Are PubMed alone and English literature only enough for a meta-analysis?

We have read with great interest the article by Tramacere et al. [1] who have analyzed the association between alcohol drinking and esophageal and gastric cardia adenocarcinoma risks, and we found some problems in the study. Recently, we have read another article by Turati et al. [2] who have analyzed the association between overweight and obesity, and esophageal and gastric cardia adenocarcinoma risks, and we found the similar problems in it. So, we would like to add some cautionary words.

The authors stated that they had carried out a literature search of all case-control and cohort studies published as original articles in English, using PubMed. The meta-analysis was based solely on English articles, thus many non-English trials might have been missed. And reported study recommended that all systematic reviews should at least attempt to identify trials reported in gray literature, which meant unpublished, randomized, controlled trials, those published in non-English language journals and those reported in gray literature and, where possible, obtain data from them [3].

It has been noted that PubMed alone may not be enough for literature searches. Researches assessing different electronic databases have demonstrated that a single search engine does not provide all the related articles, and to fully capture the complete body of available literature on the subjects might require searches of many databases, depending on the topic [4].

Therefore, to carry out the comprehensive search, particularly for performing meta-analysis, a multiple databases search will get more articles than PubMed alone. Depending on our experience, a much more comprehensive search could include PubMed, Embase, Cochrane Library, Cochrane-controlled Trials Register, Web of Science, Scopus, Google Scholar, Medline Plus, Proquest Dissertations & Theses, PsycINFO and certain specialty database. A comprehensive literature search for a systematic review should include almost all of these databases and related grey literature in different languages. Besides web searching, Richards [5] also found that hand searching was still valuable in identifying randomized trials for inclusion in systematic reviews on healthcare, particularly trials reported as abstracts and letters, those published in languages other than English, along with all reports published in journals not indexed in electronic databases.

To summarize, we should try to get all relevant studies that help us in decision-making in meta-analyses and avoid mentioning studies indexed in only one electronic database with a language we are most familiar with.

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The predictive value of BRCA1 and RAP80 mRNA expression in advanced non-small-cell lung cancer patients treated with platinum-based chemotherapy

The standard first-line treatment of metastatic non-small-cell lung cancer (NSCLC) patients with wild-type epidermal...
growth factor receptor is platinum-based chemotherapy, although characterized by great interindividual variation in outcomes. The identification of molecular markers predictive of sensitivity to platinum could thus considerably improve patient care.

Preclinical and retrospective analyses indicate that BRCA1 could confer resistance to cisplatin (Ebewe, Pharma co Auckland, NZ) [1, 2]. However, in a recent retrospective analysis by immunohistochemistry (IHC) of the protein expression of seven genes in a large cohort of NSCLC patients, Pierceall et al. [3] found that BRCA1 was not a predictive marker of outcome to cisplatin, administered in the adjuvant setting. A retrospective analysis of a subgroup of advanced NSCLC patients in a prospective phase II trial coordinated by the Spanish Lung Cancer Group found a predictive value for RAP80 mRNA expression in patients expressing low BRCA1 [4], and a phase III trial examining customized treatment according to BRCA1 and RAP80 mRNA levels in advanced disease is currently ongoing (NCT00617656).

We have retrospectively analyzed BRCA1 and RAP80 mRNA expression by a real-time PCR in paraffin-embedded tumor samples from 83 advanced NSCLC patients with ECOG performance status 0–1 treated with first-line cisplatin or carboplatin (Pfizer, New York, USA) plus gemcitabine or pemetrexed. Fifty-four patients (65%) had adenocarcinoma. Sixty-seven patients (81%) received gemcitabine. Gene expression levels were classified using tertiles as cut-off points. Expression of both the genes was successfully analyzed in 38 patients, whose characteristics were similar to those of the entire cohort.

BRCA1 mRNA expression had no predictive value when considered in isolation, consistently with the findings reported by Pierceal et al. using IHC [3]. However, the joint effect of BRCA1 and RAP80 was significant for predictive modeling. The 38 patients were divided into three groups: patients with low levels of both the genes, patients with high levels of both the genes, and patients with other combinations of gene expression. The median overall survival (OS) for all 38 patients was 11 months (95% CI 10–12), and the median progression free survival (PFS) was 7 months (95% CI 6–9). For patients with low levels of both the genes, median OS was not reached and the median PFS was 10 months (95% CI 6–15), while for those with high levels of both the genes, the median OS was 6 months (95% CI 5–7) and the PFS was 5 months (95% CI 2–8). For patients with other combinations of gene expression, the OS was 11 months (95% CI 9–12) and the PFS was 7 months (95% CI 6–9) (OS, \( P = 0.02 \); PFS, \( P = 0.01 \)) (Figure 1).

In conclusion, the present study confirms the importance of an integrated analysis of multiple DNA repair components to improve available predictive models in NSCLC and shows that BRCA1 and RAP80 can identify three groups of patients with different outcomes to first-line platinum-based chemotherapy.

<table>
<thead>
<tr>
<th>Gene expression levels</th>
<th>N</th>
<th>Median OS</th>
<th>95% CI</th>
<th>( P )</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low BRCA1 + low RAP80</td>
<td>6</td>
<td>NR</td>
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<td>0.02</td>
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<tr>
<td>Other combinations</td>
<td>29</td>
<td>11</td>
<td>9–12</td>
<td></td>
</tr>
<tr>
<td>High BRCA1 + high RAP80</td>
<td>3</td>
<td>6</td>
<td>5–7</td>
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<tr>
<th>Gene expression levels</th>
<th>N</th>
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<tr>
<td>Low BRCA1 + low RAP80</td>
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<td>3</td>
<td>5</td>
<td>2–8</td>
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Figure 1. Kaplan–Meier curves showing overall survival (OS) and progression free survival (PFS) of the study population according to BRCA1 and RAP80 mRNA expression in combination.
The major drawback of our study lies in the use of samples obtained by a conventional biopsy. Higher-quality tissue samples obtained by cryobiopsies could yield better results and enable us to gain further insight into the predictive model of BRCA1 and RAP80 in NSCLC patients treated with platinum-based chemotherapy.

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