

### What is already known on this topic

Deliberate self harm is common and costly, with repetition rates of 6-30%

Deliberate self poisoning is the commonest form of deliberate self harm

Few interventions effectively reduce repetitions of deliberate self harm

### What this study adds

A simple, inexpensive, postcard intervention for patients with deliberate self poisoning reduced the number of events per individual, but did not reduce the proportion of individual repeaters

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## Does dietary folate intake modify effect of alcohol consumption on breast cancer risk? Prospective cohort study

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### Abstract

**Objective** To evaluate the effect of dietary folate intake on the relation between alcohol consumption and breast cancer risk.

**Design** Prospective cohort study.

**Setting** Melbourne, Australia.

**Participants** 17 447 Anglo-Australian women resident in Melbourne, aged 40-69 years at recruitment in 1990-4, and followed up until 31 December 2003.

**Main outcome measure** Invasive breast cancers diagnosed during follow-up and ascertained through the Victorian cancer registry.

**Results** 537 invasive breast cancers were diagnosed. Compared with lifetime abstainers, the hazard ratio for breast cancer in women who consumed an average of 40 g or more of alcohol daily at baseline was 1.41 (95% confidence interval 0.90 to 2.23). No direct association was found between dietary folate intake and risk of breast cancer, but a high folate intake mitigated the excess risk associated with alcohol. The estimated hazard ratio of an alcohol consumption of 40 g/day or more was 2.00 (1.14 to 3.49) for women with intakes of 200 µg/day of folate and 0.77 (0.33 to 1.80) for 400 µg/day of folate (P = 0.04 for interaction between alcohol and folate).

**Conclusions** An adequate dietary intake of folate might protect against the increased risk of breast cancer associated with alcohol consumption.

### Introduction

Alcohol consumption is a known risk factor for breast cancer. Although the association is modest, its adverse effect on breast cancer is one of the most consistent findings among dietary risk factors.<sup>1</sup> The role of the B vitamin folate in colorectal carcinogenesis has been widely studied, and an inverse dose dependent relation has been found.<sup>2-4</sup> Some studies have also reported an inverse association between folate and risk of breast cancer,<sup>5-8</sup> and the protective effect of folate on breast cancer is more pronounced for heavy drinkers,<sup>9-13</sup> suggesting that folate and alcohol act in opposite directions in breast carcinogenesis. To test this hypothesis, we used the Melbourne collaborative cohort study to investigate if the association between alcohol consumption and risk of breast cancer is modified by intake of dietary folate.

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## Methods

### Participants

The Melbourne collaborative cohort study is a prospective cohort study of 41 528 people (24 479 women) aged between 27 and 75 years at baseline (99.3% aged 40-69). Recruitment took place between 1990 and 1994 in Melbourne. Participants were recruited through the electoral rolls, advertisements, and community announcements.

We excluded women with a diagnosis before baseline of invasive breast cancer (n=381), angina, heart attack, or diabetes (n=1461). Others were excluded owing to missing data on alcohol intake and dietary factors (n=439). We restricted the analyses to 17 447 women born in Australia, New Zealand, or the United Kingdom.

### Assessment of alcohol consumption and diet

At baseline we used a structured interview to obtain information on risk factors, including age, sex, country of birth, education, reproductive history, and alcohol consumption. People who had never consumed at least 12 alcoholic drinks in a year were considered lifetime abstainers. We asked non-lifetime abstainers about their current average alcohol intake and their daily intake in the previous week (diary). We categorised total alcohol consumption into lifetime abstainers, ex-drinkers, and current drinkers with low (1-19 g/day), medium (20-39 g/day), or high intake (40 g/day or more).

Participants completed a dietary questionnaire developed for the study.<sup>14</sup> We calculated nutrient, folate, and energy intake. Total energy intake included energy from food and alcohol. We calculated body mass index from measured height and weight.

### Cohort follow-up and ascertainment of invasive breast cancer cases

Cases were women notified to the Victorian cancer registry with a first diagnosis of invasive breast cancer during follow-up to 31 December 2003. We did not count women with in situ breast cancer as cases. We determined addresses and vital status of all participants by record linkage and from responses to questionnaires and newsletters. By the end of follow-up, 351 (2%) of the women were known to have left Victoria and 627 (4%) had died.

### Statistical analysis

Follow-up began at baseline and continued until diagnosis of breast cancer, death, date of leaving Victoria, or 31 December 2003. We estimated hazard ratios by using Cox regression with age as the time metric. For both alcohol consumption and folate intake, we compared linear and more complex polynomial relations with the log hazard rate (see *bmj.com*).<sup>15</sup> We studied the interaction between alcohol consumption and dietary folate intake.

We adjusted all analyses for total energy intake. Other potential confounders examined included education, body mass index, age at menarche, hormone replacement therapy, parity, and use of multivitamins. We did not include any of these variables in the final analyses, as their inclusion changed the estimated hazard ratios by less than 5%.

**Table 1** Hazard ratios for association between average alcohol consumption at baseline and breast cancer in the Melbourne collaborative cohort study

Alcohol consumption	Cases	Person years*	Hazard ratio† (95% CI)
Abstainers‡	171	56 267	Reference
Ex-drinkers§	16	5 553	1.03 (0.62 to 1.73)
1-19 g/day	286	91 274	1.12 (0.93 to 1.36)
20-39 g/day	43	17 720	0.87 (0.62 to 1.22)
≥40 g/day	21	5 313	1.41 (0.90 to 2.23)

\*Person years of follow-up of 17 447 women.

†Adjusted for total energy and folate intake and fitted as linear variable in Cox's proportional hazard model with age as time metric.

‡Women who never drank at least 12 alcoholic drinks in a year.

§Women who drank at least 12 alcoholic drinks in a year, but did not drink at baseline.

## Results

We identified 537 incident cases of invasive breast cancer over an average of 10.1 person years between 1990 and 2003. The mean age at baseline was 54.7 (SD 8.8) years; 50% were over 55 years.

Most women (86%) drank on average less than 20 g of alcohol a day, and only 538 (3%) reported an average daily intake of at least 40 g. Mean folate intake was 330 (SD 124) µg/day (see *bmj.com*). Comparison between the models using linear and fractional polynomials of current alcohol consumption provided no evidence for a departure from linearity (P=0.64). From the linear model, the hazard rate increased by 1.03 (95% confidence interval 0.95 to 1.09) times for each additional 10 g/day intake of alcohol (P=0.36). Modelling alcohol consumption as a categorical variable, the highest hazard ratio occurred in women who drank 40 g of alcohol a day or more; however, overall, the association of breast cancer incidence with alcohol was not significant (P=0.29) (table 1).

Comparison between the regression models using linear and fractional polynomials of folate intake indicated that the more complex models did not fit better than the simple linear model (P=0.27). However, folate was not significantly related to incidence of breast cancer (for 100 µg/day increment of folate, relative risk=1.01 (0.93 to 1.10); P=0.79).

We fitted a model with an interaction between alcohol and folate. Table 2 shows estimates of the hazard ratios in relation to alcohol consumption for three values of folate intake. Compared with abstainers who consumed 200 µg/day of folate, the hazard ratio was

**Table 2** Hazard ratios\* (95% confidence intervals) for association between average alcohol consumption at baseline and breast cancer by intake of dietary folate in the Melbourne collaborative cohort study

Alcohol consumption	Folic acid		
	200 µg/day	330 µg/day†	400 µg/day
Abstainers‡	Reference	Reference	Reference
Ex-drinkers§	1.06 (0.52 to 2.16)	1.03 (0.62 to 1.73)	1.02 (0.56 to 1.87)
1-19 g/day	0.93 (0.71 to 1.23)	1.12 (0.92 to 1.35)	1.23 (0.99 to 1.53)
20-39 g/day	0.94 (0.58 to 1.54)	0.85 (0.61 to 1.20)	0.81 (0.52 to 1.25)
≥40 g/day	2.00 (1.14 to 3.49)	1.08 (0.60 to 1.93)	0.77 (0.33 to 1.80)

\*Hazard ratio from Cox's proportional hazard model with age as time metric.

The model includes total energy, folate fitted as a linear variable, alcohol as categorical variable, and interaction between folate and alcohol consumption.

†Mean of distribution of folate.

‡Women who never drank at least 12 alcoholic drinks in a year.

§Women who drank at least 12 alcoholic drinks in a year, but did not drink at baseline.

twofold higher for women who consumed the most alcohol (40 g/day or more), but the hazard ratios for lower levels of consumption were not elevated. None of the hazard ratios was elevated for any other categories of alcohol consumption or for women in the highest category of consumption who had higher levels of folate intake ( $P=0.04$  for interaction). The model in which alcohol and folate were both linear did not give a better fit ( $AIC=9138$  v  $AIC=9138$ , alcohol as categorical and folate as linear). The test for the interaction between alcohol and folate was not significant ( $P=0.42$ ), probably because the interaction between alcohol and folate was not a simple linear term.

## Discussion

Overall in this prospective cohort study, we did not observe a significant association of breast cancer with either alcohol consumption or folate intake, but we found a significant interaction between alcohol and folate intakes. Women who had high alcohol consumption and low intake of folate had an increased risk of breast cancer, but those women who had high alcohol consumption and moderate to high levels of folate intake had no increased risk.

### Strengths and limitations

The strengths of our study include its prospective nature, extensive information on potential confounding variables, minimal loss to follow-up, and virtually complete ascertainment of cases through the population cancer registry. Limitations include the small numbers of women with high levels of alcohol consumption and folate intake, use of a single measure of self reported alcohol consumption at baseline, and limitations in the assessment of folate intake.

We measured folate intake at baseline, but changes in folate intake may have occurred during the follow-up period. Use of multivitamin supplements at baseline was not common, but we had no information on subsequent use of supplements containing folic acid.

### Comparison with other studies

Evidence for an effect of alcohol consumption on risk of breast cancer has been summarised in a reanalysis of data from 53 epidemiological studies.<sup>16</sup> Compared with women who reported drinking no alcohol, the relative risk of breast cancer was 1.46 (95% confidence interval 1.33 to 1.61) for those consuming on average  $\geq 45$  g/day, a result in general agreement with our finding of a hazard ratio of 1.41 (0.90 to 2.23) for those consuming  $\geq 40$  g/day. According to the collaborative reanalysis, the relative risk of breast cancer increased by 7% for each additional 10 g/day intake of alcohol. Our weaker association of a 3% increase is consistent with another reanalysis of six prospective studies restricted to women who drank less than 60 g/day of alcohol, which found increases of 3-16% across individual studies.<sup>17</sup>

Few other studies have investigated the interaction between folate and alcohol.<sup>9-12</sup> Two reports showed a higher risk of breast cancer in women with high intake of alcohol and low intake of folate,<sup>9, 12</sup> whereas two others focused on the protective effect of folate when associated with high alcohol.<sup>10, 11</sup>

## What is already known on this topic

Alcohol consumption is a known risk factor for breast cancer

Some studies have reported that folate is inversely associated with breast cancer risk

Whether folate intake can mitigate the adverse effects of alcohol on risk of breast cancer is not well established

## What this study adds

This study strengthens the evidence that an adequate dietary intake of folate might protect against the increased risk of breast cancer associated with alcohol consumption

### Possible mechanisms

Consistent evidence from animal experiments shows that ethanol modulates chemically induced carcinogenesis.<sup>18</sup> The mechanisms by which alcohol induces carcinogenesis are hypothesised to include the induction of cytochrome P-4502E1 (CYP2E1), which metabolises ethanol to acetaldehyde and is involved in the metabolism of various procarcinogens, nutritional deficiencies including folate deficiency, and alcohol mediated increases in oestradiol.<sup>18</sup> Acetaldehyde is carcinogenic and mutagenic, binds to DNA and proteins, destroys folate, and causes hyperproliferation.<sup>19</sup> How these mechanisms are involved in breast carcinogenesis is not clear, but the impact of alcohol on hormonal status is likely to be a major contributor.<sup>1</sup> It is also not clear whether the effect of folate is an early or late stage effect or whether total dose is important.<sup>3</sup>

### Conclusion

Our results support the hypothesis that alcohol consumption may increase the risk of breast cancer through an interaction with folate and suggest that any adverse effect of alcohol consumption may be reduced by sufficient dietary intake of folate.

This study was made possible by the contribution of many people, including the original investigators and the diligent team who recruited the participants and who continue working on follow-up. Finally, we thank the many thousands of Melbourne residents who continue to participate in the study.

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## Tacrolimus versus ciclosporin as primary immunosuppression for kidney transplant recipients: meta-analysis and meta-regression of randomised trial data

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### Abstract

**Objective** To compare the positive and negative effects of tacrolimus and ciclosporin as initial treatment for renal transplant recipients.

**Design** Systematic review.

**Data sources and study selection** Reports of comparative randomised trials of tacrolimus and ciclosporin identified by searches of Medline, Embase, the Cochrane Register of Controlled Trials, the Cochrane Renal Group Specialist Register, and conference proceedings.

**Data extraction and synthesis** Two reviewers assessed trials for eligibility and quality and extracted data independently. Data were synthesised (random effects model) and results expressed as relative risk (RR), with values < 1 favouring tacrolimus. Subgroup analysis and meta-regression were used to examine potential effect modification by differences in trial design and immunosuppressive co-interventions.

**Results** 123 reports from 30 trials (4102 patients) were included. At six months, graft loss was significantly reduced in tacrolimus treated recipients (RR = 0.56, 95% confidence interval 0.36 to 0.86), and this effect persisted up to three years. The relative reduction in graft loss with tacrolimus diminished with higher concentrations of tacrolimus (P = 0.04) but did not vary with ciclosporin formulation (P = 0.97) or ciclosporin concentration (P = 0.38). At one year, tacrolimus treated patients had less acute rejection (RR = 0.69, 0.60 to 0.79) and less steroid resistant rejection (RR = 0.49, 0.37 to 0.64) but more diabetes mellitus requiring insulin (RR = 1.86, 1.11 to 3.09), tremor, headache, diarrhoea, dyspepsia, and vomiting. The relative excess of diabetes increased

with higher concentrations of tacrolimus (P = 0.003). Ciclosporin treated recipients had significantly more constipation and cosmetic side effects. No differences were seen in infection or malignancy.

**Conclusions** Treating 100 recipients with tacrolimus instead of ciclosporin for the first year after transplantation avoids 12 patients having acute rejection and two losing their graft but causes an extra five patients to develop insulin dependent diabetes. Optimal drug choice may vary between patients.

### Introduction

The introduction of ciclosporin improved one year graft survival after renal transplantation from 60% to more than 80%.<sup>1,2</sup> Tacrolimus later emerged as an alternative calcineurin inhibitor.<sup>3</sup> However, pronounced global differences in use of tacrolimus exist; 63% of new renal transplant recipients in the United States receive tacrolimus for primary immunosuppression compared with 22% in Australia.<sup>2</sup>

Despite the impact of calcineurin inhibitors on initial outcome, longer term graft survival is little changed and atherogenic risk factors are more common in the renal transplant population.<sup>1,4,5</sup> To what degree recipient mortality and graft loss can be attributed to these risk factors, to the direct toxicity of immunosuppression, or to cumulative effects of infection and rejection is debated.<sup>6</sup> Tacrolimus and ciclosporin affect these risk factors differentially. Tacrolimus is associated more



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