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Beware of Kinked Frontiers: A Systematic Review of the Choice of Comparator Strategies in Cost-Effectiveness Analyses of Human Papillomavirus Testing in Cervical Screening

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ABSTRACT

Objectives: To systematically review the choice of comparator strategies in cost-effectiveness analyses (CEAs) of human papillomavirus testing in cervical screening. **Methods:** The PubMed, Web of Knowledge, and Scopus databases were searched to identify eligible model-based CEAs of cervical screening programs using human papillomavirus testing. The eligible CEAs were reviewed to investigate what screening strategies were chosen for analysis and how this choice might have influenced estimates of the incremental cost-effectiveness ratio (ICER). Selected examples from the reviewed studies are presented to illustrate how the omission of relevant comparators might influence estimates of screening cost-effectiveness. **Results:** The search identified 30 eligible CEAs. The omission of relevant comparator strategies appears likely in 21 studies. The ICER estimates in these cases are probably lower than would be estimated had more comparators been included. Five of the 30 studies restricted relevant comparator strategies to sensitivity analyses or other subanalyses not part of the principal base-case analysis. Such exclusion of relevant strategies from the base-case analysis can result in cost-ineffective strategies being identified as cost-effective. **Conclusions:** Many of the CEAs reviewed appear to include insufficient comparator strategies. In particular, they omit strategies with relatively long screening intervals. Omitting relevant comparators matters particularly if it leads to the underestimation of ICERs for strategies around the cost-effectiveness threshold because these strategies are the most policy relevant from the CEA perspective. Consequently, such CEAs may not be providing the best possible policy guidance and lead to the mistaken adoption of cost-ineffective screening strategies.

Keywords: cervical screening, comparator choice, cost-effectiveness analysis, model specification.

Introduction

This review considers the choice of screening strategies compared in cost-effectiveness analyses (CEAs) of cancer screening programs. It investigates how the choice of which strategies are compared can influence cost-effectiveness estimates and resulting policy advice. Specifically, this review addresses the choice of comparator strategies against which the cost-effectiveness of a given screening strategy is estimated. This issue is considered in the particular context of CEAs of cervical cancer screening using testing for the human papillomavirus (HPV).

The primary measure of cost-effectiveness is the incremental cost-effectiveness ratio (ICER), which is the ratio of additional costs to additional health effects of an intervention relative to its next best alternative (once strategies subject to simple and extended dominance have been eliminated) [1,2]. Because the ICER is an incremental measure, it depends not only on the costs and effects of the strategy for which it is estimated but also on those of the comparator strategy.

Typically, decision makers use ICERs in conjunction with a cost-effectiveness threshold, which indicates the maximum willingness to pay for an additional (quality-adjusted) life-year [3]. The strategy with the highest ICER within the threshold is optimal from the cost-effectiveness perspective because it is the most effective intervention that does not exceed the willingness-to-pay limit. More broadly, those strategies with ICERs closest to the threshold are defined here as the CEA-relevant strategies because they yield more net health benefit than do strategies with ICERs far above or below the threshold. It is the adequacy of the choice of comparators for these CEA-relevant strategies that is the focus of this review.

A particular characteristic of screening especially relevant to CEA modeling is that it can often be applied at a wide range of

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intensities, depending on the screening interval, screening age range, type of tests used, and the diagnostic criteria for follow-up. As a result, CEAs considering a wide range of screening intensities can yield a wide range of ICERs, varying from those well below the threshold through to those around the threshold and then on to well above the threshold.

What is already well appreciated in CEA theory is the importance of including relevant comparators for the reliable estimation of ICERs. Indeed, the Washington Panel on Cost-Effectiveness in Health and Medicine uses a cancer screening example to illustrate the importance of including relevant comparators [4]. It notes that to correctly estimate the ICER of annual screening, it must be compared with biennial screening rather than with no screening. The general principle is that to appraise the cost-effectiveness of a given screening strategy, the next best strategy should be included as a comparator against which to estimate the ICER. If less intense comparators are omitted, then the estimated ICER is likely to be lower than that in a more complete comparison, thereby giving an unrepresentatively favorable impression of the strategy's cost-effectiveness.

The motivation for this review was an observation that although most models used in CEAs of HPV screening are carefully constructed and well described, many include relatively few comparator screening strategies. Consequently, they may fail to adequately estimate the cost-effectiveness of certain strategies. This, in turn, could lead decision makers to mistakenly adopt cost-ineffective policies, thereby wasting health care resources. Therefore, the aim of this study was to systematically assess the adequacy of the choice of comparator strategies in CEAs of HPV testing in cervical screening. It seeks to demonstrate the importance of appropriately chosen comparators for the reliable estimation of ICERs. Although the review addresses the specific case of cervical screening, it is hoped that the example will illustrate the importance of including relevant comparators in CEAs in general to both analysts and decision makers alike.

The Example of Cervical Screening

Cervical screening has proved highly successful in reducing cancer incidence and mortality [5]. Cervical screening is widely practiced in developed countries, either through organized programs or on an ad-hoc basis [6,7]. There is a wide variety of possible screening strategies because alternative screening intervals and start and stop ages can be used. Similarly, screening may use different tests, such as conventional Papanicolaou cytology or the more recent alternative of liquid-based cytology. Furthermore, there are alternative combinations of primary screening tests and triage testing for inconclusive primary screen results and alternative classifications of borderline results. In practice, there are large variations between countries in screening recommendations. For example, the German recommendations are for annual screening from age 20 years, whereas the Dutch screening program has used screening every 5 years from age 30 years [8,9].

The range of possible strategies continues to expand, in part because of the recent advent of HPV DNA testing. HPV testing offers better sensitivity for the detection of high-grade lesions, but at the cost of lower specificity [10–12]. HPV testing is typically used in conjunction with cytology, for example, using HPV and cytology as the primary test and the triage test, respectively. Some proposed strategies also involve a switch in the order the tests are used [8], using cytology as the primary test and HPV as the triage test, in younger women in whom transient HPV infections are more prevalent. Importantly, for this review, HPV testing has been recognized as offering the potential for longer screening because a negative HPV test result is associated with a longer period of reduced risk of precancerous lesions than is negative cytology [13].

Another relevant development is the HPV vaccine, which has been implemented in many countries recently. Although current vaccines are expected to reduce the incidence of cervical cancer, the level of protection is not anticipated to be sufficient to abandon screening [14]. Reduced incidence will reduce the cost-effectiveness of current screening services, so screening intervals may need to lengthen for screening to be cost-effective [15].

Table 1 – The PubMed version of the search string.

Cervi*[tiab] OR pap[tiab] OR cytolog*[tiab] OR (cervi*[tiab] AND cancer[tiab])
AND (HPV[tiab] OR "Human Papillomavirus"[tiab])
AND (screen*[tiab] OR prevent*[tiab])
AND (cost-effect*[tiab] OR "cost effect*"[tiab] OR CEA[tiab] OR CUA [tiab] OR HTA[tiab]OR "health technology assessment"[tiab] OR "health economic"[tiab])
AND English[lang]
AND ("1995/01/01"[PDAT] : "2013/10/01"[PDAT])

Methods

The PubMed, Web of Knowledge, and Scopus databases were searched for model-based CEAs of cervical screening using HPV testing. The search string from the PubMed search is given in Table 1. Figure 1 shows the search protocol. The search was restricted to English language academic articles published between January 1995 and September 2013. The search excluded conference proceedings, government reports, and gray literature.

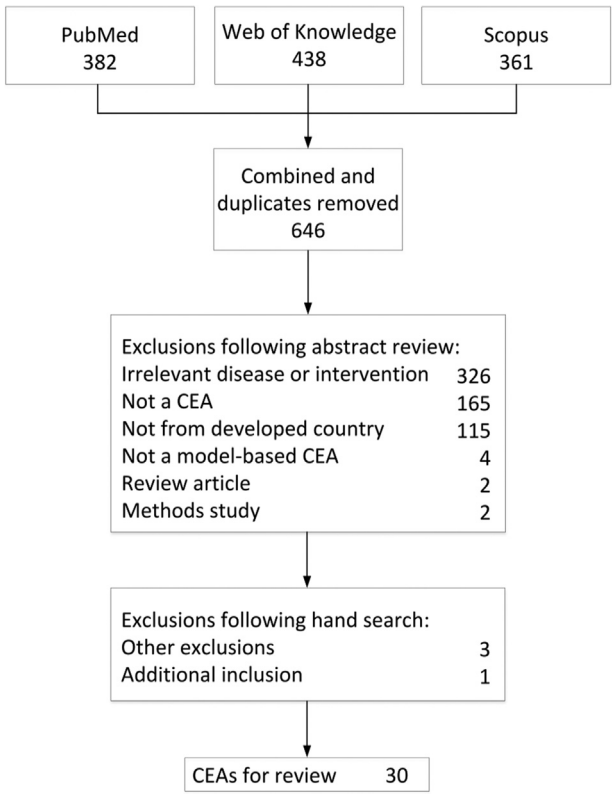

Fig. 1 – Composition of literature search and exclusions. CEA, cost-effectiveness analysis.