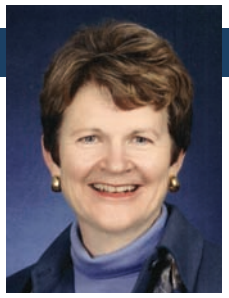

Julie M. Jones
St. Catherine University
St. Paul, MN, U.S.A.

The Whole-Grain Conundrum

According to most epidemiological studies, whole grains are associated with reduced risk of many chronic diseases. However, large randomized clinical trials have failed to substantiate a number of the associations observed in epidemiological studies. Thus, there is much discussion about confounding in the data, methodologies, and mechanisms. For example, health-promoting dietary and lifestyle patterns among whole-grain eaters create confounding in epidemiological studies. Methodological differences among studies, such as the criteria used to determine what is a whole-grain food and the strategies employed to capture whole-grain intake using various food intake instruments, also create confounded data. In many studies the associations observed between whole grains and a particular health endpoint are the same as those for cereal fiber. Although this is not surprising since whole grain is an important delivery vehicle for cereal fiber and dietary fiber overall, it does beg the question of whether it is the cereal fiber complex or something unique about the whole grain that creates the benefit. This column discusses each of these issues in detail and features some new whole-grain studies.

Confounding in Observational Studies

Observational studies, even though they stem from prospective cohort trials and many diverse populations, invariably present the challenge of confounding in the data. Those in the highest quintiles of whole-grain intake often have a cluster of positive dietary patterns and health behaviors, each of which can impact disease risk reduction. For example, many studies show that whole-grain eaters ingest more fruits and vegetables, eat less red meat, and are more likely to meet recommendations regarding amounts and types of fat, be physically active, and be of normal weight. Although the statistical models attempt to account for these behaviors, it is impossible to state that all such confounders and their interactions have been addressed.

Data continue to show that those who consume whole grains have better overall nutritional intakes (12). In an analysis of the 1999–2004 National Health and Nutrition Examination Survey (NHANES), U.S. adults over 19 years of age (n = 13,276) who ate the most whole grains scored better on nearly every dietary metric and health outcome. As anticipated, diet quality and intake of energy, all micronutrients (except vitamin B_{12}), dietary fiber, and recommended fats were significantly higher for those consuming the most servings of whole grains. Intake of added sugars, saturated fatty acids, monounsaturated fatty acids, and cholesterol was significantly lower in those consuming the most servings of whole grains. These data show that whole-grain eaters seem to do "everything right."

Cluster analysis of dietary and health behaviors is one way to look at several behaviors at once. This was done recently in the Health, Aging, and Body Composition Study (1). In this prospective cohort study of 3,075 older adults, higher whole-grain intake was one of the components of the "healthy foods" cluster. This cluster was associated with superior nutritional status, quality of life, and survival in older adults. However, the food grouping was also characterized by higher intake of low-fat dairy products, fruit, poultry, fish, and vegetables than other patterns. As a result, the cluster analysis is interesting but raises its own issues of confounding. Based on these data we can state that a healthier diet reduces risk, but we do not know which component makes it healthier or if all the components are working in synergy.

Studies continue to show that whole grains are associated with lower rates of chronic disease and obesity. However, some studies show it may not just be the result of the amount of whole grains consumed. It may be related to the specific foods selected. NHANES data from 2003–2006 show that grain-based desserts and pizza were two of the top three providers of calories in the diets of children 2–18 years of age (15). Grain-based desserts provided 138 kcal/day, and pizza provided 136 kcal/day compared with the other top contributor, sugar-sweetened beverages (soda and fruit drinks combined), which provided 173 kcal/day. Since most grain-based desserts, in the time period studied, would have been formulated with refined grains and could potentially represent inclusion of foods that are poorer nutritional choices, the positive impact seen in whole-grain eaters may in part have been a reflection of foods not chosen rather than a reflection of foods chosen. The findings from the cluster analysis and NHANES survey data still beg the question of what actually causes the differences in health outcomes observed for whole-grain eaters—the whole grain itself or the combination of characteristics of a whole-grain eater.

Thus, it can be argued that associations between whole-grain ingestion and a specific health endpoint may not be entirely attributable to whole grains. In fact, whole-grain ingestion may simply be a marker for a person who makes better dietary choices and engages in a number of health-promoting behaviors. The question remains regarding dietary advice and whole grains for those not engaging in other health-promoting behaviors: will adding whole grains to otherwise less than ideal diet or optimal lifestyle choices reduce the risk of a number of chronic diseases?

How Much Whole Grain in a Food Makes It a Whole Grain?

No consistent methodology has been used among studies to determine what foods should be considered whole-grain foods or how much whole grain needs to be in a product for it to be counted as a whole-grain food. For example, some studies actually count items that either are clearly not whole grain (e.g., bran cereal), rarely whole grain (e.g., cous cous), or may not be whole grain (e.g., dark bread). Further analysis of epidemiological stud-

doi:10.1094/CFW-56-3-0124

ies by the Life Sciences Research Office group showed that when foods such as bran were omitted from the analysis, the association between whole grains and diabetes and cardiovascular disease (CVD) was not significant (3).

Epidemiological Studies Versus Intervention Studies

Another source of controversy is the fact that randomized clinical trials and interventions have failed to show an impact of whole grains. For example, many epidemiological studies show that whole-grain foods are associated with a lower incidence of markers for inflammation and lower rates of CVD and diabetes. However, interventions with whole grains do not always show an impact. In a Swedish study, subjects either with normal or impaired glucose tolerance substituted whole-grain sourdough bread for white sourdough bread. During the 6-week period of the study, the subjects showed no changes in markers for CVD such as plasminogen activator inhibitor-1 (9). This study showed only one impact—the glucose tolerance test curve was 19% lower. There were no differences in fasting glucose, insulin, or glucagon in any of the subjects. In another recently reported intervention (18), more than 200 middle-aged healthy subjects ate 3 servings of whole grain (either whole wheat or wheat and oats) per day for 3 months. In the whole-grains group compared with the control group, mean systolic blood pressure was significantly reduced by 6 mm Hg. Other markers for CVD risk were unaffected, with the exception of cholesterol levels. These decreased slightly but significantly for those eating refined grains.

In the United Kingdom whole-grain consumption showed no effect on CVD endpoints in more than 300 overweight subjects (2). The lack of changes in these endpoints was observed despite documented increases over the course (4+ months) of the study in whole-grain intake from <1 serving/day to >6 servings/day.

In another recent 3-month intervention study, more than 200 overweight subjects ate 2 servings of a ready-to-eat oat whole-grain cereal (delivering 3 g of β-glucan per day) as part of a calorie-restricted diet (10). Those eating the whole-grain oat cereal showed a significant reduction in total and LDL cholesterol compared with those eating low-fiber foods. This study adds to the robust body of evidence showing that cereals containing whole-grain oats and β-glucan can lower cholesterol. What the study does not do is help to reveal the relationship of all whole-grain foods to blood lipids. It may affirm that only certain whole grains, such as oats, can lower cholesterol.

This study fails to explain the results of epidemiological data collected in the United States and most countries in Europe, where wheat is the primary source of whole grains. These epidemiological studies clearly show an association between whole-grain intake, lower risk of coronary heart disease (CHD) and lower blood lipids, which forces us to ask several questions. 1) Is there something problematic about intervention studies in terms of the subjects selected, length of time, and dose and type of whole grain? 2) What are the various mechanisms for lowering cholesterol and CHD and diabetes risks? 3) Is it the fiber or the fiber complex? And if so, how do the different fiber complexes behave in different food products? 4) Do studies, like diets, need to contain a variety of grain-based foods and not just a single food (e.g., sourdough bread)? 5) Is there a Hawthorne effect at work? For instance, why did the subjects eating refined sourdough bread show lower cholesterol levels? 6) How important is a single grain and do we need to know more about what grains contain? 7) How good are the extrapolations?

One study concluded that the inclusion of whole grains resulted in a small (6 mm) but significant decrease in mean systolic blood pressure and that this "could decrease the incidence of coronary artery disease and stroke by ≥15% and 25%, respectively" (18). Authors of another study that showed no positive impacts on CVD endpoints concluded that "public health messages may need to be clarified to consider the source of WG and/or other diet and lifestyle factors linked to the benefits of whole-grain consumption seen in observational studies."

In summary, the data in aggregate suggest that all whole grains are not alike and that the effects and mechanisms must be looked at separately. The varying effects of different whole grains also raise questions regarding whether it is the fiber, the phytochemicals, the phytochemicals in some native matrix, or some other combination of the whole-grain food and other salutary parts of the diet and lifestyle.

New Research on Various Whole Grains and Their Components

When it comes to fiber and phytochemicals, different whole grains vary markedly.

Wheat. The outer layers of wheat, in addition to being the gold standard for studies on laxation, are also an excellent source of many phytochemicals. Two potential whole wheat components are being actively investigated: betaine and the fiber arabinoxylan. Betaine is an important osmolyte and methyl donor. Wheat bran contains at least twice as much, and as much as five times more, betaine than either oats or barley, while corn contains no betaine. Betaine in wheat is highly concentrated in the aleurone layer. As a methyl donor, it is involved in the production of homocysteine and has been related in some studies to improved heart health. Lack of betaine is associated with metabolic syndrome, lipid disorders, and diabetes and may play a role in vascular and other diseases, especially if choline content is high and betaine content is low (8,19).

Grain processors are separating bran layers to produce a highly purified component of the bran, isolated aleurone. Feeding aleurone-rich grain products (27 g/day) to ≈80 healthy subjects for 4 weeks versus control cereal products balanced for fiber and macronutrients significantly raised serum betaine and lowered plasma total homocysteine (14). Higher betaine in the diet was also accompanied by higher levels of methylation products such as methionine. This feeding study demonstrates just one role of one phytochemicals in whole-grain wheat and wheat bran. Studies such as this also bring up the issue of whether dietary advice should stick rigidly to stating that a product must contain whole grain to deliver nutritional benefits or whether portions of the exterior of the grain that can deliver a physiological benefit should be recommended with equal vigor.

Rice. There are also questions about the impact of whole grains in countries where rice is the predominant grain consumed. Most epidemiological data are from Western countries where rice is not the predominant staple. Recent studies from countries where rice is the predominant grain consumed showed that using both brown rice and pregerminated brown rice (5,16) lowered cholesterol in rats and humans compared with diets containing white rice exclusively. Because brown rice contains little or no β-glucan and is the whole grain lowest in fiber, some other mechanism for lipid lowering and reduction of CHD must be operating. Data from the Women's Health Studies I and II and the Male Health Professionals Study (≈200,000 men and women overall) showed that regular consumption of brown rice compared with regular consumption of white rice was associated with a lower risk of diabetes (17). The authors of this study estimated that substitution of 50 g (1/3 cup) of brown rice for white rice would reduce the risk of diabetes by 15%. However, similar calculations that substituted other whole grains for white rice would

reduce diabetes risk by 36%. Since these data are from Western subjects, it would be useful to obtain data from countries where rice consumption predominates.

Oats—Beyond β-Glucan. Much research exists on the health benefits of the major fiber found in oats—β-glucan. However, just as with wheat bran and betaine, oats provide benefits that are not due only to fiber. Oats are a source of unique, anti-inflammatory compounds called avenanthramides. In a study with a number of different human cancer cell lines, these unique polyphenols inhibited cell proliferation of many, but not all, cell lines (4). In terms of mechanism, avenanthramides inhibited the prostaglandin E2 pathway, which is known to be pro-inflammatory. However, it did not inhibit another well-known inflammatory pathway in cancer proliferation through the COX-2 mechanisms. The authors emphasize that these results imply that the benefits of consuming oats and oat bran are due not only to their high-fiber, β-glucan content but also to avenanthramides, which attenuate proliferation of colonic cancer cells.

Rye, Cancer, and Satiety. Rye has special properties with respect to cancer and satiety. In animal models, rye whole-grain and bran intake had beneficial effects on prostate cancer progression. Consumption of rye resulted in lower tumor rates, smaller tumor volumes, and reduced prostate-specific antigen (PSA) concentrations. Plasma total PSA concentrations were lower in men with prostate cancer after treatment with rye (6). In this human crossover design study, the men consumed either 50% of calories as rye whole-grain and bran products or refined wheat products with added cellulose. In addition to lower PSA, fasting plasma insulin and excretion of inflammatory marker urinary C-peptide were also reduced after consumption of a whole rye diet versus a wheat-cellulose diet. Lignan excretion was also higher with the rye diet. The authors suggest that the lower PSA associated with the whole-grain rye diet lowered prostate cancer progression due to decreased exposure to insulin, as indicated by plasma insulin and urinary C-peptide excretion.

Ingestion of whole-grain, high-fiber rye bread appeared to impact satiety in women much more than a similar amount of white bread (7). In 39 hypercholesterolemic, postmenopausal women, rye bread (20% of the diet for 8 weeks) increased metabolites associated with hunger-decreasing serotonin. Researchers profiled the high-fiber rye bread and identified 540 metabolites. Women eating rye bread showed increased levels of several rye metabolites—ribitol, ribonic acid, and indoleacetic acid. The authors focused on ribonic acid because it correlates positively with tryptophan, which is a precursor for the biosynthesis of hunger-depressing serotonin. The authors suggested that ingestion of high-fiber rye bread increased metabolites that might mediate the positive effects of rye bread on satiety and weight maintenance.

Whole Grains and Weight. Several recent studies have added to the body of evidence concerning the association of whole grains with weight. Two studies involving adult populations showed an inverse association with various measures of body weight and adipose. One study involving children showed a less clear association. In 2,834 adults in the Framingham Heart Study, both abdominal subcutaneous adipose tissue (SAT) and visceral adipose tissue (VAT) were inversely related to whole-grain intake (11). In contrast, refined-grain intake was positively associated with VAT. Because VAT is considered problematic both in terms of type 2 diabetes and CHD, these findings are important.

Increased consumption of whole grains was associated with lower body mass index (BMI), waist circumference, and percent overweight/obese in analysis of data from the 1999–2004 NHANES. These data on more than 13,000 adults 19–50 years of age showed another source of confounding: the positive association of whole grain was no longer significant when cereal fiber was added as a covariate (13). Thus, the questions continue. Is it the whole grain, the fiber, the dietary fiber complex in the matrix, or some phytochemicals found in the bran/germ layers?

When analyzing the same database but looking at the associations for nearly 9,000 children and adolescents, consumption of <3 servings of whole grain was not associated with body weight measures. Surprisingly consumption of 1.5 to <3 servings was positively associated with all weight measures. Only in adolescents was there an inverse association between the highest whole-grain intake and BMI (20).

The NHANES database used for these studies reflects consumption data occurring before the 2005 USDA Dietary Guidelines emphasized the importance of whole-grain consumption. It is important to note that the mean intake of whole grain at that time was just over 0.5 servings/day for adults 19–51 years of age and was slightly higher with 0.77 servings of whole grains per day for those over 51 years of age. (Alas, it has not gone up nearly enough since the push for whole-grain consumption began.) These data also showed that the major source of cereal fiber is whole grains. The one exception is cereals that are high in bran. The results confirmed that adults who consumed the most servings of whole grains had lower body weight measures. The results also suggested that fiber in whole-grain foods may mediate associations with weight measures in adults. Since many diets are woefully short of both, it is my contention that the responsible thing to do is to recommend consumption of both whole grains and fiber. Further, recommendations must be made so these foods replace calories and do not add to diets that already contain too many calories.

Summary

The smattering of studies discussed here reflects the state of the literature. It shows the confounding that occurs in studies linking whole grains with health outcomes and highlights where intervention studies have failed to support findings from epidemiological studies. It also shows that different major whole grains have very different components and can have very different health outcomes.

We, as cereal chemists and health professionals, should consider a number of whole grains and fibers when developing whole-grain products and giving advice on nutrition. We need to emphasize the importance of including a variety of grains. We also need to encourage dietary choices that include more whole grains and dietary fiber without encouraging consumers to choose more calories or championing one dietary "star" (e.g., whole grain) while dismissing another (e.g., fiber). The intakes of both are pathetically low.

The whole-grain movement began because many diets were devoid of whole-grain foods and dietary fiber. The intent of the movement was to improve diets by helping people to choose better options. As with many movements, there have been some unintended consequences of the whole-grain movement. In some cases, regulations for government food programs may favor, and in many cases require, inclusion of whole-grain food products. The unintended consequences of such regulations have meant the elimination of cereals long known to deliver fiber in the diet, e.g., the exclusion of a whole array of bran cereals, which by their very definition are not whole grain. Another troubling aspect is the championing by some of a rigid whole-grains definition, when data show that scoring or fractioning of the aleurone provides many of the same health benefits in a product with fewer toxicants, is better absorbed, and is more readily accepted. Another potential for problems is seen in the indulgent foods category. Formulating indulgent foods with whole grains has the poten-

tial of increasing their fiber and microcomponents. However, it could have unintended consequences if consumers note that their favorite indulgent food is made with whole grains and erroneously assume that these products should be eaten to meet whole-grain requirements. The net result is that indulgent foods containing whole grains, while being a slightly better choice than their refined-grain counterparts, may fail to demonstrably increase whole-grain intake or improve the diet. Further, there is the potential problem of the "Snackwell effect," where consumers over consume indulgent foods containing whole grains believing that these foods are helping them meet dietary guidelines.

The newly released USDA Dietary Guidelines focus heavily on naturally fiber-rich foods. Consumers know that whole grains provide a variety of nutrients and phytochemicals that are important for health. However, many believe that all whole grains are a good source of fiber. The new guidelines contain a contentious statement: "Fiber is sometimes added to foods and it is unclear if added fiber provides the same health benefits as naturally occurring sources." We in the food industry need to do a better job of highlighting the evidence that does exist for added fibers. It is my position that we eat less than one-third to one-half of the amount of fiber that we need, so we need to encourage the consumption of all types of whole-grain and high-fiber foods.

Dietary guidance encouraging consumers to replace part of their refined grains with whole grains is an important strategy for improved intake of a number of micronutrients and phytochemicals and may increase dietary fiber consumption. The industry may need to move slowly when considering the use of whole grains in products in the indulgent foods category. Whole-grain snacks can contribute to the diet, but care must be exercised so the presence of whole grains does not become a consumer excuse to over consume high-calorie items. On the other hand, whole-grain options, especially high-fiber options as recommended in the 2010 USDA Dietary Guidelines, for breads, cereals, pastas, rices and other sides, and crackers can make important dietary contributions and address both the fiber and whole-grain consumption gaps.

References

1. Anderson, A. L., Harris, T. B., Tylavsky, F. A., Perry, S. E., Houston, D. K., Hue, T. F., Strotmeyer, E. S., and Sahyoun, N. R. Health ABC Study: Dietary patterns and survival of older adults. J. Am. Diet. Assoc. 111:84, 2011.
2. Brownlee, I. A., Moore, C., Chatfield, M., Richardson, D. P., Ashby, P., Kuznesof, S. A., Jebb, S. A., and Seal, C. J. Markers of cardiovascular risk are not changed by increased whole-grain intake: The WHOLEheart Study, a randomised, controlled dietary intervention. Br. J. Nutr. 104:125, 2010.
3. De Moura, F. F., Lewis, K. D., and Falk, M. C. Applying the FDA definition of whole grains to the evidence for cardiovascular disease health claims. J. Nutr. 139:2220S, 2009.
4. Guo, W., Nie, L., Wu, D., Wise, M. L., Collins, F. W., Meydani, S. N., and Meydani, M. Avenanthramides inhibit proliferation of human colon cancer cell lines in vitro. Nutr. Cancer 62:1007, 2010.
5. Hsu, T. F., Kise, M., Wang, M. F., Ito, Y., Yang, M. D., Aoto, H., Yoshihara, R., Yokoyama, J., Kunii, D., and Yamamoto, S. Effects of pre-germinated brown rice on blood glucose and lipid levels in free-living patients with impaired fasting glucose or type 2 diabetes. J. Nutr. Sci. Vitaminol. (Tokyo) 54:163, 2008.
6. Landberg, R., Andersson, S. O., Zhang, J. X., Johansson, J. E., Stenman, U. H., Adlercreutz, H., Kamal-Eldin, A., Aman, P., and Hallmans, G. Rye whole grain and bran intake compared with refined wheat decreases urinary C-peptide, plasma insulin, and prostate specific antigen in men with prostate cancer. J. Nutr. 140:2180, 2010.
7. Lankinen, M., Schwab, U., Seppänen-Laakso, T., Mattila, I., Juntunen, K., Mykkänen, H., Poutanen, K., Gylling, H., and Oresic, M. Metabolomic analysis of plasma metabolites that may mediate effects of rye bread on satiety and weight maintenance in postmenopausal women. J. Nutr. 141:31, 2011.
8. Lever, M., and Slow, S. The clinical significance of betaine, an osmolyte with a key role in methyl group metabolism. Clin. Biochem. 43:732, 2010.
9. Mackay, K. A., Tucker, A. J., Duncan, A. M., Graham, T. E., and Robinson, L. E. Whole grain wheat sourdough bread does not affect plasminogen activator inhibitor-1 in adults with normal or impaired carbohydrate metabolism. Nutr. Metab. Cardiovasc. Dis., Dec 30, 2010. (E-publication ahead of print)
10. Maki, K. C., Beiseigel, J. M., Jonnalagadda, S. S., Gugger, C. K., Reeves, M. S., Farmer, M. V., Kaden, V. N., and Rains, T. M. Whole-grain ready-to-eat oat cereal, as part of a dietary program for weight loss, reduces low-density lipoprotein cholesterol in adults with overweight and obesity more than a dietary program including low-fiber control foods. J. Am. Diet. Assoc. 110:205, 2010.
11. McKeown, N. M., Troy, L. M., Jacques, P. F., Hoffmann, U., O'Donnell, C. J., and Fox, C. S. Whole- and refined-grain intakes are differentially associated with abdominal visceral and subcutaneous adiposity in healthy adults: The Framingham Heart Study. Am. J. Clin. Nutr. 92:1165, 2010.
12. O'Neil, C. E., Nicklas, T. A., Zanovec, M., and Cho, S. Whole-grain consumption is associated with diet quality and nutrient intake in adults: The National Health and Nutrition Examination Survey, 1999–2004. J. Am. Diet. Assoc. 110:1461, 2010.
13. O'Neil, C. E., Zanovec, M., Cho, S. S., and Nicklas, T. A. Whole grain and fiber consumption are associated with lower body weight measures in US adults: National Health and Nutrition Examination Survey 1999–2004. Nutr. Res. 30:815, 2010.
14. Price, R. K., Keaveney, E. M., Hamill, L. L., Wallace, J. M., Ward, M., Ueland, P. M., McNulty, H., Strain, J. J., Parker, M. J., and Welch, R. W. Consumption of wheat aleurone-rich foods increases fasting plasma betaine and modestly decreases fasting homocysteine and LDL-cholesterol in adults. J. Nutr. 140:2153, 2010.
15. Reedy, J., and Krebs-Smith, S. M. Dietary sources of energy, solid fats, and added sugars among children and adolescents in the United States. J. Am. Diet. Assoc. 110:1477, 2010.
16. Roohinejad, S., Omidizadeh, A., Mirhosseini, H., Saari, N., Mustafa, S., Yusof, R. M., Hussin, A. S., Hamid, A., and Abd Manap, M. Y. Effect of pre-germination time of brown rice on serum cholesterol levels of hypercholesterolaemic rats. J. Sci. Food Agric. 90:245, 2010.
17. Sun, Q., Spiegelman, D., van Dam, R. M., Holmes, M. D., Malik, V. S., Willett, W. C., and Hu, F. B. White rice, brown rice, and risk of type 2 diabetes in US men and women. Arch. Intern. Med. 170:961, 2010.
18. Tighe, P., Duthie, G., Vaughan, N., Brittenden, J., Simpson, W. G., Duthie, S., Mutch, W., Wahle, K., Horgan, G., and Thies, F. Effect of increased consumption of whole-grain foods on blood pressure and other cardiovascular risk markers in healthy middle-aged persons: A randomized controlled trial. Am. J. Clin. Nutr. 92:733, 2010.
19. Ueland, P. M. Choline and betaine in health and disease. J. Inherit. Metab. Dis. 34:3, 2011.
20. Zanovec, M., O'Neil, C. E., Cho, S. S., Kleinman, R. E., and Nicklas, T. A. Relationship between whole grain and fiber consumption and body weight measures among 6- to 18-year-olds. J. Pediatr. 157:578, 2010.

Julie Miller Jones, a board-certified (CNS) and licensed nutritionist, is a professor in the Department of Family, Consumer and Nutritional Sciences at St. Catherine University in St. Paul, MN. She writes and speaks on issues regarding nutrition and food safety, with special emphasis on whole grains and dietary fiber, carbohydrates and glycemic index, and dieting. Jones is an AACC Intl. member and can be reached at juliemjones@comcast.net.