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VALUE IN HEALTH

Cost-Effectiveness versus Cost–Utility Analysis of Interventions for Cancer: Does Adjusting for Health-Related Quality of Life Really Matter?

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ABSTRACT

Objective: The US Public Health Service Panel on Cost-Effectiveness has recommended the use of quality-adjusted life-years (QALYs) as the best way to estimate outcomes in a cost-effectiveness analysis. We evaluate the importance of this recommendation by assessing whether adjusting for health-related quality of life affects the ultimate resource allocation decision implied by the cost-effectiveness ratio for interventions aimed at cancer prevention and control.

Methods: We identified 110 interventions in 39 articles for which both cost/life-year and cost/QALY were reported. Interventions were forms of prevention, early detection, or treatment of cancer. We calculated a Spearman correlation to assess the ordinal relationship between cost/life-year and cost/QALY. In addition, we employed various decision thresholds to assess whether the use of cost/life-year would yield different resource allocation decisions than the use of cost/QALY.

Results: The correlation between cost/life-year and cost/QALY is 0.96 ($P < .0001$). Assuming a \$50,000 decision threshold, adjustment for quality of life would affect the implied choice in 5% of cases. With a \$400,000 threshold, adjustment for quality of life would affect choice for 2% of interventions.

Conclusions: For interventions aimed at cancer, the outcome measures of cost/life-year and cost/QALY are highly correlated with one another. Although adjusting for quality of life can make an important difference in the evaluation of alternative approaches to cancer prevention and control, it often does not.

Keywords: cost-effectiveness analysis, cost–utility analysis, quality-adjusted life-year, quality of life, utility assessment.

Introduction

Cost-effectiveness analysis has emerged as the most common form of economic analysis in the fields of medicine and public health, usurping even cost–benefit analysis [1]. In a cost-effectiveness analysis, the incremental cost and incremental effectiveness of an intervention are calculated relative to a comparator and a ratio is computed. The numerator of the ratio is generally the net direct resource consumption, often from the societal perspective. The denominator is usually either years of life saved or quality-adjusted life-years (QALYs) saved. Economic analyses that measure effectiveness as life-years saved are commonly called “cost-effectiveness analyses” whereas those reporting QALYs are referred to as “cost–utility analyses.”

“Life-years” are saved when an intervention reduces the risk of premature death. For example, if a death is averted at age 50 and the person lives until age 85, then the intervention “saves” 35 years of life. QALYs, on the other hand, are essentially a measure of multiattribute utility. The two attributes are survival and health status. For each health state experienced, analysts assess a numerical utility, or preference weight, on an interval scale where the lower bound, often death, is 0 and the upper bound, often perfect health, is 1. Analysts multiply this utility by the number of years over which that health state is experienced. Health states might be acute health problems such as pneumonia or injury, chronic diseases such as AIDS or depression, or side effects such as pain or nausea. Utilities are assessed with techniques such as the rating scale, time tradeoff, or standard gamble or through the use of health status instruments such as the Health Utilities Index, Quality of Well Being Scale, or EQ-5D.

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The US Public Health Service Panel on Cost-Effectiveness in Health and Medicine [1] developed a set of recommendations intended to increase the uniformity and rigor of methods used in cost-effectiveness analysis. As the preferred outcome measure, the Panel recommended QALYs over life-years. As a way of measuring effectiveness, QALYs have certain advantages and disadvantages relative to life-years. Their most important advantage is that they capture changes in morbidity as well as mortality. The inclusion of morbidity allows analysts to factor in outcomes such as the gradual decline in health status with disease as well as the side effects from treatment. On the other hand, QALYs have certain limitations, both theoretical [2–8] and practical. One practical issue is that there is little agreement about how to measure the utilities that are incorporated into QALYs. Utilities measured or estimated by different authors vary considerably, even for the same severity of the same disease. For example, utilities reported in the literature for major stroke range from 0.02 to 0.71, moderate stroke 0.12 to 0.81, and minor stroke 0.45 to 0.92 [9]. Utilities for AIDS range from 0.24 to 0.79, symptomatic HIV 0.48 to 0.82, and asymptomatic HIV 0.69 to 0.88 [10]. This variation becomes problematic when different authors choose different utilities for the same health state and incorporate those weights into a QALY measure. The result is variation in cost–utility ratios for different interventions—variation that does not reflect the true relative value of the interventions. It is conceivable that the cost/QALY for a new cancer treatment might be lower than the cost/QALY for a competing treatment, not because the innovation offers better value for money, but because different utilities were used for the same type and severity of cancer.

Quality-adjusting life-years can change a cost-effectiveness ratio dramatically. QALYs can be larger or smaller than life-years for the same intervention. For example, the incremental QALYs offered by an intervention relative to a comparator will exceed the incremental life-years when the intervention improves quality of life but does not improve survival. QALYs will also exceed life-years when survival is improved, but the increase in quality of life is large in comparison. Conversely, incremental life-years can exceed incremental QALYs when a treatment extends life but at the expense of undesirable side effects that reduce overall quality of life. It can also occur when an intervention offers survival improvements that are large in comparison to improvements in quality of life.

It is evident that the inclusion of utilities in a cost-effectiveness analysis can dramatically change the final ratio. Nevertheless, although quality of life can affect the ratio, it remains an open empirical question whether it generally does have important impact on the final result of the economic analysis. Such information would be relevant for journal reviewers and editors, payers, and the analysts themselves as they seek to assess whether quality adjustment is necessary. Indeed, this work is particularly timely because in February 2003 the US Office of Management and Budget, which reviews all regulations including those that reduce environmental and occupational exposure to carcinogens, announced that they are considering requiring that regulatory agencies standardize on QALYs [11].

The objective of this research is to aid decision-makers in assessing the importance of adjusting for health-related quality of life in economic analyses of cancer prevention and control.

Methods

To compare cost/life-year with cost/QALY ratios, we turned to our existing Cancer Cost-Effectiveness Database, which contains information for more than 1500 interventions aimed at cancer prevention, screening, and treatment. We identified all studies in this database for which both cost-effectiveness and cost–utility analyses were performed. We identified analyses in the database by searching the National Health Service (NHS), Economic Evaluation Database [12], MEDLINE, and bibliographies of review articles [13]. In addition, when reviewing each analysis, we noted other cancer-related articles that were likely to have cost-effectiveness information and retrieved those as well.

Our inclusion criteria were as follows: articles had to be written in English, peer reviewed, and full length (i.e., not conference abstracts) and report both cost/life-year and cost/QALY. Of the 353 articles in our Cancer Cost-Effectiveness database, 39 of them met the inclusion criteria for this study [14–52]. Some documents contained cost-effectiveness information for more than one intervention, so we identified a total of 110 pairs of ratios.

To create the Cancer Cost-Effectiveness Database, we recorded more than 200 different pieces of information for each intervention, but used only a subset of data for this analysis. When necessary, costs were converted from foreign currencies to US dollars using historical exchange rates and updated to 2001 dollars using the US medical consumer price index. Two readers read each study and then met and came to consensus on the content of the document. The principal investigator then verified the accuracy of their work.

To assess the importance of quality of life in cost-effectiveness analysis we used two strategies. First, we computed a Spearman correlation to assess the ordinal relationship between cost/life-year and cost/QALY. This was intended to assess whether a league table ranked by cost/QALY would differ from a table ranked by cost/life-year.

We also adopted a second strategy to consider the importance of quality of life in informing resource allocation decisions: in this strategy, we sought to determine whether the inclusion of quality-of-life information affected the ultimate decision implied by the ratio. To implement this strategy, we used several decision thresholds. For each plausible threshold we considered whether the use of each cost/life-year ratio would imply a different decision than that implied by the corresponding cost/QALY ratio. For example, if the decision threshold is assumed to be $50,000 and the assessed cost/QALY of an intervention is $45,000, then this suggests that we should invest in the intervention because $45,000 is favorable compared to the $50,000 threshold. If the cost/life-year ratio is $55,000, then this suggests that we should not invest as $55,000 is above the $50,000 threshold. Thus, in this case, the decision would differ depending on whether we use cost/QALY or cost/life-year ratios; that is, the inclusion of utility information affects the resource allocation decision. Note, however, that if the decision threshold were instead $200,000, then both ratios would be below the threshold and the same choice to invest would be made regardless of the ratio used. In this latter instance we would say that the inclusion of utilities did not affect the resource allocation decision.

The question of whether utilities affect decisions may depend on the choice of the decision threshold. Thus, in implementing this second strategy, we used several thresholds for cost/QALY ranging from $50,000 through $400,000. The lowest figure of $50,000 was chosen because of its historical significance. The largest figure was chosen as an approximation of the largest willingness-to-pay (WTP) estimate mentioned in a recent review [53]. For each threshold, we counted the number of interventions for which 1) both ratios are below the threshold; 2) both are above the threshold; 3) cost/life-year is below but cost/QALY is above; and 4) cost/QALY is below but cost/life-year is above.

Note that WTP for a life-year and WTP for a QALY may differ. Because one QALY is equivalent to an additional year of life in perfect health, or 2 years of life with 0.5 quality of life, 4 years with 0.25 quality of life, etc., the value of a QALY exceeds that of a life-year because the latter might be in some state of health short of "perfect." Hirth et al. [53] used existing WTP estimates for a life to derive WTP for a QALY. Consequently, to derive WTP for a life-year, we used an estimation procedure. First, we noted that Fryback et al. [54,55], who elicited utilities with the time tradeoff method from more than 1000 persons, found that the average utility of subjects in their sample was between 0.8 and 0.94 depending on age and sex. Erickson et al. [56] used information from the Healthy People 2000 survey and found that the average utility of persons age 45 to 50 was 0.86, and age 65 to 70 was 0.77. Based on these studies we estimated that the average life-year is roughly equivalent to 0.8 QALY. WTP for a life-year might therefore be approximately 20% smaller than WTP for a QALY. For example, if WTP for a QALY is $50,000, then we estimate WTP for a life-year to be approximately $40,000. For each decision threshold for a QALY that we considered, we derived the corresponding decision threshold for a life-year.

Results

The relationship between cost/life-year and cost/QALY for 110 interventions is depicted in Figure 1. Cost/life-year exceeded cost/QALY in 38% of cases whereas cost/QALY exceeded cost/life-year in 62% of cases. The rank order correlation between these two measures is 0.94 ($P < .0001$).

Next, we considered whether the decision implied by the two ratios differs for alternate decision thresholds. As shown in Table 1, if the threshold was $50,000 for both ratios, then 76 of the 110 interventions would be sufficiently cost-effective to warrant adoption regardless of whether cost/life-

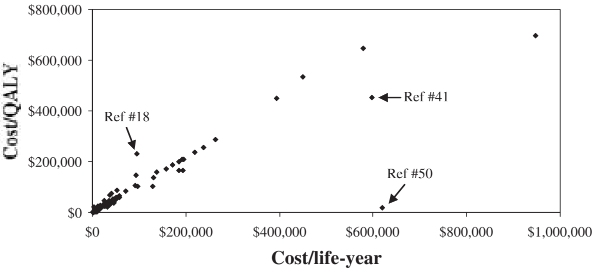

Figure 1 The relationship between cost per quality-adjusted life-year (QALY) and cost per year of life saved for interventions aimed at cancer prevention and control ($n = 110$).

Table 1 Decision thresholds based on willingness to pay (WTP) for life-years (LY) and quality-adjusted life-years (QALY) and the investment decision implied depending on ratio used

WTP life-year	WTP QALY	C/LY < WTP C/QALY < WTP	C/LY ≥ WTP C/QALY ≥ WTP	C/LY < WTP C/QALY ≥ WTP	C/LY ≥ WTP C/QALY < WTP
$40,000	$50,000	70	32	1	7
$50,000	$50,000	76	29	1	4
$160,000	$200,000	94	11	1	4
$200,000	$200,000	97	8	4	1
$320,000	$400,000	104	5	0	1
$400,000	$400,000	104	4	1	1

year or cost/QALY was used; 29 would not be judged cost-effective regardless of the measure; 1 would be judged cost-effective only if cost/life-year were used; and 4 would be considered cost-effective only if cost/QALY were considered. This suggests that the implied decision about whether or not to adopt the technology would be affected by quality of life adjustment in 5% of cases but not in the remaining 95%. If a somewhat lower decision threshold of $40,000 is used for life-years, then 70 interventions would be implemented regardless of the ratio used; 32 would not be adopted in any case; 1 would be chosen only if cost/life-year were used; and 7 would be implemented only if cost/QALY were used. The decision would be affected in 7% of cases. If a larger threshold such as $400,000 were assumed for both life-years and QALYs, then 104 of the 110 interventions would warrant adoption regardless of the measure used. The decision would be affected by the inclusion of quality-of-life data in 2% of cases.

Discussion

For interventions aimed at cancer prevention, screening, or treatment, we identified a strong ordinal relationship between cost-effectiveness and cost utility. This implies that a ranking by cost/life-year will be quite similar to a ranking by cost/QALY. Further, if resources are limited and funding decisions are made by investing first in interventions that are more cost-effective before proceeding to interventions that are less cost-effective, then the composition of the investment portfolio is likely to be similar regardless of whether cost-effectiveness or cost–utility ratios are used. We also found that when there is no fixed budget per se, and decisions are made using a decision threshold, cost-effectiveness and cost–utility estimates will generally lead to similar implied investment decisions. This was true regardless of the threshold adopted.

We sought to understand why cost/life-year is so often similar to cost/QALY, leading to similar implied investment decisions. First, note that since the numerators are identical, cost-effectiveness and cost–utility ratios for the same intervention can differ only in their denominators. Apparently, in most cases, the incremental gain in life-years of the intervention relative to a comparator is similar to the incremental gain in QALYs. Why is this? Consider Figure 2, which depicts a hypothetical, "QALY-space" of life-years on the horizontal axis and quality of life on the vertical axis. Suppose that we want to calculate the gain in health from some intervention relative to a comparator. Those receiving the comparator live L_1 life-years at Q_1 quality; thus area C represents the QALYs associated with the comparator. Imagine that the intervention improves QOL from Q_1 to Q_2 and life-years from L_1 to L_2. Thus the area B + C + E + F represents the QALYs lived by those who receive the intervention. The incremental gain in QALYs is therefore B + E + F.

Now imagine that this gain is measured not with QALYs, but with life-years. The incremental gain in life-years is clearly the difference between L_2 and L_1. Equivalently, life-years are the same as QALYs if the QOL is assumed to be 1.0 and thinking of it this way allows us to conceive of life-years as an area rather than a horizontal distance in Figure 2. Thus, with the comparator life-years would be A + B + C and with the intervention life-years would be A + B + C + D + E + F. The incremental

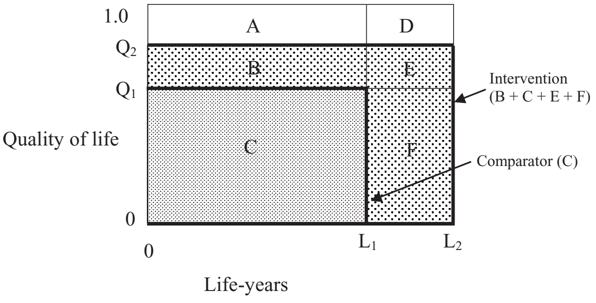

Figure 2 Comparison of a the Incremental gain in QALYs (B + E + F) with the gain in life-years (D + E + F).

gain in life-years is therefore D + E + F. Now compare the incremental gain in QALYs (B + E + F) with the incremental gain in life-years (D + E + F) and notice that they differ by only one term (B vs. D). This implies that the incremental gain in QALYs vs. life-years will be similar when the area of B is similar to the area of D and/or when B and D are relatively small in comparison to E + F.

We can use the diagram in Figure 2 to understand why the three "outlier" studies labeled in Figure 1 found such markedly different cost/life-year and cost/QALY ratios. In one case, Kim et al. [41] evaluated the cost-effectiveness of alternate triage strategies for atypical squamous cells of undetermined significance and found that cost/QALY was considerably more favorable than cost/life-year. The authors assumed that local cancer had a utility of 0.68, regional cancer 0.56, and distant cancer 0.48. They also assumed women without cancer over age 40 would have a utility consistent with that of the national average for women in that age group. Women under age 40 who were cancer-free were assumed to have a 1.0 utility. The authors modeled a hypothetical cohort of young women over a lifetime starting at age 13. In this study, the large differential between QALYs and life-years may be due to two factors: First, utility estimates appear to be somewhat lower than utilities for cancer found in the general literature [9]. Exacerbating this effect, the differential in the utility between cancer states and noncancer states is quite large before age 40 because of the perfect 1.0 utility assigned to women who are cancer-free. Second, and perhaps most importantly, the model begins at an early age, so that QALYs accumulate over a long time horizon. Referring to Fig. 2, these factors mean that $Q_2 = 1.0$ for women under 40 and Q_2 is distant from Q_1 for all women making the vertical height of B quite large. Further, because QOL is improved over a long time horizon, the horizontal width of B is also large. The result is that the area of B far exceeds the area of D, ensuring that QALYs gained are much larger than life-years gained. The outcome is that cost/QALY is much lower than cost/life-year.

In a second "outlier" study, Tengs et al. [50] performed an economic analysis of school-based antitobacco education. The authors assigned a lower health-related utility to smokers than to nonsmokers, basing utility weights on a survey of current, former, and never smokers of various ages and genders. Current smokers in these surveys reported lower utility than former smokers, and former smokers reported lower utility than those who had never smoked. Because smoking occurs over many years, utility gains from not smoking are accrued over a long period even before the survival implications of smoking become evident. As with the first outlier case, the horizontal width of B is large so that the area of B is again large in comparison to D. The result is that the QALYs gained far exceed life-years gained so cost/QALY is much lower than cost/life-year.

Unlike the studies by Kim et al. and Tengs et al., Coley et al. [18] found that cost/life-year was considerably more favorable than cost/QALY. The authors evaluated the cost-effectiveness of digital rectal examination and the measurement of prostate-specific antigen for early detection of prostate cancer. They assumed utility estimates of 0.5 and 0.8 for hormonally refractive or responsive metastatic cancer, 0.7 for incontinence, 0.95 for impotence, and 0.85 for treatment-related bowel injury caused by prostatectomy. It is likely that the exhaustive capture of the iatrogenic effects of surgery in this analysis accounted for the large differential between QALYs and life-years. Referring to Figure 2, this means that Q_2 is actually less than Q_1; thus B is quite different from D. The result is that QALYs gained are less than life-years gained and, again, cost-effectiveness and cost–utility ratios are quite different.

The close examination of these three "outlier" economic analyses combined with the review of the diagram in Figure 2 offers some insight into when cost-effectiveness and cost utility will differ greatly. When the intervention starts early in life and affects or prevents some chronic health state over a long time horizon, QALYs can far exceed life-years. Some additional examples of situations in which this might occur include psychotherapy or drug therapy for mental illness or traffic safety measures to reduce the likelihood of spinal cord and other nonfatal injuries. Further, the careful accounting of treatment-caused disutility can also yield a large difference between QALYs and life-years, but in the opposite direction. Examples include prophylactic mastectomy for carriers of the BRCA1 or BRCA2 breast cancer genes, kidney dialysis, or pharmaceutical care when the side effects of medication are chronic and unpleasant. In cases like these there will tend to be a large difference between cost/life-year and cost/QALY ratios.

The examination of Figure 2 should prove useful to investigators who want to make a decision *ex ante* about whether to go to the trouble of gathering utility data and incorporating QOL into their economic analysis. Analysts should reason about whether the areas of B and D are likely to be relatively large and different from one another. If so, incorporating QOL is probably wise. If not, it may be unnecessary. Nevertheless, although helpful, the diagram necessarily depicts the survival and QOL implications in a rather stylized fashion. For example, the area comprising QALYs is generally not rectangular because QOL often decreases gradually over time. Nevertheless, this diagram is useful in illustrating the main reasons why the gain in QALYs is generally similar to, but occasionally different from, the gain in life-years.

Although we found that quality adjustment tends to not affect the implied resource allocation decision in most cases, several caveats are important in interpreting our findings. One limitation of our research is that the interventions included in our sample are not a random sample of all medical and public health interventions. This is in part because, since this study is part of a larger funded project, the interventions we examined were chosen because of their relevance to a specific disease—cancer. Further, there many public health and medical interventions that have not been subjected to economic analysis and so would not be reflected in our larger database or in this data subset. Additionally, although interventions for which authors reported only cost/life-year or only cost/QALY are available in our larger database, they are not included in the present data subset used in this analysis for obvious reasons. This may influence our findings because it may be that when there are important morbidity implications, authors calculate only cost/QALY and not cost/life-year. For example, interventions such as palliative care that are solely intended to improve QOL would, by definition, not be included in our data subset because only cost/QALY can be calculated for these kinds of interventions. Similarly, it may be that when the intervention improves survival and has no implications for quality of life, authors report only cost/life-year. Thus, to get a sense of whether our data subset was representative the database as a whole, we performed a kind of *post hoc* analysis on the categories represented. We found that although the current data subset contains 21% primary prevention, 50% screening, and 29% treatment, the complete database contains 24% primary prevention, 41% screening, and 34% treatment. As for specific interventions, 15% of the subset involves interventions for smoking cessation, 12% cervical cancer screening, 10% breast cancer screening, 5% colorectal cancer screening, 8% chemotherapy, and 50% other interventions. The larger database contains 4% smoking cessation, 7% cervical cancer screening, 7% breast cancer screening, 2% colorectal cancer screening, 16% chemotherapy, and 64% other interventions. Thus, while it is certainly possible to find specific interventions that do not appear in our data subset, the overall composition of the categories of interventions we used in this study is similar to the categories in the complete database. This implies that the categories of interventions for which both cost/life-year and cost/QALY are reported do not differ substantially from the categories of interventions for which only one ratio is reported. Our data subset therefore is fairly representative of the overall data set.

In addition, we also performed a *post hoc* examination of the extent to which the rigor of the analyses in our subset was similar to the quality of those in the database as a whole. For all articles in the database, we coded whether each of the Gold et al. [1] recommendations was "completely," "partially," or "not" met. We then developed a variety of quality metrics, the simplest of which was the percentage of recommendations that were completely met. Although the average for the database a whole was 48%, the average for this data subset was 59%. In fact, all but three of the articles in the present data set had above average quality. Thus, it is clear that the quality of our data subset is not representative of the quality of the entire database—it is of higher quality. This also means that it is unlikely that an absence of methodologic rigor in the studies we examined, for example, in incorporating QOL, accounts for the results.

To assess whether utility adjustment affects the implied resource allocation decision, we used a series of plausible decision thresholds. Because the value of a QALY exceeds the value of a life-year, we also assessed the implications of using different thresholds for cost/life-year ratios than for cost/QALY ratios. To arrive at the appropriate thresholds, we estimated the average utility of the life-years gained as 0.8 as that was roughly the average health status of the adult US population. In reality, some interventions offer an extension of life in very good health, some extend life in average health, and some, as in the case of certain cancer treatments, extend life with cancer and so offer a gain in life-years in relatively poor health. We believe that the 0.8 estimate and the assumption that life-years are worth about 20% less than QALYs is appropriate in the context of this study because it represents a kind of reasonable average. Nevertheless, if an individual investigator wanted to identify an appropriate decision threshold for cost/life-year by estimating the relative worth of QALYs versus life-years specific to their intervention, they would essentially have to estimate QOL over added life-years. Interestingly, in doing so, they are effectively incorporating utilities into their assessment, albeit indirectly, to arrive at this threshold. Thus, it can be argued, the analyst might as well incorporate utilities at the outset, calculate cost/QALY, and use a decision threshold appropriate to a cost/QALY ratio. Although this argument is logically appealing, we found empirically that, like quality adjustment, the precise decision threshold is also relatively unimportant. Our results reveal that even when the decision thresholds for cost/QALY and cost/life-year are, somewhat inappropriately, assumed to be the same, the portfolio of interventions chosen does not differ much from when they are assumed to differ by 20%. Thus, although logically sound, this concern may be unimportant in practice.

Another caveat in interpreting our results is that some economic evaluations for cancer treatments are carried out before survival gains are established empirically. Nevertheless, note that our data set includes a broad mix of preventive interventions and screening, as well as treatment. For many interventions a model is developed to estimate cost-effectiveness, generally over the long term. In cases where survival gains are not established empirically, authors may have under- or overestimated them with their model. The same is true of quality of life. Authors, for various reasons, may under- or overestimate QOL. Nevertheless, despite any noise in cost/life-year and cost/QALY estimates, our results show that the ratios are remarkably similar.

Finally, although the present study considers hypothetical decisions made by comparing ratios to decision thresholds, actual decisions are not generally made using such a stark criterion. Some observers have pointed out that cost-effectiveness information is not typically used at all. Further, when it is used, it may be that decision makers, such as payers deciding what treatments to cover or hospital formulary managers deciding what drugs to include on their list of approved medications, consider analyses more trustworthy if side effects and other quality of life considerations are incorporated into the analysis. On the other hand, the opposite might be true. Decision-makers might believe that utility estimates lack the objectivity of survival estimates and so might assign more trust to analyses that omit quality of life.

This research has several important implications. First, we stress that our results do not imply that health status is unimportant or that survival alone matters. Clearly, both are valued. Rather, these results should be taken as empirical evidence that the improvements in health status offered by cancer-related interventions for which economic analyses are performed, are often related, perhaps even proportional, to improvements in survival.

Conclusion

We found that adjusting for health-related quality of life often does not make a large difference in the economic analysis of interventions aimed at cancer prevention, screening, and treatment. Cost-effectiveness and cost–utility estimates are highly correlated with each other and do not generally lead to different implied resource allocation decisions. We have offered a way of estimating *ex ante* whether the incorporation of quality of life estimates will greatly affect the cost-effectiveness ratio. In particular, when an intervention has important side effects that lower quality of life significantly or improves quality of life over a long time horizon, it is particularly important to incorporate utilities. In other instances, adjustment for quality of life may not be necessary and the estimation of cost per year of life saved may suffice.

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