Original Article

Plantago Ovata Consumption and Colorectal Mortality in Spain, 1995–2000

José Carlos López, Rosa Villanueva, David Martínez-Hernández, Romana Albaladejo, Enrique Regidor, and María Elisa Calle

Department of Preventive Medicine and Public Health and History of Science, Faculty of Medicine, Complutense University, Madrid, Spain

ABSTRACT

Background: Consumption of *Plantago ovata* may protect against colorectal cancer. To test this hypothesis, an ecological study was performed to determine mortality rates and distribution of colorectal cancer, and the consumption and distribution of *P ovata,* in different provinces in Spain. The putative association between *P ovata* consumption and mortality from colorectal cancer was then evaluated.

Methods: We conducted a comparative ecological study of Spanish provinces, with colorectal cancer mortality as the dependent variable and per capita consumption of *P ovata* by province and year as the independent variable. Associations were analyzed by calculating Spearman's correlation coefficients and a Poisson multiple regression model.

Results: Consumption of *P ovata* tended to be inversely correlated with mortality from colorectal cancer. In the Poisson regression analysis this tendency remained and reached statistical significance for the top quintile of *P ovata* consumption in the adjusted analysis ($P = 0.042$).

Conclusions: Our results show an inverse trend between the consumption of *P ovata* and colorectal cancer mortality. We recommend additional observational studies of individuals, in order to better control confounding factors.

Key words: colorectal cancer; *Plantago ovata*; ecological study; population study

INTRODUCTION

Tumors of the colon and rectum are generally analyzed jointly because it is difficult to establish clear differences between them, particularly for tumors of the rectosigmoid region.[1,2] There is an upward trend in incidence rates for these tumors in the developed world; however, mortality rates have stabilized or begun to decrease, as is the case in the United States.[2] In Spain, colorectal cancer was responsible for 11% of cancer deaths in men, and 15% of cancer deaths in women, in the year 2000.[3] It is estimated that the number of new cases is approximately 21 000 per year in both sexes, with a total of 11 900 deaths. Mortality has continued to increase since 1975 and is very high. Colorectal cancer is now regarded as the second most frequent cancer in both men and women.[3]

The most important known etiologic factors for colorectal cancer are genetic predisposition and diet. The dietary risk factors include greater consumption of red and processed meat ("convincing" risks) and animal fats (a "limited" risk),[4] whereas consumption of garlic, vegetables, and foods containing dietary fiber and calcium is believed to be protective.[4]

More than 30 years ago, the research of Trowell[5] and Burkitt[6] gave rise to the fiber theory, which suggested that a high-fiber diet could protect against a range of diseases and conditions, such as colon cancer, constipation, diverticulosis, diabetes, obesity, and cardiovascular disease.

With respect to clinical practice, fiber is classified as soluble or insoluble. A specific variety of fiber is present in the *Plantago* family, among which *Plantago ovata* is the most frequently used variety. The seeds of *P ovata* contain a 20/80 ratio of soluble and insoluble fibers, and the husks a 70/30 ratio. The US Food and Drug Administration recommends that the dietary fiber component of a balanced diet should comprise 70% to 75% insoluble fiber and 25% to 30% soluble fiber, which makes the seeds of *P ovata* an ideal source of fiber.[7]

Address for correspondence. Dr. Rosa Villanueva, Department of Preventive Medicine and Public Health and History of Science, Faculty of Medicine, Complutense University, Ciudad Universitaria sn 28040 Madrid, Spain (e-mail: mrvillan@med.ucm.es).

Various commercial preparations derived from *P ovata* are used in Spain. Their therapeutic indications include conditions characterized by alternate episodes of diarrhea and constipation (irritable colon, diverticulosis); functional diarrheas; ulcerous colitis in remission; proctological processes; habitual, chronic, or secondary constipation (due to travel or in bedridden patients); and regulation of evacuation in post-colostomy patients. *P ovata* can also be consumed to complement daily fiber intake.[8]

The consumption of *P ovata* improves the postprandial glucose curve in patients with diabetes, especially those with type II diabetes. This effect has been demonstrated in a number of experimental studies, in which the husks had the greatest effect. Clinical trials have confirmed this hypoglycemic effect.[9]

A total of 16 cohort studies and 91 case-control studies[4] have reported findings which indicate that a diet rich in fiber protects against colon cancer. This protective effect has been ascribed to the production of butyric acid in the colonic fermentation of dietary fiber.[10] Butyric acid produces acetylation, induces apoptosis, favors cellular differentiation, and regulates the expression of some oncogenes. Butyrate also has antineoplastic properties in colon cancer and is the preferred oxidative substrate for colonocytes. Increased production of butyric acid has been observed after ingestion of *P ovata*. This acts on sterol metabolism to reduce the concentration of plasma cholesterol, and increases elimination of biliary acids.[11] The effects in both cases depend on continued intake of the *P ovata* preparation.[11]

It is considered likely that certain dietary factors, possibly including consumption of *P ovata*, play a protective role in colon cancer, as was observed in a previous study carried out by the present research team.[12] Based on these findings, we investigated both the consumption of *P ovata* and mortality from colorectal cancer by age group and sex in each province of Spain during the period from 1995 through 2000. The putative association between consumption of *P ovata* and mortality from colorectal cancer was then evaluated.

METHODS

We conducted an ecological study that compared time trends in colorectal cancer mortality and consumption of *P ovata* in Spanish provinces. Age-adjusted colorectal cancer mortality was the dependent variable; the independent variable was per capita consumption of *P ovata* by province and year.

Colorectal mortality rates by sex and age were collected for the 50 provinces of Spain for the period from 1995 through 2000.[13] The mortality rates were standardized in accordance with the European population, by sex and age, using the indirect method. Specific mortality rates for colorectal cancer were calculated, by province and year, in the following age groups: 0 to 4, 5 to 14, 15 to 24, 25 to 34, 35 to 44, 45 to 54, 55 to 64, 65 to 74, and ≥75 years. The mean mortality

quintiles (Qmean) were also calculated, where 1 has the lowest mortality and 5 has the highest.

The information needed to calculate the per capita fiber consumption for each province and for each year of the study period (1995–2000) was obtained from data taken from the sales records for preparations containing *P ovata* as an active ingredient. These records were supplied by the pharmaceutical laboratories that produce this preparation in Spain and by the Spanish Medicine Agency.[14] The total amount (in milligrams) of *P ovata* contained in each preparation studied (Cenat, Plantaben, Agiolax, Plantago Ovata Davur) was obtained. This amount was multiplied by the number of units sold in each province and year, and then divided by the Spanish Statistical Institute (INE) population projections for each year. Based on these calculations of per capita consumption per year, mean consumption was obtained for each province over the period examined. The mean quintiles of fiber consumption (QmeanF) were also calculated, where 1 is the lowest consumption and 5 is the highest. The association between mortality from colorectal cancer and consumption of *P ovata* was analyzed by calculating Spearman's correlation coefficients.

Also included in the study were a series of co-variables which could affect the associations. These were obtained from the *Disabilities, Deficiencies and Health Status Survey of 1999* (INE), a survey of 220 000 people that are representative of the resident population in Spain.[15] The relevant variables for the study were selected and then converted into dichotomous variables, as shown in Table 1. The variables were also analyzed using a Poisson multiple regression model.[16,17,18] First, the unadjusted relative risk of colorectal cancer mortality was calculated for each quintile of fiber consumption. The final model thus obtained was then adjusted for the other independent variables; educational level and regular physical activity were included in the final model. Data processing and analysis were performed using the SAS 9.1 and SPSS 15.0 statistical packages.

RESULTS

The mean adjusted mortality rate for colorectal cancer during the period from 1995 through 2000 was 22.93 per 100 000 population in men and 18.34 in women; the combined rate was 20.93. With respect to mean colorectal mortality rate per province for the study period (Figure 1), there was a north-to-south distribution (higher-to-lower mortality).

Regarding the average consumption of *P ovata* during the period analyzed, the highest average intakes per person were in Segovia and Navarra, and the lowest were in Cuenca and Murcia (Figure 2).

Regarding the association between mean per capita consumption of *P ovata* and mean mortality rate in each province, lower consumption tended to be associated with higher mortality (Figure 3). The correlation between sex and

Table 1. Coding in the present study of variables included in "Disabilities, Deficiencies and Health Status Survey" (INE)

DEMOGRAPHIC VARIABLES

CIVIL STATUS: MARRIED = 0; SINGLE OR WIDOWED = 1
NATIONALITY: SPANISH = 0; OTHER = 1
INCOME LEVEL: MONTHLY INCOME >195 000 pesetas = 0; ≤195 000 pesetas = 1
EDUCATIONAL LEVEL: VOCATIONAL TRAINING LEVEL 2, SECONDARY or tertiary education = 0; OTHER (ILLITERATE, NO SCHOOLING, PRIMARY education, OR VOCATIONAL TRAINING LEVEL 1) = 1

LIFESTYLE VARIABLES

TOBACCO CONSUMPTION: DAILY SMOKER = 1; OTHER (OCCASIONAL SMOKER, FORMER SMOKER, or Never SMOKER) = 0
ALCOHOL CONSUMPTION: DAILY DRINKER = 1; OTHER (DRINKER 4–6 TIMES PER WEEK, 2–3 TIMES PER WEEK, ONCE A WEEK, LESS THAN ONCE A WEEK, FORMER DRINKER, or Never DRINKER) = 0
PHYSICAL Exertion IN MAIN WORK ACTIVITY: WORK REQUIRING heavy PHYSICAL EXERTION = 0; OTHER (SEATED MOST OF DAY, STANDING MOST OF DAY, LITTLE MOVEMENT OR EXERTION, WALKING with WEIGHT, OR MOVING AROUND FREQUENTLY) = 1
PHYSICAL EXERCISE: ENGAGES IN PHYSICAL EXERCISE OR SPORT SEVERAL TIMES PER WEEK = 0; OTHER (NO EXERCISE, COMPLETELY SEDENTARY, or ENGAGES IN PHYSICAL ACTIVITY OCCASIONALLY OR SEVERAL TIMES PER MONTH) = 1

HEALTH VARIABLES

SELF-PERCEIVED STATE OF HEALTH: VERY GOOD OR GOOD = 0; FAIR, POOR, OR VERY POOR = 1
CHOLESTEROL LEVEL: HYPERCHOLESTEROLEMIA YES = 1; NO = 0
BODY MASS INDEX: QUETELET INDEX <30 = 0; ≥30 = 1
CHRONIC ILLNESS: SUFFERS FROM CHRONIC disorder YES = 1; NO = 1

Figure 1. Mean annual mortality per 100 000 population in Spain, 1995–2000. Distribution in quintiles: ■ <15.00; ■ 15.00–19.99; ■ 20.00–24.99; ■ 25.00–29.99; ■ >30.00
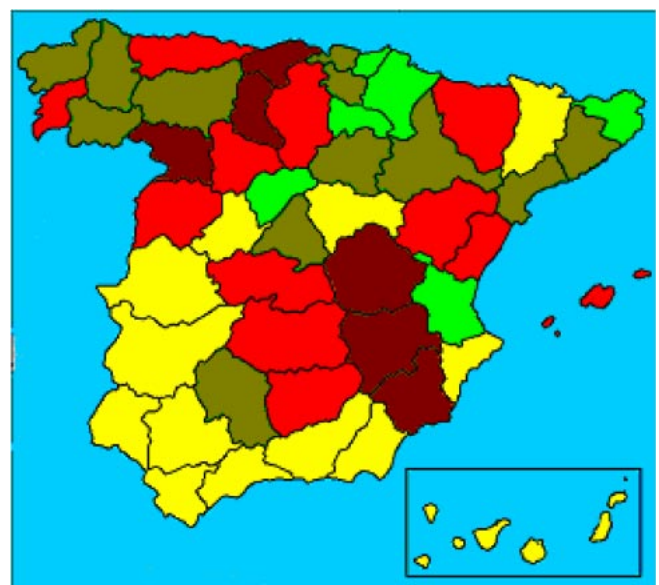

Figure 2. Average annual consumption rate of *P ovata* (mg) in Spain, 1995–2000. Distribution in quintiles: ■ <20.000; ■ 20.000–29.999; ■ 30.000–39.999; ■ 40.000–49.999; ■ ≥50.000

colorectal cancer mortality showed a negative trend, but this trend was not statistically significant (Figure 3).

In the Poisson multiple regression model, there was a tendency for high consumption of *P ovata* to be protective against colorectal cancer in the raw model (Table 2). In the adjusted model, this protective trend remained, and the association was significant for the top quintile (*P* = 0.042) (Table 2).

DISCUSSION

Despite decades of epidemiological research, there is insufficient evidence for a causal relation between diet and

cancer in general, and colorectal cancer in particular—with the exception of a few dietary factors. Most information on these associations comes from ecological studies of mortality, which are considered the most appropriate first step for developing new hypotheses. Statistics on deaths by cause of death are one of the most important sources of information for the study of the characteristics of population health and disease. Standard disease categories are used for all countries (International Classification of Diseases, 10th revision), and mortality statistics provide the basic data for such studies.

Scattered diagram of colorectal cancer mortality rate by average consumption rate of P. ovata
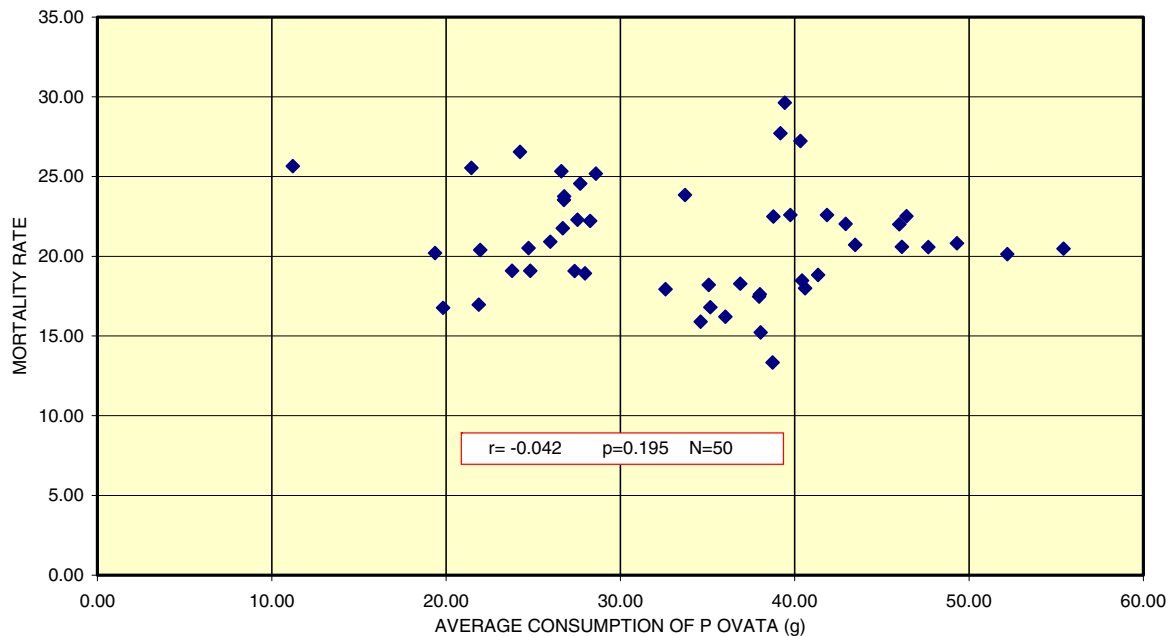
Figure 3. Scatter plot of average consumption of *P ovata* and colorectal cancer mortality for all Spanish provinces, 1995–2000

Table 2. Crude and adjusted relative risks for colorectal cancer mortality by fiber consumption, in quintiles

	RR	95% CI	P
RR CRUDE ANALYSIS			
QmeanFO1	1	1–1	
QmeanFO2	0.909	0.555–1.380	0.220
QmeanFO3	1.091	0.624–1.540	0.121
QmeanFO4	0.606	0.578–1.018	0.060
QmeanFO5	0.939	0.575–1.044	0.063
RR ADJUSTED* ANALYSIS			
QMEDIAFO1	1	1–1	
QMEDIAFO2	0.817	0.452–1.476	0.388
QMEDIAFO3	0.940	0.534–1.430	0.120
QMEDIAFO4	0.747	0.370–1.023	0.061
QMEDIAFO5	0.746	0.416–0.908	0.042

Abbreviations: RR, Relative Risk; QMEDIAF, Quintiles of fiber consumption (01 - lowest consumption; 05 - highest consumption).
*Adjusted for educational level and physical activity.

Another advantage of ecological studies is that when there is little variation in exposure among individuals in a particular geographic area, as is the case with certain types of dietary intake, studies of individuals are unable to investigate a sufficiently wide range of individuals, with different exposure levels, to allow epidemiological associations to be determined. Therefore, an ecological study that encompasses a large number of geographic areas, with variation in exposure to variables such as diet, can be a valid option.[19,20] That is why we selected this type of epidemiological design for the present study.

We found considerable variation in adjusted mortality rates between provinces. For the years studied, rates were higher in the north—the area with the highest level of per capita income and industrialization. A close association was found between per capita income and physical activity (both at work and leisure), and seems to be a protective factor in colorectal cancer. However, this association is subject to confounding factors—such as sedentary lifestyle, diet, fat consumption, body weight, and lifestyles associated with physical activity (such as low use of tobacco and alcohol)—which are also related to educational level.[21–24] For these reasons, physical activity and educational level are included in the subsequent Poisson analysis.

Previous ecological studies have shown that industrialization is accompanied by higher rates of colorectal cancer, and that industrialization is positively correlated with greater consumption of vegetable oil, chicken, poultry, and pork. However, there was no such correlation between industrialization and mean intakes of fish, cereals, and fresh vegetables, which remained stable.[25] These data suggest that dietary changes, particularly increased consumption of foods containing animal fats, play a role in the increased incidence of colorectal cancer.[4,25–27]

Geographic differences in mortality rates may also be due to other dietary factors that have been implicated in tumorigenesis, such as total fiber consumption and fiber source,[28,29] which vary widely between countries. For example, the main source of fiber is vegetables in France; fruit in Italy; and fruit, legumes, and potatoes in Spain.[30]

The *Second Expert Report: Food, Nutrition, Physical Activity and the Prevention of Cancer* categorized different fiber-rich foods, including garlic, as probable protective factors against colorectal cancer.[4] For other foods —including fruit, legumes, and potatoes—the evidence of a preventive role against colorectal cancer was described as limited.[4]

The mechanisms by which fiber inhibits carcinogenesis are well established. Fiber is known to increase fecal weight, reduce intestinal transit time, and dilute carcinogenic substances in the colon by osmosis.[31] Fiber also provides a substrate for bacterial activity, and generates short-chain fatty acids such as acetate, propionate, and butyrate, which exert anti-carcinogenic effects by reducing fecal mutagenicity.[32–34] Furthermore, butyrate in the distal colon reduces cellular proliferation and induces apoptosis; both mechanisms inhibit the transformation of colonic epithelium to carcinoma.[30] For all these reasons, the World Cancer Research Fund and the American Institute for Cancer Research assert that the evidence supports a probable relation between a high level of fiber consumption and lower risk of colorectal cancer.[4]

Although much research has been done on the overall role of fiber, few epidemiological studies have examined the anti-carcinogenic role played by each nutrient or each dietary supplement.[12,35,36] This is why we examined the role of the fiber supplement *P ovata* in reducing mortality from colorectal cancer.

We have already noted that *P ovata* is an ideal source of fiber. A large proportion of the fiber in the seeds and husks of this plant is fermentable in the colon, which gives rise to different protective mechanisms. First, *P ovata* inhibits bacterial β-glucuronidase, thereby reducing the incidence of colorectal tumors by decreasing the hydrolysis of glucuronide-conjugated carcinogens.[37–39] Second, the seeds increase the elimination of biliary acids from the feces, which also contributes to decreasing the risk of colorectal tumors. Third, a clinical trial in Spain showed that *P ovata* is effective in maintaining remission in ulcerative colitis, which has some etiopathogenic mechanisms in common with carcinogenesis.[40] These processes may be due not only to an increase in the previously mentioned protective mechanisms, but also by a reduction in inflammatory mediators such as TNF-α and NO.[41] Fourth, other studies have shown that consumption of *P ovata* increases production of butyrate and acetate by the intestinal flora, and results in higher levels of these fatty acids in the feces of patients who had undergone intestinal resection due to colon cancer.[40,42]

A preliminary study showed an inverse trend between *P ovata* consumption and mortality from colorectal cancer.[12] In the present study, when the Poisson regression analysis was completed, a protective trend associated with increased intake of *P ovata* was noted in the adjusted model. This association was statistically significant in the top quintile of *P ovata* consumption ($P = 0.042$).

Although ecological designs permit only limited epidemiological inferences, the international dissemination of these studies has helped to identify associations between diet and disease that were later confirmed by subsequent studies. Our results showed a tendency toward an inverse association between *P ovata* intake and colorectal cancer mortality; however, the study period was likely too short to confirm the protective effect of fiber consumption. Therefore, we believe that continued research, particularly observational studies of individuals, is warranted. Such research would be capable of confirming the putative association of *P ovata* consumption with colorectal cancer mortality and would allow for better control of confounding factors.

ACKNOWLEDGMENTS

REFERENCES

1. López Abente G, Pollán M, Escolar A, Errezola M, Abraira V. Atlas of Cancer Mortality and other causes of Death in Spain 1978–1992. Fundacion Científica de la Asociación Española Contra el Cáncer. Madrid 1996.
2. López-Abente G, Pollán M, Aragonés N, Pérez-Gómez B, Hernández V, Lope V, et al. Plan Integral del Cáncer: Situación del cáncer en España. Madrid: Ministerio de Sanidad y Consumo. 2005.
3. Centro Nacional de Epidemiología. Área de Epidemiología Ambiental y Cáncer. Mortalidad por Cáncer en España, 2000. Available at: http://cne.isciii.es/cancer/mort2000.txt.
4. World Cancer Research Fund, American Institute for Cancer Research. The Second Expert Report. Food, Nutrition, Physical Activity and the Prevention of Cancer: A Global Perspective. Available at: http://www.dietandcancerreport.org, 2007.
5. Trowell H. The development of the concept of dietary fiber in human nutrition. Am J Clin Nutr. 1978;31:S3–11.
6. Burkitt DP, Walker AR, Painter NS. Dietary fiber and disease. JAMA. 1974;229(8):1068–74.
7. Food and Drug Administration (FDA) news. P04-100, November 2004.
8. Ficha técnica de Plantaben®, Diciembre 2001. Laboratorio MADAUS S.A.
9. Pastors JG, Blaisdell PW, Balm TK, Asplin CM, Pohl SL. Psyllium fiber reduces rise in postpandrial glucose and insulin concentrations in patients with non-insulin-dependent diabetes. Am J Clin Nutr. 1991;53:1431–5.
10. Lupton JR. Is fiber protective against colon cancer? Where the research is leading us. Nutrition. 2000;16:558–61.
11. Gelissen IC, Brodie B, Eastwood MA. Effect of Plantago ovata (psyllium) husk and seeds on sterol metabolism: studies in normal and ileostomy subjects. Am J Clin Nutr. 1994;59:395–400.
12. Juarranz M, Calle-Purón ME, González-Navarro A, Regidor-

Poyatos E, Soriano T, Martínez-Hernandez D, et al. Physical exercise, use of Plantago ovata and aspirin, and reduced risk of colon cancer. Eur J Cancer Prev. 2002;11(5):465–72.

13. Instituto Nacional de Estadística (INE). Defunciones por provincia, edad y sexo 1995–2000. Available at: http://www.ine.es/inebmem/indice.htm.

14. Agencia Española del Medicamento y Productos Sanitarios. Available at: http://www.agemed.es/aplicaciones/home.htm.

15. Instituto Nacional de Estadística. Encuesta sobre Discapacidades, Deficiencias y Estado de Salud 1999. Madrid: INE. 2002.

16. Monge-Corella S, García-Pérez J, Aragonés N, Pollán M, Pérez-Gómez B, López-Abente G. Lung cancer mortality in towns near paper, pulp and board industries in Spain: a point source pollution study. BMC Public Health. 2008;8:288.

17. Cordier S, Monfort C, Miossec L, Richardson S, Belin C. Ecological analysis of digestive cancer mortality related to contamination by diarrhetic shellfish poisoning toxins along the coasts of France. Environ Res. 2000;84:145–50.

18. Marque S, Jacqmin-Gadda H, Dartigues JF, Commenges D. Cardiovascular mortality and calcium and magnesium in drinking water: an ecological study in elderly people. Eur J Epidemiol. 2003;18:305–9.

19. Willet. Nutritional epidemiology (2ª ed). University Press, New York: Oxford. 1998.

20. Bolúmar F, Vioque J, Rebagliato M. Estudios descriptivos ecológicos. Estudios transversales. In Medicina Preventiva y Salud Pública (ed Piédrola Gil); Masson, Barcelona, 2001: 87–100.

21. Giovannucci E. Modifiable risk factors for colon cancer. Gastroenterol Clin North Am. 2002;31:925–43.

22. Giovannucci E. Obesity, gender and colon cancer. Gut. 2002;51:147.

23. González CA, Navarro C, Martínez C, Quirós JR, Dorronsoro M, Barricarte A, et al. El estudio prospectivo europeo sobre cáncer y nutrición (EPIC). Rev Esp Salud Publica. 2004;78:167–76.

24. IARC Working Group on the Evaluation of Cancer-Preventive Agents. *Weight control and physical activity*. Handbooks of cancer prevention, vol. 6. Lyon: IARC Press. 2002.

25. You WC, Jin F, Devesa S, Schatzkin A, Yang G, Rosenberg P, et al. Rapid increase in colorectal cancer rates in urban Shangai, 1972–97, in relation to dietary changes. J Cancer Epidemiol Prev. 2002;7(3):143–6.

26. Kono S. Secular trend of colon cancer incidence y mortality in relation to fat and meat intake in Japan. Eur J Cancer Prev. 2004;13:127–32.

27. Wynder EL, Cohen LA, Winters RD. The challenges of assessing fat intake in cancer research investigations. J Am Diet Assoc. 1997;97(S):S5–S8.

28. Bingham SA. Diet and colorectal cancer prevention. Biochem Soc Trans. 2000;28:12–6.

29. Pylkas AM, Juneja LR, Slavin JL. Comparison of different fibers for in vitro production of short chain fatty acids by intestinal microflora. J Med Food. 2005;8:113–6.

30. Bingham SA, Day NE, Luben R, Ferrari P, Simani N, Norat T, et al. Dietary fiber in food and protection against colorectal cancer in the European Prospective Investigation into Cancer and Nutrition: an observational study. Lancet. 2003;361:1496–501.

31. Alabaster O, Tang Z, Shivapurkar N. Dietary fiber and the chemopreventive modelation of colon carcinogenesis. Mutat Res. 1996;350:185–97.

32. Jacobs LR. Relationship between dietary fibre and cancer: metabolic, physiologic, and cellular mechanisms. Proc Soc Exp Biol Med. 1986;183:299–310.

33. Clausen MR, Bonnen H, Mortensen PB. Colonic fermentation of dietary fiber to short chain fatty acids in patients with adenomatous polyps and colonic cancer. Gut. 1991;32:923–8.

34. Donaldson MS. Nutrition and cancer: a review of the evidence for anticancer diet. Nutr J. 2004;3:19–40.

35. Woods SE, Basho S, Engel A. The influence of gender on colorectal cancer stage: the state of Ohio, 1996–2001. J Womens Health. 2006;15:877–81.

36. Wakai K, Hirose K, Matsuo K, Ito H, Kuriki K, Suzuki T, et al. Dietary Risk Factors for Colon and Rectal Cancers: a comparative case-control study. J Epidemiol. 2006;16:125–35.

37. Quinn MJ, d'Onofrio A, Moller B, Black C, Martínez-García, Moller H, et al. Cancer mortality trends in the EU and acceding countries up to 2015. Ann Oncol. 2003;14:1148–52.

38. Sun Y, Li Y. Induction of β-glucuronidase activity during dimetylhhydrazine and additive effects of cholic acid and indole. Cancer Lett. 1988;39:69–76.

39. Nordgaard I, Hove H, Claisen MR, Mortensend PB. Colonic production of butyrate in patients with previous colonic cancer during long-term treatment with dietary fibre (Plantago ovata seeds). Scand J Gastroenterol. 1996;31:1011–20.

40. Fernandez-Bañares F, Hinojosa J, Sánchez-Lombrana JL, Navarro E, Martínez-Salmerón JF, García-Pugés, et al. Randomized clinical trial of Plantago ovata seeds (dietary fiber) as compared with mesalamine in maintaining remission in ulcerative colitis. Spanish Group for the Study of Crohn's Disease and Ulcerative Colitis (GETECCU). Am J Gastroenterol. 1999;94:427–33.

41. Rodriguez-Cabezas ME, Gálvez J, Lorente MD, Concha A, Camuesco D, Azzouz S, et al. Dietary fiber down-regulates colonic tumor necrosis factor-α and nitric oxide production in trinitrobenzenesulfonic acid-induced colitic rats. J Nutr. 2002;132:3263–71.

42. Plantago ovata (Psyllium). Altern Med Rev. 2002;7:155–9.