REVIEW ARTICLES

Searching one or two databases was insufficient for meta-analysis of observational studies

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Abstract

Objective: To address methodologic issues in searching for observational studies by presenting database search methods and results.

Study Design and Setting: Results of two literature searches for publications reporting on observational studies of alcohol consumption and the risk of breast cancer and large bowel cancer were compared, to evaluate the sensitivity of various bibliographic databases and search strategies, including hand-searching reviews and meta-analyses.

Results: The target sensitivity of 90\% of publications in the breast cancer search was achieved by starting with Medline, then adding Biosis, Embase, and SCI EXPANDED–SSCI, which provided a total of 72 (91\%) of the 79 relevant publications. To reach a similar 89\% sensitivity for large bowel cancer, at least Biosis, Dissertation Abstracts Online, Embase, ETOH, and Medline had to be searched, with the addition of hand search of reviews and meta-analyses.

Conclusion: Limiting a search to one or two databases when conducting meta-analyses of observational studies will not provide a thorough summary of the existing literature. The findings support recommendations to implement a comprehensive search of electronic databases and the reference lists of recent review articles and meta-analyses. © 2005 Elsevier Inc. All rights reserved.

Keywords: Meta-analysis; Bibliographic databases; Epidemiologic studies; Sensitivity; Cancer; Alcohol drinking

1. Introduction

In 1904, Karl Pearson performed the first reported meta-analysis. He derived a quantitative summary estimate for the efficacy of a vaccine against enteric fever \cite{1}. One hundred years later, researchers continue to wrestle with methodologic issues in the conduct and interpretation of meta-analyses and their application in public health. Although the general approach to the conduct of meta-analysis has been extensively described \cite{2}, most work addressing key issues has focused on statistical methods rather than data collection. Of those investigators who have examined methodologic issues pertaining to data collection, most have relied solely on Medline and have limited consideration to randomized control trials \cite{2}. Recently, however, more meta-analyses have drawn on observational data \cite{3}. In 2000, Stroup et al. \cite{4} published guidelines for the reporting of meta-analyses of observational studies (although they did not specifically address searching and data collection methods). To date, there still are no standard guidelines for creating a search strategy, defining exclusion–inclusion criteria, determining which electronic databases to search, or reporting the results of a literature search. With the present study, we address the issue of searching for observational studies by considering database search methods and results. We compared the results of two literature searches for publications reporting on observational studies of alcohol consumption and the risk of breast cancer and large bowel cancer, with the particular aim of exploring the sensitivity of various bibliographic databases and search strategies, including hand searching of reviews and meta-analyses.

2. Methods

Following standard practices for conducting meta-analysis \cite{5}, we identified publications on the relationship between alcohol consumption and breast and large bowel cancer, respectively, by searching several electronic databases and checking reference lists of meta-analyses and reviews.
As recommended by Smith et al. [6], we consulted with reference librarians at Countway Library, Harvard’s medical library, and investigators at the U.S. National Institute of Alcohol Abuse and Alcoholism (NIAAA) regarding possible databases to search. We chose databases based on their access to biomedical journal articles and research reports. For both meta-analyses, we searched nine databases. Details about each database are summarized in Table 1.

In addition to completing courses on the use of multiple electronic databases for literature searching, we discussed search strategies with reference and education services librarians at the Countway Library. As advised, we experimented with different word combinations for alcohol consumption (e.g., including liquor, wine, beer) in each database to determine standard alcohol-related subject headings and text words for the literature search phase of each meta-analysis. We intended to use a strategy that would be exhaustive and that would have high sensitivity. Each database used different alcohol-related search terms. Some databases mapped words in a tree structure with standardized subject headings; others relied solely on text words. To decide which alcohol-related search terms to use, we entered a variety of alcohol-related words, one at a time, into the search box of each database. Each search was downloaded separately into EndNote libraries (Thomson ResearchSoft, Carlsbad, CA, USA). We used the search terms that were the most inclusive.

For example, in Biosis we found 550 publications in a search using the text words alcohol AND breast cancer. We compared the results of this search to a search using the text words liquor AND breast cancer, which found only eight publications. Because all eight had duplicates in the previous search, we did not include the word liquor; in Biosis, the term alcohol would include publications reporting on liquor as well. We repeated this procedure for numerous other alcohol-related search terms, including wine and beer. If a search term did not yield any unique or relevant publications, or if it did not yield any publications at all, we did not use the word as an alcohol-related search term (see Table 2).

Prior to running each literature search, we formulated questions about how alcohol intake influences both breast and large bowel cancer [5,7]. Each question included the exposure, alcohol consumption, and the outcome of interest (breast or large bowel cancer). For example, the question about the relationship between alcohol consumption and breast cancer was, “What is the relationship between the average daily amount of alcohol consumption and the risk of breast cancer?”

After breaking down the research question into searchable terms, we searched each database using the alcohol-related subject headings and text words specified in Table 2, combined with the search terms breast cancer or breast neoplasms. For example, the search in Medline was as follows:

1. exp alcoholic beverages/ OR alcoholic intoxication/ OR alcohol drinking/ OR alcoholism/ OR ethanol/ OR alcohol consumption.tw
2. breast neoplasms/
3. 1 AND 2
4. limit 3 to human

Table 1

<table>
<thead>
<tr>
<th>Database (full name), URL</th>
<th>Types of sources</th>
<th>Size, no. of records</th>
<th>Time period</th>
</tr>
</thead>
<tbody>
<tr>
<td>Biosis (Biological Abstracts), <a href="http://www.biosis.org/">http://www.biosis.org/</a></td>
<td>Journal articles, meeting and conference reports, books, patents</td>
<td>&gt;13 million</td>
<td>1969–date</td>
</tr>
<tr>
<td>Dissertation Abstracts Online, <a href="http://www.il.proquest.com/hp/Products/Dissertations.html">http://www.il.proquest.com/hp/Products/Dissertations.html</a></td>
<td>Dissertations</td>
<td>&gt;1.6 million</td>
<td>1861–date</td>
</tr>
<tr>
<td>ETOH (NIAAA Alcohol and Alcohol Problems Science Database), <a href="http://etho.niaaa.nih.gov/">http://etho.niaaa.nih.gov/</a></td>
<td>Journal articles, books, dissertation abstracts, conference papers and proceedings, reports and studies, and chapters in edited works</td>
<td>&gt;110,000</td>
<td>1899–2003</td>
</tr>
<tr>
<td>Pre-Medline (current citations before indexing is completed; “in process” tag), <a href="http://www.ncbi.nlm.nih.gov/entrez/query.fcgi/">http://www.ncbi.nlm.nih.gov/entrez/query.fcgi/</a></td>
<td>Journal articles</td>
<td>&gt;180,000</td>
<td>Most recent several days</td>
</tr>
<tr>
<td>SCI EXPANDED–SSCI (Science Citation Index and Social Sciences Citation Index), <a href="http://www.isinet.com/cgi-bin/jmlist/">http://www.isinet.com/cgi-bin/jmlist/</a> [options.cgi]?PC=D</td>
<td>Journal articles</td>
<td>&gt;30 million</td>
<td>1945–date</td>
</tr>
</tbody>
</table>

a PubMed and Ovid are two different interfaces that can search Medline exclusively—either interface may be used.
b As references prior to 1966 are added to the database, they are tagged “OLDMEDLINE for pre-1966” unless an abstract is available.
c If a reference from NIH CRISP seemed relevant, we contacted the principal investigator to see if there were any preliminary results.
Table 2

<table>
<thead>
<tr>
<th>Database</th>
<th>Alcohol-related search terms</th>
<th>Breast cancer search terms</th>
<th>Large-bowel cancer search terms</th>
</tr>
</thead>
<tbody>
<tr>
<td>Biosis</td>
<td>alcohol OR alcoholic beverage OR alcoholism OR wine; limits: human</td>
<td>Breast cancer</td>
<td>Colon cancer, colorectal cancer, large bowel cancer, rectal cancer</td>
</tr>
<tr>
<td>Dissertation Abstracts Online</td>
<td>alcohol OR alcoholic beverages</td>
<td>Breast cancer</td>
<td>Colon cancer, colorectal cancer, rectal cancer</td>
</tr>
<tr>
<td>Embase</td>
<td>alcohol OR alcohol abuse OR alcoholic beverage# OR alcohol consumption OR alcohol intoxication OR alcoholism; limits: human</td>
<td>Breast cancer</td>
<td>Colon-cancer, rectum-cancer</td>
</tr>
<tr>
<td>ETOH</td>
<td>Type the name of the health condition into the “all fields” search box</td>
<td>Breast cancer</td>
<td>Colon cancer, colorectal cancer, large bowel cancer, rectal cancer</td>
</tr>
<tr>
<td>Medline</td>
<td>exp alcoholic beverages/ OR alcohol consumption.tw OR alcohol drinking/ OR alcoholic intoxication/ OR alcoholism/ OR ethanol/; limits: human</td>
<td>Breast neoplasms</td>
<td>Colorectal neoplasms</td>
</tr>
<tr>
<td>NIH CRISP</td>
<td>$alcohol</td>
<td>Breast cancer</td>
<td>Colon cancer, colorectal cancer</td>
</tr>
<tr>
<td>NTIS</td>
<td>alcohol</td>
<td>Breast cancer OR breast neoplasms</td>
<td>Colon cancer, colorectal cancer, large bowel cancer, rectal cancer</td>
</tr>
<tr>
<td>Pre-Medline</td>
<td>alcohol OR alcoholism OR ethanol</td>
<td>Breast cancer</td>
<td>Colon cancer, colorectal cancer, large bowel cancer, rectal cancer</td>
</tr>
<tr>
<td>SCI EXPANDED–SSCI</td>
<td>TS = (alcohol OR alcohol* beverage* OR alcohol consumption OR alcohol drinking OR alcoholism OR beverage consumption)</td>
<td>Breast cancer</td>
<td>Colon cancer, colorectal cancer, large bowel cancer, rectal cancer</td>
</tr>
</tbody>
</table>

Our choice of search terms can be further explained, as follows:

“Exp” means explode alcoholic beverages to include beer, wine, and absinthe in the search. (Note that hard liquor and liquor are not medical subject headings in Medline. When entered as text words, neither yielded additional publications.)

Include ethanol, because some countries use the term ethanol for the beverage alcohol.

Do not explode ethanol, to avoid yielding additional publications related to the effect of the metabolism of alcohol on the health condition.

No additional medical subject headings lie below alcoholic intoxication, alcohol drinking, or alcoholism in Medline’s tree structure.

Use alcohol consumption as a text word to account for publications not catalogued under the other alcohol-related subject headings.

Breast neoplasms is the subject heading used for breast cancer in Medline.

Limit the search to “human,” to avoid yielding publications on animal and alcohol experimentation.

We did not specify the type of epidemiologic study (e.g., case-control, cohort) or the type of effect estimate (e.g., relative risk, odds ratio), because a more sensitive search is generated without using them as search terms.

Because electronic databases are both dynamic and prone to human error, there is always the possibility that further searching will identify potentially relevant publications. To complete the project in a timely manner, we set cutoff dates to regulate the time frame within which publications would be accepted into each analysis. Publications with dates that fell on or before the last day of the electronic search were considered for the meta-analyses. We conducted the breast cancer search on September 9, 2003 and the large bowel cancer search on October 28, 2003.

We limited our search to modern studies (defined as those dated from January 1, 1950, onward), because studies conducted prior to 1950 differ in historical context and research paradigms [8,9].

Each electronic database is a different size, searches different types of sources, and searches a different time period. The databases are updated daily (Medline, Pre-Medline, Embase, NTIS), weekly (SCI EXPANDED–SSCI, NIH CRISP), bimonthly (Biosis), or monthly (ETOH, Dissertation Abstracts Online).

Two of the authors (A.R.L. and R.E.B.) independently appraised each downloaded reference first according to the title and then the abstract. As detailed in the Appendix, we assessed the essential characteristics, publication period, language, and type of publication, and evaluated each paper for relevancy to each meta-analysis. We included study types such as cohort and case-control studies if they directly examined the relationship of alcohol consumption to the specified health condition [7]. We included publications if they described the results of research performed among any type of adult population (e.g., nonalcoholics or alcoholics), but we excluded studies if they did not provide usable data. We excluded intervention studies, ecological studies, individual case reports, methodological publications, meta-analyses, reviews, editorials, and news items, as none of these provide usable data.

We excluded publications if they did not address human alcohol consumption and breast or large bowel cancer.
Among those excluded were publications that addressed
treatment or management, pathophysiology or pharmacol-
ogy, or the natural history, prognosis, or complications of
the cancer. These excluded publications did not address the
specific aims of the meta-analysis.

After the inclusion–exclusion criteria were applied inde-
pendently to the titles, duplicates were identified. Whichever
reference had the most useful data for abstract review or full
publication retrieval was placed into a library for the next
round of the literature search. The other duplicates were
stored in a separate library and were used later for calculating
the sensitivity of each database (see Table 3). There were
no inconsistencies in determining which records were dupli-
cates. We then reviewed bibliographies of pertinent review
papers and recent meta-analyses to ensure that no potentially
relevant publications had been overlooked. In addition, an
advisory committee expert reviewed publication references
deemed potentially relevant to approve or modify the final
list.

We repeated the above search strategy for large bowel
cancer. All search terms are specified in Table 2.

The analysis is based on the final set of eligible studies
as the total number of publications. We estimated the sensi-
tivity of each database against the total pool of relevant
publications, defining sensitivity as the number of relevant
publications found in each database divided by total number of
relevant publications found across all the data-
bases. We also calculated exact 95% binomial confidence
intervals (CI) using Stata software, version 8.2 (StataCorp,
College Station, TX, USA). We did not focus on specificity,
because our primary focus was on the comprehensiveness
of our search strategy.

3. Results

We identified a total of 79 relevant reports on alcohol
consumption and breast cancer published up to September
9, 2003. The flow chart in Fig. 1 summarizes the steps in
the search, with exclusion criteria applied and duplicate
reports from a single study eliminated. The sensitivity of
the search strategy across the databases varied substantially
from a high of 82% (95% CI 72%–90%) for Medline, to
0% for Dissertation Abstracts Online and NTIS. The most
sensitive databases for this topic (Medline, SCI-EXPANDED–
SSCI, Embase, and Biosis) all performed above 75%, with
little variability among them either in terms of the estimates
of sensitivity or the individual publications identified (see
Table 3).

Of the 79 publications identified through searching data-
bases and reference lists of meta-analyses and reviews, 68
appeared in more than one database. In nine cases, a publica-
tion was found in only one of the databases. Biosis had three
of these nine uniquely-identified studies, SCI-EXPANDED–
SSCI had two, Pre-Medline had one, Embase had two,
and Medline had one. Two additional publications were
identified by searching reference lists of published meta-
analyses and reviews [10,11]. Biosis had access to both of
these publications, but our search did not yield them.

Following the same approach, we identified 56 large
The sensitivity of the leading databases ranged from 57%
(95% CI 43%–70%) for SCI-EXPANDED–SSCI to 66%
(95% CI 52%–78%) for Medline. Pre-Medline, NTIS, and
NIH CRISP each contributed zero publications. Of the 56
publications identified, 12 (∼21%) were found in only one
of the databases. Three additional publications were identi-
fied by searching reference lists of published meta-analyses
and reviews [12–14].

We then sought to determine how many databases should
be searched to achieve a target sensitivity of 90% of relevant
publications. For breast cancer, starting with Medline and
adding Biosis, Embase, and SCI EXPANDED–SSCI
yielded 72 of the 79 relevant publications (91%). For large

<table>
<thead>
<tr>
<th>Database</th>
<th>Breast cancer</th>
<th></th>
<th>Large bowel cancer</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Found, no.</td>
<td>Relevant, no.</td>
<td>Sensitivity, %</td>
<td>95% CI</td>
</tr>
<tr>
<td>Biosis</td>
<td>642</td>
<td>62</td>
<td>78</td>
<td>68–87</td>
</tr>
<tr>
<td>Dissertation Abstracts</td>
<td>44</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Pre-Medline</td>
<td>21</td>
<td>2</td>
<td>3</td>
<td>0–9</td>
</tr>
<tr>
<td>Sci-Expanded–SSCI</td>
<td>1,032</td>
<td>64</td>
<td>81</td>
<td>71–89</td>
</tr>
<tr>
<td>Total from all databases</td>
<td>3,607</td>
<td>79</td>
<td>81</td>
<td>71–89</td>
</tr>
</tbody>
</table>

Identified according to database searched, number of relevant publications found, sensitivity of the database search strategy, and the number of unique publications identified in each database. Sensitivity is defined as the number of relevant publications found in each database divided by total number of relevant publications found.
bowl cancer, however, these four databases combined to give only 42 of the 56 relevant publications (75%). To reach 89% sensitivity, we had to search at least Biosis, Dissertation Abstracts Online, Embase, ETOH, and Medline, with the addition of a hand search of reviews and meta-analyses.

Medline alone would have found 82% of the relevant breast cancer publications, but only 65% of the relevant large bowel cancer publications.

4. Discussion

Through the application of standard and explicit search strategies for observational studies, we saw that several common databases performed at only 60% to 80% sensitivity for the identification of research reports relating alcohol to either breast or large bowel cancer. Because we do not have a complete ideal list of the publications, the sensitivity estimates are likely biased upward; the numbers are inflated because we took the number of relevant identified publications as the total. In addition, sensitivity for each database was higher for breast cancer than for large bowel cancer.

Importantly, Biosis, Embase, Dissertation Abstracts Online, ETOH, Medline, Pre-Medline, and SCI-EXPANDED–SSCI contributed unique reports to the total pool of relevant publications. Biosis, Embase, ETOH, Medline and SCI-EXPANDED–SSCI consistently proved to have high sensitivities. NTIS and NIH CRISP neither contributed unique reports, nor did they contribute any relevant publications to the final pool, proving to have low value.

We recognize that there is a cost to searching multiple databases. Not only does it take time to search more than one database, but also access to some can be expensive.

We gained access to Embase through Dialog DataStar, an online provider of information services. The cost is not low; each reference costs about $2.50 to download, and there are additional separate time-sensitive fees for accessing DataStar and Embase.

There are several limitations to our empirical evidence on the performance of searching for observational studies. Our results were obtained by searching each electronic database with specific search terms determined with the help of medical librarians. The sensitivity of each database was therefore based not on the publications to which each database had access, but rather on what was found in each search given the chosen search terms. This applies to the unique publications found in the databases as well.

The publications found in only one database were not unique with regard to access by the other databases to each reference, but rather to our particular search strategy. For example, in the breast cancer search, Medline and Biosis had access to the two publications found uniquely in SCI-Expanded–SSCI [15,16]. Given our choice of search terms, however, as well as keyword coding at the database level, only SCI-Expanded was able to find the publications. Medline could not locate them in the search on breast cancer and alcohol consumption because alcohol was not coded as a subject heading. Rather, subject headings included smoking, life-style, risk factors, and diet. Had we included these exposure-related terms in our search in addition to the alcohol-related terms, the pool of potentially eligible references would have increased from 537 to >9,000—a very large number of references to pick through for one database. Other examples of miscoding at the database level included failing to code breast cancer as a keyword or failing to code any keywords at all. In the final reference lists of breast and large bowel cancer, a total of 28 SCI EXPANDED–SSCI, 24 Embase, and 27 ETOH citations did not include keywords.
Dissertation Abstracts Online does not provide any keywords. In Pre-Medline, the frequent absence of keywords is a consequence of the competing and primary goal of providing rapid access to records, prior to indexing. The publications found during the cross-check of the reference lists of the reviews and meta-analyses were not accessible solely through this method of searching. The titles either originally appeared in one or more of the databases but were prematurely discarded because of seemingly irrelevant titles, or the databases had access to the publications but did not yield them because of our choice of search terms or the miscoding of keywords. Had these publications been found during the electronic database search phase rather than during the cross-check of reference lists of recent meta-analyses and reviews, the sensitivity of certain databases would have increased.

Publication bias may play a significant role in determining the sensitivity of each electronic database. In the alcohol and large bowel cancer search, three publications were found in Dissertation Abstracts Online. Only one of the three dissertations reported a statistically significant association between alcohol consumption and large bowel cancer. Often, only statistically significant results are published, as confirmed by the majority of these unpublished dissertations [17]. We rechecked each database and confirmed that only one of these dissertations was published elsewhere [18]. Although the dissertation had significant alcohol and large bowel results, the published report did not include results on alcohol and thus did not appear in our final list of relevant large bowel publications [19]. These three dissertations had a substantial impact on overall sensitivity. Three out of 56 publications constitutes an approximate 5% decrease in the potential sensitivity of all other databases. For example, SCI EXPANDED–SSCI’s sensitivity would have improved from 57% to >60% had these three publications not been found in Dissertation Abstracts Online.

Because our findings were based on observational studies of alcohol and cancer and were limited to two sites, the classification of other exposures may be more or less precise in the keywords, leading to a broader or narrower range of sensitivity. Outcomes of interest in observational studies may also vary in their precision for classification, contributing to potentially greater variability if this approach is applied in other settings.

In summary, this empirical evidence provides strong support for using a broad search strategy when identifying original publications for inclusion in a meta-analysis or systematic review of observational studies. Our results suggest that limiting a search to a single database will not provide a thorough summary of the existing literature, and support recommendations made by researchers of meta-analyses on randomized clinical trials to implement a comprehensive search of both electronic databases and the references in recent review articles and meta-analyses [20–22]. Based on our case studies, searches for observational studies limited to one or two databases—which appears to be the current standard practice [23–43]—will retrieve only 60%–80% of the pertinent publications. Further research is required to demonstrate the appropriate use of databases for searches in other topic areas and with a range of health conditions beyond cancer. We recommend that researchers report methods for constructing the search strategy and choosing search terms in the literature search phase of meta-analyses of observational studies. Standard reporting of search strategies will help guide researchers toward greater efficiency and accuracy in data collection.

Acknowledgments

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Appendix

Criteria for identifying potentially relevant publications

Essential characteristic: The publication must address alcohol consumption and the risk of breast or large bowel cancer in humans.

Publication period [8,9]: Beginning date, 1950; end date, the last day of the electronic search for each outcome.

Languages [7,8]: The languages of publications included in the meta-analyses are languages that allow access to research conducted in countries that have populations with similar risk factor and disease distribution as the U.S., or that have substantial scientific activity on alcohol-related conditions. To access research activity in places that fall into 1 or both of these categories, we searched for publications in languages including, but not limited to, English, Spanish, Portuguese, Italian, French, Hebrew, German, Japanese, and Chinese. Otherwise-eligible publications from any of the countries of the former Soviet Union and Japan had to be published in English or have an English abstract to be considered for inclusion.

Types of publications [8]: Journal articles; books and book chapters; conference papers and proceedings; dissertations; research project reports; technical reports; unpublished manuscripts.

References


