No Evidence of Increased Risk of Stroke with Consumption of Refined Grains: A Meta-analysis of Prospective Cohort Studies

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Objectives: Results of the relationships between dietary consumption of refined grains and the risk of stroke are mixed. This study was based on a meta-analysis of prospective cohort studies. *Methods:* We systematically searched the MEDLINE (from January 1, 1966) and EMBASE (from January 1, 1974) databases up to November 30, 2014. Random-effects models were used to calculate summary relative risks (SRRs) and 95% confidence intervals (CIs). Between-study heterogeneity was assessed using Cochran's Q and I^2 statistics. *Results:* Eight prospective studies (7 publications) with a total of 410,821 subjects and 8284 stroke events were included in the meta-analysis. Overall, a diet containing greater amounts of refined grains was not associated with risk of stroke, with no evidence of heterogeneity among studies (SRR = 1.02; 95% CI, .93-1.10; $P_{\text{heterogeneity}} = .970$; $I^2 = 0$). In addition, no significant associations between consumption of refined grains and risk of stroke were found for both women and men, for both hemorrhagic and ischemic strokes, and for both incident and fatal strokes. These null results are consistent with those of linear dose–response meta-analyses (SRR = .98; 95% CI, .73-1.03 for per 3 servings/day). Consumption of white rice was not associated with risk of stroke (SRR = 1.01; 95% CI, .93-1.11; $P_{\text{heterogeneity}} = .966$; $I^2 = 0$). *Conclusions:* The current meta-analysis provides some evidence for the hypothesis that consumption of refined grains was not associated with risk of stroke and its subtypes. **Key Words:** Refined grains—hemorrhagic stroke—ischemic stroke—meta-analysis.

Introduction

Stroke remains an important cause of mortality and the most common cause of disability in both developed and developing countries.[1] In addition, stroke is becoming a great health burden in future decades, consuming large amounts of health resources and leading to significant economic burden.[2] For instance, in the United States, it is the fourth leading cause of mortality, with 795,000 estimated cases of incident stroke annually.[3] It is, therefore, imperative to identify and implement healthcare policies that can reduce the risk of stroke.[4]

A substantial body of evidence has shown that diet is related to risk of stroke.[4] Whole grain consists of 3 botanically defined parts: the bran, the germ, and the endosperm; the former two parts (bran and germ) are sources of dietary fiber and various micronutrients, minerals, and phytochemicals. Refined grains, which primarily consist of starch, are produced when removing the outer bran and germ portions of whole grains. It is reported that high intake of refined carbohydrates may be the reason why Asian populations tend to develop diabetes at a younger age and a lower body mass index (BMI) than white populations.[5] High intake of energy-dense foods, such as refined grains, has

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adverse effects on lipid and glucose metabolism, thereby creating potential worries with regard to increased risk of weight gain/obesity, dyslipidemia, and hypertension,[6,7] all of which are major intermediate end points for stroke.

Several epidemiological studies have directly examined the relationship between consumption of refined grains and risk of stroke and its subtypes with inconsistent results.[8-14] Up to now, no systematic reviews and meta-analyses have looked into the effects of consumption of refined grains on the risk of stroke. We therefore undertook a meta-analysis of prospective cohort studies to quantitatively assess such an association following the Meta-analysis of Observational Studies in Epidemiology guidelines.[15]

Methods

Literature Search

Two investigators (W.D.M. and G.Y.X.) made a systemic search of MEDLINE (from January 1, 1966) and EMBASE (from January 1, 1974) up to November 30, 2014 to identify all published articles using the following medical subject headings or key words: (1) cereals OR grains OR rice OR sweets OR desserts OR white bread OR pasta OR muffins OR biscuits OR pancakes OR waffles OR pizza; (2) cerebrovascular accident OR brain ischemia OR intracranial hemorrhages OR cerebral hemorrhage OR subarachnoid hemorrhage OR stroke. The search was limited to studies in English. Furthermore, the reference lists of retrieved articles were scrutinized to identify additional relevant studies.

Study Selection

The studies had to meet the following criteria to be included in the meta-analysis: (1) the prospective cohort studies were published as original articles; (2) the exposure of interest was refined grains or specific subtypes; the outcome was nonfatal or fatal stroke and its subtypes; and (3) the studies reported relative risks (RRs) and corresponding 95% confidence intervals (CIs) for at least 3 quantitative categories of intake of refined grains. Case–control studies, animal studies, in vitro researches, case reports, ecological studies, and reviews were not considered eligible. If multiple papers reported results from the same cohort, we included the one with the largest number of cases. Studies on foods that were based on components of individual grains, such as bran or germ, were excluded. W.D.M. and G.Y.X. independently reviewed all potentially relevant articles to determine whether an article met the general inclusion criteria, and disagreement was resolved by discussion.

Data Extraction

From each study, W.D.M. and G.Y.X. extracted the following characteristics: first author's surname, publication year, study location, duration of follow-up, number of participants, participants' age and sex, methods used for collection of data on exposure, number of events, outcome assessment, confounding factors, and RR estimates with the corresponding 95% CI for the highest versus the lowest category of intake of refined grains. If separate risk estimates for men and women and for subtypes of stroke were available in one study, we treated it as separate studies.[12,13] From each study, we extracted the risk estimates with the greatest number of adjustments.

Assessment of Study Quality

W.D.M. and G.Y.X. assessed the quality of each selected study using the Newcastle–Ottawa Scale (NOS).[16] For cohort studies, the NOS consist of 3 parameters of quality: selection (4 points), comparability (2 points), and outcome (3 points); a maximum of 9 points reflect the highest quality. A total score of 7 or greater indicated high-quality studies and a total score of 6 or smaller indicated low-quality studies.

Statistical Methods

We used the statistical program STATA, version 11.0 (STATA, College Station, TX) for the analysis. A two-tailed P value of less than 0.05 was considered statistically significant. We used the method of a random-effects model, which accounts for heterogeneity among studies,[17] to calculate summary relative risks (SRRs) and 95% CIs for the high versus low and dose–response analysis. We converted the RRs in each study by using their natural logarithms, and the standard errors were calculated from their corresponding 95% CIs. Publication bias was assessed by using funnel plots and Begg's adjusted rank correlation and Egger's regression asymmetry tests; results were considered to indicate potential publication bias if the P value is less than .10.[18,19]

Statistical heterogeneity among studies was assessed using both the Q statistic and the I^2. Results were considered significantly heterogeneous if the P values are less than .10. I^2 is the amount of total variation that is explained by between-study variation, with values of approximately 25%, 50%, and 75% considered to indicate low, moderate, and high heterogeneity, respectively.[20] To explore the sources of heterogeneity, subgroup and metaregression analyses were performed according to sex; geographic locations; duration of follow-up; number of cases; stroke outcome; and adjustments for confounding factors, including a history of type 2 diabetes, dyslipidemia, and total energy intake. Sensitivity analyses were performed by excluding one study from the meta-analysis and calculating a pooled estimate for the remainder of the studies to evaluate whether the results were significantly affected by a single study.

The dose–response results in the forest plots are presented for a 3-servings-per-day increment. We used the