Public Health Nutrition: 14(12A), 2316–2322 doi:10.1017/S1368980011002576

Wholegrain cereals and bread: a duet of the Mediterranean diet for the prevention of chronic diseases

Angel Gil[1,*], Rosa M Ortega[2] and José Maldonado[3]

[1]Department of Biochemistry and Molecular Biology II, Centre for Biomedical Research (CIB), Institute of Nutrition and Food Technology, University of Granada, Avda. del Conocimiento s/n, 18100 Armilla, Granada, Spain: [2]Department of Nutrition, School of Pharmacy, Complutense University of Madrid, Spain: [3]Department of Paediatrics, School of Medicine, University of Granada, Spain

Submitted 13 May 2011: Accepted 7 September 2011

Abstract

Objective: The promotion of healthy lifestyles is one of the major goals of governments and international agencies all over the world. Wholegrain cereals are rich in nutrients and many phytochemical compounds, with recognised benefits for health, including dietary fibre, a number of phenolic compounds, lignans, vitamins and minerals and other bioactive components. The aim of the present work is to review the fundamental studies that support the consumption of wholegrain cereals and bread to prevent chronic diseases.
Design: Descriptive review considering human studies.
Setting and subjects: Subjects included in randomised intervention trials and cohort studies from different countries published up to 2010.
Results: Several studies show consistently that subjects who ingest three or more portions of foods per day based on wholegrain cereals have a 20–30 % lower risk of CVD than subjects who ingest low quantities of cereals. This level of protection is not observed with the ingestion of refined cereals, these being even higher than with the intake of fruit and vegetables. Likewise, high intake of wholegrain cereals and their products, such as whole-wheat bread, is associated with a 20–30 % reduction in the risk of type 2 diabetes. Finally, protection against the risk of colorectal cancer and polyps, other cancers of the digestive tract, cancers related to hormones and pancreatic cancer has been associated with the regular consumption of wholegrain cereals and derived products.
Conclusions: The regular intake of wholegrain cereals can contribute to reduction of risk factors related to non-communicable chronic diseases.

Keywords
Bread
Cereals
Chronic disease
Grains
Diet
Mediterranean

Foods based on wholegrain cereals, including bread, play an important part in health and well-being. Thus, research consistently indicates that the regular consumption of wholegrain cereals reduces the risk of CVD, type 2 diabetes mellitus (DM2) and certain types of cancer, as well as several gastrointestinal pathologies[1–5].

Wholegrain cereals, those containing all the parts of the grain (bran, germ and endosperm), are rich in nutrients and phytochemical compounds, with recognised benefits for health, such as dietary fibre, antioxidants, including phenolic compounds, phytoestrogens including lignans, vitamins and minerals. In fact, the advantages of wholegrain cereals are related not only to greater fibre content but also to higher content of essential fatty acids, vitamin-B complex, vitamin E, Fe, K, Mg, Zn, Se and other bioactive components[2,6].

Most of the substances that promote health in wholegrain cereals are found in the germ and bran. It is believed that these compounds exert an additive, synergetic effect on health when consumed together[7]. In particular, cereals contain various non-amylaceous polysaccharides, namely cellulose, pentosans and β-glucans. These compounds are hydrolysed by endogenous digestive enzymes and, being cell-wall constituents, abound in the external parts of the grain. Therefore, their content is greater in wholegrain or less processed flours.

The major compound in bread is starch. Starch is classified into rapidly digestible starch (RDS), slowly digestible starch (SDS) and resistant starch (RS)[8] according to the rate of glucose release and its absorption in the gastrointestinal tract. SDS, which leads to a slower entry of glucose into the blood stream and a lower glycaemic response, is digested completely in the small intestine at a lower rate as compared to RDS, whereas RS is the starch portion that cannot be digested in the small intestine, but is fermented in the large intestine. Experimentally, each starch fraction can be quantified on the

*Corresponding author: Email agil@ugr.es

basis of the *in vitro* Englyst method[8,9]: starch digested within 20 min belongs to RDS, whereas SDS represents the digested starch between 20 and 120 min, and the remaining fraction is RS. Bread has a variable proportion of SDS and of RS, according to the variety of grain. In white breads, the proportion of RS is high, reaching 5·6–8·1 % due to the incomplete gelatinisation of the starch in the crust. Starch in bread tends to retrograde, so that from the moment the bread is made, the portion of resistant starch increases over time, this being more pronounced in pre-cooked breads[10]. Some varieties of French bread (the traditional baguette) have lower insulinaemic index in healthy subjects, and lower glycaemic index (GI) in type 2 diabetic subjects, than that of the other varieties; these results might be due to bread processing difference rather than fibre content[11].

Soluble fibres present in bread are partially hydrolysed and used as a substrate by the intestinal microbiota, augmenting the mass of colon bacteria and the synthesis of volatile fatty acids – acetic, propionic and butyric acids – as well as gases such as nitrogen and methane. These fatty acids can be used by the colonocyte as an energy source. Its ingestion in the appropriate quantity is associated with lower levels of plasma cholesterol and TAG as well as a lower postprandial peak of glucose and insulin[9].

The aim of the present study is to review the fundamental studies, concerning both epidemiology as well as intervention, which support the consumption of wholegrain cereals and bread to prevent CVD, DM2, colorectal cancer and other cancers, as well as certain gastrointestinal pathologies.

CVD

There is ample epidemiological and clinical evidence that relates the consumption of wholegrain cereals with a reduced risk of coronary disease[10,11]. Subjects who ingest three or more rations of foods per day based on integral cereals have a 20–30 % lower risk than subjects who ingest low quantities of cereals, and this level of protection is not observed with the ingestion of refined cereals, these being even higher than with the intake of fruits and vegetables[1,6,12–16].

Morris *et al.*[17], after studying 337 subjects for 10–20 years, concluded that the reduction in the risk of CVD was attributable to a greater consumption of cereal fibre, whereas other sources of soluble fibre such as pectin and guar gum did not present the same effect. In addition, an analysis of several cohort studies on dietary fibre and coronary disease risk showed that the consumption of dietary fibre from cereals and fruits was inversely associated with the risk of coronary disease[18]. Other large surveys have found a moderate association between the intake of wholegrain cereal and the lowering of CVD risk. In an extensive prospective health study in Iowa (USA), 34 492 postmenopausal women aged 55–69 years and free of CVD were tracked to determine the occurrence of mortality by CVD (n 387) from 1986 to 1994[15]. The lowering of the risk in the highest quintile of wholegrain cereal intake was controlled for more than fifteen variables and was not explained by the adjustment of the consumption of dietary fibre. This suggests that other components of wholegrain cereal that are not dietary fibre may reduce the risk of CVD.

A Finnish study of 21 930 men who smoked (50–69 years of age) was monitored for 6·1 years[16]. The lower risk of CVD was associated with the increase in the intake of products containing rye. Rimm *et al.*[19] examined the association between cereal consumption and the risk of myocardial infarction (MI) in 43 757 health professionals in the USA, aged 40–75 years. Cereal fibre was the factor most strongly associated with a reduced risk of MI, with a 0·71 decline in the risk per 10 g increase in the ingestion of cereal fibre.

The Nurses' Health Study, an extensive prospective cohort study tracking women in the USA for 10 years, was also used to examine the relationship between cereal consumption and cardiovascular risk[1]. A total of 68 782 women aged between 37 and 64 years without prior diagnosis of angina, MI, apoplexy, cancer, hypercholesterolaemia or diabetes were examined at the beginning of the study. The authors controlled for age, cardiovascular risk factors, dietary factors and the use of multivitamin supplements. For an increase of 10 g/d in the total consumption of fibre, the risk of CVD was 0·81 (95 % CI 0·66, 0·99). Among the different sources of dietary fibre (cereal, vegetables and fruit), only cereal fibre proved to be strongly associated with a lower risk of CVD.

As wholegrain cereals are a major source of dietary fibre in many countries, it is difficult to separate the protection of dietary fibre from that of wholegrain cereals. In a study tracking health professionals, Jensen *et al.*[6] examined the consumption of wholegrain cereals, bran and germ in relation to the risk of coronary disease from the data on food consumption frequency. Added germ was not associated with CVD risk, leading the authors to conclude that the study supported the association of the benefits described between the consumption of wholegrain cereals and the reduction of CVD, suggesting that the bran of wholegrain cereal could be a key factor in this relation. The regular consumption of foods that include wholegrain cereals appears to protect against CVD. Van Dam *et al.*[20] reported that the consumption of refined diets that did not include wholegrain cereals was associated with higher levels of blood cholesterol and lower consumption of micronutrients. Prudent eating habits, including the intake of wholegrain cereals, was associated with a lower level of reactive protein C and endothelial dysfunction, an early step in the development of atherosclerosis[21]. The consumption of foods based on wholegrain cereals was also associated with lower reactive protein-C concentrations in the Nurses' Health Study[22]. In addition, a prospective

cohort study of post-menopausal women found that the consumption of cereal fibre and the ingestion of wholegrain cereal reduced the progression of atherosclerosis in the coronary artery[23]. In a subsample of the Study Tracking Health Professionals and the Nurses' Health Study II, a broad range of biomarkers related to CVD[24] was measured. Greater consumption of wholegrain cereal was associated with lower homocisteine and total cholesterol. Thus, these results suggest a lower risk of cardiac disease in persons who consume diets high in whole grains. In this sense, Sayoun *et al.*[25], have published a significant inverse trend between the intake of wholegrain cereal and mortality by CVD, independently of demography, lifestyle or dietary factors. In addition, glucose while fasting and the BMI diminished as the quartiles increased in the category of wholegrain consumption.

Type 2 diabetes mellitus

Nutrition is considered by health professionals to be a basic tool to control the blood glucose levels and therefore to treat diabetes. Several epidemiological studies have shown that the high intake rates of wholegrain cereals and their products, such as whole-wheat bread, are associated with a 20–30 % reduction in the risk of DM2[25,26]. Furthermore, evidence from observational and interventional studies indicates that the consumption of wholegrain cereals improves the plasma glucose levels as well as insulinaemia, reducing tissue resistance to insulin[2,26]. On the other hand, the data available indicate that the components of wholegrain cereals overall are responsible for the lowering of risk, as the fibre from fruit and vegetables does not exert the same effects[27]. In fact, Montonen *et al.*[27] found an inverse relation between the intake of total fibre, especially cereal fibre, and the risk of type 2 diabetes, whereas fibre derived from fruit or vegetables did not have an effect on diabetes risk. Adjustment for cereal fibre considerably weakened the association between wholegrain consumption and type 2 diabetes risk, which suggests that the relation of whole grain may be due to cereal fibre or to factors related to cereal fibre intake.

With the exception of a few foods, most contain carbohydrates in different proportions. However, from the nutritional standpoint, not only the quantity is important but also the speed with which it is absorbed, this being influenced by a number of factors such as the type of carbohydrate (glucose, fructose, sucrose, lactose), the nature of the starch (amylose, amylopectin, RS), the method of preparation (manner and time of cooking, quantity of heat used), the degree of processing of the foods (degree of gelatinisation of the starch, particle size, the form of the food) and other components (e.g. natural substances that slow down digestion like pectins, phytates and tannins)[8,11].

With the aim of comparing the effects of specific foods in the blood sugar response, in 1981 the concept of GI was introduced. For this index to be established, healthy volunteers who had fasted for the night had their glycaemia levels measured after ingesting a set quantity of the food in question (the quantity of food was adjusted to provide 50 g of glycaemic or biologically available carbohydrate). The glycaemia was measured in previously established time intervals up to a maximum of 120 min. These measurements were compared with those of a reference product such as glucose (50 g), to which an index of 100 was arbitrarily assigned. The quotient between the areas of the respective curves was called the GI[3]. Initially, the reference product for the determination of the GI was white bread, but the bread generated a variable glycaemic curve, depending on its composition and preparation, especially the variable content of RS. In fact, traditional white breads can vary their GI with respect to glucose from 74 % to 100 %[8].

The concept of GI appears to be a useful tool for glycaemic tracking in diabetic patients. In addition, diets with a low GI have the capacity to reduce the secretion of insulin and diminish blood lipid concentrations, as demonstrated in several clinical tests[28]. Diabetic patients who ingested bread having a low GI and made with the addition of fibre from wholegrain cereals registered a reduction in the blood glucose values[29] as well as in the cholesterol and TAG levels, compared with those who followed a diet with a high GI[5,30]. However, the GI did not take into account the quantity of carbohydrates consumed, an important determinant of the glycaemic response. For example, most fruits have a high GI and would appear not to be a good choice as part of a diet with a low GI. Nevertheless, fruit usually have a low content of carbohydrates, and therefore their glycaemic effect is minimal. Given that foods differ in carbohydrate content, Willett *et al.* defined the glycaemic load (GL) in 1997 as the arithmetic product of GI and the quantity of carbohydrates ingested[3].

Another important concept is that of the glycaemic glucose equivalent (GGE) of a food. The GGE refers to the relative tendency of a given quantity of food consumed at a single time, such as a portion, to induce a postprandial glycaemic response. The GGE is measured directly by the quantity of reference glucose necessary to give the same glycaemic response as a relevant quantity of a given food[31].

Bread belongs to a group of foods that increase the insulin response, as its main carbohydrate is gelatinised starch, easily digested by human amylases, and therefore usually gives rise to high glycaemic responses. Wholegrain breads have a lower GL than do corresponding white breads and therefore offer better control for postprandial glycaemia[8].

Breads made with wholegrain cereals, for reasons discussed for the whole grains in terms of their content of fibre and resistant starches, present lower GI values. The incorporation of soluble fibre in great quantities (bread made of oat bran) augments viscosity of the bolus, limits

the access of amylotic enzymes and diminishes the diffusion of the glucose through the mucosa, giving these products a far lower GI. In addition, rye breads made with sour dough, due to the presence of organic acids, appear to diminish postprandial glycaemia and insulinaemia. In addition, flatbread has a more compact structure and therefore slower digestion and a lower GI. For all the above, breads made traditionally with high fibre contents are useful for controlling postprandial glycaemia in subjects with intolerance to glucose and with diabetes[8].

It has been reported that the ingestion of fibre from wholegrain cereals is inversely related to DM2. In a long-term study of almost 90 000 women[31], and in a similar study of nearly 45 000 men[32], it was found that those who consumed more cereal fibre had an approximately 30 % lower risk of developing DM2, compared with those with lower consumption. In addition, in the study on women's health in Iowa (USA), it was found that the consumption of dietary fibre and wholegrain cereal protected against DM2[33]. In another study, individuals who consumed mainly refined cereals and little wholegrain cereal had a 57 % greater risk of DM2 than those who consumed higher quantities of wholegrain cereals[34]. In the Study Tracking Health Professionals, one part monitoring 42 898 men consuming approximately three rations of wholegrain cereal per day associated this consumption with a 37 % lower risk of DM2[35]. In addition, when the data were brought together for prospective cohort studies, the consumption of wholegrain cereal was found to reduce the relative risk of DM2 by 30 %[36,37].

Pereira *et al.*[38], studying hyperinsulinaemic subjects who were overweight or obese, tested the hypothesis that the consumption of wholegrain cereal improves the tissue sensibility of the insulin in overweight and obese adults. Eleven adults followed two diets, each for 6 weeks. The two diets were identical except that in one of them the products of refined cereal, mainly bread, were replaced by wholegrain products. The insulin during fasting proved 10 % lower during the diet with the integral cereal. Thus, the authors concluded that sensitivity to insulin may be an important mechanism by which foods based on whole grains reduce the risk of DM2 and cardiac disease.

Juntunen *et al.*[39] evaluated the factors affecting plasma glucose and the insulin response after the ingestion of cereal products. Several subjects consumed different cereal products: bread with wholegrain rye, wholegrain rye bread with a β-glucan concentrate from oats, pasta made of dark Durum wheat and wheat bread made from white wheat flower. The glucose responses and the index of gastric emptying after the consumption of the two rye breads and the pasta did not differ from those after the consumption of white wheat bread. However, the insulin, the glucose-dependent insulinotropic polypeptide and the peptide analogous to type-1 glucagon were lower after the consumption of the rye breads and dark pasta than after the consumption of white wheat bread. Thus, the postprandial insulin responses to cereal products may be determined by the form of the food and the botanical structure more than by the quantity of fibre or the type of cereal in the food. McKeown *et al.*[40] have reported that the consumption of wholegrain cereal in the Framingham Children's Study is inversely associated with the index of body mass and insulin during fasting.

Juntunen *et al.*[41], studying postmenopausal women who consumed high-fibre rye bread and white wheat bread, measured the glucose and insulin metabolism. The acute response of insulin significantly augmented more during the period of consuming rye bread than during that of consuming white wheat bread. This suggests that high-fibre rye bread favours the secretion of insulin. In another study, foods based on rye and wheat was offered to middle-aged overweight men[42]. The men consumed cereals low in fibre that provided 5 g of dietary fibre in the diet of refined cereals and 18 g of fibre in the diet of the wholegrain cereal, whether high in rye or wheat. All this was additional to a basal diet that contained 14 g of fibre. The postprandial insulin fell 46–49 % and postprandial glucose dipped 16–19 % after the consumption of the wholegrain diet.

Qi *et al.*[43], examining whether the ingestion of wholegrain cereals and dietary fibre was associated with inflammatory indicators among 902 diabetic women in the Nurses' Health Study, suggested that the wholegrain cereals and a diet with a low GI could reduce systemic inflammation among women with DM2. In addition, Jensen *et al.*[24] found in 938 healthy men and women that the consumption of wholegrain cereal was inversely related more strongly to the plasma markers of glycaemic control (insulin during fasting, glycosylated Hb A1c, peptide C and leptin).

Cancer

The consumption of wholegrain cereals has in several studies been associated with a reduced risk of some types of gastrointestinal cancer. In a meta-analysis on the consumption of wholegrain cereals and cancer that analysed all the studies conducted up to 1998 indicated protection against the risk of colorectal cancer and polyps, other cancers of the digestive tract, cancers related to hormones and pancreatic cancer[44]. In addition, a systematic review of case–control studies carried out using a common protocol in northern Italy between 1983 and 1996 indicated that a greater frequency in the consumption of wholegrain cereal is associated with a lower risk of cancer[45]. Wholegrain cereal is consumed primarily as wholegrain bread and some as wholegrain pasta. Cohort studies have shown a lower risk for specific cancers, such as colorectal in women[46], stomach[47], mouth/throat and the upper digestive tract[48] and endometrium[49].

A review of forty studies on gastrointestinal cancer has found a reduction in cancer risk from 21 % to 43 % in subjects with high consumption of wholegrain cereals

https://doi.org/10.1017/S1368980011002576 Published online by Cambridge University Press

compared to those with low consumption[2]. In addition, in more recent cohort studies, the intake of wholegrain cereals has been associated with a moderate reduction in colorectal cancer risk[50,51]. Furthermore, in a recent meta-analysis, it was shown that the intake of products having a low GI and GL, including products based on cereals with a high fibre content, was associated with a lower risk of colorectal, pancreatic, endometrium and breast cancer[52]. However, a recent study published jointly between the World Cancer Research Fund and the Institute for Cancer Research on the relative risk of different types of cancer in relation to different lifestyles found no association between the specific consumption of cereals and colorectal cancer[53]. On the other hand, another meta-analysis indicated that the consumption of foods with a low GI or GL was not associated with a reduction in colorectal or pancreatic cancer[54]. However, the studies that examine the association of the consumption of cereals with hormone-dependent cancers are very limited.

Several mechanisms have been proposed for the action of cereals in relation to cancer. The fibre and certain resistant starches found in cereals and their products, as in the case of bread, ferment in the colon and contribute to reduction of the intestinal transit and improvement of intestinal health. Cereals also contain antioxidants that can protect against oxidative damage, which can play a fundamental role in the development of cancer. Other bioactive compounds in wholegrain cereals may affect the hormonal levels and probably the hormone-dependent cancers. The potential mechanisms include shifts in the plasma-glucose values and weight loss[2]. In addition, the lowering of insulin levels by wholegrain cereals can be an indirect way by which cancer risk is reduced, given that several epidemiological studies have suggested that higher levels of insulin are associated with a greater risk of colon, breast and possibly other types of cancer.

Dietary factors, such as the intake of fibre, vegetables, fruits, antioxidants, vitamin B_6 and phytoestrogen, as well as lifestyle factors such as exercise, smoking and alcohol intake, which are controlled for in most epidemiological studies, do not explain the apparent protective effect of wholegrain cereals against cancer, again suggesting that it is the complete package of the wholegrain cereal that is effective[11].

Various theories have been proposed to explain the protective effects of wholegrain cereals. Thus, the increase in the faecal mass and the decrease in transit time give less opportunity to the faecal mutagens to interact with the intestinal epithelium. Secondarily, it is thought that the sequestration by fibre of the bile acids, which promote cell proliferation, can diminish the frequency of mutations. Wholegrain cereals also contain anti-nutrients, such as protease inhibitors, phytic acid, phenolic compounds and saponins, which until recently were thought to have only a negative nutritional consequence. Some of these anti-nutrient compounds may act as cancer inhibitors by preventing the formation of carcinogens and blocking the interaction of carcinogens with cells. Other potential mechanisms of wholegrain cereals to lower cancer risk include effects of lignans. Lignans are compounds that have a 2,3-dibenzylbutane structure, and there are minority constituents of many plants that form construction blocks to create lignin in the cell wall of the plant. Owing the relation of the excretion of lignans with fibre consumption, it is assumed that vegetal lignans are contained in external layers of the grain. Concentrated sources of lignans include whole wheat, whole oats and whole rye. Seeds are also a concentrated source of lignans, including flax seeds (the most concentrated source), pumpkin seeds, caraway seeds and sunflower seeds[2].

Cereals and other foods rich in fibre increase the urinary excretion of lignans, an indirect measure of the lignan content in food[55,56]. In addition, they are positively related to the consumption of products based on wholegrain cereals[57]. Similar results were found in a study in the USA[58] in which the subjects consumed either wholegrain-based foods or refined-grain foods (especially bread) for 6 weeks. Most of the increase in serum enterolactone occurred when the subjects consumed the diet based on wholegrain bread. Serum enterolactone has been associated not only with a decline in the risk of cancer, but also with a lower CVD related to all the causes of mortality in middle-aged Finnish men[59].

Gastrointestinal pathologies

The components of wholegrain cereals, including fibre, RS and oligosaccharides, play a fundamental role in the maintenance of intestinal homeostasis. Several studies have suggested that the dietary fibre from grains and whole cereals augments the weight of the stool and absorb water, and the partial fermentation of the fibre in the colon as well as of the oligosaccharides promotes the growth of beneficial bacteria in the faeces[2,27]. RS is not digested in the same way as ordinary starch, passing through the intestine to the colon, where it is fermented, and behaving in all senses like soluble dietary fibre. The main content of faecal residue facilitates intestinal peristalsis and defecation. All this helps alleviate symptoms of constipation and contributes to lowering the risk of developing diverticulosis and diverticultitis[60].

McIntosh *et al.*[42] offered foods based on rye and wheat to overweight middle-aged men and measured markers of intestinal health. The food based on rye and wheat with high fibre content increased the faecal evacuation by 33–36% and diminished the activity of faecal β-glucuronidase by 29%.

Conclusion

The regular intake of wholegrain cereals may contribute to reduction of the risk factors related to non-communicable

https://doi.org/10.1017/S1368980011002576 Published online by Cambridge University Press

chronic diseases, particularly those of CVD, DM2 and certain types of cancer, as well as several gastrointestinal pathologies.

Acknowledgements

A.G. and J.M. are funded in part by the Instituto de Salud Carlos III del Ministerio de Ciencia e Innovación. Red SAMID RETIC n. RD08/0072. The authors have no conflict of interest to declare related to the topic and content of the article. The authors thank the Mediterranean Diet Foundation for its valuable comments and suggestions.

References

1. Liu SM, Stampfer MJ, Hu FB *et al.* (1999) Whole-grain consumption and risk of coronary heart disease: results from the Nurses' Health Study. *Am J Clin Nutr* **70**, 412–429.
2. Slavin J (2004) Whole grains and human health. *Nutr Res Rev* **17**, 99–110.
3. Venn BJ & Green TJ (2007) Glycemic index and glycemic load: measurement issues and their effect on diet-disease relationships. *Eur J Clin Nutr* **61**, Suppl. 1, S122–S131.
4. Lajous M, Boutron-Ruault MC, Fabre A *et al.* (2008) Carbohydrate intake, glycemic index, glycemic load, and risk of postmenopausal breast cancer in a prospective study of French women. *Am J Clin Nutr* **87**, 1384–1391.
5. Livesey G, Taylor R, Hulshof T *et al.* (2008) Glycemic response and health – a systematic review and meta-analysis: relations between dietary glycemic properties and health outcomes. *Am J Clin Nutr* **87**, Suppl. 1, S258–S268.
6. Jensen MK, Koh-Banarjee P, Hu FB *et al.* (2004) Intakes of whole grains, bran, and germ and the risk of coronary heart disease in men. *Am J Clin Nutr* **80**, 1492–1499.
7. Pereira MA, Pins JJ, Jacobs DR *et al.* (1993) Whole grains, cereal fiber, and chronic diseases: epidemiologic evidence. In *CRC Handbook of Dietary Fiber in Human Nutrition*, pp. 461–479 [GA Spiller, editor]. Boca Raton, FL: CRC Press.
8. Englyst HN, Kingman SM & Cummings JH (1992) Classification and measurement of nutritionally important starch fractions. *Eur J Clin Nut* **46**, Suppl. 2, S33–S50.
9. Englyst HN, Kingman SM, Hudson GJ *et al.* (1996) Measurement of resistant starch in vitro and in vivo. *Br J Nutr* **75**, 749–755.
10. Rizkalla SW, Laromiguiere M, Champ M *et al.* (2007) Effect of baking process on postprandial metabolic consequences: randomized trials in normal and type 2 diabetic subjects. *Eur J Clin Nutr* **61**, 175–183.
11. Gil A, Ortega RM & Lozano JM (2010) Importancia del pan en la prevención de las enfermedades crónicas. In *Libro Blanco del Pan*, pp. 141–158 [A Gil and L Serra, editors]. Madrid: Editorial Medica Panamericana.
12. Zarzuelo A & Gálvez J (2010) Fibra dietética. In *Tratado de Nutrición*, 2nd ed., pp. 233–256 [A Gil, editor]. Madrid: Editorial Médica Panamericana.
13. Anderson JW (2002) Whole-grains intake and risk for coronary heart disease. In *Whole Grain Foods in Health and Disease*, pp. 187–200 [L Marquart, JL Slavin and RG Fulcher, editors]. St. Paul, MN: Eagan Press.
14. Truswell AS (2002) Cereal grains and coronary heart disease. *Eur J Clin Nutr* **56**, 1–14.
15. Jacobs DR, Meyer KA, Kushi LH *et al.* (1998) Whole-grain intake may reduce the risk of ischemic heart disease death in postmenopausal women: the Iowa Women's Health Study. *Am J Clin Nutr* **68**, 248–257.
16. Pietinen P, Rimm EB, Korhonen P *et al.* (1996) Intake of dietary fiber and risk of coronary heart disease in a cohort of Finnish men. The Alpha-Tocopherol, Beta-Carotene Cancer Prevention Study. *Circulation* **94**, 2720–2727.
17. Morris JN, Marr JW & Clayton DG (1977) Diet and heart: a postscript. *BMJ* **2**, 1307–1314.
18. Pereira MA, O'Reilly E, Augustsson K *et al.* (2004) Dietary fiber and risk of coronary heart disease. A pooled analysis of cohort studies. *Arch Intern Med* **164**, 370–376.
19. Rimm EB, Ascherio A, Giovannucci E *et al.* (1996) Vegetable, fruit and cereal fiber intake and risk of coronary heart disease among men. *JAMA* **275**, 447–451.
20. Van Dam RM, Grievink L, Ocké MC *et al.* (2003) Patterns of food consumption and risk factors for cardiovascular disease in the general Dutch population. *Am J Clin Nutr* **77**, 1156–1163.
21. Lopez-Garcia E, Schulze MB, Fung TT *et al.* (2004) Major dietary patterns are related to plasma concentrations of markers of inflammation and endothelial dysfunction. *Am J Clin Nutr* **80**, 1029–1035.
22. Wu T, Giovannucci E, Pischon T *et al.* (2004) Fructose, glycemic load, and quantity and quality of carbohydrate in relation to plasma C-peptide concentrations in US women. *Am J Clin Nutr* **80**, 1043–1049.
23. Erkkilä AT, Herrington DM, Mozaffarian D *et al.* (2005) Cereal fiber and whole-grain intake are associated with reduced progression of coronary-artery atherosclerosis in postmenopausal women with coronary artery disease. *Am Heart J* **150**, 94–101.
24. Jensen MK, Koh-Banerjee P, Franz M *et al.* (2006) Whole grains, bran, and germ in relation to homocysteine and markers of glycemic control, lipids, and inflammation 1. *Am J Clin Nutr* **83**, 275–283.
25. Sahyoun NR, Jacques PF, Zhang XL *et al.* (2006) Whole-grain intake is inversely associated with the metabolic syndrome and mortality in older adults. *Am J Clin Nutr* **83**, 124–131.
26. Murtaugh MA, Jacobs DR Jr, Jacob B *et al.* (2003) Epidemiological support for the protection of whole grains against diabetes. *Proceed Nutr Soc* **62**, 143–149.
27. Montonen J, Knekt P, Järvinen R *et al.* (2003) Whole-grain and fiber intake and the incidence of type 2 diabetes. *Am J Clin Nutr* **77**, 622–629.
28. Riccardi G, Rivellese AA & Giacco R (2008) Role of glycemic index and glycemic load in the healthy state, in prediabetes, and in diabetes. *Am J Clin Nutr* **87**, Suppl. 1, S269–S274.
29. Henry CJ, Lightowler HJ, Tydeman EA *et al.* (2006) Use of low-glycaemic index bread to reduce 24-h blood glucose: implications for dietary advice to non-diabetic and diabetic subjects. *Int J Food Sci Nutr* **57**, 273–278.
30. Marangoni F & Poli A (2008) The glycemic index of bread and biscuits is markedly reduced by the addition of a proprietary fiber mixture to the ingredients. *Nutr Metab Cardiovasc Dis* **18**, 602–605.
31. Monro JA & Shaw M (2008) Glycemic impact, glycemic glucose equivalents, glycemic index, and glycemic load: definitions, distinctions, and implications. *Am J Clin Nutr* **87**, Suppl. 1, S237–S243.
32. Salmerón J, Manson JE, Stampfer MJ *et al.* (1997) Dietary fiber, glycemic load, and risk of non-insulin-dependent diabetes mellitus in women. *JAMA* **277**, 472–477.
33. Salmerón J, Ascherio A, Rimm EB *et al.* (1997) Dietary fiber, glycemic load, and risk of NIDDM in men. *Diabetes Care* **20**, 545–550.
34. Meyer KA, Kushi LH, Jacobs DR Jr *et al.* (2000) Carbohydrates, dietary fiber, and incident type 2 diabetes in older women. *Am J Clin Nutr* **71**, 921–930.
35. Liu S, Manson JE, Stampfer MJ *et al.* (2000) A prospective study of whole grain intake and risk of type 2 diabetes mellitus in US women. *Am J Public Health* **90**, 1409–1415.

36. Fung TT, Hu FB, Pereira MA *et al.* (2002) Whole-grain intake and the risk of type 2 diabetes: a prospective study in men. *Am J Clin Nutr* **76**, 535–540.
37. Liu S (2003) Whole-grain foods, dietary fiber, and type 2 diabetes: searching for a kernel of truth. *Am J Clin Nutr* **77**, 527–529.
38. Pereira MA, Jacobs DJ Jr, Pins JJ *et al.* (2002) Effect of whole grains on insulin sensitivity in overweight hyperinsulinemic adults. *Am J Clin Nutr* **75**, 848–855.
39. Juntunen KS, Niskanen LK, Liukkonen KH *et al.* (2002) Postprandial glucose, insulin, and incretin responses to grain products in healthy subjects. *Am J Clin Nutr* **75**, 254–262.
40. McKeown NM, Meigs JB, Liu S *et al.* (2002) Whole-grain intake is favorably associated with metabolic risk factors for type 2 diabetes and cardiovascular disease in the Framingham Offspring Study. *Am J Clin Nutr* **76**, 390–398.
41. Juntunen KS, Laaksonen DE, Poutanen KS *et al.* (2003) High-fiber rye bread and insulin secretion and sensitivity in healthy postmenopausal women. *Am J Clin Nutr* **77**, 385–391.
42. McIntosh GH, Noakes M, Royle PJ *et al.* (2003) Whole-grain rye and wheat foods and markers of bowel health in overweight middle-aged men. *Am J Clin Nutr* **77**, 967–974.
43. Qi L, van Dam RM, Liu S *et al.* (2006) Whole-grain, bran, and cereal fiber intakes and markers of systemic inflammation in diabetic women. *Diabetes Care* **29**, 207–211.
44. Jacobs DR Jr, Marquart L, Slavin J *et al.* (1998) Whole-grain intake and cancer: an expanded review and meta-analysis. *Nutr Cancer* **30**, 85–96.
45. Chatenoud L, Tavani A, La Vecchia C *et al.* (1998) Whole-grain food intake and cancer risk. *Int J Cancer* **77**, 24–28.
46. Larsson SC, Giovannucci E, Bergkvist L *et al.* (2005) Whole grain consumption and risk of colorectal cancer: a population-based cohort of 60 000 women. *BJC* **92**, 1803–1807.
47. Terry P, Lagergren J, Ye W *et al.* (2001) Inverse association between intake of cereal fiber and risk of gastric cardia cancer. *Gastroenterology* **120**, 387–391.
48. Kasum CM, Jacobs DR Jr, Nicodemus K *et al.* (2002) Dietary risk factors for upper aerodigestive tract cancers. *Int J Cancer* **99**, 267–272.
49. Kasum CM, Nicodemus K, Harnack LJ *et al.* (2001) Whole grain intake and incident endometrial cancer: the Iowa Women's Health Study. *Nutr Cancer* **39**, 180–186.
50. Jacobs DR Jr, Andersen LF & Blomhoff R (2007) Whole grain consumption is associated with a reduced risk of non cardiovascular, non cancer death attributed to inflammatory diseases in the Iowa Women's Health Study. *Am J Clin Nutr* **85**, 1606–1614.
51. Schatzkin A, Mouw T, Park Y *et al.* (2007) Dietary fiber and whole-grain consumption in relation to colorectal cancer in the NIH-AARP Diet and Health Study. *Am J Clin Nutr* **85**, 1353–1360.
52. Gnagnarella P, Gandini S, La Vecchia C *et al.* (2008) Glycemic index, glycemic load, and cancer risk: a meta-analysis. *Am J Clin Nutr* **87**, 1793–1801.
53. World Cancer Research Fund/Institute for Cancer Research (2007) *Food, Nutrition, Physical Activity and the Prevention of Cancer – A Global Perspective.* Washington, DC: WCRF/AICR; available at http://www.dietandcancerreport.org/
54. Mulholland HG, Murray LJ, Cardwell CR *et al.* (2009) Glycemic index, glycemic load, and risk of digestive tract neoplasms: a systematic review and meta-analysis. *Am J Clin Nutr* **89**, 568–576.
55. Borriello SP, Setchell KD, Axelson M *et al.* (1985) Production and metabolism of lignans by the human faecal flora. *J Applied Bact* **58**, 37–43.
56. Adlercreutz H, Fotsis T, Bannwart C *et al.* (1986) Urinary estrogen profile determination in young Finnish vegetarian and omnivorous women. *J Steroid Biochem* **24**, 289–296.
57. Kilkkinen A, Valsta LM, Virtamo J *et al.* (2003) Intake of lignans is associated with serum enterolactone concentration in Finnish men and women. *J Nutr* **133**, 1830–1833.
58. Jacobs DR Jr, Pereira MA, Stumpf K *et al.* (2002) Whole grain food intake elevates serum enterolactone. *Br J Nutr* **88**, 111–116.
59. Vanharanta M, Voutilainen S, Rissanen TH *et al.* (2003) Risk of cardiovascular disease-related and all-cause death according to serum concentrations of enterolactone. Kuopio Ischaemic Heart Disease Risk Factor Study. *Arch Inter Med* **163**, 1099–1104.
60. Marlett JA, McBurney MI & Slavin JL (2002) Position of the American Dietetic Association: health implications of dietary fiber. *J Am Diet Ass* **102**, 993–1000.