Thematic Article

Candidate foods in the Asia–Pacific region for cardiovascular protection: fish, fruit and vegetables

Gayle S Savige DipTeach, BSc, GradDipDiet, PhD

Cardiovascular disease is a major cause of morbidity and mortality. Epidemiological studies indicate fish eaters are less likely to die prematurely compared with non-fish eaters. The protective properties in fish are likely to be related to its concentration of omega 3 fatty acids, calcium, selenium, vitamin D, taurine and coenzyme Q_{10}. A high consumption of fruits and vegetables has been shown to protect against stroke and coronary heart disease. The presence of vitamins and minerals, as well as the complex array of non-nutrient compounds, found in fruits and vegetables would play an important role in this protection.

Key words: cardiovascular disease, cardiovascular protection, fish, fruits, n-3 fatty acids, vegetables.

Introduction

Throughout the Asia–Pacific region cardiovascular disease (CVD) is a major cause of mortality, although rates differ from country to country.[1] This variation in mortality rates cannot be solely attributed to genetic and/or geographical location. It would appear that a sizeable proportion of this difference may be explained by certain food patterns as well as other lifestyle factors. Interest in the protective effects of specific foods has arisen from a number of epidemiological studies that show a relationship between food intake and CVD. For example, Inuits and Japanese living in Japan, have much lower rates of coronary heart disease (CHD) compared with other countries such as New Zealand and Australia. This difference appears to relate, at least in part, to the consumption of marine foods. A recent review investigating the effects of fruit and vegetable consumption indicate these foods are protective against CVD, in particular CVD mortality.[2] These associations have prompted a number of dietary interventions and the findings from these studies often support these observations.

Many of the risk factors associated with CVD are affected by particular food habits such as hypertension, dislipidaemia, diabetes, obesity, homocysteine, inflammation and blood clotting factors (such as fibrinogen). The intake of food itself may be influenced adversely by other cardiovascular risk factors such as smoking, physical inactivity and alcohol. Hypertension and dislipidaemia have been positively moderated by particular dietary patterns, which include the regular consumption of fish and/or a high intake of fruits and vegetables. There are a number of properties in these foods that potentially offer protection and these may operate through one or more pathways.

Observational studies in relation to fish consumption

Middle-aged men living in the Netherlands who consumed at least one to two fish meals per week suffered less CHD than those who did not eat fish.[3] Furthermore, the risk of dying from CHD decreased as the consumption of fish increased. This inverse relationship between fish consumption and CHD mortality has also been found in the elderly.[4] The Chicago Western Electric Study examined the health and food intake patterns of 1800 males.[5] During 30 years of follow-up, men who ate the equivalent of 35 g or more of fish per day had a 44% lower risk of death from a myocardial infarction compared with those who ate no fish.

In a large prospective cohort study conducted in the US (the Health Professionals Follow-up study), neither the intake of n-3 fatty acids (from fish) or the consumption of fish itself was associated with a lower risk of CHD.[6] However, the risk of a non-fatal myocardial infarct when adjusted for confounders (such as age, body mass index (BMI), smoking habits, alcohol intake, hypertension, diabetes, hypercholesterolaemia and family history of myocardial infarction), was 33% lower in men who consumed two to three fish meals per week (37 g/day) compared to those who consumed no fish.

Intervention studies with fish

While most cohort studies examining the association between fish consumption and CVD tend to indicate a protective effect, there have also been several intervention studies to further support this association. The survival of men recovering from a myocardial infarction has been favourably influenced by fish consumption or fish oil supplements. In the Dart study, men assigned to a diet including two to three fatty fish meals per week had a 29% reduction in all-cause mortality, while changes in fat or cereal fibre consumption had no such effect.[7] In the GISSI-Prevenzione trial, subjects surviving a myocardial infarction were randomly allocated to receive 1 g of n-3 polyunsaturated fat containing eicosapentaenoic acid and docosahexaenoic acid.[8] After 3½ years there was a 20% decrease in cardiovascular death, non-fatal myocardial infarction, and non-fatal stroke in those taking the n-3 polyunsaturated fatty acid (PUFA) supplements compared to the controls.

Correspondence address: Dr Gayle S Savige, FAO Centre of Excellence, C/–Department of Epidemiology and Preventive Medicine, Faculty of Medicine, Nursing and Health Sciences, Monash Medical School, Alfred Hospital, Prahran, VIC 3181, Australia.
Tel: +61 3 9903 0891, Fax: +61 3 9903 0584
Email: gayle.savige@med.monash.edu.au
Accepted 15 January 2001

Fish consumption also appears to protect against hypertension, a major risk factor for CVD. When a group of overweight, hypertensive men and postmenopausal women were randomly assigned to an energy-restricted diet with one fish meal per day (for 16 weeks), there was a drop in blood pressure over and above those assigned only to the energy-restricted diet.[9] In other words, the drop in blood pressure was substantially enhanced when fish consumption was combined with weight loss.

Mechanisms of protection (fish)

There are many properties in fish that may protect against CVD. Fish is rich in omega 3 fatty acids, calcium, selenium, vitamin D, taurine and Coenzyme Q_{10} (CoQ_{10}).

Omega 3 fatty acids

Omega 3 fatty acids have been shown to protect against arrhythmia. The survival of experimental dogs who were made to endure artificially induced ventricular fibrillation while exercising was greatly enhanced when the dogs were infused with either eicosapentaenoic acid (EPA) or docosahexaenoic acid.[10] Omega three fatty acids can also help to reduce platelet aggregation and thereby have an antithrombotic effect. Both omega 6 and omega 3 fatty acids compete for cyclooxygenase, an enzyme important in the synthesis of a number of prostaglandins. Omega 3 fatty acids suppress the synthesis of thromboxane A_2 (from arachidonic acid) and enhance the synthesis of prostacyclin (a prostaglandin that inhibits platelet adhesion and stimulates vasodilation).[11] A high concentration of triglycerides in blood, an important risk factor for CVD, can be lowered with omega 3 fatty acids. Omega 3 fatty acids inhibit the synthesis of triglycerides in the liver.[12]

Calcium

Fatty fish is a good source of calcium. Calcium may protect against CVD by favourably influencing blood pressure. One meta-analysis of randomised control trials investigating the effects of calcium supplementation on blood pressure found evidence to indicate that calcium supplementation in the order of 1000–2000 mg per day may lower systolic but not diastolic blood pressure.[13] This effect was greatest in those who had a low calcium intake to begin with.

Selenium

Fish is rich in selenium and as selenium is important in the function of a number of anti-oxidant enzymes, such as the glutathione peroxidases, it may potentially retard the development of CVD via two pathways. One pathway offering protection would be through the favourable action of anti-oxidant enzymes on the oxidation of lipids; therefore inhibiting atherosclerosis. The other pathway would involve the production of eicosanoids. In selenium deficiency, the synthesis of thromboxane (an eicosanoid that enhances vasoconstriction and platelet aggregation) is favoured over the synthesis of prostacyclin (a vasodilatory eicosanoid).[14]

Vitamin D

Fish, especially fatty fish, is one of the few foods containing vitamin D. Vitamin D is important in cell differentiation.[15] Therefore, it may play a role in dampening down atherogenesis, a process which has proliferative features.

Taurine

Taurine excretion is sometimes used as a marker of seafood intake.[16] Animal studies in rats suggest taurine may reduce serum cholesterol levels by altering the activity of certain enzymes that either influence cholesterol metabolism through bile acid synthesis or inhibit its absorption from the intestine.[17]

Coenzyme Q_{10}

Concentrations of CoQ_{10} in fish range from 4 to 64 μg/g of fish.[18] CoQ_{10} protects low-density lipoprotein (LDL) against oxidation in vitro and so may play a protective role against atherosclerosis.[18]

Ecological studies in relation to fruit and vegetable consumption

When the availability and consumption of exotic fruits, such as citrus fruits and bananas (due to imports), increased in Poland in recent years, there was a corresponding fall in ischaemic heart disease (IHD).[19] Changes in medical care, smoking, drinking and stress did not parallel this decline in IHD, suggesting changes in fruit consumption and other dietary patterns (less animal and more vegetable fat) were factors contributing to the fall observed in IHD.

Observational studies in relation to fruit and vegetable consumption

Several prospective cohort studies have shown that the intake of fruit and vegetables appears to protect against the risk of stroke. When results from the Nurses Health Study and the Health Professional Follow-up Study were pooled and analysed in relation to ischaemic stroke, subjects whose intake of fruit and vegetables fell into the highest quintile had a 31% lower risk of stroke compared with those in the lowest quintile.[20] The fruit and vegetables that appeared to be most protective were vitamin C-rich fruits and vegetables, citrus fruits and juices, green leafy vegetables and cruciferous vegetables such as broccoli, cabbage, cauliflower and brussel sprouts. When a cohort of middle-aged men were followed for 20 years, the risk of stroke was also shown to decrease for each increment of three servings of fruit and vegetables eaten per day.[21]

In the Ireland-Boston Diet-Heart Study, three cohorts of men were followed for almost two decades.[22] Those whose vegetable food score fell in the middle or highest tertile (after controlling for age and cohort) had a 43% and 46%, respectively, lower risk of dying from CHD compared with those who fell in the lowest tertile. The dietary intake of fruits and vegetables and the intake of anti-oxidant vitamins (carotene, E and C) was examined in a group of Finnish men and women in relation to mortality from heart disease. Men in the highest tertile for vegetable consumption had a 34% lower risk of dying from CHD compared with those in the lowest tertile. Among the women, vitamin C was inversely associated with CHD mortality but this association was not seen in men.[23]

After 25 years of follow-up in 16 cohorts of the Seven Countries Study, flavonoid intake was found to be inversely associated with CHD mortality.[24] Furthermore, the variance in flavonoid intake after adjusting for saturated fat and cigarette smoking accounted for 8% of the total explained variance in CHD mortality. In addition to this cross-cultural

comparison, the relationship between the dietary intake of flavonoids and CHD mortality as well as the incidence of stroke has also been examined within one of these 16 cohorts: the Zutphen Elderly Study.[25] The Zutphen Elderly Study examines Dutch men that were originally enrolled in the Seven Countries Study. When these elderly men were ranked in tertiles according to their daily intake of flavonoids, the risk of dying from CHD after adjusting for age, diet and other risk factors was 68% lower in the men who fell in the top two tertiles. In this same group of men, those with the highest intake of flavonoids were also more likely to be protected against stroke.[26] It is worth noting the major source of flavonoids in the Zutphen study came from black tea (61%), onions (13%) and apples (10%).[25]

Elevated serum homocysteine concentrations have been identified as an independent risk factor for CVD.[27] Nutrient deficiencies such as folate, vitamin B6 and B12 can raise serum homocysteine concentrations. In the Framingham study, folate status and homocysteine concentrations were inversely associated.[28] The foods that made an important contribution to folate status in this study population of elderly, included breakfast cereal, fruit, orange juice and leafy green vegetables.

A cross-sectional study, comparing two religious groups with similar lifestyles, but different food habits found differences in blood pressure between the two groups. The Seventh-Day Adventists, a religious group who follow a vegetarian diet, had lower blood pressure levels at all ages (ranging from 30 to 79 years) compared with the Mormons, a religious sect who consume an omnivore diet.[29]

Interventions in relation to fruit and vegetable consumption

In the Dietary Approaches to Stop Hypertension (DASH) study, a high intake of fruits and vegetables (around 8–10 serves per day) when consumed against a background diet low in saturated and total fat, was shown to be effective in lowering blood pressure.[30] Furthermore, when this high intake of fruit and vegetables was accompanied by a moderate intake of low-fat diary products, the blood pressure lowering effects were further enhanced. These impressive changes were also evident after following this dietary pattern for only 2 weeks.

Mechanisms of protection (fruit and vegetables)

There are many mechanisms that might explain, at least in part, the protective properties of fruits and vegetables such as energy, anti-oxidants, dietary fibre, nutrients and phytochemicals.

Energy

Obesity is a risk factor for hypertension, diabetes mellitus type II and dyslipidaemia, risk factors in the development of CVD. Diets high in saturated fat have also been shown to account for differences in CHD death rates cross-culturally.[24] Fruits and vegetables are low in fat (especially saturated fat) and energy. If they are eaten in sufficient quantity, they may displace the intake of other foods, especially those high in saturated fat. This pattern of eating may indirectly protect against CVD. However, in many studies where the consumption of fruits and vegetables is shown to be inversely associated with CVD, this association often remains after adjusting for such factors as saturated fat and energy intake, suggesting other factors in fruits and vegetables play an important role in protection.

Anti-oxidants

Fruits and vegetables contain a multitude of anti-oxidants from well-known nutrients such as vitamin C and beta-carotene to the less well studied phytochemicals such as flavonoids. Anti-oxidants can quench free radicals and prevent the oxidation and modification of LDL and other lipids.

Dietary fibre

Dietary fibre may favourably influence the risk of CVD by improving lipid profiles[31] and possibly protecting against hypertension.[32]

Nutrients

There are a number of pathways in which several nutrients found in fruits and vegetables could exert a protective effect. A variety of fruits and vegetables are a good source of folate and several are a good source of vitamin B6. These nutrients can assist in preventing the rise of homocysteine, an independent risk factor for CVD. Fruits and vegetables are also rich in potassium, magnesium and to a lesser extent calcium, minerals that may play an important role in preventing hypertension. Vitamin C acting as an anti-oxidant has been shown to protect against stroke and possible CHD, although the evidence is less convincing regarding the latter.[33]

Phytochemicals

Fruits and vegetables contain many different phytochemicals. Flavonoids, a subgroup of phenols (a major class of plant chemicals), possess several properties that potentially offer protection against CVD. This protection may be due to the anti-oxidant and platelet inhibiting effects of flavonoids.[34] Flavonoids can influence platelet aggregation by blocking cyclooxygenase, the enzyme required for prostaglandin synthesis.[35] Flavonoids can also inhibit the angiotensin-converting enzyme responsible for increasing blood pressure.[35]

Sitosterol is a major plant sterol that is similar in structure to cholesterol. It competes with cholesterol in the intestine and inhibits its absorption. If eaten in sufficient quantities, plant sterols can reduce serum cholesterol and LDL cholesterol.[36] The intake of plant sterols has been estimated to range from approximately 150 mg per day up to about 1 g per day in vegetarians.[36] Vegetable oils are also an important food source of plant sterols.

Sulfur-based compounds like allicin found in garlic may play a protective role in cardiovasuclar disease. One recent meta-analysis of randomised clinical trials investigating the effects of garlic on total cholesterol found evidence to suggest that garlic had a positive effect on lowering total cholesterol levels, although this effect was weak.[37]

Many fruit and vegetable contain *salicylates*, a family of plant chemicals to which aspirin belongs. The salicylate chemicals may exert a mildly protective effect through their antithrombotic and anti-inflammatory properties.[38]

Conclusion

There is good evidence to suggest fish, fruits and vegetables are protective against CVD especially CVD mortality. The mechanisms responsible for this protection are complex as are the properties of fish, fruits and vegetables. Consuming these properties as foods probably provides the best protection as the effects are likely to be synergistic or additive.

References

1. Khor GL. 1997 Nutrition and cardiovascular disease: an Asia Pacific perspective. Asia Pac J Clin Nutr 1997; 6: 122–142.
2. Ness AR, Powles JW, Khaw KT. Vitamin C and cardiovascular disease: a systematic review. J Cardiovasc Risk 1996; 3: 513–521.
3. Kromhout D, Bosschieter EB, de Lezenne Coulander C. The inverse relation between fish consumption and 20-year mortality form coronary heart disease. N Engl J Med 1985; 312: 1205–1209.
4. Kromhout D, Feskens EJM, Bowles CH. The protective effect of a small amount of fish on coronary heart disease mortality in an elderly population. Int J Epidemiol 1995; 24: 340–345.
5. Daviglus ML, Stamler J, Orencia AJ, Dyer AR, Liu K, Greenland P, Walsh MK, Morris D, Shekelle RB. Fish consumption and the 30-year risk of fatal myocardial infarction. N Engl J Med 1997; 336: 1046–1053.
6. Ascherio A, Rimm EB, Stampfer MJ, Giovannucci EL, Willett WC. Dietary intake of marine n-3 fatty acids, fish intake, and the risk of coronary disease among men. N Engl J Med 1995; 332: 977–982.
7. Burr ML, Fehily AM, Gilbert JF, Rogers S, Holliday RM, Sweetnam PM, Elwood PC, Deadman NM. Effects of changes in fat, fish, and fibre intakes on death and myocardial reinfarction: diet and reinfarction trial (DART). Lancet 1989; 2: 757–761.
8. GISSI-Prevenzione Investigators. Dietary supplementation with n-3 polyunsaturated fatty acids and vitamin E after myocardial infarction: results of the GISSI-Prevenzione trial. Lancet 1999; 354: 447–455.
9. Bao DQ, Mori TA, Burke V, Puddey IB, Beilin LJ. Effects of dietary fish and weight reduction on ambulatory blood pressure in overweight hypertensives. Hypertension 1998; 32: 710–717.
10. Kang JX, Leaf A. Prevention of fatal cardiac arrhythmias by polyunsaturated fatty acids. Am J Clin Nutr 2000; 71: 202S–207S.
11. Goodnight SH. The fish oil puzzle. Science and Medicine. 1996, September/October: 42–51.
12. Singleton CB, Walker BD, Campbell TJ. N-3 Polyunsaturated fatty acids and cardiac mortality. Aust NZ J Med 2000; 30: 246–251.
13. Bucher HC, Cook RJ, Guyatt GH, Lang JD, Cook DJ, Hatala R, Hunt DL. Effects of dietary calcium supplementation on blood pressure – a meta-analysis of randomized controlled trials. JAMA 1996; 275: 1016–1022.
14. Rayman MP. The importance of selenium to human health. Lancet 2000; 356: 233–241.
15. Kato S. The function of vitamin D receptor in vitamin D action. J Biochem 2000; 127: 717–722.
16. Liu LJ, Mizushima S, Ikeda K, Hattori H, Miura A, Gao M, Nara Y, Yamori Y. Comparative studies of diet-related factors and blood pressure among Chinese and Japanese: Results from the China–Japan Cooperative Research of the WHO–CARDIAC Study. Hypertens Res 2000; 23: 413–420.
17. Murakami S, Yamagishi I, Asami Y, Ohta Y, Toda Y, Nara Y, Yamori Y. Hypolipidemic effect of taurine in stroke-prone spontaneously hypertensive rats. Pharmacology 1996; 52: 303–313.
18. Weber C, Bysted A, Holmer G. The coenzyme Q_{10} content of the average Danish diet. Int J Vitam Nutr Res 1994; 67: 123–129.
19. Zatonski WA, McMichael AJ, Powles JW. Ecological study of reasons for sharp decline in mortality from ischaemic heart disease in Poland since 1991. BMJ 1998; 316: 1047–1051.
20. Joshipura KJ, Ascherio A, Manson JE, Stampfer MJ, Rimm EB, Speizer FE, Hennekens CH, Spiegelman D, Willett WC. Fruit and vegetable intake in relation to risk of ischemic stroke. JAMA 1999; 282: 1233–1239.
21. Gillman MW, Cupples LA, Gagnon D, Posner BM, Ellison RC, Castelli WP, Wolf PA. Protective effect of fruits and vegetables on development of stroke in men. JAMA 1995; 273: 1113–1117.
22. Kushi LH, Lew RA, Stare FJ, Ellison CR, el Lozy M, Bourke G, Daly L, Graham I, Hickey N, Mulcahy R, Kevaney J. Diet and 20-year mortality from coronary heart disease. The Ireland-Boston Diet-Heart Study. N Engl J Med 1985; 312: 811–818.
23. Knekt P, Reunanen A, Jarvinen R, Seppanen R, Heliovaara M, Aromaa A. Antioxidant vitamin intake and coronary mortality in a longitudinal population study. Am J Epidemiol 1994; 139: 1180–1189.
24. Hertog MGL, Kromhout D, Aravanis C, Blackburn H, Buzina R, Fidanza F, Giampaoli S, Jansen A, Menotti A, Nedeljkovic S, Pekkarinen M, Simic BS, Toshima H, Feskens EJM, Hollman PCH, Katan MB. Flavonoid intake and long-term risk of coronary heart disease and cancer in the seven countries study. Arch Intern Med 1995; 155: 381–386.
25. Hertog MGL, Feskens EJM, Hollman PCH, Katan MB, Kromhout D. Dietary antioxidant flavonoids and risk of coronary heart disease – the Zutphen elderly study. Lancet 1993; 342: 1007–1011.
26. Keli SO, Hertog MG, Feskens EJ, Kromhout D. Dietary flavonoids, antioxidant vitamins, and incidence of stroke: the Zutphen study. Arch Intern Med 1996; 156: 637–642.
27. Koehler KM, Romero LJ, Stauber PM, Pareo-Tubbeh SL, Chi Laing H, Baumgartner RN, Garry PJ, Allen RH, Stabler SP. Vitamin supplementation and other variables affecting serum homocysteine and methylmalonic acid concentrations in elderly men and women. J Am Coll Nutr 1996; 15: 364–376.
28. Tucker KL, Selhub J, Wilson PW, Rosenberg IH. Dietary intake patterns relates to plasma folate and homocysteine concentrations in the Framingham Heart Study. J Nutr 1996; 126: 3025–3031.
29. Rouse IL, Beilin LJ. Vegetarian diet and blood pressure. J Hyperten 1984; 2: 231–240.
30. Appel LJ, Moore TJ, Obarzanek E, Vollmer WM, Svetkey LP, Sacks FM, Bray GA, Vogt TM, Cutler JA, Windhauser MM, Lin PH, Karanja N. A clinical trial of the effects of dietary patterns on blood pressure. DASH Collaborative Research Group. N Engl J Med 1997; 336: 1117–1124.
31. Jenkins DJA, Kendall CWC, Vuksan V. Viscous fibers, health claims, and strategies to reduce cardiovascular disease risk. Am J Clin Nutr 2000; 71: 401–402.
32. He J, Whelton PK. Effect of dietary fiber and protein intake on blood pressure: a review of epidemiologic evidence. Clin Exp Hypertens 1999; 21: 785–796.
33. Ness AR, Powles JW, Khaw KT. Vitamin C and cardiovascular disease: a systematic review. J Cardiovasc Risk 1996; 3: 513–521.
34. Gryglewski RJ, Korbut R, Robak J, Swies J. On the mechanism of antithrombotic action of flavonoids. Biochem Pharmacol 1987; 36: 317–322.
35. Dillard CJ, German JB. Phytochemicals: nutraceuticals and human health. J Sci Food Agric 2000; 80: 1744–1756.
36. Piironen V, Lindsay DG, Miettinen TA, Toivo J, Lampi AM. Plant sterols: biosynthesis, biological function and their importance to human nutrition. J S Food Agric 2000; 80: 939–966.
37. Stevinson C, Pittler MH, Ernst E. Garlic for treating hypercholesterolemia – A meta-analysis of randomized clinical trials. Ann Inter Med 2000; 133: 420–429.
38. Ridker PM, Cushman M, Stampfer MJ, Tracy RP, Hennekens CH. Inflammation, aspirin and the risk of cardiovascular disease in apparently healthy men. N Engl J Med 1997; 336: 973–979.