Yang *et al.* (2001), they act on the formation of the prostaglandins and pro-inflammatory cytokines that intervene in the inflammatory response (Yang *et al.* 2001; Kris-Etherton *et al.* 2002). This mechanism may be important in tumours that have a component of chronic inflammation, such as colorectal cancer, stomach cancer, cancer of the pancreas and cancer of the cervix. However, there is no solid epidemiological evidence to prove these hypotheses.

Compounds that induce detoxifying metabolic enzymes in the second phase of metabolism

Among these compounds are flavonoids and possibly other phenolics such as resveratrol (Stoner & Mukhtar, 1995; Yang *et al.* 2001). The function of metabolic enzymes is to metabolize and facilitate the elimination of potentially cancerous chemical compounds or their intermediate metabolites. Although experimental studies have shown these mechanisms of action in cell cultures and animals, there is no solid evidence to corroborate how these compounds act in humans.

Compounds that act on hormonal mechanisms (phytoestrogens)

Phytoestrogens are compounds from plants that modify hormonal activity. There are two groups of phytoestrogens: isoflavonoids, consisting mainly of daidzein and genistein, the main sources of which are soya derivatives, and lignans, the main source of which are whole beans, seeds and legumes, and to a lesser extent nuts (Adlercreutz, 1995). Recent studies on the content of isoflavonoids in fruit and nuts (Liggins *et al.* 2000) have shown, however, that although nuts are not as rich in isoflavonoids as soy, such nuts as hazelnuts and Brazil nuts do contain isoflavonoids. They are also present in peanuts and chestnuts.

Several studies in animals and humans have shown that phytoestrogens have weak estrogenic activity, but can compete with endogenous estrogens by coupling to estrogenic receptors (Adlercreutz, 1995). When they bound these receptors, they prevent endogenous estrogens such as estradiol, which have much greater estrogenic power. In this way they act as 'antiestrogens'. Epidemiological studies suggest that a high consumption of soy products can reduce the risk of hormone-dependent tumours, such as breast, endometrial and prostate cancer (Greenwald *et al.* 2001), although the results are not consistent. The low incidence of breast and prostate cancer observed in China and Japan is thought to be due to the traditional high consumption of soy products in the diet

in these two countries. The consumption of isoflavonoids in European countries, however, is much lower (1 mg/d) than in Asian countries (20–100 mg/d) and also low with respect to the level at which physiological effects are expected (60–100 mg/d) (van Erp-Baart *et al.* 2003).

Dietetic fibre content

Nuts contain fibre which has various effects on the gastrointestinal system and can potentially reduce the risk of cancer. A high intake of dietetic fibre increases the volume of faeces and anaerobic fermentation, and reduces the length of intestinal transit. Therefore, intestinal mucosa is exposed to carcinogens for less time and, because the faecal volume is greater, the carcinogens in the colon are diluted.

The effect of dietary fibre intake on cancer has been controversial. In 1997, the committee of experts of the WCRF & AICR concluded that 'epidemiological and experimental evidence indicates that a high consumption of dietetic fibre may reduce the risk of cancer of the colon and rectum, breast cancer and prostate cancer'. However, subsequent prospective studies (Terry *et al.* 2001) observed no protective effect. Neither did controlled trials (Schatzkin *et al.* 2000) observe any protective effect of fibre supplements on the recurrence of adenomas and colorectal polyps. However, a new study in an American cohort, and the wide-ranging European Prospective Investigation on Nutrition and Cancer (EPIC), have provided new solid evidence (Bingham *et al.* 2003) on the protective effect of dietetic fibre, particularly for cancer of the colon.

Monounsaturated fatty acid content

Nuts have a relatively high content of monounsaturated fatty acids (MUFA) and a low content of saturated fatty acids (SFA). A high intake of MUFA and a high MUFA/SFA ratio is one of the typical components of the Mediterranean diet pattern, which has been associated to a low risk of some types of cancer (particularly colorectal, breast and prostate). Although lipids are some of the most commonly studied dietary components, both in animal research initiated in the 1940s and in epidemiological studies, their effects on cancer are still controversial and there is no conclusive evidence on the effect of MUFA intake. Olive oil, which is one of the main sources of MUFA, may have a protective effect against breast cancer, although it is not clear whether this is due to the MUFA or their high content of phenolic compounds and vitamin E. Although some case-control studies carried out in Spain, Italy and Greece have shown that olive oil has a protective effect (Martin-Moreno, 2000) against breast cancer, a subsequent study in five centres (Simonsen *et al.* 1998) did not confirm this association.

Epidemiological studies on the consumption of nuts and the risk of cancer

In an exhaustive search of Medline (Pubmed) on the consumption of nuts and the risk of cancer in humans before July 2005, we were only able to identify fifteen epidemiological studies (one cross-sectional study, eleven case-control studies and three cohort studies) which have published sixteen articles

with results on the consumption of nuts and cancer (Tables 2 and 3). One of the greatest difficulties in interpreting the results of these relatively few studies is that several of them (Pickle *et al.* 1984; Kune *et al.* 1987; Heilbrun *et al.* 1989; Peters *et al.* 1992; Jain *et al.* 1999; Petridou *et al.* 2002) present the results of nuts, seeds and legumes together, so their effects cannot be differentiated. Others include in the group of 'nuts' the results of the consumption of peanuts or peanut butter (Graham *et al.* 1978; Young & Wolf, 1988; Peters *et al.* 1992), which is a legume, not a nut. Only five studies (Trichopoulos *et al.* 1985; Mills *et al.* 1989; Hoshiyama & Sasaba, 1992; Singh & Fraser, 1998; Jenab *et al.* 2004) have evaluated the effect of nuts separately, although four (Trichopoulos *et al.* 1985; Mills *et al.* 1989; Hoshiyama & Sasaba, 1992; Singh & Fraser, 1998) do not indicate exactly which ones were included. A wide-ranging European cohort study (Jenab *et al.* 2004) considers the effect of nuts and seeds together, but it is the only one to describe the consumption according to the type of nut in each of the participating countries.

We have identified eight studies that have published results on the risk of colon and rectum cancer, most of which were carried out in the USA. Two of them (Graham *et al.* 1978; Young & Wolf, 1988) presented results exclusively on the consumption of peanut butter. Of the six studies that presented results that included the consumption of nuts, three (Pickle *et al.* 1984; Heilbrun *et al.* 1989; Peters *et al.* 1992) found no association. On the other hand, three studies (Kune *et al.* 1987; Singh & Fraser, 1998; Jenab *et al.* 2004) found a protective effect that was statistically significant. One of the studies that observed a protective effect was a population-based case control study (Kune *et al.* 1987), with a considerable number of cases. Another (Singh & Fraser, 1998) is a relatively broad study of an American cohort carried out on Seventh-Day Adventists, in which one to four intakes of nuts per week was associated with a 33 % decrease in the risk of colorectal cancer with respect to the non-consumers. Finally, the EPIC cohort study conducted in ten European countries, which included the largest number of cancer cases so far, found a protective effect that was statistically significant. A dose-response effect was also found, but only for cancer of the colon in women (31 % decrease in the risk of cancer of the colon for a daily consumption of more than 6.2 g with respect to non-consumers of nuts and seeds).

The protective effect observed only in women coincides with the result obtained in the case-control study in Austria (Kune *et al.* 1987), which the authors were unable to explain.

We found three studies on nuts and prostate cancer. The cohort study of the Seventh Day Adventists (Mills *et al.* 1989) observed a slight, though not statistically significant, protective effect. A cross-sectional ecological study carried out in fifty countries (Hebert *et al.* 1998) found a negative correlation between mortality due to prostate cancer and the calories supplied by nuts and seed oils, including soy oil (the most important source of phytoestrogens). A broad population-based case-control study in Canada (Jain *et al.* 1999), using a dietary history in order to make a good estimation of dietary intake, found a statistically significant reduction (31 %) in the risk of prostate cancer. However, the results are for the group of nuts, legumes and seeds, and their individual effects cannot be differentiated.

Table 2. Case-control studies on cancer and nuts

Study population							Remarks
Author	Country - year	Cases	Controls	Base	Tumour	Dietetic method	
Graham <i>et al.</i> EEUU 1978		256	783	Hospital	Colon Rectum	FFQ	Colon: No association Rectum: 1.51 ($P=0.003$) Colon: 1.08 (NS) Rectum: 2.04 (NS) (OR not presented) Protective effect statistically significant only in women 0.33 (0.12–0.89) Between 18 and 35 years old
Pickle <i>et al.</i> EEUU 1984		330	628	Hospital	Colon Rectum	FFQ (57 items)	
Kune <i>et al.</i> Austria 1987		58	176	Population	Colorectal	Diet history (300 items)	
Young <i>et al.</i> EEUU 1988		28	727	Population	Colorectal	FFQ	
Peters <i>et al.</i> EEUU 1992		746	746	Population	Colorectal	SQ FFQ (116 items)	0.98 (0.93–1.03) Similar results in both sexes
Jain <i>et al.</i> Canada 1999		617	636	Population	Prostate	Diet history (1129 items)	0.69 (0.53–0.91)
Trichopoulos <i>et al.</i> Greece 1985		110	100	Hospital	Stomach	SQ FFQ (80 items)	2.46 (IC not presented) Statistically significant
Hoshiyama <i>et al.</i> Japan 1992		294	294	Hospital Population	Stomach	FFQ (24 items)	0.6 (0.3–1.0)
Bueno de Mesquita <i>et al.</i> Holland 1991		164	480	Population	Pancreas	SQ FFQ (116 items)	Statistically significant tendency 1.06 (NS)
Iscovic <i>et al.</i> Argentina 1989		150	150	Population	Breast	SQ FFQ (150 items)	1.2 (NS)
Petridou <i>et al.</i> Greece 2002		84	84	Hospital	Endometrium	SQ FFQ (110 items)	0.63 (0.44–0.88)

FFQ = Food Frequency Questionnaire.

NS = Not significant.

SQ FFQ = Semi-quantitative Food Frequency Questionnaires.

Nuts not evaluated
Significant association only in males
60% of cases died
Family interview
The effects of legumes and nuts are not differentiated

No association in individuals > 35 years old
Particular effect on distal colon
The effects of peanut butter, nuts and legumes are not differentiated

Broad, population-based study
The effects of legumes, nuts and seeds are not differentiated
Mostly salted nuts

It does not state which nuts are studied
Short list of food studied

Well-designed population-based study
Good evaluation of dietary intake. It is not clear which nuts are included
Dietary intake evaluated during the last 5 years (difficult to remember)
The effects of legumes, nuts and seeds are not differentiated
It does not state which nuts are studied

Table 3. Cohort and ecological studies on cancer and nuts

Study population						
Author	Country - year	Number	Type/study	Tumour	Dietetic method	Food evaluated
Heilbrun <i>et al.</i> Hawaii 1989		8006 (162 cases)	American Japanese Cohort	Colorectal	24-h recall	Nuts, seeds and legumes
Singh <i>et al.</i> USA 1998		32 051 (157 cases)	White adventist Cohort	Colorectal	SQ FFQ (55 items)	Nuts
Jenab <i>et al.</i> 10 European countries		478 040 (1329 cases)	Cohort	Colon/Rectum	SQ FFQ (200–300 items)	Nuts and seeds
Mills <i>et al.</i> USA 1989		14 000 (180 cases)	White adventist Cohort	Prostate	SQ FFQ (55 items)	Nuts
Hebert <i>et al.</i> 59 countries America, Europe, Asia		–	Cross-sectional ecological study	Prostate mortality	Food balance sheet	Calories of nuts and seed oils
Results OR (IC 95%)						
Remarks						
Only one 24-h recall used						
No difference between the effect of legumes and seeds						
No information about which nuts have been studied						
No dose response						
Big differences in intake between countries						
Possible differences in the quality of the information registered						
Raisins and dates are included in the category of nuts						
Soya (phytoestrogens) is included in the category of seed oils						
If it is taken out, but the other seed oils maintained, the protective effect remained						

FFQ = Food Frequency Questionnaire.

SQ FFQ = Dietary questionnaire on frequencies and standard portions.

24 h = 24-h intake recall.

We identified two case-control epidemiological studies on stomach cancer. One was carried out in Greece (Trichopoulos *et al.* 1985) and surprisingly found an increase in the risk, which the authors attributed to the fact that, in their country, nuts are commonly eaten salted, and salt is a well-known risk factor of gastric cancer. The other study was relatively broad and was conducted in Japan (Hoshiyama & Sasaba, 1992). It observed a protective effect with a clear dose response.

Finally, we found a case-control study on cancer of the pancreas (Bueno de Mesquita *et al.* 1991) and another on breast cancer (Iscovich *et al.* 1989) which observed no association with the intake of nuts, while a case-control study on dietary intake and the risk of endometrial cancer in Greece (Petridou *et al.* 2002) did observe a protective effect, although the results were for the intake of nuts, seeds and legumes, and were based on a small hospital study.

When interpreting the results of the epidemiological studies that have evaluated the intake of nuts and the risk of cancer, various limitations must be taken into account. Most studies have used questionnaires on the frequency of consumption as the instrument to evaluate dietary intake. This method has been widely used in the last 20 years because it is simple, easy to use and economic; however, it is associated with measurement errors (Prentice, 2003). Therefore, the absence of an association may be due simply to an error in measuring the dietary intake with the questionnaire.

It should also be borne in mind that the process of carcinogenesis starts with mutations and damage to the DNA and is completed when the tumoural cells multiply during a silent period, which may last for 10–20 years or even more, before the tumour can be clinically detected. This long latent period makes it difficult to establish the moment at which the process of carcinogenesis begins with any accuracy and it means that any investigation into the relations between diet and cancer must estimate the dietetic intake 15, 20 or more years before the tumour was diagnosed. Case control studies take into account the diet of the year before diagnoses of cases and assume that it represents the usual past diet.

It should also be taken into account that the components of nuts that can potentially prevent cancer, and which have been described elsewhere, are not exclusive to nuts but can be found in a wide variety of fresh fruit, vegetables, legumes and cereals. This means that it is very difficult to separate the effect of consuming the various sources. From a biological point of view, it is also highly unlikely that the isolated consumption of nuts, which is relatively low (the average of a European population is 5–10 g/d), will produce a strong biological effect. Therefore, it is more likely, and biologically more relevant, that the components of nuts add to and interact with the nutritional components of fruit and vegetables. This leads us to conclude that what is really important is the dietary pattern and that the most effective strategy for preventing cancer is to encourage a high intake of a wide variety of fruit, vegetables, legumes, whole cereals and nuts.

Conclusions

Although nuts contain vitamins and micronutrients that have potential biological mechanisms of action for reducing the risk of cancer, epidemiological evidence on the effects of

nuts on the risk of cancer in humans is still limited and insufficient. The location that has been most commonly studied is the colon/rectum, an organ in which the effects of nuts are biologically plausible. Despite the inconsistent results, a protective effect on cancer of the colon and rectum is possible, although many questions persist because of the incongruence of the results according to sex and because of the absence of a dose-response effect in some studies, an important criterion of causality.

Likewise, some studies show a possible protective effect of a high consumption of nuts on prostate cancer. On the other hand, there is not enough data to draw conclusions about other tumour locations. New and better epidemiological studies are required to clarify the possible effects of nuts on cancer, particularly prospective studies that make a reliable, complete estimation of consumption and which allow their effects to be analyzed independently of the consumption of other legumes and seeds.

References

- Adlercreutz H (1995) Phytoestrogens: epidemiology and a possible role in cancer protection. *Environ Health Perspect* **103**, Suppl. 7, 103–112.
- Bingham SA, Day NE, Luben R, *et al.* (2003) Dietary fibre in food and protection against colorectal cancer in the European Prospective Investigation into Cancer and Nutrition (EPIC): an observational study. *Lancet* **361**, 1496–1501.
- Bueno de Mesquita HB, Maisonneuve P, Runia S & Moerman CJ (1991) Intake of foods and nutrients and cancer of the exocrine pancreas: a population-based case-control study in The Netherlands. *Int J Cancer* **48**, 540–549.
- Clark LC, Dalkin B, Krongrad A, *et al.* (1998) Decreased incidence of prostate cancer with selenium supplementation: results of a double-blind cancer prevention trial. *Br J Urol* **81**, 730–734.
- COMA (Committee on Medical Aspects of Food and Nutrition Policy) (1998) *Nutritional aspects of the development of cancer*. Norwick, UK: COMA.
- Correa P, Fontham ET, Bravo JC, *et al.* (2000) Chemoprevention of gastric dysplasia: randomized trial of antioxidant supplements and anti-helicobacter pylori therapy. *J Natl Cancer Inst* **92**, 1881–1888.
- Dreher ML, Maher CV & Kearney P (1996) The traditional and emerging role of nuts in healthful diets. *Nutr Rev* **54**, 241–245.
- Graham S, Dayal H, Swanson M, Mittelman A & Wilkinson G (1978) Diet in the epidemiology of cancer of the colon and rectum. *J Natl Cancer Inst* **61**, 709–714.
- Greenberg ER, Baron JA, Tosteson TD, *et al.* (1994) A clinical trial of antioxidant vitamins to prevent colorectal adenoma. Polyp Prevention Study Group. *N Engl J Med* **331**, 141–147.
- Greenwald P, Clifford CK & Milner JA (2001) Diet and cancer prevention. *Eur J Cancer* **37**, 948–965.
- Hebert JR, Hurley TG, Olendzki BC, Teas J, Ma Y & Hampl JS (1998) Nutritional and socioeconomic factors in relation to prostate cancer mortality: a cross-national study. *J Natl Cancer Inst* **90**, 1637–1647.
- Heilbrun LK, Nomura A, Hankin JH & Stemmermann GN (1989) Diet and colorectal cancer with special reference to fiber intake. *Int J Cancer* **44**, 1–6.
- Heinonen OP, Albanes D, Virtamo J, *et al.* (1998) Prostate cancer and supplementation with alpha-tocopherol and beta-carotene: incidence and mortality in a controlled trial. *J Natl Cancer Inst* **90**, 440–446.

- Hoshiyama Y & Sasaba T (1992) A case-control study of stomach cancer and its relation to diet, cigarettes, and alcohol consumption in Saitama Prefecture, Japan. *Cancer Causes Control* **3**, 441–448.
- Iscovich JM, Iscovich RB, Howe G, Shiboski S & Kaldor JM (1989) A case-control study of diet and breast cancer in Argentina. *Int J Cancer* **44**, 770–776.
- Jain MG, Hislop GT, Howe GR & Ghadirian P (1999) Plant foods, antioxidants, and prostate cancer risk: findings from case-control studies in Canada. *Nutr Cancer* **34**, 173–184.
- Jenab M, Ferrari P, Slimani N, *et al.* (2004) Association of nut and seed intake with colorectal cancer risk in the European Prospective investigation into Cancer and Nutrition. *Cancer Epidemiol Biomarkers Prev* **13**, 1595–1603.
- Kannamkumath SS, Wrobel K, Wrobel K, Vonderheide A & Caruso JA (2002) HPLC-ICP-MS determination of selenium distribution and speciation in different types of nut. *Anal Bioanal Chem* **373**, 454–460.
- Key TJ, Allen NE, Spencer EA & Travis RC (2002) The effect of diet on risk of cancer. *Lancet* **360**, 861–868.
- Kris-Etherton PM, Hecker KD, Bonanome A, Coval SM, Binkoski AE, Hilpert KF, Griel AE & Etherton TD (2002) Bioactive compounds in foods: their role in the prevention of cardiovascular disease and cancer. *Am J Med* **113**, Suppl 9B, 71S–88S.
- Kune S, Kune GA & Watson LF (1987) Case-control study of dietary etiological factors: the Melbourne Colorectal Cancer Study. *Nutr Cancer* **9**, 21–42.
- Kushi LH, Lenart EB & Willett WC (1995) Health implications of Mediterranean diets in light of contemporary knowledge. 1. Plant foods and dairy products. *Am J Clin Nutr* **61**, 1407S–1415S.
- Liggins J, Bluck LJ, Runswick S, Atkinson C, Coward WA & Bingham SA (2000) Daidzein and genistein content of fruits and nuts. *J Nutr Biochem* **11**, 326–331.
- Martin-Moreno JM (2000) The role of olive oil in lowering cancer risk: is this real gold or simply pinchbeck? *J Epidemiol Commun Health* **54**, 726–727.
- Mills PK, Beeson WL, Phillips RL & Fraser GE (1989) Cohort study of diet, lifestyle and prostate cancer in Adventist men. *Cancer* **64**, 598–604.
- Omenn GS (2000) Chemoprevention of lung cancer is proving difficult and frustrating, requiring new approaches. *J Natl Cancer Inst* **92**, 959–960.
- Peters RK, Pike MC, Garabrant D & Mack TM (1992) Diet and colon cancer in Los Angeles County, California. *Cancer Causes Control* **3**, 457–473.
- Petridou E, Kedikoglou S, Koukoulomatis P, Dessypris N & Trichopoulos D (2002) Diet in relation to endometrial cancer risk: a case-control study in Greece. *Nutr Cancer* **44**, 16–22.
- Pickle LW, Greene MH, Ziegler RG, Toledo A, Hoover R, Lynch HT & Fraumeni JF Jr (1984) Colorectal cancer in rural Nebraska. *Cancer Res* **44**, 363–369.
- Prentice RL (2003) Dietary assessment and the reliability of nutritional epidemiology reports. *Lancet* **362**, 182–183.
- Schatzkin A, Lanza E, Corle D, *et al.* (2000) Lack of effect of a low-fat, high-fiber diet on the recurrence of colorectal adenomas. Polyp Prevention Trial Study Group. *N Engl J Med* **342**, 1149–1155.
- Simonsen NR, Fernandez-Crehuet NJ, Martin-Moreno JM, *et al.* (1998) Tissue stores of individual monounsaturated fatty acids and breast cancer: the EURAMIC study. European Community Multicenter Study on Antioxidants, Myocardial Infarction, and Breast Cancer. *Am J Clin Nutr* **68**, 134–141.
- Singh PN & Fraser GE (1998) Dietary risk factors for colon cancer in a low-risk population. *Am J Epidemiol* **148**, 761–774.
- Stoner GD & Mukhtar H (1995) Polyphenols as cancer chemopreventive agents. *J Cell Biochem Suppl* **22**, 169–180.
- Terry P, Giovannucci E, Michels KB, Bergkvist L, Hansen H, Holmberg L & Wolk A (2001) Fruit, vegetables, dietary fiber, and risk of colorectal cancer. *J Natl Cancer Inst* **93**, 525–533.
- Trichopoulos D, Ouranos G, Day NE, Tzonou A, Manousos O, Papadimitriou C & Trichopoulos A (1985) Diet and cancer of the stomach: a case-control study in Greece. *Int J Cancer* **36**, 291–297.
- van Erp-Baart MA, Brants HA, Kiely M, Mulligan A, Turrini A, Sermoneta C, Kilkkinen A & Valsta LM (2003) Isoflavone intake in four different European countries: the VENUS approach. *Br J Nutr* **89**, Suppl. 1, S25–S30.
- WCRF, & AICR: World Cancer Research Fund & American Investigation of Cancer Research (1997) *Food, Nutrition and the Prevention of Cancer: a global perspective*. Menasha, USA: BANTA Book Group.
- World Health Organization (2004) *The world health report 2004: changing history*. Geneva: WHO.
- Yang CS, Landau JM, Huang MT & Newmark HL (2001) Inhibition of carcinogenesis by dietary polyphenolic compounds. *Annu Rev Nutr* **21**, 381–406.
- Young TB & Wolf DA (1988) Case-control study of proximal and distal colon cancer and diet in Wisconsin. *Int J Cancer* **42**, 167–175.