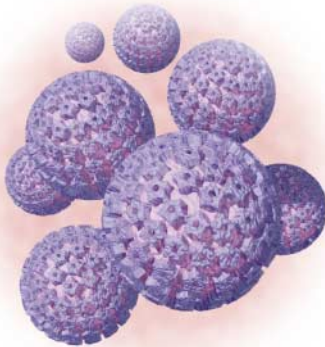




This Week in the Journal

April 11, 2002



Male Circumcision, Penile Human Papillomavirus Infection, and Cervical Cancer

It is uncertain whether male circumcision reduces the risk of penile human papillomavirus (HPV) infection and of cervical cancer in a man's female partner. The authors studied women and their male partners enrolled in seven case-control studies of cervical carcinoma in situ and cervical cancer in five countries in Europe, South America, and Asia. Circumcised men were significantly less likely than uncircumcised men to have penile HPV infection. Women whose partners had six or more lifetime sexual partners were less likely to have cervical cancer if their partners were circumcised than if they were uncircumcised.

These data suggest that male circumcision may reduce the risk of penile HPV infection in men and the risk of cervical cancer in female partners of sexually promiscuous men.

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“The $n-3$ fatty acids found in fish are strongly associated with a reduced risk of sudden death.”

$n-3$ Fatty Acids and the Risk of Sudden Death

Fish contains long-chain $n-3$ polyunsaturated fatty acids, which are believed to have antiarrhythmic properties and may reduce the risk of sudden death after myocardial infarction. This study shows that men without cardiovascular disease who have higher blood levels of $n-3$ fatty acids have a reduced risk of sudden death.

Fish consumption, or dietary supplementation with $n-3$ fatty acids, may be appropriate for the prevention of sudden death in persons at risk, whether or not they have evidence of cardiovascular disease.

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PERSPECTIVE

Fish — Food to Calm the Heart

In the Book of Genesis, fish appeared in the waters on the fifth day of creation, after dry land and water separated. This may be the first reference to a functional, indeed lifesaving, food for humans. In the 19th century, New England ships harvested marine oil not for food but to light lamps. Fast forward to the 20th century and the identification of the “Eskimo paradox,” which refers to the extremely low rates of death from cardiovascular disease among the Inuit, as compared with their northern European counterparts, despite similarly high intakes of fat — about 40 percent of calories. Fish and fish-eating mammals, however, were the main sources of fat among the Inuit. Travel to the island of Crete,

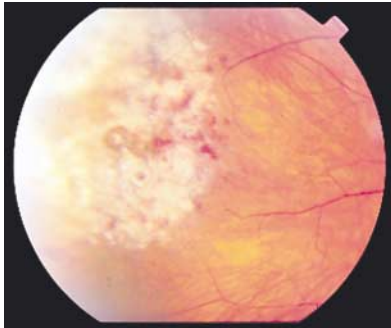
where the extremely low rates of death from cardiac disease are attributed to dietary factors, not least the intake of unsaturated fatty acids from marine and unusual plant sources. These unsaturated fatty acids are a central element in the diet-heart hypothesis, which emerged in the mid-20th century and has dominated public health discourse in nutrition ever since.

Common to this mix of myth, paradox, and science are the marine or fish oils in the diet and their apparent protective effects against death from cardiovascular disease, the number-one killer in the industrialized world, resulting in 250,000 sudden deaths yearly in the United States. The article by Albert et al. in this issue of the *Journal* (pages 1113–1118) is yet another addition to the growing body of evidence, including data from intervention trials, that eating long-chain n-3 polyunsaturated fatty acids, largely from fish, may provide protection against sudden death from cardiovascular causes. The emerging story of how n-3 fatty acids prevent

ventricular arrhythmias and sudden death is our focus here, although lipid metabolism, blood-pressure regulation, brain and retinal development, immune modulation, platelet function, and clotting are other targets of these multifunctional substances.

What are these long-chain polyunsaturated fatty acids, the main actors in this story? The structure and nomenclature of the three lead actors are shown in the figure. By 1930, it was clear that some fatty acids not only were sources of energy (as a result of oxidation), but also were essential in the diet — thus, the term “essential fatty acids.” Our focus is on long-chain n-3 fatty acids, which are characterized by the presence of a double bond three carbons from the n end of the molecule. Two such acids — docosahexaenoic acid (DHA) and eicosapentaenoic acid (EPA) — derived largely from marine species, especially fatty fish (salmon, bluefish, mackerel, arctic char, and swordfish), are mainly responsible for the protective effects of this group of

n-3 Fatty acid	Formula	Dietary source
α -Linolenic acid (C18:3n-3)		Some vegetable oils (canola, soybean), nuts (walnuts), seeds (flaxseed)
Eicosapentaenoic acid (C20:5n-3)		Fish and shellfish
Docosahexaenoic acid (C22:6n-3)		Fish and shellfish



Valganciclovir for Treatment of Cytomegalovirus Retinitis

This randomized trial involved 160 patients with the acquired immunodeficiency syndrome (AIDS) and newly diagnosed cytomegalovirus retinitis. After four weeks, the response to induction therapy was satisfactory in 72 percent of patients who received oral valganciclovir, as compared with 77 percent of those who received intravenous ganciclovir. The median time to progression of retinitis was 160 days for the valganciclovir group and 125 days for the ganciclovir group.

Valganciclovir is a prodrug that can be taken orally and is rapidly hydrolyzed to ganciclovir. This more convenient form of medication appears to be as effective as ganciclovir as induction therapy for cytomegalovirus retinitis, the leading cause of visual loss in patients with AIDS.

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substances, although they can be made from shorter-chain α -linolenic acid, which is present in some vegetable oils, nuts, and seeds.

In the past decade, the mechanism by which DHA and EPA counter potentially fatal cardiac arrhythmias has emerged from studies in laboratory animals. The connection between fish in the diet and protection from sudden death due to cardiac arrhythmias is not, as might be assumed from the title of the study by Albert et al., the result of the protective action of n-3 fatty acids in blood (these substances are really markers of dietary patterns, as the authors point out), but rather the effect of diet on the fatty-acid content of phospholipids in heart-cell membranes in the functionally critical SN2 position.

In the event of severe physiological stress, such as that caused by the loss of blood supply to a portion of the heart early in an ischemic attack,

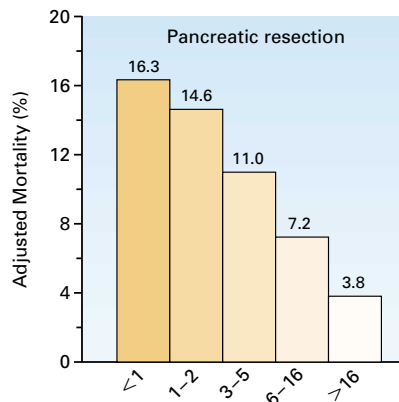
the DHA or EPA occupying the SN2 position in phospholipids is released and protects the heart cell locally from participating in the genesis and propagation of ventricular tachycardia, which can result in cardiac arrest and sudden death. This protective effect, which is absent if other fatty acids derived from the diet occupy the SN2 position, depends on the unique ability of these n-3 fatty acids to stabilize all contractile heart cells electrically and thus protect against sudden death from arrhythmias.

What are the nutritional and health implications of this compelling scientific narrative? One is that the diet-heart relation is more complex than that reflected by recommendations about total dietary fat and cholesterol or even saturated fat. The mechanism underlying the prevention of sudden death from cardiac causes differs from that of prevention of atherosclerotic heart

disease, and n-3 fatty acids play a critical part. It is both safe and prudent to eat, as recommended by the American Heart Association, at least two servings of fish per week, especially fatty fish, as we strive for an intake of n-3 fatty acids approaching 1 g per day. There are also likely to be other beneficial effects of the intake of n-3 fatty acids that are not discussed by Albert et al., including those on blood triglyceride levels, the immune system, the developing central nervous system (by the transmission of fatty acids through breast milk), clotting mechanisms, and blood pressure. This result is a model for any scientific effort to identify a functional food.

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Special Article: Hospital Volume and Surgical Mortality

For surgical procedures, operative mortality varies inversely with the number of procedures performed at a hospital. This study quantified the relation between volume and outcome among Medicare patients for 14 different surgical procedures. The relative effect of surgical volume on outcome varied markedly among types of procedures. For pancreatic resection, the absolute difference in mortality rates between the highest-volume and the lowest-volume hospitals was over 12 percent, whereas for carotid endarterectomy, the difference was only 0.2 percent.

In selecting a hospital for a surgical procedure, Medicare patients should consider the number of procedures performed at that hospital, among other measures of surgical quality.

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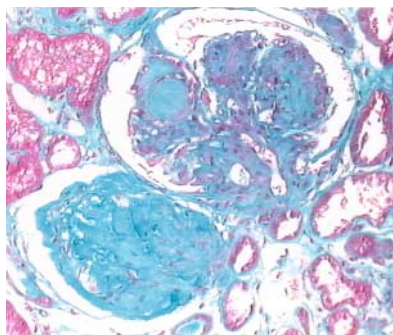
“Our results suggest the need for more careful scrutiny of adverse outcomes in prostate cancer.”

Special Article: Variations in Outcome after Radical Prostatectomy

Radical prostatectomy is commonly performed in men with early-stage prostate cancer. This study assessed the outcome of surgery in relation to the number of prostatectomy procedures performed at individual hospitals (hospital volume) and by individual surgeons (surgeon volume). Neither hospital volume nor surgeon volume was related to operative mortality. However, postoperative complications and late urinary complications were more common in patients treated at low-volume hospitals or by low-volume surgeons than in those treated at high-volume hospitals or by high-volume surgeons.

This study adds to a growing body of information that hospital volume and surgeon volume have significant effects on outcome — in this case, on important measures of postoperative complications that may affect patients’ quality of life.

see page 1138 (editorial, page 1161)



Clinical Practice: Nephropathy in Patients with Type 2 Diabetes

A 60-year-old man with recently diagnosed type 2 diabetes mellitus has a serum creatinine level of 1.5 mg per deciliter (133 μmol per liter), and a dipstick test shows proteinuria (++) . His blood pressure is 150/90 mm Hg. He smokes half a pack of cigarettes daily. What can be done to reduce the risk of progressive renal disease?

This Clinical Practice article reviews strategies for preventing the development or progression of nephropathy in patients with type 2 diabetes.

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