

logical analysis and if immunoglobulin deposition and complement activation are observed, possibly as a pathogenic factor, the elimination of damaging inflammatory factors should help and improve the neurological deficit. The conditions are, however, very strict and therefore the adherence to a good diagnostic protocol and selection of patients is important. Unfortunately, a brain biopsy was used. By comparison with other current diagnostic measures, biopsies decrease the compliance for patients considerably, therefore surrogate markers are needed (figure).

We do not know how total plasma-exchange works. The technique might eliminate pathogenic molecules or induce and restore beneficial humoral factors. This issue might be addressed in future studies by prospectively investigating, for example, complement-factor consumption, alterations of immunoglobulins, acute-phase reactants, cytokines, and balances between matrix metalloproteinases and inhibitors. In addition, the collection of individual plasma exchanges after informed consent might constitute an ideal opportunity to discover the elusive humoral pathogenic factor(s). By the study of autoantigens and antibodies in single patients, so-called nagged antibodies<sup>12</sup> or novel antigens might be discovered.

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- 1 Keegan M, König F, McClelland R, et al. Relation between humoral pathological changes in multiple sclerosis and response to therapeutic plasma exchange. *Lancet* 2005; **366**: 579–82.
- 2 Hohlfeld R, Wekerle H. Autoimmune concepts of multiple sclerosis as a basis for selective immunotherapy: from pipe dreams to (therapeutic) pipelines. *Proc Natl Acad Sci USA* 2004; **101**: 14599–606.
- 3 Opdenakker G, Van Damme J. Cytokine-regulated proteases in autoimmune diseases. *Immunol Today* 1994; **15**: 103–07.
- 4 Buntinx M, Stinissen P, Steels P, Ameloot M, Raus J. Immune-mediated oligodendrocyte injury in multiple sclerosis: molecular mechanisms and therapeutic interventions. *Crit Rev Immunol* 2002; **22**: 391–424.
- 5 Opdenakker G, Nelissen I, Van Damme J. Functional roles and therapeutic targeting of gelatinase B and chemokines in multiple sclerosis. *Lancet Neurol* 2003; **2**: 747–56.
- 6 Corboy JR, Goodin DS, Frohman EM. Disease-modifying therapies for multiple sclerosis. *Curr Treat Options Neurol* 2003; **5**: 35–54.
- 7 Munari L, Lovati R, Boiko A. Therapy with glatiramer acetate for multiple sclerosis. *Cochrane Database Syst Rev* 2004; **1**: CD004678.
- 8 Poser CM, Paty DW, Scheinberg L, et al. New diagnostic criteria for multiple sclerosis: guidelines for research protocols. *Ann Neurol* 1983; **13**: 227–31.
- 9 Paemen L, Olsson T, Söderström M, Van Damme J, Opdenakker G. Evaluation of gelatinases and IL-6 in the cerebrospinal fluid of patients with optic neuritis, multiple sclerosis and other inflammatory neurological diseases. *Eur J Neurol* 1994; **1**: 55–63.
- 10 Vamvakas EC, Pineda AA, Weinshenker BG. Meta-analysis of clinical studies of the efficacy of plasma exchange in the treatment of chronic progressive multiple sclerosis. *J Clin Apheresis* 1995; **10**: 163–70.
- 11 Lassmann H, Bruck W, Lucchinetti C. Heterogeneity of multiple sclerosis pathogenesis: implications for diagnosis and therapy. *Trends Mol Med* 2001; **7**: 115–21.
- 12 Opdenakker G, Van den Steen PE, Laureys G, Hunnink K, Arnold B. Neutralizing antibodies in gene-defective hosts. *Trends Immunol* 2003; **24**: 94–100.

## Vegetables, fruit, and cancer

A role for plant foods in the maintenance of health has been known for several thousand years. Plants and plant extracts also provide the bulk of the pharmacopoeia. In 1991, Steinmetz and Potter<sup>1,2</sup> summarised the available (largely case-control) data on cancer, vegetables, and fruit, concluding that the evidence was consistent with higher consumption being associated with a lower risk of many epithelial cancers. The 1997 World Cancer Research Fund report,<sup>3</sup> reviewing the available literature to the end of 1996, concluded that vegetables and fruit were probably or convincingly associated with a lower risk of cancers of mouth, oesophagus, lung, stomach, colorectum (vegetables only), larynx, pancreas, breast, and bladder. In October 2004, Hsin-Chia Hung and colleagues,<sup>4</sup> using data from the Harvard Nurses Health and Health Professionals follow-up studies,<sup>5</sup> concluded that vegetables and fruit were associated with a lower risk

of cardiovascular disease, but that the relation with cancer, overall, was null. Clearly there is an inconsistency here. Is there an explanation?

First, is Hung and colleagues' report<sup>4</sup> consistent with earlier findings from the Harvard investigators? Previously, Walter Willett's group at Harvard had reported lower risks in association with high intakes of vegetables and fruit for premenopausal, but not postmenopausal, breast cancer (and, in 1993, a reduced risk for all breast cancer with vegetables alone<sup>6</sup>), female lung cancer,<sup>7</sup> male bladder cancer but only for cruciferae,<sup>8</sup> non-Hodgkin lymphoma,<sup>9</sup> and prostate cancer (for fruit only).<sup>10</sup> Only for colon cancer have they previously reported no association with vegetables and fruit.<sup>11</sup>

In other cohort studies of breast cancer, high intake of vegetables and fruit was not associated with risk in the Leisure World Study<sup>12</sup> but showed reduced risk in the

Canadian National Breast Screening study (relative risk 0.68, 95% CI, 0.46–1.00).<sup>13</sup> The overall picture for colon cancer in cohort studies is one of reduced risk, particularly for women, where nine of ten estimates of association with vegetables and fruit are less than 1.0, although most 95% CIs include 1.0.<sup>12,14–18</sup> For lung cancer, cohort studies again suggest, if any association, a lower risk for women but not men,<sup>12,19–25</sup> by far the largest study (n about 500 000) shows a reduced risk associated with fruit consumption (0.60, 0.46–0.78), but not vegetables.<sup>25</sup>

The Harvard findings for cardiovascular disease had essentially already been reported and are not a surprise.<sup>26,27</sup>

So there is something of a paradox. The literature up to 1997 was sufficient to conclude that vegetables and fruit were associated with a lower risk of various cancers.<sup>3</sup> The earlier Harvard findings were included in the World Cancer Research Fund review, but even as a separate body of literature, this group has, as noted above, independently reported lower risks for several cancers. Against the background of all findings, there are several possible conclusions about the results of Hung and colleagues.<sup>4</sup>

The first possibility is that there really is an association between lower risk of cardiovascular disease and intake of vegetables and fruit, but none between such intake and cancer, and earlier papers, including those of the Harvard group, are somehow in error. In support of this position, the tone used to describe findings in earlier papers is revealing. For breast cancer, “consumption of fruits and vegetables high in specific carotenoids and vitamins may reduce premenopausal breast cancer risk” accompanies a relative risk estimate for highest versus lowest quintile of 0.70 (0.58–1.02);<sup>5</sup> and for lung cancer, “high fruit and vegetable intakes were associated with lower risks of lung cancer in women” (0.79, 0.59–1.06);<sup>7</sup> but for bladder cancer, “consumption of vegetables other than cruciferae may not confer appreciable benefit” (0.72, 0.47–1.09).<sup>8</sup> So has the Harvard group never been sure which way to jump about cancer and vegetables and fruit?

Alternatively, there is an association with cardiovascular disease and, earlier, there was an association with cancers, but this latter association has changed over time due to the increasing error in measurement, as greater and greater time has elapsed between the exposure and outcome. This explanation would also imply that there is a difference in the way measurement error affects the relation with cardiovascular disease versus cancer.



However, Hung and colleagues specifically used a concatenated measure of exposure, using not only the baseline data, but also subsequent updates (only the second cancer paper in which the Harvard group have done this<sup>11</sup>).

Another possible reason why the relation with intake of vegetables and fruit might have seemingly gone away is a genuine change in the exposure, such that the constituents of vegetables and fruit that fight cardiovascular disease remain, but the cancer-preventing properties have been eliminated or reduced by changes in food sources, plant breeding, or harvesting, transport, and storage. This explanation would suggest that plant constituents that are active against cardiovascular diseases are different from putative cancer preventives, and remains a plausible explanation for the discrepancies between studies in different parts of the world; this explanation, if true, might give some clues as to which constituents are key to which prevention strategies.

There are, however, other considerations worthy of our attention. First, Hung and colleagues implicitly use the discrepancy in findings for cardiovascular disease and cancer to argue that null findings cannot be solely a measurement-error problem; measurement error would show itself with all outcomes. There is some merit to this argument, although the Harvard group earlier used exactly this argument to show that their finding that fat was unrelated to breast cancer<sup>28</sup> was not due to measurement error because there was still an association between fat and colon cancer.<sup>29</sup> Subsequently, in the Harvard studies, the association between fat and colon cancer has gone away<sup>30,31</sup> and an association between

saturated fat and breast cancer has emerged,<sup>32</sup> though not in all settings.<sup>33</sup>

Second, cardiovascular disease is a small cluster of diseases, whereas cancer is a much larger and more heterogeneous collection of outcomes. The heterogeneity is increasing as we develop molecular disease-classification systems. There is heterogeneity in the associations of reproductive variables with breast cancer when stratified on receptor subtype<sup>34</sup> and the smoking associations with colon cancer when stratified on microsatellite stability.<sup>35</sup> Collapsing across all cancer types and subtypes to examine the relation with a single exposure is an increasingly doubtful proposition, especially because we know that cancers (and cancer subtypes) have different associations with intake of vegetables and fruit. For example, stomach cancer, a relatively rare cancer in the USA and Canada, and uncommon in the Harvard cohorts, is related to vegetable and fruit intake.<sup>36–38</sup>

Third, the median intake of vegetables and fruit in the Harvard cohorts is greater than five servings a day for both men and women, much higher than the US norm. If the relation of risk with vegetables and fruit intake plateaus but at different doses for different diseases, this very-high-intake population might be a poor test of all of the aspects of the relation between plant foods and disease.

Finally, whilst it might be useful to collapse across all cancers to make a public-health point, any given individual's risk will be elevated for a much smaller subset of cancers; grouping sites thus obscures not only important biology, but also useful information for individuals.

We still have an unclear picture of the relation between diet and chronic disease, the role of specific foods, specific meal patterns, and changes over time, whether due to changes in foods themselves or changes in behaviours. We have yet to take advantage of the complete range of human behaviours, genetic variability, and disease patterns; all of our cohort studies are confined to fragments of the complete human experience. We need a large ( $n > 10^6$ ) international cohort study that takes advantage of the complete pattern of human genetic susceptibility and resistance, that identifies, and measures well, dietary and other exposures, and that establishes more precise, molecular, disease phenotypes.<sup>39,40</sup> We now have the tools to do this. Do we have the collective determination to get it done?

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I declare that I have no conflict of interest.

- Steinmetz KA, Potter JD. Vegetables, fruit, and cancer I: epidemiology. *Cancer Causes Control* 1991; **2**: 325–57.
- Steinmetz KA, Potter JD. Vegetables, fruit, and cancer II: mechanisms. *Cancer Causes Control* 1991; **2**: 427–42.
- World Cancer Research Fund Panel. Food, nutrition and the prevention of cancer: a global perspective. Washington, DC: American Institute for Cancer Research, 1997.
- Hung HC, Josphipura KJ, Jiang R, et al. Fruit and vegetable intake and risk of major chronic disease. *J Natl Cancer Inst* 2004; **96**: 1577–84.
- Zhang S, Hunter DJ, Forman MR, et al. Dietary carotenoids and vitamins A, C, and E and risk of breast cancer. *J Natl Cancer Inst* 1999; **91**: 547–56.
- Hunter DJ, Manson JE, Colditz GA, et al. A prospective study of the intake of vitamins C, E, and A and the risk of breast cancer. *N Engl J Med* 1993; **329**: 234–40.
- Feskanich D, Ziegler RG, Michaud DS, et al. Prospective study of fruit and vegetable consumption and risk of lung cancer among men and women. *J Natl Cancer Inst* 2000; **92**: 1812–23.
- Michaud DS, Spiegelman D, Clinton SK, Rimm EB, Willett WC, Giovannucci EL. Fruit and vegetable intake and incidence of bladder cancer in a male prospective cohort. *J Natl Cancer Inst* 1999; **91**: 605–13.
- Zhang SM, Hunter DJ, Rosner BA, et al. Intakes of fruits, vegetables, and related nutrients and the risk of non-Hodgkin's lymphoma among women. *Cancer Epidemiol Biomarkers Prev* 2000; **9**: 477–85.
- Giovannucci E, Rimm EB, Wolk A, et al. Calcium and fructose intake in relation to risk of prostate cancer. *Cancer Res* 1998; **58**: 442–47.
- Michels KB, Edward G, Josphipura KJ, et al. Prospective study of fruit and vegetable consumption and incidence of colon and rectal cancers. *J Natl Cancer Inst* 2000; **92**: 1740–52.
- Shibata A, Paganini-Hill A, Ross RK, Henderson BE. Intake of vegetables, fruits, beta-carotene, vitamin C and vitamin supplements and cancer incidence among the elderly: a prospective study. *Br J Cancer* 1992; **66**: 673–79.
- Rohan TE, Howe GR, Friedenreich CM, Jain M, Miller AB. Dietary fiber, vitamins A, C, and E, and risk of breast cancer: a cohort study. *Cancer Causes Control* 1993; **4**: 29–37.
- Steinmetz KA, Kushi LH, Bostick RM, Folsom AR, Potter JD. Vegetables, fruit, and colon cancer in the Iowa Women's Health Study. *Am J Epidemiol* 1994; **139**: 1–15.
- Thun MJ, Calle EE, Namboodiri MM, et al. Risk factors for fatal colon cancer in a large prospective study. *J Natl Cancer Inst* 1992; **84**: 1491–500.
- Terry P, Giovannucci E, Michels KB, et al. Fruit, vegetables, dietary fiber, and risk of colorectal cancer. *J Natl Cancer Inst* 2001; **93**: 525–33.
- Voorrips LE, Goldbohm RA, van Poppel G, Sturmans F, Hermus RJ, van den Brandt PA. Vegetable and fruit consumption and risks of colon and rectal cancer in a prospective cohort study: the Netherlands Cohort Study on Diet and Cancer. *Am J Epidemiol* 2000; **152**: 1081–92.
- Flood A, Velie EM, Chatterjee N, et al. Fruit and vegetable intakes and the risk of colorectal cancer in the Breast Cancer Detection Demonstration Project follow-up cohort. *Am J Clin Nutr* 2002; **75**: 936–43.
- Wang LD, Hammond EC. Lung cancer, fruit, green salad and vitamin pills. *Chin Med J (Engl)* 1985; **98**: 206–10.
- Kromhout D. Essential micronutrients in relation to carcinogenesis. *Am J Clin Nutr* 1987; **45** (suppl 5): 1361–67.
- Fraser GE, Beeson WL, Phillips RL. Diet and lung cancer in California Seventh-day Adventists. *Am J Epidemiol* 1991; **133**: 683–93.
- Steinmetz KA, Potter JD, Folsom AR. Vegetables, fruit, and lung cancer in the Iowa Women's Health Study. *Cancer Res* 1993; **53**: 536–43.
- Kvale G, Bjelke E, Gart JJ. Dietary habits and lung cancer risk. *Int J Cancer* 1983; **31**: 397–405.
- Liu Y, Sobue T, Otani T, Tsugane S. Vegetables, fruit consumption and risk of lung cancer among middle-aged Japanese men and women: JPHC study. *Cancer Causes Control* 2004; **15**: 349–57.
- Miller AB, Altenburg HP, Bueno-de-Mesquita B, et al. Fruits and vegetables and lung cancer: findings from the European Prospective Investigation into Cancer and Nutrition. *Int J Cancer* 2004; **108**: 269–76.

- 26 Joshipura KJ, Ascherio A, Manson JE, et al. Fruit and vegetable intake in relation to risk of ischemic stroke. *JAMA* 1999; **282**: 1233–39.
- 27 Joshipura KJ, Hu FB, Manson JE, et al. The effect of fruit and vegetable intake on risk for coronary heart disease. *Ann Intern Med* 2001; **134**: 1106–14.
- 28 Willett WC, Stampfer MJ, Colditz GA, Rosner BA, Hennekens CH, Speizer FE. Dietary fat and the risk of breast cancer. *N Engl J Med* 1987; **316**: 22–28.
- 29 Willett WC, Stampfer MJ, Colditz GA, Rosner BA, Speizer FE. Relation of meat, fat, and fiber intake to the risk of colon cancer in a prospective study among women. *N Engl J Med* 1990; **323**: 1664–72.
- 30 Giovannucci E, Rimm EB, Stampfer MJ, Colditz GA, Ascherio A, Willett WC. Intake of fat, meat, and fiber in relation to risk of colon cancer in men. *Cancer Res* 1994; **54**: 2390–97.
- 31 Giovannucci E, Willett W. Dietary factors and risk of colon cancer. *Ann Med* 1994; **26**: 443–52.
- 32 Smith-Warner S, Spiegelman D, Adami H, et al. Types of dietary fat and breast cancer: a pooled analysis of cohort studies. *Int J Cancer* 2001; **92**: 767–74.
- 33 Holmes MD, Hunter DJ, Colditz GA, et al. Association of dietary intake of fat and fatty acids with risk of breast cancer. *JAMA* 1999; **281**: 914–20.
- 34 Potter J, Cerhan J, Sellers T, et al. Progesterone and estrogen receptors and mammary neoplasia in the Iowa Women's Health Study: how many kinds of breast cancer are there? *Cancer Epidemiol Biomarkers Prev* 1995; **4**: 319–26.
- 35 Slattery M, Curtin K, Anderson K, et al. Associations between cigarette smoking, lifestyle factors, and microsatellite instability in colon tumors. *J Natl Cancer Inst* 2000; **92**: 1831–36.
- 36 Kato I, Tominaga S, Matsumoto K. A prospective study of stomach cancer among a rural Japanese population: a 6-year survey. *Jpn J Cancer Res* 1992; **83**: 568–75.
- 37 Nomura AM, Stemmermann GN, Chyou PH. Gastric cancer among the Japanese in Hawaii. *Jpn J Cancer Res* 1995; **86**: 916–23.
- 38 Kobayashi M, Tsubono Y, Sasazuki S, Sasaki S, Tsugane S. Vegetables, fruit and risk of gastric cancer in Japan: a 10-year follow-up of the JPHC Study Cohort I. *Int J Cancer* 2002; **102**: 39–44.
- 39 Collins F. The case for a US prospective study of genes and environment. *Nature* 2004; **429**: 475–77.
- 40 Potter J. Toward the last cohort. *Cancer Epidemiol Biomarkers Prev* 2004; **13**: 895–97.

## Risk stratification in Brugada syndrome

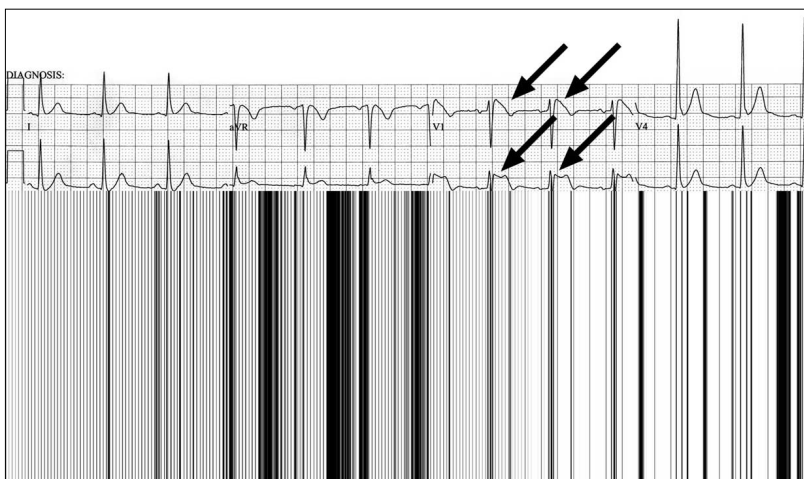
It is easy to recommend an implantable cardioverter-defibrillator to a patient who has just survived a cardiac arrest, but what do you tell his asymptomatic brother who has the same genetic disease? In this age of gene testing and sophisticated technology, such questions arise frequently, and the answers are complex.

Lars Eckardt and colleagues recently addressed this question of risk stratification for asymptomatic patients with Brugada syndrome.<sup>1</sup> Brugada syndrome is a genetic disease characterised by mutations in the cardiac sodium-channel (*SCN5A*), which cause a loss of function of the channel.<sup>2–4</sup> Patients with Brugada syndrome have normal

heart function but are prone to cardiac arrhythmias and sudden death, especially in middle-aged men. The syndrome is one of the leading causes of death for young men in south-east Asia, where the mutation is particularly common.<sup>5</sup>

Like most such genetic causes of sudden death, Brugada syndrome is an autosomal dominant disease, meaning that 50% of the progeny will inherit the mutation (and risk of sudden death) from the affected proband. Thus there will probably be more silent carriers of the mutation who may never exhibit disease symptoms (syncope, cardiac arrest, or sudden death) than symptomatic probands. Although drugs such as quinidine and sotalol have been tried in patients with Brugada syndrome, the only real treatment is placement of an implantable cardioverter-defibrillator to prevent sudden death.<sup>6,7</sup> Diagnosis of these patients is also problematic because the characteristic ECG findings (figure) may be absent. Genetic testing will only reveal the mutation in 20% of patients with Brugada syndrome. How to treat these asymptomatic patients is controversial.<sup>8</sup>

Two major research groups have studied Brugada syndrome and provide much of the available data. The first group is an international registry spearheaded by the Brugada brothers, who initially described the disease in 1992.<sup>9</sup> Their cohort of patients is the largest but appears to be one at relatively high-risk for sudden death. Their group reported the clinical prognosis of 547 patients with Brugada syndrome over 24 (SD 33) months of follow-up.<sup>2</sup> Despite the short follow-up, 8% of the initially



**Figure: 12-lead ECG**  
46-year old man with family history of sudden death in men. Asymptomatic patient was originally admitted for stab wound to neck and was found to have this ECG classic for Brugada syndrome. Note pseudodirect bundle-branch-block pattern and ST-elevation in leads V1–V3 (arrows). Electrophysiology study easily induced ventricular fibrillation, and implantable defibrillator was placed.