Effect of 2 pieces of nutritional advice on folate status in Swedish women: a randomized controlled trial

Veronica E Öhrvik, Johan C Olsson, Birgitta E Sundberg, and Cornelia M Witthöft

ABSTRACT
Background: Ten years after the introduction of mandatory folic acid fortification in the United States, Canada, and Costa Rica, the issue is still under debate in several countries, and Sweden recently decided against mandatory fortification.

Objective: The objective was to determine the folate status of women after an intervention involving 2 Swedish dietary recommendations: a food recommendation (bread) and a complete meal recommendation (breakfast).

Design: Fifty-one free-living women with normal folate status participated in a 12-wk controlled intervention trial. Subjects were randomly assigned to one of the following interventions: apple juice (control group; n = 17), a breakfast providing 125 μg folate (breakfast group; n = 17), or 5 slices of whole-meal bread to be eaten over the course of the day, which provided 70 μg folate (bread group; n = 17). Folate status was assessed on the basis of concentrations of erythrocyte folate, serum folate, and plasma total homocysteine (tHcy) at baseline and at weeks 8 and 12 of the trial.

Results: In the breakfast group, initial median concentrations of erythrocyte folate (805 nmol/L) increased by 172 nmol/L (95% CI: 24, 293; P = 0.02) relative to the control. The relative increase in initial serum folate (2 nmol/L, 95% CI: 0.5; P = 0.06) was nonsignificant. The initial tHcy concentration (8.7 μmol/L) decreased by 2.3 μmol/L (95% CI: −1, −3.4; P < 0.01). In the bread group, the initial tHcy concentration (9.1 μmol/L) decreased nonsignificantly by 1.4 μmol/L (95% CI: 0, −2.8; P = 0.08) relative to the control group, whereas other outcomes were stable.

Conclusions: The folate status of the subjects improved after regular consumption of the breakfast meal. The additional folate intake from the bread maintained the folate status but was not sufficient to improve it.

INTRODUCTION
To reduce the prevalence of neural tube defects (NTDs), mandatory fortification of staple foods with folic acid was implemented in countries such as the United States and Canada. Fortification has successfully improved folate status in the United States (1) and has reduced the prevalence of NTDs in Canada (2). The Swedish authorities decided against mandatory folic acid fortification because of the ambiguous role of synthetic folic acid in the prevention and promotion of colorectal cancer (3), for example, and other potential adverse health effects (4, 5). However, data from the Swedish Dietary Survey (6) indicate a large gap between actual and recommended folate intakes, and measures to improve folate status are thus required.

Folic acid–fortified foods effectively improve folate status (7–9). However, results from controlled intervention trials using nonfortified foods are inconsistent. Some studies have reported improved folate status (10–15), whereas others have reported no effects (7, 16, 17) or inconsistent responses in different indicators of folate status (18, 19). In Sweden and several other European countries, additional intake of 50–180 μg/d would be sufficient to reach the recommended dietary intake of 300–400 μg/d (20). However, controlled trials on the effects of low additional food folate intakes (<180 μg/d) on folate status are scarce (11, 17, 19), and none of these trials assessed erythrocyte folate concentrations—an indicator of the long-term status of folate.

The implementation of nutritional advice concerning nutrient levels is difficult (21). Therefore, in the Swedish Nutrition Recommendations Objectified (SNO), nutrition recommendations are converted into foods and a 4-wk menu for healthy women and men (22). Whether these recommendations are useful in terms of improving folate status is unknown. Therefore, the objective of the present trial was to determine the effect on folate status of 2 SNO recommendations with minor modifications: a food recommendation (175 g whole-grain bread/d) and a complete meal (breakfast).

SUBJECTS AND METHODS

Subjects
Healthy women aged 25–60 y were recruited by a local newspaper advertisement on 25 June 2006. Subjects were interviewed (Figure 1) and excluded if they were allergic to the intervention foods or regularly consumed folic acid–fortified foods or vitamin B supplements. (To ensure no regular consumption of folic acid–

1 From the Department of Food Science, Swedish University of Agricultural Sciences, Uppsala, Sweden (VEÖ and CMW), and KPL Good Food Practice AB, Uppsala, Sweden (JCO and BES).
2 Supported by the Swedish Research Council Formas and the Cerealia Foundation R&D. Lantmännen (Sweden) donated the breads and breakfast cereals, JO Bolaget (Sweden) donated the orange and apple juices, and Merck Eprova AG (Schaffhausen, Switzerland) donated the folate standards.
3 Reprints not available. Address correspondence to VE Öhrvik, Department of Food Science, Swedish University of Agricultural Sciences, Box 7051, SE-750 07 Uppsala, Sweden. E-mail: veronica.ohrvik@lmv.slu.se.

fortified foods or vitamin B supplements, the subjects were given a list of folic acid supplements and fortified food products in Sweden, which consisted of a few breakfast cereals, juices, and snacks.) Other exclusion criteria were use of medication interfering with folate metabolism (eg, antiepileptics), a body mass index (BMI; in kg/m²) < 18 and > 30, weight loss or gain > 10% of body weight during the past 6 mo, pregnancy, planned conception, or lactation. The health check (Figure 1) required a normal range of the following measures for inclusion in the trial: hemoglobin, serum ferritin, plasma glucose, liver status (aspartate transaminase, c-glutamyl transferase activities), serum folate, erythrocyte folate, plasma total homocysteine (tHcy), and vitamin B-12. BMI, blood pressure and smoking habits were recorded. Of the initial subjects (n = 101), 51 were included in the study (Figure 1). Subject characteristics did not differ significantly between groups at screening or at baseline (Table 1).

**Study design**

A randomized, controlled, parallel intervention trial with 2 active groups (bread and breakfast) and one control group was carried out for 12 wk (September to December). For an increase in erythrocyte folate concentrations of 100 nmol/L with 80% power (2-sided P < 0.05) (23), 17 subjects had to complete each intervention diet, as calculated from the SDs of another intervention trial (92 nmol/L) with similar doses (9). Subjects were randomly assigned into groups by using a block design based on screening concentrations of erythrocyte folate (6 blocks per group). Concentrations of erythrocyte folate, serum folate, and tHcy were measured at baseline (day 1), 8 wk (day 56 ± 4), and 12 wk (day 84 ± 4; Figure 1). The study protocol was approved by the Regional Ethical Review Board in Uppsala.

**Blood sampling and analysis**

Blood samples for folate status were collected into coded sterile tubes from BD Vacutainer (Belliver Industrial Estate, Plymouth, United Kingdom) by research nurses at KPL Good Food Practice AB in Uppsala, Sweden, after the subjects had fasted for 12 h. Whole blood samples for erythrocyte folate status were collected into 3.0-mL EDTA-containing tubes and were analyzed by using Immunoassay Plus (BioRad, Sundbyerg, Sweden) and a Vitros ECI instrument (range: 270–3882 nmol/L; intraassay CV: 3%). Hematocrit was also measured. Erythrocyte folate concentrations were not corrected for serum folate concentrations. Plasma tHcy samples were collected in 3.0-mL EDTA-containing tubes, centrifuged in a swing-out rotor (2000 × g, 11 min), and transferred to cryotubes (Nunc, Roskilde, Denmark) within 30 min. Plasma tHcy was measured by using a CardiacMark 1/2/3 (Bio-Rad) and an Immulite 2000 instrument (range: 2–50 μmol/L; intraassay CV: 10%). Serum folate samples were collected into 3.5-mL SST tubes, left to coagulate for 30 min before centrifugation (2000 × g, 11 min, B Braun Biotech International centrifuge, Melsungen, Germany), and analyzed by using Immunoassay Plus (BioRad) and a Vitros ECI instrument (range: 0.5–45.0 nmol/L; intraassay CV: 12%). Samples were kept at 8°C until analyzed. A routine laboratory (Quintiles AB, Uppsala, Sweden) certified for ISO/IEC 17025 and accredited by Swedac (Swedish Board for Accreditation and Conformity) for analysis of serum folate and tHcy analyzed the samples.

**Intervention foods**

All intervention foods were regularly provided to subjects in anonymous packages. The total folate content of the intervention foods was determined in duplicate by using an accredited (Swedac; intraassay CV: 18%) microbiological assay (MA; Swedish Food Administration). Subjects in the control group were given 250 mL apple juice (JO Bolaget, Stockholm, Sweden) to consume with their habitual diet. The folate content of the juice was unknown to the subjects, but HPLC (24) detected no folate. The apple juice was produced in a single batch and stored in individual portions at 4°C. According to SNO recommendations, > 50% of the recommended bread intake (for women 6 slices/d, 150 g) should contain > 6 g fiber/100 g bread. This trial used only whole-meal bread (fiber content: 7.5–8 g/100 g) because of its higher folate content. Subjects in the bread group replaced all bread in their diet with 2 sorts of whole-meal bread, but otherwise maintained their habitual diet (Figure 1). Subjects consumed 5 slices (~175 g) daily, which provided 70 μg additional folate (analyzed; MA) and 1800 kJ/d (calculated). The breads supplied were produced in one batch (Linfrö/omega 3, 43% rye whole meal; Lantmännen AXA,
INTERVENTION WITH LOW DOSES OF FOOD FOLATE

TABLE 1
Characteristics of subjects in each group at screening and baseline

<table>
<thead>
<tr>
<th>Variable (range)</th>
<th>Time</th>
<th>Median (n = 17)</th>
<th>Q1</th>
<th>Q3</th>
<th>Median (n = 17)</th>
<th>Q1</th>
<th>Q3</th>
<th>Median (n = 17)</th>
<th>Q1</th>
<th>Q3</th>
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<tbody>
<tr>
<td>Intervention dose (µg/d)</td>
<td>During trial</td>
<td>0</td>
<td>70</td>
<td>125</td>
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<td></td>
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<tr>
<td>Estimated folate intake (µg/d)</td>
<td>Screening</td>
<td>239.4</td>
<td>210.3</td>
<td>278.0</td>
<td>308.5</td>
<td>201.3</td>
<td>330.4</td>
<td>312.1</td>
<td>250.4</td>
<td>375.2</td>
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<td>Serum vitamin B-12</td>
<td>Screening</td>
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<td>244.5</td>
<td>328.0</td>
<td>245.0</td>
<td>221.5</td>
<td>425.5</td>
<td>288.0</td>
<td>203.5</td>
<td>390.0</td>
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<td>142–725 pmol/L F</td>
<td>Screening</td>
<td>23.8</td>
<td>21.7</td>
<td>26.5</td>
<td>23.1</td>
<td>21.7</td>
<td>26.1</td>
<td>23.5</td>
<td>22.5</td>
<td>27.0</td>
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<td>Screening</td>
<td>48</td>
<td>38</td>
<td>57</td>
<td>47</td>
<td>40</td>
<td>55</td>
<td>49</td>
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<td>53</td>
</tr>
<tr>
<td>Age (y)</td>
<td>Screening</td>
<td>382.0</td>
<td>654.5</td>
<td>1021.0</td>
<td>805.0</td>
<td>625.0</td>
<td>952.5</td>
<td>764.0</td>
<td>613.0</td>
<td>920.5</td>
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<tr>
<td>Erythrocyte folate</td>
<td>Baseline</td>
<td>900.0</td>
<td>646.5</td>
<td>1079.0</td>
<td>855.0</td>
<td>634.5</td>
<td>991.5</td>
<td>805.0</td>
<td>742.0</td>
<td>908.5</td>
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<tr>
<td>6–22 nmol/L F</td>
<td>Baseline</td>
<td>12.0</td>
<td>10.5</td>
<td>14.5</td>
<td>12.0</td>
<td>9.0</td>
<td>15.5</td>
<td>12.0</td>
<td>10.0</td>
<td>16.0</td>
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<td>Plasma total homocysteine</td>
<td>Baseline</td>
<td>8.6</td>
<td>5.8</td>
<td>10.0</td>
<td>8.2</td>
<td>6.0</td>
<td>10.1</td>
<td>7.4</td>
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<tr>
<td>2–14 µmol/L F</td>
<td>Baseline</td>
<td>9.3</td>
<td>8.6</td>
<td>11.5</td>
<td>9.1</td>
<td>7.8</td>
<td>11.3</td>
<td>8.7</td>
<td>7.2</td>
<td>10.5</td>
</tr>
</tbody>
</table>

1 At screening, there was no significant difference between the groups for any variable according to a Kruskal-Wallis test. The median plasma homocysteine concentration increased significantly in the control group from screening to baseline (Wilcoxon’s signed-rank test) but was not significantly different from the increase in other groups (Kruskal-Wallis test). Q, quartile.
2 Intervention dose (analyzed) in addition to regular dietary habits.
3 Estimated with a 3-mo food-frequency questionnaire at screening.
4 Reference range from a certified laboratory.
5 Conversion factor from nmol/L to ng/mL is 0.460^{-1} (based on the molecular weight of 5-CH₃-CH₂folate).

Eskilstuna, Sweden) or 2 batches (Harmoni, 44% wheat and rye whole meal; Lantmännen AXA) and stored at −20°C. Subjects received equal amounts of frozen bread and were instructed to thaw it overnight in darkness.

Subjects in the breakfast group received a meal consisting of one slice of each bread (in total ~70 g), 30 g whole-meal breakfast cereal (Lantmännen, Järna, Sweden), 250 mL orange juice (JO Bolaqet), ≥15 g liver pâté (38% liver, 13% fat; ICA, Solna, Sweden), one kiwifruit (~65 g, chosen because of its higher folate content than the banana recommended by the SNO), and one portion of a self-selected dairy product (Figure 1). The breakfast provided 125 µg additional folate daily (analyzed; MA) and 2600 kJ/d (calculated). Breakfast cereals and orange juice were packed in individual portions and stored at 4°C. Dairy products, liver pâté and kiwifruit were purchased at local supermarkets.

To ensure that the folate content of intervention foods did not change as a result of storage or batch variation, individual foods were analyzed in duplicate during the trial. H₄folate, 5-CH₃-H₂folate, 10-HCO-folic acid, and 5-HCO-H₂folate were quantified, modified for quantification of 10-HCO-folic acid according to Pfeiffer et al (25), by using HPLC–mass spectrometry or HPLC–fluorescence detection after sample preparation, heat extraction, deconjugation using rat serum, and purification using either strong anion-exchange columns or affinity chromatography columns (24). The folate content of orange juice, breads, and cereals did not change during storage (data not shown). Batch variations were found for kiwifruit (18%) and liver pâté (22%); however, because these foods contributed only slightly to the total folate intake, the effect of batch variation on folate content in the breakfast was <10%.

Total folate intake before and during the trial

A food-frequency questionnaire (FFQ) consisting of 71 semi-quantitative questions was completed by subjects at screening (3-mo recall) and 8 wk (2-mo recall; Figure 1) for crude estimation of median folate intake. Folate intakes were estimated by using Dietist XP software (version 3.0; Kost och näringsdata, Bromma, Sweden) with data from the Swedish food-composition database (26) and food industries. The analyzed folate contents (MA) of the intervention foods were used to estimate folate intakes during intervention (day 56). To measure compliance, subjects kept daily records of consumption of the intervention foods and of their general health.

Statistical analysis

Data were expressed as medians, lower quartiles (Q1) and upper quartiles (Q3), or percentages. Response variables were not normally distributed, so nonparametric methods were used. Wilcoxon’s-Mann-Whitney rank-sum test was used to compare changes in each active group from baseline to 8 wk and to 12 wk with the changes in the control group (status indicators). Wilcoxon’s signed-rank test was used to compare changes from baseline within groups (status indicators). The Jonckheere-Terpstra test (StatXact-4 version 4.0.1; Cytel Software Corporation, Cambridge, MA) was used to detect possible dose-response effects. Because an increase in the folate content was expected to increase erythrocyte folate and serum folate concentrations and decrease tHcy concentrations, the test was one-sided. To check for interaction effects on the response of the initial folate status (ie, erythrocyte folate concentrations at screening divided into 6 blocks per group) and intervention group as detected by Vahteristo et al (9), a nonparametric test based on ranks aligned for block and group effects was used (27). A 2-sided P value <0.05 was regarded as statistically significant.
RESULTS

The baseline characteristics did not differ significantly between groups (Table 1); the median age was 48 y (Q1 = 39, Q3 = 54), median BMI was 23.5 (Q1 = 22.3, Q3 = 26.4), and median folate intake was 265 µg/d (Q1 = 222, Q3 = 330). During the trial, the subjects’ habitual diets did not change substantially, as indicated by the absence of changes in BMI at the end of the trial (0.01; Q1 = −0.02, Q3 = 0.07; P = 0.48).

The intervention was performed as a parallel study with 3 groups: control, bread, and breakfast (n = 17 in each group). Folate status, based on concentrations of erythrocyte folate and tHcy, improved significantly in the breakfast group compared with changes in the control group (Figure 2) at 12 wk but not at 8 wk. In the control group, there were no significant changes in concentrations of erythrocyte folate (−18%; P = 0.07), tHcy (3%; P = 0.98), and serum folate (0%; P = 0.37) at 84 d. In the bread group, there were no significant changes in concentrations of erythrocyte folate (−18%; P = 0.12) and serum folate (0%; P = 0.33), but tHcy was lower (−21%; P = 0.02) at 12 wk. However, this decrease in tHcy was not significant compared with the control group (P = 0.08; Figure 2). In the breakfast group, the tHcy concentration decreased (−23%; P < 0.01), whereas concentrations of erythrocyte folate (12%; P = 0.12) and serum folate (8%; P = 0.16) did not change significantly. A dose-response effect of the intervention foods was found at 12 wk for the tHcy-lowering capacity (P = 0.03) but not for increases in concentrations of erythrocyte folate (P = 0.39). There were no interaction effects between screening erythrocyte folate concentrations and intervention diets on the erythrocyte folate response (P = 0.70).

The subjects’ daily records of consumption of intervention foods and regular contacts during food delivery indicated full compliance. Median folate intakes estimated by FFQ increased for both active groups during the intervention. In the bread group, folate intake increased by 40 µg/d (Q1 = −16, Q3 = 99; P = 0.04) because of an increase in folate intake from bread (P < 0.01). In the breakfast group, median folate intake increased by 79 µg/d (Q1 = 25, Q3 = 136; P = 0.03) because of an increased folate intake from fruit and juice (P < 0.01), meat and fish (P < 0.01), and bread (P < 0.01), which reflected an increased consumption of the intervention foods (orange juice, kiwifruit, liver paté, and bread). In the control group, folate intake did not change (7 µg/d; Q1 = −62, Q3 = 56; P = 0.38).

DISCUSSION

This controlled dietary intervention showed that a breakfast following SNO recommendations (Figure 1) can improve folate status in healthy women, based on concentrations of erythrocyte folate and tHcy. However, the diet had to be consumed for >2 months before effects were observed. This slow response might have been the result of a combination of low additional folate intake and a good initial folate status of the subjects (Table 1), because the subjects’ concentrations of erythrocyte folate at screening were ≈30% higher than those for American women, despite mandatory folic acid fortification in the United States (1). However, although the initial status was good, only 24% of subjects in the breakfast group had erythrocyte folate concentrations associated with the lowest risk of NTD (>900 nmol/L) according to Daly et al (28). By 12 wk, nearly 60% of subjects in the breakfast group had concentrations >900 nmol/L. The increase in median erythrocyte folate concentration (from 805 to 990 nmol/L) was slightly higher than that in other trials using nonfortified foods (7, 10, 17, 18), although Fenech et al (14) reported an increase in erythrocyte folate concentrations from 509 to 768 nmol/L. In 2 trials (10, 17), the lower response in erythrocyte folate was most likely due to the short duration of the trial (4 wk). Because erythrocyte folate is a long-term indicator of folate status, the increase could be expected to continue if these trials were prolonged.

Folic acid supplements are known to reduce tHcy concentrations, and several interventions using folate-rich diets have shown significant positive effects (10–15). In this trial, median tHcy concentrations decreased significantly from 8.7 to 6.7 µmol/L in the breakfast group (Figure 2). In a previous meta-analysis (25 randomized controlled trials; n = 2596) (29), considerably larger doses of folic acid supplements were required to obtain the tHcy reductions observed in the present study (0.4 and 0.8 mg folic acid for the bread group and breakfast group, respectively). The

FIGURE 2. Differences in absolute changes [from baseline to 8 (solid symbols) and 12 wk (open symbols)] in erythrocyte folate, serum folate, and plasma homocysteine concentrations (medians and 95% nonparametric CIs) between the control group and the bread (circles) and breakfast (squares) groups. Significant differences in the absolute changes between each active group and the control group were determined by Wilcoxon’s Mann-Whitney rank-sum test (**P < 0.05, ***P < 0.001). In the control group, no significant changes were observed from baseline to 8 and 12 wk (Wilcoxon’s signed-rank test). In the control group (n = 17), median concentrations of erythrocyte folate were 838 nmol/L [quartile (Q) 1 = 621, Q3 = 1065] at 8 wk (56 ± 4 d) and 735 nmol/L (Q1 = 529, Q3 = 892) at 12 wk (84 ± 4 d), of serum folate were 13 nmol/L (Q1 = 11, Q3 = 15) at 8 wk and 12 nmol/L (Q1 = 9, Q3 = 15) at 12 wk, and of plasma homocysteine were 9.9 µmol/L (Q1 = 8.9, Q3 = 12.8) at 8 wk and 9.6 µmol/L (Q1 = 7.3, Q3 = 11.7) at 12 wk. The conversion factor from nmol/L to ng/mL is 0.460 L (based on the molecular weight of 5-CH3-H4folate).
pronounced effect might be explained in part by the fact that our subjects were women, who respond more efficiently to supplemental folic acid (29). However, other components in the diets probably further improved the homocysteine-lowering effect of folate. For example, whole-grain bread was inversely related to tHcy concentrations in the Hordaland Homocysteine Study (30) and in a controlled intervention trial using whole grain–legume powder (31). Furthermore, an inverse relation between tHcy concentration and intake of supplements containing the methyl donor betaine has been reported from clinical trials (32). Bread is a good betaine source, and, according to the Atherosclerosis Risk in Communities Study (n = 14 430), bread contributed >40% of betaine intake (33). Nevertheless, the dose-response effect indicated that folate was essential to tHcy lowering in our trial. According to a meta-analysis by Wang et al (34), the observed reductions in tHcy concentrations (21–23%) are associated with a stroke-preventive effect (relative risk: 0.77).

Daily supplements of 100 μg folic acid increase serum folate by ∼2 nmol/L according to the meta-analysis by Wald et al (35). Other intervention trials using low additional folate intakes (62–104 μg/d) also report minor but significant increases in plasma folate concentrations compared with the control (<2 nmol/L) in more subjects (≥39) (11, 19). In our trial the relative increase of 2 nmol/L (P = 0.06; Figure 2) in median serum folate concentration in the breakfast group (initial concentration: 12 nmol/L) was nonsignificant because of high interindividual variation. To establish a significant relation for serum folate, this trial would have needed more subjects. Therefore, no conclusions could be drawn on the effects of the intervention on serum folate.

Foods were chosen according to SNO recommendations (150 g bread/d or breakfast; Figure 1) because they were expected to be generally acceptable. This was confirmed by the full compliance of the subjects. The subjects’ BMIs did not change during the trial, which suggested only minor changes in energy intake. Some subjects commented that they would not normally consume 5 slices of bread daily, so they possibly unintentionally reduced their consumption of other food items. In addition, most of our subjects already consumed similar types of whole-mead diets in their habitual diet, and the breakfast group replaced their ordinary consumption of other food items. In addition, most of our subjects already consumed similar types of whole-mead diets in their habitual diet, and the breakfast group replaced their ordinary breakfast rolls fortified with folic acid the effect on folate status in women during a 3-month intervention. Eur J Nutr 2002;41:279–86.

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References


