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Peadar N Kirke, James L Mills, Anne M Molloy, Lawrence C Brody, Valerie B O'Leary, Leslie Daly, Sharon Murray, Mary Conley, Philip D Mayne, Owen Smith and John M Scott

BMJ 2004;328:1535-1536; originally published online 21 May 2004; doi:10.1136/bmj.38036.646030.EE

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Impact of the MTHFR C677T polymorphism on risk of neural tube defects: case-control study

Peadar N Kirke, James L Mills, Anne M Molloy, Lawrence C Brody, Valerie B O’Leary, Leslie Daly, Sharon Murray, Mary Conley, Philip D Mayne, Owen Smith, John M Scott

Homozgyosity for the T allele of the C677T polymorphism of the gene encoding the folate dependent enzyme 5,10-methylenetetrahydrofolate reductase (MTHFR) is a risk factor for neural tube defects.1 Both the homozygous (TT) and heterozygous (CT) genotypes are associated with lower tissue concentrations of folate, higher homocysteine concentrations, and lower enzyme activity than the wild type (CC) genotype; these effects are more marked in homozgyotes. Low folate and raised homocysteine levels in early pregnancy are risk factors for neural tube defects.2 We investigated the possibility that the CT genotype would also increase the risk of these malformations.

Participants, methods, and results

We recruited 397 individuals with spina bifida aperta (380) or encephalocele (17) throughout Ireland. Participants were aged between 5 months and 52 years (mean 16.8 years). We drew blood for analysis of DNA. We derived the controls from a random sample of 1000 newborn screening cards collected on all Irish births. Of these 1000, DNA was successfully extracted from 855 cards. We successfully genotyped 395 (99.5%) cases and 848 (99.2%) controls.

We calculated population attributable fractions, broadly interpreted as the percentage of the disease in a population that is “caused by” a risk factor, for heterozygotes and homozgyotes separately comparing each to the wild type.

The heterozygous genotype is associated with an increased risk of neural tube defects (odds ratio 1.52; P = 0.0015; table). Risk is also raised for the homozygous TT genotype (2.56; P < 0.0001), confirming our earlier finding.3 Population attributable fraction calculations reveal that the CT genotype is responsible for at least as many neural tube defects in the population as the TT genotype (14.9% vs 11.3%; table). This arises because a much greater proportion of the population are heterozygous for this allele (about 38% of the general population are CT compared with 10% who are TT; table).

Comment

Heterozygosity for the MTHFR polymorphism, which is present in 38% of the population, increases the risk of neural tube defects. Most studies of MTHFR C677T and neural tube defects and other conditions have focused on the risk associated with T allele homozygosity. The possibility that heterozygosity might also increase neural tube defect risk has gone unrecognised except for a small study in which an association between CT and these malformations was thought to be due to the higher than expected proportion of CC control subjects.4

The combined CT and TT genotypes account for about 26% of neural tube defects in Ireland. Folate or folic acid is estimated to be involved in about 50% to 70% of these defects. Thus up to a half of the folate related neural tube defects may be explained by this single genetic variant.

These findings have two important implications. Firstly, MTHFR C677T heterozygosity needs to be considered as a risk factor for other conditions where homozgyosity has been shown to be associated with increased risk, for example, ischaemic heart disease.5 Secondly, the population at risk, and the population that will benefit from food fortification, is much larger than previously believed. Based on pooled data from published studies, about 50% of the European population and 53% of the North American population have either CT or TT genotypes.6 Both the lower folate and increased homocysteine concentrations associated with CT and TT genotypes can be corrected by folic acid, even in relatively small doses. Therefore, our study provides new data underscoring the importance of public health intervention programmes of folic acid supplementation and food fortification targeted at all women of childbearing age to prevent neural tube defects. Such intervention may also turn out to have other public health benefits—for example, in the prevention of cardiovascular disease.

We thank Deborah Watson, Marie Sutton, Maev Royston, Helen Burke, and Mary-Patricia McKeever for subject recruitment and data collection and the Irish Association for Spina Bifida and Hydrocephalus for their help with subject recruitment.

Contributors: PNK, JLM, AMM, LCB, LD, MC, and JMS designed the study, analysed and interpreted the data, and wrote the paper.

This article was posted on bmj.com on 21 May 2004: http://bmj.com/cgi/doi/10.1136/bmj.38036.646030.EE

Papers

Risk of neural tube defect by the 5,10-methylenetetrahydrofolate reductase C677T genotype

<table>
<thead>
<tr>
<th>Genotype</th>
<th>No of cases (%)</th>
<th>No of controls (%)</th>
<th>Odds ratio (95% CI)</th>
<th>P value</th>
<th>Population attributable fraction</th>
</tr>
</thead>
<tbody>
<tr>
<td>CC (wild type)</td>
<td>151 (38.2)</td>
<td>439 (51.8)</td>
<td>1.00</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>CT (heterozygous)</td>
<td>171 (43.3)</td>
<td>526 (38.4)</td>
<td>1.52 (1.16 to 2.00)</td>
<td>0.0015</td>
<td>14.9 (6.1 to 23.7)</td>
</tr>
<tr>
<td>TT (homozygous)</td>
<td>73 (18.5)</td>
<td>83 (8.8)</td>
<td>2.56 (1.75 to 3.74)</td>
<td>&lt;0.0001</td>
<td>11.3 (6.7 to 15.8)</td>
</tr>
<tr>
<td>CT or TT</td>
<td>244 (61.8)</td>
<td>609 (48.2)</td>
<td>1.73 (1.40 to 2.14)</td>
<td>&lt;0.001</td>
<td>26.2 (15.7 to 36.6)</td>
</tr>
<tr>
<td>Total</td>
<td>395 (100)</td>
<td>848 (100)</td>
<td>—</td>
<td>—</td>
<td>—</td>
</tr>
</tbody>
</table>
Delays in publication of cost utility analyses conducted alongside clinical trials: registry analysis

Dan Greenberg, Allison B Rosen, Natalia V Olchanski, Patricia W Stone, John Nadai, Peter J Neumann

Economic evaluations conducted alongside randomised controlled trials enable analysis of detailed, patient level data on efficacy, cost, and quality of life in a controlled setting. They can provide timely and reliable assessments of value for money, to inform decisions on coverage and reimbursement.1,2

The BMJ recently decided to consider trial based economic evaluations for publication only if the clinical results are submitted to the journal as well.3 We assessed the extent to which cost utility analyses are conducted alongside trials, estimated the time lag between the publication of trials’ clinical and economic results, and compared the characteristics of journals publishing the clinical trial data and the cost utility analyses.

Methods and results

We conducted a systematic search for original English language cost utility analyses published in 1976–2001 by using Medline and other electronic databases. Two readers independently reviewed each study and came to a consensus on whether the analysis was conducted alongside a trial (data on both efficacy and resource use from the trial were used for the analysis). We identified the journal and publication date for each cost utility analysis and the corresponding trial. To assess the study’s potential readership and dissemination we used paired sample t tests to compare the mean impact factors of journals in which studies were published and the extent to which publications were subsequently cited by other authors.

Of 533 cost utility analyses identified, 45 (8%) were trial based economic evaluations and covered a variety of clinical areas, particularly cardiovascular disease, cancer, and psychiatry (a full list of studies is available at www.hsph.harvard.edu/cearegistry). We could not determine the lag in publication between the trial and the economic evaluation for four studies, for which a specific trial could not be identified or trial results were published only in abstract form. In cases where the clinical trial results and economic evaluation were reported in the same article or in the same issue of the journal (n=7), we assumed no lag.

On average, cost utility analyses were published almost two years after the publication of the corresponding trial (mean (SD) 1.8 (1.4) years; range 0–7.5 years) (figure). Journal impact factors were higher for trials published) was also higher for clinical trials than for economic evaluations (27.4 vs 3.3; t = −3.197 (df=30); 95% confidence interval for the difference −39.24 to −8.64; P=0.003).