Systematic review of the association between dietary acid load, alkaline water, and cancer

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<td>bmjopen-2015-010438</td>
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<td>Complete List of Authors:</td>
<td>Fenton, Tanis; University of Calgary, Department of Community Health Sciences, O'Brien Institute of Public Health, Alberta Children's Hospital Research Institute; Alberta Health Services, Nutrition Services Huang, Tian; Alberta Health Services, Nutrition Services; University Of Alberta, Faculty of Agriculture, Life and Environmental Sciences, Edmonton Clinic Health Academy</td>
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<td>Dietary Acids, Alkaline Diet, Alkaline water, Acid base equilibrium, Cancer, Neoplasm</td>
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Systematic review of the association between dietary acid load, alkaline water, and cancer

Tanis R Fenton 1,2,*, Tian Huang 2,3

1 Department of Community Health Sciences, O’Brien Institute for Public Health, Alberta Children’s Hospital Research Institute, University of Calgary
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Keywords: dietary acid, alkaline diet, alkaline water, acid base equilibrium, cancer, neoplasm

Word count: 2451, excluding title page, abstract, references, and table
Abstract:

Objectives: To evaluate the evidence for a causal relationship between dietary acid/alkaline and alkaline water, for both the etiology and treatment of cancer.

Design: A systematic review was conducted on published and grey literature for human randomized intervention and observational studies with either varying acid-base dietary intakes and/or alkaline water with any cancer outcome or for cancer treatment.


Results: No randomized trials were located. One prospective cohort study met the inclusion criteria, a study of bladder cancer. No studies were located that examined dietary acid or alkaline or alkaline water for cancer treatment. The included study revealed no association between the diet acid load with bladder cancer (Odds ratio (OR) = 1.15, confidence interval (CI) = 0.86 to 1.55, p = 0.36), even among long term smokers (OR = 1.72, CI = 0.96 to 3.10, p = 0.08).

Conclusion: This systematic review of the literature revealed a lack of evidence for an association between a diet acid load and/or alkaline water for the initiation or treatment of cancer. Promotion of alkaline diet and alkaline water to the public for cancer prevention or treatment is not justified.

Article Summary

Strengths and Limitations of this study:

- A strength of this study is its broad search of both the published and unpublished literature for studies for consideration of inclusion into this systematic review.

- It is a limitation of this study that we only located one observational study which fit the inclusion criteria
Introduction

The general public is being encouraged that to prevent cancer, they must assess the acidity of their urine and/or saliva as an assessment of the acidity of their body, and then to modify their diets accordingly [9][1–6]. The alkaline diet, or acid-ash diet, is being promoted based on the claims that modern diets acidify the body [1–11] causing diseases including cancer, osteoporosis, and cardiovascular disease [1–12]. Promoters of this diet claim that changing food choices to more “alkaline” selections prevents all of these conditions [1–9,11] and has the ability to treat cancer once it has developed [5,10,12,13]. This diet is based on the concept that mineral components of foods make the body acidic, alkaline, or neutral [14]. This marketing of the alkaline diet promotes not only a diet, but also the sale of related supplements and water alkalinizer machines through almost every media medium, including websites, books, and videos [1–7]. In our experience, cancer patients are approached by salespeople who are promoting water alkalinizers as a way to treat their cancer.

There is some evidence that some cancer cells and tumors grow well in an acidic environment in the laboratory[15,16]. While the alkaline diet is being promoted to correct the acid state that the modern diet creates, the American Institute of Cancer Research and the Canadian Cancer Society have stated that the body tightly regulates systemic pH and that food choices will only affect urine pH and not body acidity [17,18]. Studies show that while urine pH changes in response to diet changes, blood pH does not [19,20].

As acid/base forming potential of foods does alter urinary pH[19,20], cancers of the urinary tract may be an important focus in investigating claims of the alkaline diet to prevent and treat cancer.

Studies suggest that a substantial and growing number of patients use the internet to obtain health information [21,22], which may not be innocuous. Oncologists report that cancer patient internet use contributes to confusion and anxiety among cancer patients [22].

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As far as we are aware, no systematic review has been done to evaluate the evidence for an association between dietary acid and/or alkaline, or the effectiveness of alkaline water, for the etiology or treatment of cancer. The purpose of this systematic review is to conduct an extensive search of the published and unpublished literature to determine if evidence of a causal relationship exists between dietary acid or alkaline and the etiology of cancer and/or the treatment of this disease.

METHODS

Eligibility Criteria

Randomized interventions and observational human studies of acid-base intakes of diet, supplemental salts to change systemic pH (such as potassium bicarbonate or potassium citrate), and consumption of alkaline water, with cancer outcomes (both etiology and treatment) were sought. No language or publication date restrictions were imposed. Human participants of all ages and backgrounds were considered. Studies with no original research (narrative reviews, editorials) and non-human studies were excluded from this review.

Literature Search

Two reviewers conducted independent literature searches, one with the assistance of a librarian (J.P.), in an attempt to find all human studies of the ash-acid diet hypothesis or an alkaline diet with any type of cancer as the outcome. Studies were identified through search text words and Medical subject headings: diet, dietary, acid, acidic, alkaline, acid-base, acid-base equilibrium, acid-ash, “net acid excretion”, “potential renal acid load, water, cancer, neoplasm. For published literature, databases searched included Ovid Medline, Pubmed, CINAHL, and Embase up to April 2015. No limits were applied to searches and studies reported in all languages were considered. In an effort to include all available studies, reference lists for the located articles were reviewed. For grey literature, Cochrane Register of
Clinical Trials, Current Controlled Trials, Canadian Cancer Trials, Google, and Google Scholar were manually searched up to April 2015.

Both authors examined the article titles for relevance to the topic and potential fit to the inclusion criteria independently, with the plan to use discussion and resolution by reaching consensus of any differences in assessments. When the title was not clear regarding the potential fit, both reviewers reviewed the abstracts. For abstracts which suggested relevance, the full text of the article was reviewed. Both researchers extracted data independently. There was no indication of unpublished data from the search, so authors were not contacted.

Data extracted included exposures to estimates of acid generated from diet, among humans, and with the outcome of any cancer.

Results with p-values < 0.05 were considered to be statistically significant, and relative risks > 2.0 were considered clinically relevant if confounding was considered controlled for or > 5.0 with narrow confidence intervals if serious concerns about bias existed [23]. We used the Newcastle-Ottawa Scale (NOS) to assess the included studie(s) for risk of bias [24].

RESULTS

Description of studies

A total of 8278 citations were identified, 252 abstracts were reviewed for potential fit; only one study met the inclusion criteria [25], and was included in this systematic review. There were no disagreements about articles fit to the inclusion criteria between the reviewers. The literature search also located a systematic review which found no evidence for the alkaline diet [25] and two narrative reviews discussing the acid-ash/alkaline diet and cancer [26,27]. No relevant unpublished studies were found.

The included study, by Wright et al was a prospective cohort study, nested within the
alpha-Tocopherol, Beta-Carotene Cancer Prevention Study, a randomized controlled trial [25]. This study examined the diet acid load and the occurrence of bladder cancer. The exposure used in this study was an estimate of renal net acid excretion, based on dietary intakes and anthropometrics. No studies were found that examined any other cancer or neoplastic outcomes with dietary acid, alkalinity, alkaline water, or the use of an alkaline diet, alkaline water, or change of the diet acid load for cancer treatment.

Wright et al. [25] examined the relationship between diet-estimated renal net acid excretion (NAE) using a food frequency questionnaire (and measured height and weight for the estimation of urinary organic acid excretion) with the risk of bladder cancer in a large cohort of 27,096 male smokers [25]. The relative risk (RR) estimate for bladder cancer was 1.15 (CI = 0.86 to 1.55, p= 0.38) for individuals in the most acidic versus the least acidic NAE quintile as assessed in a multivariate proportional hazards model, a not statistically significant relationship. These researchers also tested whether acidic urine was associated with an increased risk of bladder cancer in a subset of long-term smokers. Among men who smoked for more than 45 years there was a non-significant adjusted relative risk of bladder cancer of 1.72 (CI = 0.96 to 3.10, p = 0.08) with higher NAE levels.

**Risks of bias assessment**

In the included study, the exposure of net acid excretion, which was used to define the exposed and non-exposed cohorts, was categorized using a food frequency tool [25]. With respect to representativeness of the cohort, the subjects were recruited through a mailed invitation to the Alpha-Tocopherol, BetaCarotene Lung Cancer Prevention Study from the total population from 14 areas in southwest Finland, using addresses in the Central Population Register [28]. Thus for the Selection section of the NOS, the study was rated with 3 of a possible 4 points since we considered it reasonably representative of the population, the exposed and non-exposed were drawn from the same community, the food frequency
questionnaire was a written self-report, and the subjects were required to be cancer free at the start of the study. We reduced the score from a full 4/4 since food frequency questionnaires are not perfect at describing exposure to nutrients [29] due to reporting bias and poor reliability.

Several variables were assessed for effect medication (Table 1) and numerous potentially confounding variables were controlled for in the analysis of the included study (Table 1) [25]. Due to this comprehensive confounding control, we assessed this study as at a low risk of bias (1 of a possible 2 points) in the Comparability section of the NOS, since observational studies usually have some residual confounding.

<table>
<thead>
<tr>
<th>Study</th>
<th>Population</th>
<th>Outcome</th>
<th>Results</th>
<th>Study design</th>
<th>Potential modifiers or confounders</th>
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<tr>
<td>Wright, 2005</td>
<td>29,133 male residents of southwestern Finland aged 50-69 who smoked 5 or more years</td>
<td>Relative risk of bladder cancer.</td>
<td>The relative risk (RR) for bladder cancer was 1.15 (confidence interval = 0.86 to 1.55, p = 0.38), suggesting that urine pH is not a major risk factor for bladder cancer</td>
<td>Prospective cohort study.</td>
<td>Energy intake, age, number of cigarettes smoked daily, number of years of smoking, alpha tocopherol and beta carotene supplementation, BMI, total fluid intake, education level, place of residence, pack years of smoking, smoking inhalation, smoking cessation, calcium, magnesium, and/or potassium supplements. Effect modification by smoking duration, smoking dose, total fluid intake, BMI and intervention group was evaluated in stratified analysis.</td>
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</table>

In terms of outcome assessment, the included study assessed the bladder cancer outcome using the Finnish Cancer Registry and the Register of Causes of Death to identify cases of
bladder cancer (ICD-9 code 188 and 233.7) [25]. Once possible cases were identified, “all relevant medical records were obtained and reviewed independently by one or two study physicians” [25]. They found that of the 473 cases of bladder cancer identified in the median of 14 years of follow-up, 446 (94%) had complete baseline data [25]. We rated the Wright et al study with 3 of a possible 3 points on the NOS scale for outcome assessment since they used records, reviewed independently, and had the high rate of complete data on the cases.

Overall, we rated the Wright study [25] as having a low risk of bias since it warranted a score of 7 out of a possible 9 on the NOS [24]. Additionally, since the study by Wright et al. [25] was a prospective observational study, this study had the strength of temporality, since the exposure (estimated urine acidity) preceded the outcome (bladder cancer risk). The study relied on estimated renal net acid excretion to determine urine acidity, which could potentially result in misclassification of individuals.

DISCUSSION

This systematic review, based on only one relevant observational study, did not find support for the acid-ash hypothesis which suggests that acid from the diet causes or contributes to cancer development [1–6]. The GRADE Working Group recommends that any associations from observational data are weak evidence unless the results show at least a two-fold risk with no concerns about confounding, or a five-fold risk with narrow confidence intervals when there are serious concerns about bias [23]. The estimates of effect between the diet acid load and bladder cancer in this study were not statistically significant, and the estimates of effect were low relative to the GRADE guidelines.

The included Wright study [25] was rated as having a low risk of bias since it warranted a score of 7 out of a possible 9 on the NOS [24]. Additionally, the study had
temporality between the exposure (net acid excretion) and bladder cancer risk and controlled for several potentially confounding variables. These study strengths provide support that the study reached accurate conclusions.

Our thorough literature search did not locate any studies of this acid/alkali hypothesis for any other forms of cancer, or cancer treatment. Additionally, our literature search failed to locate any studies that evaluated whether alkaline water has a role in prevention or treatment of cancer. Thus, there is a lack of support for any advice to the public about the acid-ash hypothesis, the alkaline diet, and/or alkaline water and their relationships to cancer. By searching the published and unpublished literature for studies on this topic we decreased the risk of bias due to publication bias. It is a limitation of this study that we only located one observational study.

Some review articles suggest that alterations in acid-base homeostasis in the tumor microenvironment are common in the pathology of cancer [15,16] and that tumor interstitial fluid has a reduced buffering capacity compared with normal tissues, and along with high rates of production of metabolic end products, tumours may cause an acidic extracellular environment [16]. Further, cancer therapy may be influenced by pH. Some in vitro and animal studies have suggested that metabolic alkalosis may be useful in enhancing some cancer treatment regimens [30].

However, these in vitro examinations and animal studies of cancer cell behaviour are at the hypothesis generating phase and should not be extrapolated to human health. These cell culture studies do not address the questions or provide evidence regarding cancer etiology or treatment. Studies have demonstrated that alkaline supplements [20] or alkaline-promoting diets [19] can alter urine pH, however, they do not appreciably change overall systemic pH [19,20]. Three studies of acid load interventions have measured both urine and blood pH changes as a result of various interventions, including changes in food intake [19], ingesting a
bicarbonate salt [20], or a phosphate salt [31]. In each case, the urine pH increased markedly, from 0.2 to 1.2 pH units, while blood pH did not change minimally, by 0.01 [19,20] to 0.02 [31] pH units. The urine pH changes were 7.5 [31] to 177 [20] multiples of the blood pH changes. This comparison shows that kidneys are effective at excreting acid to maintain systemic pH balance, and that urine pH does not provide a measurement of systemic pH.

In spite of finding no human studies of alkaline water and cancer, our search did locate some studies of alkaline water, none of which supported the promotions that suggest alkaline water supports good health. We found outcomes from alkaline water included: In humans: inhibited gastric secretion [32], reduced gall bladder emptying [33], and toxic reactions [34]; In rat pups: cardiac necrosis [35] and growth restriction [36]. Therefore, the promotion of alkaline water as health promoting is not supported by evidence.

There may be a safety concern involving eating an “alkaline diet” and subsequently to increase urine pH of bladder cancer patients. For instance, Ciprofloxacin’s influence on human bladder cell lines suggests that the antiproliferative potential and antitumor effect of this drug may be superior at low urine pH [37]. Overall, safety considerations for increasing urinary pH in bladder cancer patients undergoing certain cancer therapy treatments needs to be evaluated before patients should undertake urine pH alterations.

In contrast to our findings of no association between dietary acid or alkaline and bladder cancer, there is convincing evidence to suggest that smoking is an important risk factor for bladder cancer [38].

The alkaline diet emphasizes, to varying degrees, fresh fruits, vegetables, roots and tubers, and legumes. It is possible that some of these foods may have cancer protective effects, not through their acidity/alkaline promoting qualities but rather due to nutrient and non-nutritive compounds. A systematic review and meta-analysis of prospective studies show that a high intake of dietary fibre is associated with reduced risk of colorectal cancer [41]. A
review and meta-analysis of epidemiological research on physical activity, diet and adiposity found that a prudent dietary pattern of high intakes of fruits, vegetables, whole grains, legumes, and fish appeared protective against breast cancer [42]. However, the alkaline diet promotes the exclusion of many foods, several of which contribute many beneficial nutrients and have health benefits.

5. Conclusions

A systematic review of the literature revealed a lack of association between a diet acid load or alkaline water for cancer risk and no studies alkaline treatment for cancer. Promotion of alkaline diet and alkaline water to the public for cancer prevention or treatment is not justified.

Contributorship statement: TRF conceptualized and designed the study, TH assisted in the conceptualization and design of the study and drafted the initial manuscript. Both authors conducted comprehensive literature searches, conducted the analysis and interpretation of data for the work, reviewed and revised the manuscript, approved the final manuscript as submitted, and agree to be accountable for all aspects of the work.

Competing interests: The authors have no competing interests.

Funding statement: This research received no specific grant from any funding agency in the public, commercial or not-for-profit sectors.

Data sharing statement: Dataset available from the Dryad repository, DOI: [doi:10.5061/dryad.35pj0]
References


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<td>Structured summary</td>
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<td>Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.</td>
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<td>Rationale</td>
<td>3</td>
<td>Describe the rationale for the review in the context of what is already known.</td>
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<td>Objectives</td>
<td>4</td>
<td>Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).</td>
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<td>Protocol and registration</td>
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<td>Eligibility criteria</td>
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<td>Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.</td>
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<td>Information sources</td>
<td>7</td>
<td>Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.</td>
<td>4,5</td>
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<tr>
<td>Search</td>
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<td>Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.</td>
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<tr>
<td>Study selection</td>
<td>9</td>
<td>State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).</td>
<td>5</td>
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<tr>
<td>Data collection process</td>
<td>10</td>
<td>Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.</td>
<td>5</td>
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<tr>
<td>Data items</td>
<td>11</td>
<td>List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.</td>
<td>5</td>
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<td>Risk of bias in individual studies</td>
<td>12</td>
<td>Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.</td>
<td>5</td>
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<tr>
<td>Summary measures</td>
<td>13</td>
<td>State the principal summary measures (e.g., risk ratio, difference in means).</td>
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<tr>
<td>Synthesis of results</td>
<td>14</td>
<td>Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I² for each meta-analysis).</td>
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# PRISMA 2009 Checklist

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<td>Risk of bias across studies</td>
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<td>Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).</td>
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<td>Additional analyses</td>
<td>16</td>
<td>Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.</td>
<td>N/A</td>
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## RESULTS

| Study selection | 17 | Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.                                                                                     | 5                 |
| Study characteristics | 18 | For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.                                                                                           | 5,6               |
| Risk of bias within studies | 19 | Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).                                                                                                                                 | 6,7               |
| Results of individual studies | 20 | For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.     | 6                 |
| Synthesis of results | 21 | Present results of each meta-analysis done, including confidence intervals and measures of consistency.                                                                                                                   | 6                 |
| Risk of bias across studies | 22 | Present results of any assessment of risk of bias across studies (see Item 15).                                                                                                                                 | 6.7               |
| Additional analysis | 23 | Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).                                                                                                      | N/A               |

## DISCUSSION

| Summary of evidence | 24 | Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).                                         | 6,7               |
| Limitations | 25 | Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).                                                              | 8-11              |
| Conclusions | 26 | Provide a general interpretation of the results in the context of other evidence, and implications for future research.                                                                                                      | 9                 |

## FUNDING

| Funding | 27 | Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.                                                                                  | N/A               |

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Keywords: dietary acid, alkaline diet, alkaline water, acid base equilibrium, cancer, neoplasm

Word count: 2595, excluding title page, abstract, references, and table
Abstract:

Objectives: To evaluate the evidence for a causal relationship between dietary acid/alkaline and alkaline water for the etiology and treatment of cancer. The alkaline diet is also promoted for conditions including diabetes and hypertension.

Design: A systematic review was conducted on published and grey literature separately for randomized intervention and observational studies with either varying acid-base dietary intakes and/or alkaline water with any cancer outcome or for cancer treatment.


Results: 8278 citations were identified, 252 abstracts were reviewed; one study met the inclusion criteria and was included in this systematic review. No randomized trials were located. No studies were located that examined dietary acid or alkaline or alkaline water for cancer treatment. The included cohort study, had a low risk of bias. It revealed no association between the diet acid load with bladder cancer (Odds ratio (OR) = 1.15; 95% CI = 0.86 to 1.55, p = 0.36), even among long term smokers (OR = 1.72; 95% CI = 0.96 to 3.10, p = 0.08).

Conclusion: Despite the promotion of the alkaline diet and alkaline water by the media and salespeople, there is almost no actual research to either support or disprove these ideas. This systematic review of the literature revealed a lack of evidence for or against diet acid load and/or alkaline water for the initiation or treatment of cancer. Promotion of alkaline diet and alkaline water to the public for cancer prevention or treatment are not justified.

Article Summary

Strengths and Limitations of this study:

- A strength of this study is its broad search of both the published and unpublished literature for studies to include in this systematic review.

- It is a limitation of this study that we only located one observational study which fit the inclusion criteria.
Introduction

The general public is being encouraged by the lay press that to prevent cancer, they are persuaded to assess the acidity of their urine and/or saliva as an assessment of the acidity of their body, and then to modify their diets accordingly [1–7]. The alkaline diet, or acid-ash diet, is being promoted based on the claims that modern diets acidify the body [1–11] causing diseases including cancer, osteoporosis, and cardiovascular disease [1–12]. The alkaline diet is also promoted for conditions including diabetes and hypertension. Promoters of this diet claim that changing food choices to more “alkaline” selections prevents all of these conditions [1–9,11] and has the ability to treat cancer once it has developed [5,10,12,13]. This diet is based on the concept that mineral components of foods make the body acidic, alkaline, or neutral [14].

The alkaline diet is designed to provide more alkaline ions after metabolism, based on the acid-ash hypothesis developed over 100 years ago [15]. The acid-ash hypothesis suggests that to achieve a more alkaline load, one must consume more fruit and vegetables with only a moderate intake of protein. While the marketing of this diet implies that the diet changes will raise systemic pH, a well-conducted randomized trial of these diet changes only altered systemic pH by 0.014 pH units, while the urine pH increased by 1.02 units [16]. This study reveals that diet changes can alter urine pH but does not change blood pH [16]. Further, the fact that the effect of phosphorus on calcium metabolism is opposite to that predicted by the hypothesis [17], raises questions about the validity of the hypothesis. Additionally, a review of the body of evidence regarding the acid-ash/alkaline hypothesis for bone health found that the hypothesis is not supported and there is no evidence that altering the diet acid load improves bone health [18].

The marketing of the alkaline diet promotes not only a diet, but also the sale of related supplements and water alkalinizer machines through almost every media medium, including
websites, books, and videos [1–6,8]. In our experience, cancer patients are approached by
salespeople who are promoting water alkalinizers as a way to treat their cancer.

There is some evidence that some cancer cells and tumors grow well in an acidic
environment in the laboratory [19,20]. While the alkaline diet is being promoted to correct
the acid state that the modern diet creates, the American Institute of Cancer Research and the
Canadian Cancer Society have stated that the body tightly regulates systemic pH and that
food choices will only affect urine pH and not body acidity [21,22]. Studies show that while
urine pH changes in response to diet changes, blood pH does not [16,23].

As acid/base forming potential of foods does alter urinary pH [16,23], cancers of
the urinary tract may be an important focus in investigating claims of the alkaline diet to
prevent and treat cancer.

Studies suggest that a substantial and growing number of patients use the internet to
obtain health information [24,25], which may not be innocuous. Oncologists report that
cancer patient internet use contributes to confusion and anxiety among cancer patients [25].

As far as we are aware, no systematic review has been done to evaluate the evidence
for an association between dietary acid and/or alkaline, or the effectiveness of alkaline water,
for the etiology or treatment of cancer. The purpose of this systematic review is to conduct an
extensive search of the published and unpublished literature to determine if evidence of a
causal relationship exists between dietary acid or alkaline and the etiology of cancer and/or
the treatment of this disease.

METHODS

Eligibility Criteria

Randomized interventions and observational human studies of acid-base intakes of
diet, supplemental salts to change systemic pH (such as potassium bicarbonate or potassium
citrate), and consumption of alkaline water, with cancer outcomes (both etiology and
treatment) were sought. No language or publication date restrictions were imposed. Human participants of all ages and backgrounds were considered. Studies with no original research (narrative reviews, editorials) and non-human studies were excluded from this review.

**Literature Search**

Two reviewers conducted independent literature searches, one with the assistance of a librarian (J.P.), in an attempt to find all human studies of the ash-acid diet hypothesis or an alkaline diet with any type of cancer as the outcome. Studies were identified through search text words and Medical subject headings: *diet, dietary, acid, acidic, alkaline, acid-base, acid-base equilibrium, acid-ash, “net acid excretion”, “potential renal acid load, water, cancer, neoplasm* (Supplemental file). For published literature, databases searched included Ovid Medline, Pubmed, Cochrane Register of Clinical Trials, CINAHL, and Embase up to April 2015. No limits were applied to searches and studies reported in all languages were considered. In an effort to include all available studies, reference lists for the located articles were reviewed. For grey literature, Current Controlled Trials, Canadian Cancer Trials, Google, and Google Scholar were manually searched up to April 2015.

Both authors examined the article titles for relevance to the topic and potential fit to the inclusion criteria independently, with the plan to use discussion and resolution by reaching consensus of any differences in assessments. When the title was not clear regarding the potential fit, both reviewers reviewed the abstracts. For abstracts which suggested relevance, the full text of the article was reviewed. Both researchers extracted data independently. There was no indication of unpublished data from the search, so authors were not contacted.

Data extracted included exposures to estimates of acid generated from diet, among humans, and with the outcome of any cancer.
Results with p-values < 0.05 were considered to be statistically significant, and Relative Risks > 2.0 with no plausible residual confounding were considered clinically relevant [26]. We used the Newcastle-Ottawa Scale to assess the included study for risk of bias [27].

RESULTS

Description of studies

A total of 8278 citations were identified, 252 abstracts were reviewed for potential fit; only one study met the inclusion criteria [28], and was included in this systematic review. There were no disagreements about articles fit to the inclusion criteria between the reviewers. The literature search also located a systematic review which found no evidence for the alkaline diet [29] and two narrative reviews discussing the acid-ash/alkaline diet and cancer [30,31]. No relevant unpublished studies were found.

The systematic review, published in 2014, reported finding four articles on the alkaline diet and cancer in a google search but they did not report findings from these articles or their references [29].

The two narrative reviews did not include any human studies of an association between diet acid/alkaline and cancer. The narrative review by Robey et al concluded: “there are numerous systemic pathways affected by diet-induced acidosis that may be cancer promoting, but a causal role is poorly defined” [31]. The review by Lee et al suggested a post hoc analogy between the traditional Chinese medicine concepts of yin and yang with the acid/alkaline diet but did not cite any studies of the acid/alkaline diet and cancer [30].

The included study, by Wright et al was a prospective cohort study, nested within the alpha-Tocopherol, Beta-Carotene Cancer Prevention Study, a randomized controlled trial (Table 1) [28]. This study examined the diet acid load and the occurrence of bladder cancer. The exposure used in this study was an estimate of renal net acid excretion, based on dietary
intakes and anthropometrics. No studies were found that examined any other cancer or neoplastic outcomes with dietary acid, alkalinity, alkaline water, or the use of an alkaline diet, alkaline water, or change of the diet acid load for cancer treatment.

<table>
<thead>
<tr>
<th>Study</th>
<th>Population</th>
<th>Outcome</th>
<th>Results</th>
<th>Study design</th>
<th>Potential modifiers or confounders</th>
<th>Other risk of bias</th>
</tr>
</thead>
<tbody>
<tr>
<td>Wright, 2005</td>
<td>29,133 male residents of southwestern Finland aged 50-69 who smoked 5 or more years</td>
<td>Relative risk of bladder cancer</td>
<td>The relative risk (RR) for bladder cancer was 1.15 (confidence interval = 0.86 to 1.55, p = 0.38), suggesting that urine pH is not a major risk factor for bladder cancer</td>
<td>Prospective cohort study.</td>
<td>Energy intake, age, number of cigarettes smoked daily, number of years of smoking, alpha tocopherol and beta carotene supplementation, BMI, total fluid intake, education level, place of residence, pack years of smoking, smoking inhalation, smoking cessation, calcium, magnesium, and/or potassium supplements.</td>
<td>Used renal NAE based on a validated formula based on nutrient intake and anthropometric information to estimate true urine pH</td>
</tr>
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</table>

Table 1: Included study

Wright et al. [28] examined the relationship between diet-estimated renal net acid excretion (NAE) using a food frequency questionnaire (and measured height and weight for the estimation of urinary organic acid excretion) with the risk of bladder cancer in a large cohort of 27,096 male smokers [28]. The Relative Risk estimate for bladder cancer was 1.15 (CI = 0.86 to 1.55, p= 0.38) for individuals in the most acidic versus the least acidic NAE quintile as assessed in a multivariate proportional hazards model, a not statistically significant relationship. These researchers also tested whether acidic urine was associated with an increased risk of bladder cancer in a subset of long-term smokers. Among men who smoked for more than 45 years there was a non-significant adjusted Relative Risk of bladder cancer of
1.72 (CI = 0.96 to 3.10, p = 0.08) with higher NAE levels.

Risks of bias assessment

Overall, we rated the Wright study [28] as having a low risk of bias since it warranted a score of 7 out of a possible 9 on the Newcastle-Ottawa Scale [27]. We reduced the score from a full 9/9 since food frequency questionnaires are imperfect descriptions of exposure to nutrients [32], and due possible residual confounding. Additionally, since the study by Wright et al. [28] was a prospective observational study, this study had the strength of temporality, since the exposure (estimated urine acidity) preceded the outcome (bladder cancer risk). The study relied on estimated renal net acid excretion to determine urine acidity, which could potentially result in misclassification of individuals.

DISCUSSION

This systematic review, based on only one relevant observational study, did not find support for the acid-ash hypothesis which suggests that acid from the diet causes or contributes to cancer development [1–6]. The GRADE Working Group recommends that any associations from observational data are weak evidence unless the results show at least a two-fold risk with no concerns about confounding, or a five-fold risk with narrow confidence intervals when there are remaining concerns about bias [26]. The estimates of effect between the diet acid load and bladder cancer in this study were not statistically significant, and the estimates of effect were low relative to the GRADE guidelines.

The included Wright study [28] had strengths of having a low risk of bias on the Newcastle-Ottawa Scale [27] and temporality between the exposure (net acid excretion) and bladder cancer risk and controlled for several potentially cofounding variables. These study strengths provide support that the study reached accurate conclusions.

Our thorough literature search did not locate any studies of this acid/alkali hypothesis for any other forms of cancer, or cancer treatment. Additionally, our literature search failed to
locate any studies that evaluated whether alkaline water has a role in prevention or treatment of cancer. Thus, there is a lack of support for any advice to the public about the acid-ash hypothesis, the alkaline diet, and/or alkaline water and their relationships to cancer. By searching the published and unpublished literature for studies on this topic we decreased the risk of bias due to publication bias. It is a limitation of this study that we only located one observational study.

Some review articles suggest that alterations in acid-base homeostasis in the tumor microenvironment are common in the pathology of cancer [19,20] and that tumor interstitial fluid has a reduced buffering capacity compared with normal tissues, and along with high rates of production of metabolic end products, tumours may cause an acidic extracellular environment [20]. Further, cancer therapy may be influenced by pH. Some in vitro and animal studies have suggested that metabolic alkalosis may be useful in enhancing some cancer treatment regimens [33].

However, these *in vitro* examinations and animal studies of cancer cell behaviour are at the hypothesis generating phase and should not be extrapolated to human health. These cell culture studies do not address the questions or provide evidence regarding cancer etiology or treatment. Studies have demonstrated that alkaline supplements [23] or alkaline-promoting diets [16] can alter urine pH, however, they do not appreciably change overall systemic pH [16,23]. Three studies of acid load interventions have measured both urine and blood pH changes as a result of various interventions, including changes in food intake [16], ingesting a bicarbonate salt [23], or a phosphate salt [34]. In each case, the urine pH increased markedly, from 0.2 to 1.2 pH units, while blood pH did not changed minimally, by 0.01 [16,23] to 0.02 [34] pH units. The urine pH changes were 7.5 [34] to 177 [23] multiples of the blood pH changes. This comparison shows that kidneys are effective at excreting acid to maintain systemic pH balance, and that urine pH does not provide a measurement of systemic pH.
In spite of finding no human studies of alkaline water and cancer, our search did locate some studies of alkaline water, none of which supported the promotions that suggest alkaline water supports good health. We found outcomes from alkaline water included: In humans: inhibited gastric secretion [35], reduced gall bladder emptying [36], and toxic reactions [37]; In rat pups: cardiac necrosis [38] and growth restriction [39]. Therefore, the promotion of alkaline water as health promoting is not supported by evidence.

There may be a safety concern involving eating an “alkaline diet” and subsequently to increase urine pH of bladder cancer patients. For instance, Ciprofloxacin’s influence on human bladder cell lines suggests that the antiproliferative potential and antitumor effect of this drug may be superior at low urine pH [40]. Overall, safety considerations for increasing urinary pH in bladder cancer patients undergoing certain cancer therapy treatments needs to be evaluated before patients should undertake urine pH alterations.

Future study direction may focus on systematic reviews to examine the relationships between the alkaline diet and other health conditions. Several observational prospective studies have suggested a relationship between acid load and risk of type 2 diabetes [41,42] as well as hypertension [43,44]. However, in all 3 of these studies the estimates of effect are of low magnitude, below the threshold of the Relative Risk of 2, the minimum considered to indicate important associations [26]. Further, these studies had large sample sizes (1732 to 66,485); small significant p-values are likely in studies with large sample sizes even when there is no important effect [45]. Other prospective studies have suggested a lack association between the dietary acid load and both of these conditions: risks of type 2 diabetes [46] as well as hypertension [47]. Further, in observational studies, residual confounding is likely [26], many lifestyle variables are interrealted, and therefore it is not recommended to suggest that the findings from such studies represent independent causal relationships [48]. It must be
noted that although observational studies are important in generating hypotheses, intervention studies are required to investigate and confirm associations between diet and disease.

The alkaline diet emphasizes, to varying degrees, fresh fruits, vegetables, roots and tubers, and legumes with only a moderate protein intake. It is possible that some of these foods may have cancer protective effects, not through their acidity/alkaline promoting qualities but rather due to nutrient and non-nutritive compounds. A systematic review and meta-analysis of prospective studies show that a high intake of dietary fibre is associated with reduced risk of colorectal cancer [49]. A review and meta-analysis of epidemiological research on physical activity, diet and adiposity found that a prudent dietary pattern of high intakes of fruits, vegetables, whole grains, legumes, and fish appeared protective against breast cancer [50]. However, the alkaline diet promotes the exclusion of many foods, several of which contribute many beneficial nutrients and have health benefits.

5. Conclusions

Despite the promotion of the alkaline diet and alkaline water by the media and salespeople, there is almost no actual research to either support or disprove them. A systematic review of the literature revealed a lack of evidence of an association between a diet acid load or alkaline water for cancer risk and no studies alkaline treatment for cancer. Promotion of alkaline diet and alkaline water to the public for cancer prevention or treatment is not justified.

Contributorship statement: TRF conceptualized and designed the study, TH assisted in the conceptualization and design of the study and drafted the initial manuscript. Both authors conducted comprehensive literature searches, conducted the analysis and interpretation of data for the work, reviewed and revised the manuscript, approved the final manuscript as submitted, and agree to be accountable for all aspects of the work.

Competing interests: The authors have no competing interests.

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Data sharing statement: Dataset available from the Dryad repository, DOI: [doi:10.5061/dryad.35pj0]
References


For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml


Supplementary information file

Search strategy for PubMed search engine of MedLine

In an attempt to find all published literature on the topic, human studies relating to the acid-ash diet hypothesis and cancer were identified through computerized searches using, but not limited to, the following medical subject headings and textwords in Medline back to 1966 using the PubMed search engine:

1. acid OR alkaline OR acid-ash OR acid-base OR “acid-base equilibrium” OR “acid excretion” OR “net acid excretion” OR “potential renal acid load”
2. diet
3. cancer or neoplasms
4. Not: not “folic acid” not “ascorbic acid” not “fatty acid” not “amino acid”
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<th>#</th>
<th>Checklist item</th>
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<td>Title</td>
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<td>Identify the report as a systematic review, meta-analysis, or both.</td>
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<td>ABSTRACT</td>
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<td>Structured summary</td>
<td>2</td>
<td>Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.</td>
<td>2</td>
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<td>INTRODUCTION</td>
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<tr>
<td>Rationale</td>
<td>3</td>
<td>Describe the rationale for the review in the context of what is already known.</td>
<td>3</td>
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<tr>
<td>Objectives</td>
<td>4</td>
<td>Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).</td>
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<td>METHODS</td>
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<td>Protocol and registration</td>
<td>5</td>
<td>Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.</td>
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<td>Eligibility criteria</td>
<td>6</td>
<td>Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.</td>
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<tr>
<td>Information sources</td>
<td>7</td>
<td>Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.</td>
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<tr>
<td>Search</td>
<td>8</td>
<td>Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.</td>
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<tr>
<td>Study selection</td>
<td>9</td>
<td>State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).</td>
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</tr>
<tr>
<td>Data collection process</td>
<td>10</td>
<td>Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.</td>
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<tr>
<td>Data items</td>
<td>11</td>
<td>List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.</td>
<td>5</td>
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<tr>
<td>Risk of bias in individual studies</td>
<td>12</td>
<td>Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.</td>
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<tr>
<td>Summary measures</td>
<td>13</td>
<td>State the principal summary measures (e.g., risk ratio, difference in means).</td>
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<td>Synthesis of results</td>
<td>14</td>
<td>Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I² for each meta-analysis).</td>
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<td>Risk of bias across studies</td>
<td>15</td>
<td>Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).</td>
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<td>Additional analyses</td>
<td>16</td>
<td>Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.</td>
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<td>Study selection</td>
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<td>Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.</td>
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<td>Study characteristics</td>
<td>18</td>
<td>For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.</td>
<td>5,6</td>
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<td>Risk of bias within studies</td>
<td>19</td>
<td>Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).</td>
<td>6,7</td>
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<tr>
<td>Results of individual studies</td>
<td>20</td>
<td>For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.</td>
<td>6</td>
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<tr>
<td>Synthesis of results</td>
<td>21</td>
<td>Present results of each meta-analysis done, including confidence intervals and measures of consistency.</td>
<td>6</td>
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<td>Risk of bias across studies</td>
<td>22</td>
<td>Present results of any assessment of risk of bias across studies (see Item 15).</td>
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<tr>
<td>Additional analysis</td>
<td>23</td>
<td>Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).</td>
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<td>Summary of evidence</td>
<td>24</td>
<td>Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).</td>
<td>6,7</td>
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<tr>
<td>Limitations</td>
<td>25</td>
<td>Discuss limitations at study and outcome level (e.g., risk of bias), and at review level (e.g., incomplete retrieval of identified research, reporting bias).</td>
<td>8-11</td>
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<tr>
<td>Conclusions</td>
<td>26</td>
<td>Provide a general interpretation of the results in the context of other evidence, and implications for future research.</td>
<td>9</td>
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<tr>
<td>Funding</td>
<td>27</td>
<td>Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.</td>
<td>N/A</td>
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For more information, visit: [www.prisma-statement.org](http://www.prisma-statement.org)
Systematic review of the association between dietary acid load, alkaline water, and cancer

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Systematic review of the association between dietary acid load, alkaline water, and cancer

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Tel.: +1-403-680-8595

Keywords: dietary acid, alkaline diet, alkaline water, acid base equilibrium, cancer, neoplasm

Word count: 2595, excluding title page, abstract, references, and table
Abstract:

Objectives: To evaluate the evidence for a causal relationship between dietary acid/alkaline and alkaline water for the etiology and treatment of cancer.

Design: A systematic review was conducted on published and grey literature separately for randomized intervention and observational studies with either varying acid-base dietary intakes and/or alkaline water with any cancer outcome or for cancer treatment.


Results: 8278 citations were identified, 252 abstracts were reviewed; one study met the inclusion criteria and was included in this systematic review. No randomized trials were located. No studies were located that examined dietary acid or alkaline or alkaline water for cancer treatment. The included study was a cohort study with a low risk of bias. This study revealed no association between the diet acid load with bladder cancer (Odds ratio (OR) = 1.15:95% CI = 0.86 to 1.55, p = 0.36). No association was found even among long term smokers. (OR = 1.72:95% CI = 0.96 to 3.10, p = 0.08)

Conclusion: Despite the promotion of the alkaline diet and alkaline water by the media and salespeople, there is almost no actual research to either support or disprove these ideas. This systematic review of the literature revealed a lack of evidence for or against diet acid load and/or alkaline water for the initiation or treatment of cancer. Promotion of alkaline diet and alkaline water to the public for cancer prevention or treatment are not justified.
Article Summary

Strengths and Limitations of this study:

- A strength of this study is its broad search of both the published and unpublished literature for studies to include in this systematic review.

- It is a limitation of this study that we only located one observational study which fit the inclusion criteria.
Introduction

The general public is being encouraged by the lay press that to prevent cancer, they are persuaded to assess the acidity of their urine and/or saliva as an assessment of the acidity of their body, and then to modify their diets accordingly [1–7]. The alkaline diet, or acid-ash diet, is being promoted based on the claims that modern diets acidify the body [1–11] causing diseases including cancer, osteoporosis, and cardiovascular disease [1–12]. The alkaline diet is also promoted for conditions including diabetes and hypertension. Promoters of this diet claim that changing food choices to more “alkaline” selections prevents all of these conditions [1–9,11] and has the ability to treat cancer once it has developed [5,10,12,13] This diet is based on the concept that mineral components of foods make the body acidic, alkaline, or neutral [14].

The alkaline diet is designed to provide more alkaline ions after metabolism, based on the acid-ash hypothesis developed over 100 years ago [15]. The acid-ash hypothesis suggests that to achieve a more alkaline load, one must consume more fruit and vegetables with only a moderate intake of protein. While the marketing of this diet implies that the diet changes will raise systemic pH, a well-conducted randomized trial of these diet changes only altered systemic pH by 0.014 pH units, while the urine pH increased by 1.02 units [16]. This study reveals that diet changes can alter urine pH but does not change blood pH [16]. Further, the fact that the effect of phosphorus on calcium metabolism is opposite to that predicted by the hypothesis [17], raises questions about the validity of the hypothesis. Additionally, a review of the body of evidence regarding the acid-ash/alkaline hypothesis for bone health found that the hypothesis is not supported and there is no evidence that altering the diet acid load improves bone health [18].

The marketing of the alkaline diet promotes not only a diet, but also the sale of related supplements and water alkalinizer machines through almost every media medium, including websites, books, and videos [1–6,8]. In our experience, cancer patients are approached by
salespeople who are promoting water alkalinizers as a way to treat their cancer. Studies suggest that a substantial and growing number of patients use the internet to obtain health information [24,25], which may not be innocuous. Oncologists report that cancer patient internet use contributes to confusion and anxiety among cancer patients [25].

There is some evidence that some cancer cells and tumors grow well in an acidic environment in the laboratory [19,20]. While the alkaline diet is being promoted to correct the acid state that the modern diet creates, the American Institute of Cancer Research and the Canadian Cancer Society have stated that the body tightly regulates systemic pH and that food choices will only affect urine pH and not body acidity [21,22]. Studies show that while urine pH changes in response to diet changes, blood pH does not [16,23]. As acid/base forming potential of foods does alter urinary pH [16,23], cancers of the urinary tract may be an important focus in investigating claims of the alkaline diet to prevent and treat cancer.

As far as we are aware, no systematic review has been done to evaluate the evidence for an association between dietary acid and/or alkaline, or the effectiveness of alkaline water, for the etiology or treatment of cancer. The purpose of this systematic review is to conduct an extensive search of the published and unpublished literature to determine if evidence of a causal relationship exists between dietary acid or alkaline and the etiology of cancer and/or the treatment of this disease.

METHODS

Eligibility Criteria

Randomized interventions and observational human studies of acid-base intakes of diet, supplemental salts to change systemic pH (such as potassium bicarbonate or potassium citrate), and consumption of alkaline water, with cancer outcomes (both etiology and treatment) were sought. No language or publication date restrictions were imposed. Human
participants of all ages and backgrounds were considered. Studies with no original research (narrative reviews, editorials) and non-human studies were excluded from this review.

**Literature Search**

Two reviewers conducted independent literature searches, one with the assistance of a librarian (J.P.), in an attempt to find all human studies of the ash-acid diet hypothesis or an alkaline diet with any type of cancer as the outcome. Studies were identified through search text words and Medical subject headings: *diet, dietary, acid, acidic, alkaline, acid-base, acid-base equilibrium, acid-ash, “net acid excretion”, “potential renal acid load, water, cancer, neoplasm* (Supplemental file). For published literature, databases searched included Ovid Medline, Pubmed, Cochrane Register of Clinical Trials, CINAHL, and Embase up to April 2015. No limits were applied to searches and studies reported in all languages were considered. In an effort to include all available studies, reference lists for the located articles were reviewed. For grey literature, Current Controlled Trials, Canadian Cancer Trials, Google, and Google Scholar were manually searched up to April 2015.

Both authors examined the article titles for relevance to the topic and potential fit to the inclusion criteria independently, with the plan to use discussion and resolution by reaching consensus of any differences in assessments. When the title was not clear regarding the potential fit, both reviewers reviewed the abstracts. For abstracts which suggested relevance, the full text of the article was reviewed. Both researchers extracted data independently. There was no indication of unpublished data from the search, so authors were not contacted.

Data extracted included exposures to estimates of acid generated from diet, among humans, and with the outcome of any cancer.

Results with p-values < 0.05 were considered to be statistically significant, and Relative Risks > 2.0 with no plausible residual confounding were considered clinically
relevant [26]. We used the Newcastle-Ottawa Scale to assess the included study for risk of bias [27].

RESULTS

Description of studies

A total of 8278 citations were identified, 252 abstracts were reviewed for potential fit; only one study met the inclusion criteria [28], and was included in this systematic review. There were no disagreements about articles fit to the inclusion criteria between the reviewers. The literature search also located a systematic review which found no evidence for the alkaline diet [29] and two narrative reviews discussing the acid-ash/alkaline diet and cancer [30,31]. No relevant unpublished studies were found.

The systematic review, published in 2014, reported finding four articles on the alkaline diet and cancer in a google search but they did not report findings from these articles or their references [29].

The two narrative reviews did not include any human studies of an association between diet acid/alkaline and cancer. The narrative review by Robey et al concluded: “there are numerous systemic pathways affected by diet-induced acidosis that may be cancer promoting, but a causal role is poorly defined” [31]. The review by Lee et al suggested a post hoc analogy between the traditional Chinese medicine concepts of yin and yang with the acid/alkaline diet but did not cite any studies of the acid/alkaline diet and cancer [30].

The included study, by Wright et al was a prospective cohort study, nested within the alpha-Tocopherol, Beta-Carotene Cancer Prevention Study, a randomized controlled trial (Table 1) [28]. This study examined the diet acid load and the occurrence of bladder cancer. The exposure used in this study was an estimate of renal net acid excretion, based on dietary intakes and anthropometrics. No studies were found that examined any other cancer or neoplastic outcomes with dietary acid, alkalinity, alkaline water, or the use of an alkaline diet,
alkaline water, or change of the diet acid load for cancer treatment.

<table>
<thead>
<tr>
<th>Study</th>
<th>Population</th>
<th>Outcome</th>
<th>Results</th>
<th>Study design</th>
<th>Potential modifiers or confounders</th>
<th>Other risk of bias</th>
</tr>
</thead>
<tbody>
<tr>
<td>Wright, 2005</td>
<td>29,133 male residents of southwestern Finland aged 50-69 who smoked 5 or more years</td>
<td>Relative risk of bladder cancer.</td>
<td>The relative risk (RR) for bladder cancer was 1.15 (confidence interval = 0.86 to 1.55, p = 0.38), suggesting that urine pH is not a major risk factor for bladder cancer</td>
<td>Prospective cohort study.</td>
<td>Energy intake, age, number of cigarettes smoked daily, number of years of smoking, alpha tocopherol and beta carotene supplementation, BMI, total fluid intake, education level, place of residence, pack years of smoking, smoking inhalation, smoking cessation, calcium, magnesium, and/or potassium supplements. Effect modification by smoking duration, smoking dose, total fluid intake, BMI and intervention group was evaluated in stratified analysis.</td>
<td>Used renal NAE based on a validated formula based on anthropometric information to estimate true urine pH</td>
</tr>
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</table>

Table 1: Included study

Wright et al. [28] examined the relationship between diet-estimated renal net acid excretion (NAE) using a food frequency questionnaire (and measured height and weight for the estimation of urinary organic acid excretion) with the risk of bladder cancer in a large cohort of 27,096 male smokers [28]. The Relative Risk estimate for bladder cancer was 1.15 (CI = 0.86 to 1.55, p= 0.38) for individuals in the most acidic versus the least acidic NAE quintile as assessed in a multivariate proportional hazards model, a not statistically significant relationship. These researchers also tested whether acidic urine was associated with an increased risk of bladder cancer in a subset of long-term smokers. Among men who smoked for more than 45 years there was a non-significant adjusted Relative Risk of bladder cancer of 1.72 (CI = 0.96 to 3.10, p = 0.08) with higher NAE levels.

Risks of bias assessment
Overall, we rated the Wright study [28] as having a low risk of bias since it warranted a score of 7 out of a possible 9 on the Newcastle-Ottawa Scale [27]. We reduced the score from a full 9/9 since food frequency questionnaires are imperfect descriptions of exposure to nutrients [32], and due possible residual confounding. Additionally, since the study by Wright et al. [28] was a prospective observational study, this study had the strength of temporality, since the exposure (estimated urine acidity) preceded the outcome (bladder cancer risk). The study relied on estimated renal net acid excretion to determine urine acidity, which could potentially result in misclassification of individuals.

DISCUSSION

This systematic review, based on only one relevant observational study, did not find support for the acid-ash hypothesis which suggests that acid from the diet causes or contributes to cancer development [1–6]. The GRADE Working Group recommends that any associations from observational data are weak evidence unless the results show at least a two-fold risk with no concerns about confounding, or a five-fold risk with narrow confidence intervals when there are remaining concerns about bias [26]. The estimates of effect between the diet acid load and bladder cancer in this study were not statistically significant, and the estimates of effect were low relative to the GRADE guidelines.

The included Wright study [28] had strengths of having a low risk of bias on the Newcastle-Ottawa Scale [27] and temporality between the exposure (net acid excretion) and bladder cancer risk and controlled for several potentially cofounding variables. These study strengths provide support that the study reached accurate conclusions.

Our thorough literature search did not locate any studies of this acid/alkali hypothesis for any other forms of cancer, or cancer treatment. Additionally, our literature search failed to locate any studies that evaluated whether alkaline water has a role in prevention or treatment of cancer. Thus, there is a lack of support for any advice to the public about the acid-ash
hypothesis, the alkaline diet, and/or alkaline water and their relationships to cancer. By searching the published and unpublished literature for studies on this topic we decreased the risk of bias due to publication bias. It is a limitation of this study that we only located one observational study.

Some review articles suggest that alterations in acid-base homeostasis in the tumor microenvironment are common in the pathology of cancer [19,20] and that tumor interstitial fluid has a reduced buffering capacity compared with normal tissues, and along with high rates of production of metabolic end products, tumours may cause an acidic extracellular environment [20]. Further, cancer therapy may be influenced by pH. Some in vitro and animal studies have suggested that metabolic alkalosis may be useful in enhancing some cancer treatment regimens [33].

However, these in vitro examinations and animal studies of cancer cell behaviour are at the hypothesis generating phase and should not be extrapolated to human health. These cell culture studies do not address the questions or provide evidence regarding cancer etiology or treatment. Studies have demonstrated that alkaline supplements [23] or alkaline-promoting diets [16] can alter urine pH, however, they do not appreciably change overall systemic pH [16,23]. Three studies of acid load interventions have measured both urine and blood pH changes as a result of various interventions, including changes in food intake [16], ingesting a bicarbonate salt [23], or a phosphate salt [34]. In each case, the urine pH increased markedly, from 0.2 to 1.2 pH units, while blood pH did not changed minimally, by 0.01 [16,23] to 0.02 [34] pH units. The urine pH changes were 7.5 [34] to 177 [23] multiples of the blood pH changes. This comparison shows that kidneys are effective at excreting acid to maintain systemic pH balance, and that urine pH does not provide a measurement of systemic pH.

In spite of finding no human studies of alkaline water and cancer, our search did locate some studies of alkaline water, none of which supported the promotions that suggest
alkaline water supports good health. We found outcomes from alkaline water included: In humans: inhibited gastric secretion [35], reduced gall bladder emptying [36], and toxic reactions [37]; In rat pups: cardiac necrosis [38] and growth restriction [39]. Therefore, the promotion of alkaline water as health promoting is not supported by evidence.

There may be a safety concern involving eating an “alkaline diet” and subsequently to increase urine pH of bladder cancer patients. For instance, Ciprofloxacin’s influence on human bladder cell lines suggests that the antiproliferative potential and antitumor effect of this drug may be superior at low urine pH [40]. Overall, safety considerations for increasing urinary pH in bladder cancer patients undergoing certain cancer therapy treatments needs to be evaluated before patients should undertake urine pH alterations.

Future study direction may focus on systematic reviews to examine the relationships between the alkaline diet and other health conditions. Several observational prospective studies have suggested a relationship between acid load and risk of type 2 diabetes [41,42] as well as hypertension [43,44]. However, in all 3 of these studies the estimates of effect are of low magnitude, below the threshold of the Relative Risk of 2, the minimum considered to indicate important associations [26]. Further, these studies had large sample sizes (1732 to 66,485); small significant p-values are likely in studies with large sample sizes even when there is no important effect [45]. Other prospective studies have suggested a lack association between the dietary acid load and both of these conditions: risks of type 2 diabetes [46] as well as hypertension [47]. Further, in observational studies, residual confounding is likely [26], many lifestyle variables are interrelated, and therefore it is not recommended to suggest that the findings from such studies represent independent causal relationships [48]. It must be noted that although observational studies are important in generating hypotheses, intervention studies are required to investigate and confirm associations between diet and disease.
The alkaline diet emphasizes, to varying degrees, fresh fruits, vegetables, roots and tubers, and legumes with only a moderate protein intake. It is possible that some of these foods may have cancer protective effects, not through their acidity/alkaline promoting qualities but rather due to nutrient and non-nutritive compounds. A systematic review and meta-analysis of prospective studies show that a high intake of dietary fibre is associated with reduced risk of colorectal cancer [49]. A review and meta-analysis of epidemiological research on physical activity, diet and adiposity found that a prudent dietary pattern of high intakes of fruits, vegetables, whole grains, legumes, and fish appeared protective against breast cancer [50]. However, the alkaline diet promotes the exclusion of many foods, several of which contribute many beneficial nutrients and have health benefits.

5. Conclusions

Despite the promotion of the alkaline diet and alkaline water by the media and salespeople, there is almost no actual research to either support or disprove them. A systematic review of the literature revealed a lack of evidence of an association between a diet acid load or alkaline water for cancer risk and no studies alkaline treatment for cancer. Promotion of alkaline diet and alkaline water to the public for cancer prevention or treatment is not justified.

Contributorship statement: TRF conceptualized and designed the study, TH assisted in the conceptualization and design of the study and drafted the initial manuscript. Both authors conducted comprehensive literature searches, conducted the analysis and interpretation of data for the work, reviewed and revised the manuscript, approved the final manuscript as submitted, and agree to be accountable for all aspects of the work.

Competing interests: The authors have no competing interests.

Funding statement: This research received no specific grant from any funding agency in the public, commercial or not-for-profit sectors

Data sharing statement: Dataset available from the Dryad repository, DOI: [doi:10.5061/dryad.35pj0]
References


Supplementary information file

Search strategy for PubMed search engine of MedLine

In an attempt to find all published literature on the topic, human studies relating to the acid-ash diet hypothesis and cancer were identified through computerized searches using, but not limited to, the following medical subject headings and textwords in Medline back to 1966 using the PubMed search engine:

1. acid OR alkaline OR acid-ash OR acid-base OR “acid-base equilibrium” OR “acid excretion” OR “net acid excretion” OR “potential renal acid load”
2. diet
3. cancer or neoplasms
4. Not: not “folic acid” not “ascorbic acid” not “fatty acid” not “amino acid”
# PRISMA 2009 Checklist

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<th>Section/topic</th>
<th>#</th>
<th>Checklist item</th>
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<td><strong>TITLE</strong></td>
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<tr>
<td>Title</td>
<td>1</td>
<td>Identify the report as a systematic review, meta-analysis, or both.</td>
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<td><strong>ABSTRACT</strong></td>
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<td>Structured summary</td>
<td>2</td>
<td>Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.</td>
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<tr>
<td><strong>INTRODUCTION</strong></td>
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<td>Rationale</td>
<td>3</td>
<td>Describe the rationale for the review in the context of what is already known.</td>
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<td>Objectives</td>
<td>4</td>
<td>Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).</td>
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<td><strong>METHODS</strong></td>
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<td>Protocol and registration</td>
<td>5</td>
<td>Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.</td>
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<td>Eligibility criteria</td>
<td>6</td>
<td>Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.</td>
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<td>Information sources</td>
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<td>Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.</td>
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<td>Search</td>
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<td>Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.</td>
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<td>Study selection</td>
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<td>State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).</td>
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<td>Data collection process</td>
<td>10</td>
<td>Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.</td>
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<tr>
<td>Data items</td>
<td>11</td>
<td>List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.</td>
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<tr>
<td>Risk of bias in individual studies</td>
<td>12</td>
<td>Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.</td>
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<td>Summary measures</td>
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<td>State the principal summary measures (e.g., risk ratio, difference in means).</td>
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<td>Synthesis of results</td>
<td>14</td>
<td>Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I², for each meta-analysis).</td>
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<td>Risk of bias across studies</td>
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<td>Specify any assessment of risk of bias that may affect the cumulative evidence</td>
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<td>(e.g., publication bias, selective reporting within studies).</td>
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<td>Additional analyses</td>
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<td>Describe methods of additional analyses (e.g., sensitivity or subgroup</td>
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<td>analyses, meta-regression), if done, indicating which were pre-specified.</td>
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<td>RESULTS</td>
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<td>Study selection</td>
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<td>Give numbers of studies screened, assessed for eligibility, and included in</td>
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<td>the review, with reasons for exclusions at each stage, ideally with a flow</td>
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<td>diagram.</td>
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<td>Study characteristics</td>
<td>18</td>
<td>For each study, present characteristics for which data were extracted</td>
<td>5, 6</td>
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<td>(e.g., study size, PICOS, follow-up period) and provide the citations.</td>
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<td>Risk of bias within studies</td>
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<td>Present data on risk of bias of each study and, if available, any outcome</td>
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<td>level assessment (see item 12).</td>
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<td>Results of individual studies</td>
<td>20</td>
<td>For all outcomes considered (benefits or harms), present, for each study:</td>
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<td>(a) simple summary data for each intervention group (b) effect estimates and</td>
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<td>confidence intervals, ideally with a forest plot.</td>
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<td>Synthesis of results</td>
<td>21</td>
<td>Present results of each meta-analysis done, including confidence intervals</td>
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<td>and measures of consistency.</td>
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<td>Risk of bias across studies</td>
<td>22</td>
<td>Present results of any assessment of risk of bias across studies (see Item</td>
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<td>Additional analysis</td>
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<td>DISCUSSION</td>
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<td>Summary of evidence</td>
<td>24</td>
<td>Summarize the main findings including the strength of evidence for each main</td>
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<td>outcome; consider their relevance to key groups (e.g., healthcare providers,</td>
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<td>users, and policy makers).</td>
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<td>Limitations</td>
<td>25</td>
<td>Discuss limitations at study and outcome level (e.g., risk of bias), and at</td>
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<td>review level (e.g., incomplete retrieval of identified research, reporting</td>
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<td>bias).</td>
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<tr>
<td>Conclusions</td>
<td>26</td>
<td>Provide a general interpretation of the results in the context of other</td>
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<td>evidence, and implications for future research.</td>
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<td>Funding</td>
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<td>Describe sources of funding for the systematic review and other support</td>
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<td>(e.g., supply of data); role of funders for the systematic review.</td>
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Systematic review of the association between dietary acid load, alkaline water and cancer

Tanis R Fenton and Tian Huang

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