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Primary prevention of age related macular degeneration

Current evidence does not support a protective role for dietary antioxidant vitamins

In this week’s *BMJ*, Chong and colleagues present a systematic review and meta-analysis of the effectiveness of dietary antioxidants, including supplements, in the primary prevention of age related macular degeneration.1

Age related macular degeneration is one of the most important causes of visual loss in older people. The number of people affected will increase as populations age.2 Two types of age related macular degeneration exist. Geographic atrophy is a sharply demarcated area of depigmentation caused by atrophy of the retinal pigment epithelium; neovascular degeneration occurs when new blood vessels grow under the retinal pigment epithelium leading to haemorrhage and scarring. Age related macular degeneration is diagnosed in people aged 50 or more when no other obvious cause for degeneration exists.

New treatments are being developed rapidly. In the past two years, intraocular injections of agents that interfere with angiogenesis have been licensed for use in this condition.3 These bind to vascular endothelial growth factors to prevent endothelial cell proliferation and neovascularisation. Although improved treatments are always encouraging for people with age related macular degeneration, visual loss arising from the growth of new vessels is usually permanent, and no effective treatments exist for geographic atrophy. Research into why age related macular degeneration develops, with a view to preventing it, continues.

The incidence of many diseases increases exponentially with age. One common theory for the aetiology of many age related diseases, including age related macular degeneration, is that they arise as a result of the cumulative effects of oxidative stress.4 The systematic review by Chong and colleagues summarises the results of seven prospective studies and three randomised controlled trials evaluating the association between dietary intake of antioxidant vitamins and minerals (such as vitamin C, vitamin E, various types of carotenoids, and zinc) or dietary supplements (vitamin E and β carotene) and age related macular degeneration.5 This is the first such review of usual dietary intake—previous reviews have considered randomised controlled trials of supplements.5

The prospective studies show that people with relatively high dietary intakes of antioxidant nutrients are no more or less likely to develop the condition than those with relatively low intakes. The possible exception to this is high dietary intake of vitamin E, which was associated with a 20% reduced odds of age related macular degeneration. The significance of this finding depended on which studies were included in the meta-analysis. Further studies are needed to confirm its relevance.

Dietary intake is difficult to measure accurately. In observational studies it is difficult to be sure that a fair comparison is being made, because people with different diets also differ in many other ways. In spite of these caveats, evidence of a strong protective effect of the dietary antioxidants studied was lacking. Obviously, a well balanced diet containing fruit and vegetables has many other health benefits and should still be recommended. In addition, included studies were carried out on relatively well nourished populations in the United States, Australia, and Europe, and the results may not apply to populations with different dietary intakes.

Three randomised controlled trials provide good evidence that vitamin E or β carotene supplements do not prevent age related macular degeneration (one of these trials is included in abstract form in the review but has since been published6). Although generally regarded as safe, vitamin supplements may have harmful effects. People who smoke may be at increased risk of lung cancer if they take β carotene,7,8 and vitamin E supplements may increase risk of heart failure in people with diabetes or vascular disease.9

While antioxidant vitamin supplements cannot be recommended as a public health measure to reduce the incidence of age related macular degeneration, people with early stage disease may benefit from supplements containing vitamin C, vitamin E, β carotene, and zinc.10 The recommended combination and doses of antioxidant vitamins and minerals is found in only a few commercial supplements and should be taken on specialist advice,11 with appropriate consideration of the possible benefits and harms for the individual.

Do other options exist for primary prevention of age related macular degeneration? The strongest risk factors for this condition—age and genetic factors—are not preventable, although genetic research will provide new insights into the causes of the disease and therefore its prevention. High concentrations of polyunsaturated fats are found in the retina, but evidence for a protective effect of dietary fatty acids in this condition is inconsistent.12 Smoking is the only preventable risk factor that has been associated with the condition in most observational studies.13 Currently, reducing the prevalence of smoking is probably the most effective method of reducing the population burden of this common cause of visual loss in older people.

*All references are on bmj.com*
Data sources and performance measurement

Measuring outcomes is necessary but difficult to get right

In this week’s BMJ, Westaby and colleagues compare the value of two sources of data for determining mortality 30 days after congenital cardiac surgery—hospital episode statistics (HES) and the central cardiac audit database.1 They find that the central cardiac audit database is more complete than HES, but that individual centres need investment to improve the completeness and accuracy of their data. Their investigation follows a study published in the BMJ in 2004 that used HES to compare mortality from congenital heart surgery in different UK centres.2 The study suggested that Oxford had significantly higher mortality than the national average, and the results were reported widely by the media. So have we learnt anything new about the relative value of routinely collected versus specifically collected sources of data?

Routinely collected patient data are regularly analysed to investigate outcome. Equally regularly the results are contested by the specifically collected dataset, which is often designed to measure the very thing being looked for. So why use routinely collected data to draw clinical conclusions at all? The advantages include pragmatism, wide coverage, low cost, and easy access. The disadvantages include superficial or inaccurate coding and potentially damaging generalisations.

HES data from the National Health Service (NHS) are widely used to produce outcome information and more recently to publicise differences between hospitals. Data produced for administrative and financial purposes that are centred on the organisation not the patient may never be as complete as data derived from clinicians.

Huge datasets also invite misuse of statistical method—the significance of correlations is a product of the number of data points, not necessarily its relative importance. Chance findings will occur if many tests are done on the same data; association is not the same as causality. Nonetheless, the sheer scale of the HES database makes it attractive and it has become a rich source of hypotheses generation and evidence on outcomes. The database has been used to investigate associations between case volume and outcome (for example, oesophagectomy3 and repair of aortic aneurysms4), to search for potentially useful predictors of outcome (for example, excess mortality associated with delay in operation after hip fracture5), to carry out quasi-longitudinal studies to track changes in outcome related to changes in clinical practice (for example, acute urinary retention and prostatectomy,6 follow-up after emergency admission,7 and changes in mortality after paediatric cardiac surgery8), and increasingly to predict individual outcomes in patients at high risk.

Results that conflict with HES data have often been reported—for example, the relation between hospital volume and outcome9 10 and the predictive factors for poorer outcome in certain patients.10 This is not just a contest of science and statistics but of politics, hearts, and minds. As Westaby and colleagues note, the media rapidly picked up on the conclusion based on HES data that Oxford had significantly higher mortality after paediatric cardiac surgery than the national average.

While recognising that there are problems in special datasets too—timescales and numbers of episodes are often smaller, making it more likely to miss a rare event or true difference, and collecting outcome data on your own performance may bias the case mix of patients selected for intervention—Westaby and colleagues conclude that HES data should not be used for comparisons within specialties.

Patients do not necessarily trust official data sources.11 We need to know if they will trust information collected by doctors who analyse their own data and claim that their performance is sound. The NHS has recently appointed a new medical director, Professor Sir Bruce Keogh, who is famous for his leadership of British cardiothoracic surgeons in measuring outcomes and making them public. This appointment sends a clear signal to staff, the public, and the media about the importance of measuring outcomes.

It is unclear how much patients change their choice of provider based on such knowledge, or how much employers manage their clinical staff with an eye on comparative performance, however intuitively it seems important. With all its potential problems, HES has more to offer than league tables of performance. Better knowledge will flow from a collaboration of all sound analyses, based on complete data, that are accurately coded by clinicians who have an interest in the outcome. This can only lead to more complete and contextualised data being released into the public domain.

Participation in mammography screening

Women should be encouraged to decide what is right for them, rather than being told what to do

In April 2007, the American College of Physicians—the largest medical specialty society in the United States—issued new guidelines on screening mammography for women aged 40-49. Rather than calling for universal screening, the guidelines recommend that women make an informed decision after learning about the benefits and harms of mammography.¹

The last time a major US policy organisation made such a recommendation all hell broke loose. In 1997, a consensus panel of the National Institutes of Health concluded “that the data currently available do not warrant a universal recommendation for mammography for all women in their forties. Each woman should decide for herself whether to undergo mammography.” This recommendation generated intense reactions in the press, public, and government.² Most stories in the press suggested that women should be screened and others directed anger at the panel for “failing” to recommend screening. The panel’s chair was summoned before congress, and a US senate resolution in favour of screening was unanimously passed—a rare act of bipartisanship. After a few months of intense political pressure, the National Cancer Institute contravened the panel’s conclusions and recommended that women in their 40s should be screened.

In contrast, the reaction to the recent guidelines was muted. The press carried a few stories—a few of which were critical—but there were no senate resolutions and no hearings to cross examine the leadership of the American College of Physicians.

The possible reasons for these dramatically different reactions are that the American College of Physicians may not have the same visibility as the National Institutes of Health panel; journalists and readers may be preoccupied with other matters. But a more positive explanation is that the public and profession increasingly accept that cancer screening has both benefits and harms. Perhaps we are finally moving beyond the debate about what women should do and are ready to focus on how to help women make the best decision for themselves.

So how can clinicians help? The first step—exemplified by the recent guideline—is to acknowledge that women face a real choice. Screening entails trade-offs that are hidden by slogans such as “If you haven’t had a recent mammogram, you may need more than your breasts examined.” These messages are meant to persuade women to do what is right, as decided by the people who write them. But no right choice exists, because screening has mixed effects—some women will benefit (by avoiding death from breast cancer) but others will be harmed. So the next step is to ensure that women understand what is likely to happen if they do or do not undergo screening.

The table shows estimates of the benefits and harms of screening mammography for women in their 40s and (for context) older women. Despite the wealth of published literature, the numbers are still controversial, and any of the figures could be criticised. The table is not meant to be the final word on mammography but to convey the order of magnitude of its effects. Furthermore, the data are based on averages, so the risks will be different for women at high risk (such as those with a strong family history of early breast cancer). And of course, the numbers are only a start. If we seriously want to promote informed decisions, we must ensure that women understand the data and have some context for judging how big (or small) these numbers are.¹⁰,¹¹

The main benefit of screening is to avoid death from breast cancer. The relative risk of death from breast cancer for women who are screened is 0.85 for those in their 40s and 0.78 for those 50 and older.¹ These figures may underestimate the efficacy of screening because

| Summary of data on benefits and harms of screening mammography every 1-2 years for 10 years |
|---------------------------------------------|-----------------|-----------------|
| Benefits and harms                          | 40-49           | 50-69           |
| Benefits                                    |                 |                 |
| 10 year risk of death from breast cancer*   |                 |                 |
| No screening                                | 3.3/1000 (0.33%)| 8.9/1000 (0.89%)|
| Screening                                   | 2.5/1000 (0.25%)| 6.0/1000 (0.6%) |
| Avoidance of death from breast cancer       | 0.8/1000 (0.08%)| 3/1000 (0.30%)  |
| Harms                                       |                 |                 |
| Patient has at least one false positive screening examination that results in additional testing¹ | 100-500/1000 (10-50%) | 100-500/1000 (10-50%) |
| Patient has at least one false positive screening examination that results in unnecessary diagnosis and treatment for breast cancer¹ | 2-5/1000 (0.25-0.5%) | 3-9/1000 (0.30-0.90%) |

*The 10 year chance of dying from breast cancer for American women aged 40-49 and 50-69 (2002-4) came from the National Cancer Institute. We calculated the risk for the two sets of women using the risk reduction of mammography for each age group² after adjusting for non-compliance in trials³ and national estimates of mammography uptake in each age group about 10 years earlier according to the National Center for Health Statistics. This approach assumes that the total risk of death from breast cancer is the weighted average of the risks faced by women who are and are not screened.

¹We applied estimates of the proportion of screen detected cancers that are overdiagnoses (low 10%, high 30%) to the rate of screen detected breast cancers in trials of women ≥55 and those 40-49.²
Screening for abdominal aortic aneurysm

Can save lives but only if operative mortality is low

A recent Cochrane review has updated our knowledge about screening asymptomatic people for abdominal aortic aneurysm, with respect to their mortality, subsequent treatment for the aneurysm, and the cost effectiveness of screening. Four completed randomised controlled studies—Chichester, Viborg, Western Australia, and the multicentre aneurysm screening study (MASS)—with 127,891 men and 9342 women (only the Chichester trial included women) aged from 65-83 years were included to a cut-off date of 26 January 2007. This excluded the more recent seven year follow-up of men in MASS. Acceptance rates (of people agreeing to be screened) ranged from 63.1% (Western Australia) to 80.2% (MASS).

In men aged 65-79 years screening significantly reduced the risk of mortality related to aneurysm (relative risk 0.53 (confidence interval 0.42 to 0.68). This was achieved at the expense of doubling the rate of aneurysm surgery. However, for studies in men, the review reported no significant reduction in all cause mortality. Although the Western Australia trial found a reduction in all cause mortality (from the time of screening and not randomisation), the authors note that the interval between randomisation and screening could have introduced a bias, such that screening did not account for the reduction. However, the recent update from MASS also hints at a possible benefit in all cause mortality in men who were screened (estimated hazards ratio 0.96, 95% confidence interval 0.93 to 1.00), so a further update of the Cochrane review may be needed.

MASS produced a cost effectiveness analysis at four years with 47 fewer deaths from aneurysm equating to £28 400 (€42 000; $58 000) per life year gained and £36 000 per quality adjusted life year. At seven years this had fallen to £12 334 per life year gained and is likely to fall even further after 10 years. The Viborg trial derived a very different figure (£620 per life year saved), and the reason for this disparity seems opaque, although health economists should be able to shed some light on the reasons for the disparity.

The trials have provided evidence to suggest that screening in itself does not impair quality of life, although this is not covered in the Cochrane review. Data are still lacking on the potential benefits of...
“Although a deeply damaging episode for British medicine, from this experience must come a recommitment to optimal standards of postgraduate medical education and training. This can only occur if a new partnership is struck between the profession and the DH [Department of Health], and between Health and Education. Each constituency has been found wanting thus far. In future, each must play its part. An aspiration to clinical excellence in the interests of the health of the population must be paramount.”

So concludes Professor Sir John Tooke’s inquiry into Modernising Medical Careers (MMC).1 2 This initiative, “an honest attempt to accelerate training and assure the fundamental abilities of the next generation of doctors” almost founded over the failure of its main component, the centralised selection into run-through specialist training. In response, the government announced an independent inquiry into MMC, the interim report of which was released this week. While Tooke’s report runs through the reasons for the failure of the medical training application service (MTAS), these have been extensively covered in a previous report.1 Sir John’s canvas was much wider. His panel “explored the background and context—in medical terms the predisposing or aetiological factors—that may have contributed to the perceived problems with MMC, rather than simply focusing on MTAS.”

So, what went wrong? Wherever Sir John shone his torch he found debilitating vagueness and frailty. He found no evidence of a consensus on the educational principles guiding postgraduate medical training and that mechanisms for creating such a consensus are weak. The management of postgraduate training is hampered by unclear principles, a weak contractual base, a lack of cohesion, a fragmented structure, and, in England, deficient relationships between academia and service. No consensus exists over doctors’ roles at various career stages, which hampers planning of the medical workforce. A vacuum exists in policy regarding the potentially massive increase in trainee numbers. And so on.

At the press conference launching his report, Sir John refused to name and shame the guilty parties, but because he listed governance and risk management as most at fault they are most likely to reside at the Department of Health. In mitigation, responsibility for MMC was split between two people and the biggest headaches—MTAS’s and the surfeit of eligible international medical graduates—were outside the responsibilities of both of them.

This week, the government announced that there would be no national IT system for job applications
next year and that it was launching a consultation exercise over training jobs for medical graduates from outside the European Economic Area. How had the stewardship of medical training deteriorated to such an extent at the Department of Health? Benign or malign neglect? Conspiracy to further depprofessionalise doctors or cock-up? Once again Sir John would not be drawn, but the manifest organisational failures of the department would suggest that conspiracy was beyond its skill set.

The bottom line is that the department has wrested control of doctors’ training from the medical profession and has proved itself unequal to the task. One of Tooke’s “corrective actions” concerns the Postgraduate Medical Education and Training Board, set up to regulate postgraduate medical education in the wake of the Bristol inquiry. He wants it merged with the General Medical Council, which already regulates two of the three components of medical education (undergraduate education and continuing professional development). Crucially, “it is a body that reports to Parliament, rather than through the monopoly employer [Department of Health].”

Doctors don’t emerge unscathed. “Forensic” analysis of meeting records shows they were well represented on the various delivery and advisory boards—one figure in the report lists an alphabet soup of 19 different representative bodies, with their dates of attendance. But in sum their influence was “suboptimal.” Their frequent calls for trialling and delay went largely unheeded, and they reported being deterred from questioning policies. On occasion, they weakened their impact by speaking up for their individual consistencies rather than for the profession as a whole, according to the report.

The report recommends that the medical profession urgently needs to develop a way of providing coherent advice on matters that affect the entire profession, without giving details of what this might look like. And it wants a consensus on the role of doctors to be agreed by the end of 2008. Sir John admits it’s a tall order, but it would coincide with the 150th anniversary of the Medical Act, something that obviously appeals to a doctor who quotes William Osler and medical historian Roy Porter in his foreword.

For the doctor on the ward or in the clinic the biggest changes will be those recommended for the structure of postgraduate training. The need for a broad based beginning, flexibility, and the promotion of excellence recur like a mantra throughout the report. Sir John says this part of the report was heavily influenced by the workshops he held throughout the United Kingdom, which involved 450 trainee doctors. They said that they wanted to be much better than “just good enough” for their jobs (hence the report’s title, Aspiring to Excellence).

The report recommends that the link between foundation years one and two is broken, allowing the second foundation year to become the first of a three year core training programme (along with the current first and second years of specialist training HST1 and ST2). Up to half a dozen defined core programmes (including ones in surgery, medicine, and general practice) are envisaged, which would involve six appointments of six months each. These core programmes would serve as stems for subsequent specialty training.

Entry into higher specialty training after the core programme would be based on marks obtained in national assessment centres for the specialty in question, together with structured CVs and interviews for shortlisted candidates at deanery level.

General practice training “must be extended to five years to assure the skill base of that part of the medical workforce that is going to become increasingly important, with rising longevity, increasing co-morbidity, and shifts of care to the community.” And the future of doctors in fixed term specialty training appointments and in the non-consultant career grade needs to be sorted out.

If Tooke’s recommendations for the early years of training sound familiar it is because they resemble the proposals for senior house officer training set out in Unfinished Business, a consultation paper dating from 2002. Its principles were that training in these early years should begin with a broad based programme and be flexible to trainees’ needs, providing opportunities to leave and re-enter. However, a subsequent document reported that “thinking had moved beyond the basic specialist programmes foreseen in Unfinished Business” towards a single “run-through approach,” a shift recently discussed in these pages. Tooke’s comment, “although whose thinking and with what authority is not entirely clear,” could stand as his verdict on this whole sorry chapter of Modernising Medical Careers.

And as to the next chapter? Richard Hayward captures the challenges well in his personal view this week, “the MTAS fiasco (for which all parties must share responsibility) stands as a dire warning to government and medical profession alike of trying to reform health care without cooperation between the two. Expect the current rocky ride to continue until and unless the government and the community of independent medical practitioners find common ground—something that will require a shift of culture on both sides if the NHS is really to benefit.” Tooke has provided the roadmap for postgraduate medical education and training.