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RESEARCH ARTICLE

Cost-Effectiveness of Cancer Screening: Health and Costs in Life Years Gained

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Introduction: Studies reporting on the cost-effectiveness of cancer screening usually account for quality of life losses and healthcare costs owing to cancer but do not account for future costs and quality of life losses related to competing risks. This study aims to demonstrate the impact of medical costs and quality of life losses of other diseases in the life years gained on the cost-effectiveness of U.S. cancer screening.

Methods: Cost-effectiveness studies of breast, cervical, and colorectal cancer screening in the U.S. were identified using a systematic literature review. Incremental cost-effectiveness ratios of the eligible articles were updated by adding lifetime expenditures and health losses per quality-adjusted life year gained because of competing risks. This was accomplished using data on medical spending and quality of life by age and disease from the Medical Expenditure Panel Survey (2011–2015) combined with cause-deleted life tables. The study was conducted in 2018.

Results: The impact of quality of life losses and healthcare expenditures of competing risks in life years gained incurred owing to screening were the highest for breast cancer and the lowest for cervical cancer. The updates suggest that incremental cost-effectiveness ratios are underestimated by $10,300–$13,700 per quality-adjusted life year gained if quality of life losses and healthcare expenditures of competing risks are omitted in economic evaluations. Furthermore, cancer screening programs that were considered cost saving, were found not to be so following the inclusion of medical expenditures of competing risks.

Conclusions: Practical difficulties in quantifying quality of life losses and healthcare expenditures owing to competing risks in life years gained can be overcome. Their inclusion can have a substantial impact on the cost-effectiveness of cancer screening programs.

INTRODUCTION

Screening for breast, cervical, and colorectal cancer is recommended in many countries. Economic evaluations have suggested that cancer screening programs are cost effective and sometimes even cost saving.[1–10] Economic evaluations are important tools to support decision making in health care by identifying the most efficient way of deploying healthcare resources using the incremental cost–effectiveness ratio (ICER) as the main outcome.[11] The ICER represents incremental costs per unit of incremental health effects, which allows interventions to be ranked by relative cost-effectiveness. Ideally, the ICER is expressed as the cost per quality-adjusted life year (QALY) gained to allow the comparison of interventions across different disease areas.[12] The economic evaluations of screening programs for cancer require models to simulate the

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lifetime impact of prevention of cancer or early diagnosis on the remaining life expectancy, quality of life, and cancer-related healthcare expenditures of a population.

For interventions that extend life, such as cancer screening programs, it is essential to estimate the cost-effectiveness correctly with the appropriate assessment of costs, as well as the health effects in life years gained.[13–18] If an individual is saved from death (e.g., colorectal death) because of screening and lives additional years, during these gained years, there is the competing risk of acquiring diseases unrelated to the intervention under evaluation (e.g., Alzheimer disease). As a result, a person may incur decrements in the quality of life and consume health care, which can be labeled as the incurred medical costs of other aging-related diseases.[18] If one ignores these quality of life losses and healthcare costs of diseases in the life years gained in economic evaluations, it implicitly assumes that the life years gained are lived in perfect health, which leads to an underestimation of costs, and an overestimation of health benefits, and, consequently, to an underestimation of the ICER.[19] Considering that the life years gained because of cancer screening are gained in old age, when the quality of life is generally low and healthcare use is high, this issue is of particular importance when assessing the cost-effectiveness of cancer screening.

The inclusion of future unrelated medical costs has been a topic of debate in the area of economic evaluation, and, in practice, these costs are often ignored.[13–18] However, there has been a growing consensus to include such costs, as it has been shown that their exclusion could lead to decisions that result in losses in population health. Several pharmacoeconomic guidelines, such as the newest U.S. guidelines from the Second Panel on Cost-Effectiveness in Health and Medicine, now recommend the inclusion of this type of cost in cost-effectiveness analyses.[11] In practice, many economic evaluations have also ignored the impact of diseases in life years gained on quality of life.[20] The aim of this study is to update the cost-effectiveness estimates of U.S. cancer screening programs by including future medical costs and quality of life losses for competing diseases in the life years gained.

METHODS

The study consisted of several steps. First, previously published cost-effectiveness studies of screening for breast, cervical, and colorectal cancers were searched in the literature. Second, age-specific estimates of the quality of life and medical expenditures were estimated. Third, the impact of screening on the length of life was approximated using cause-deleted life tables. Finally, these results were used to update the ICERs of the eligible articles found in Step 1. All the analyses were performed in 2018.

Literature Search

First, cost-effectiveness studies of screening for breast, cervical, and colorectal cancers in the U.S. were systematically searched in MEDLINE. The search was conducted in May 2018. The search strategy and review process are presented in Appendix Text 1 (available online). After assessing the eligible studies, data on the incremental costs, incremental QALYs, and the age of starting screening were extracted from the studies. To avoid double counting, studies already including medical costs and quality of life losses owing to competing risks in life years gained were excluded.

Study Sample

Age-specific per capita estimates of the quality of life and healthcare costs owing to competing diseases (all diseases except breast/colorectal/cervical cancer) were estimated using data from the Medical Expenditure Panel Survey (MEPS) from 2011 to 2015. MEPS is a nationally representative survey of the U.S. civilian noninstitutionalized population containing information on healthcare utilization; medical conditions; and various social, demographic, and economic characteristics.[21] The health status of the respondents in the survey is assessed using the standardized questionnaire Short-Form 12 version 2. For this study, the 6-dimension health state classification (SF-6D) was used to estimate health-related quality of life, which was derived from the Short-Form 12 version 2 with the algorithm proposed by Brazier et al.[22] The expenditures in 2011–2014 were adjusted to 2015 U.S. dollars using the Personal Consumption Expenditure Health index.[23] To model healthcare expenditures not related to cancers, all the respondents who reported that they had been diagnosed with breast, cervical, or colorectal cancer or currently had cancer according to their medical conditions data file were excluded from the analysis. The final sample consisted of 107,431 respondents to model the quality of life and 127,273 respondents to model the healthcare expenditures.

Statistical Analysis

To estimate the per capita age-specific quality of life losses and healthcare expenditures for the competing diseases, two-part regression models were fitted, because the distributions of both outcomes were skewed.[24,25] The first part of the model predicted the probability of the outcome variable being 1 (for the quality of life data) or 0 (for the healthcare expenditure data). The second part modeled the values for those who were not at the bounds of the outcome variable. To model the quality of life, a logistic regression was used for the first part and standard ordinary least squares for the second part. For the healthcare expenditures, a logistic regression model was used for the first part and a generalized linear model with log link (gamma distribution) for the second part. Models were fitted separately for male and female respondents. To capture the nonlinear pattern of the quality of life and expenditures by age, the models included the age and polynomials of age as predictors.

As there was no access to the original models of the eligible articles, the impact of screening on length of life was approximated using cause-deleted life tables.[26,27] Life tables enable the estimation of survival curves and life expectancy based on the population mortality rates. A cause-deleted life table provides estimates of the life expectancy of the population if cancer deaths were eliminated. For the unscreened cohorts, it was assumed that the mortality rates were not affected by screening, so the all-cause

mortality rates were used to calculate life expectancy. For the screened cohorts, it was assumed that because of screening, cancer was eliminated as a cause of death, and the life expectancy was then recalculated as if the eliminated cancer had never occurred. The recalculated life expectancy was then compared with the all-cause life expectancy to approximate the life years gained because of the screening. By linking age-specific per capita estimates of the quality of life and healthcare costs to these life table cohorts, quality-adjusted life expectancy (QALE) and medical costs of competing risks in the life years gained were estimated. This approximation works well because the main outcome of interest was the ratio of healthcare expenditure of competing risk per QALE and not the absolute amounts. Prediction intervals were estimated using parametric bootstrapping with the regression coefficients and their covariance as input.[28]

Deaths (all causes and cancer-specific) by single-year age group and sex were derived from the Centers of Disease Control and Prevention WONDER database for the last available year, 2016.[29] The Human Mortality Database was used to extract the population size by single-year age group and sex because, for the subset of those aged 85–≥100 years, the population sizes and consequently the mortality rates, were not available.[30] The cause-deleted mortality rates were calculated by subtracting cancer-specific mortality rates from the all-cause mortality rates. Cohorts were followed up from the age of starting screening until age 100 years or death. Life tables were constructed separately for breast, cervical, and colorectal cancer screening programs.

Published cost-effectiveness estimates from the original studies were updated by adding lifetime healthcare expenditures and quality of life losses owing to competing risks to the ICERs with the formula: $\text{ICER} = \Delta\frac{cost}{\Delta}\ QALYs + \frac{\Delta CCs}{\Delta QALE}$ (Appendix Text 3 available online), where $\Delta costs$ are the incremental costs extracted from the original articles and inflated to the year 2015 using the Personal Consumption Expenditure Health index;[23] $\Delta QALYs$ are the incremental QALYs extracted from the original articles, and ΔCC and $\Delta QALE$ are the estimated incremental future healthcare expenditures and gains in the QALE of the competing risks estimated using the life tables. Lifetime health effects and healthcare costs were discounted with the 3% annual rate suggested by the Second Panel on Cost-Effectiveness in Health and Medicine.[11] Note that this updating procedure is similar to the one used in several papers by Meltzer and colleagues.[15,31,32]

Several univariate sensitivity analyses were performed. In the first, cancer mortality was decreased with 10% instead of eliminating the mortality for all cancers. In the other sensitivity analysis, the impact of using different estimates of spending[33] and quality of life[34] was assessed.

RESULTS

The literature search identified 669 articles, of which 71 seemed eligible based on the title. Based on the full-text articles, 17 studies were found to be eligible, of which another 7 were excluded because the study did not compare screening with no screening (n=5), QALYs and healthcare costs were presented in total (n=1), or both the costs and quality of life losses of competing risks were already included (n=1).[35] In total, 10 articles reporting on the cost-effectiveness of screening for breast, cervical, and colorectal cancer in the U.S. were included in this study.[36–45]

The mean observed and predicted values for health-related quality of life and healthcare expenditures by age for men and women are presented in Figure 1. The quality of life decreased with age for both sexes, and the healthcare expenditures increased with age presuming higher costs for men than for women at advanced ages. More details on the estimated coefficients of the two-part models for the quality of life and healthcare expenditures can be found in Appendix Text 2 available online.

The estimates of the gains in the life expectancy, QALE, and lifetime healthcare expenditures of competing risks for various ages of starting screening are shown in Table 1. The gains in life expectancy and in QALE were the highest for breast cancer and the lowest for cervical cancer. The healthcare expenditures of the competing risks incurred from screening were also the highest for breast cancer and the lowest for cervical cancer. The incremental costs per QALE gained reflect how much the actual ICER in the original publication is underestimated. Values for the costs per QALE for the base case analysis ranged from $10,300 per QALE gained for a cohort screened for cervical cancer at age 18 years to

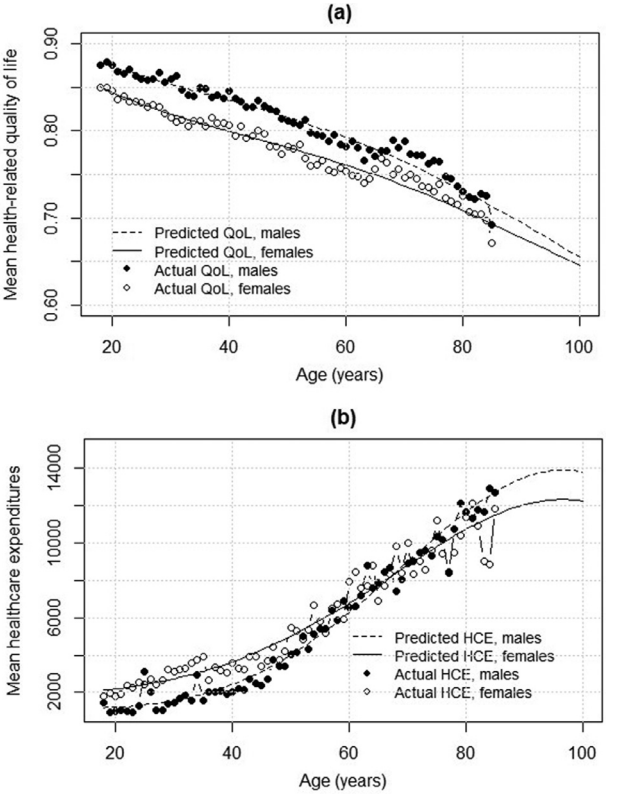

Figure 1. (a) Actual (dots) and predicted mean QoL and (b) HCEs in U.S. dollars by age for males and females.
HCE, healthcare expenditure; QoL, quality of life.

Table 1. Estimated Incremental Results of Including Competing Risks (Base Case Analysis and Sensitivity Analyses), Starting Age of Screening

Variable	Breast cancer	Cervical cancer		Colorectal cancer	
	Age 40 years	Age 50 years	Age 18 years	Age 30 years	Age 50 years
Base case analysis					
ΔLE, undiscounted	0.397	0.347	0.0531	0.051 5	0.209
ΔQALE, undiscounted	0.283 (0.281, 0.285)	0.245 (0.244, 0.247)	0.0388 (0.0386, 0.0389)	0.037 5 (0.037 4, 0.037 7)	0.150 (0.149, 0.151)
ΔHCE, undiscounted[a]	3,980 (3,730, 4,310)	3,591 (3,344, 3,893)	470 (450, 510)	460 (440, 500)	2,260 (1,950, 2,670)
Costs/QALY gained, discounted (ΔHCE/ΔQALE)	12,710	13,620	10,260	10,510	13,700
10% decrease mortality[b]					
ΔLE, undiscounted	0.039	0.035	0.005	0.005	0.021
ΔQALE, undiscounted	0.028	0.0244	0.0039	0.0038	0.015
ΔHCE, undiscounted[a]	396	358	47	46	220
Costs/QALY gained, discounted (ΔHCE/ΔQALE)	12,700	13,620	10,260	10,510	13,660
Different quality of life and cost values[c]					
ΔQALE, undiscounted	0.302	0.2614	0.0417	0.0403	0.161
ΔHCE, undiscounted[a]	9,140	8,419	987	969	5,040
Costs/QALY gained, discounted (ΔHCE/ΔQALE)	25,120	27,692	18,469	18,970	26,780

[a]In 2015 U.S. dollars.
[b]Instead of eliminating cancer as a cause, cancer mortality is only reduced by 1%.
[c]Costs taken from Lassman et al.(2014)[33] and quality of life values taken from Heijink et al.(2011)[34].
HCE, healthcare expenditures; LE, life expectancy; QALE, quality adjusted life expectancy; QALY, quality adjusted life years.

$13,700 per QALE gained for a cohort screened for colorectal cancer at age 50 years. Table 1 also shows that results are quite robust to different assumptions with the exception of using cost values from a different study, which increased the costs per QALE by a factor of 2.

Table 2 shows the original and updated ICERs for the studies identified in the literature review. Only a selection of the results is presented, but all the results are available in Appendix Table 4 (available online). All the screening alternatives are displayed in relative cost-effectiveness based on 2015 U.S. dollar ICERs from the most to the least cost effective. The selected studies suggest that colorectal cancer screening strategies were the most cost effective, followed by cervical cancer screening and breast cancer screening strategies. The updated ICERs, including the quality of life losses and healthcare expenditures of competing risks, were higher compared with the original ICERs. Furthermore, by including the healthcare expenditures of competing risks in the life years gained, interventions that appeared to be cost saving were no longer cost saving, as the additional spending in the life years gained outweighed the savings in the care for cancer.

DISCUSSION

This study aimed to update the cost-effectiveness of breast, cervical, and colorectal cancer screening programs in the U.S. by including quality of life losses and healthcare costs owing to disease other than cancer in the life years gained. The review on published studies reporting the cost-effectiveness of breast, cervical, and colorectal cancer showed that almost all the studies did not account for medical expenditures and quality of life losses owing to competing diseases in life years gained at old age. The ICERs of breast, cervical, and colorectal cancer screening were underestimated by approximately $10,300–$13,700 per QALY gained if the quality of life losses and healthcare expenditures of competing risks are omitted in economic evaluations. The ICERs of the breast and colorectal cancer screening programs were more sensitive to the exclusion of the healthcare expenditures of competing risks, whereas the ICERs of cervical cancer screening were more sensitive to the exclusion of quality of life losses. This suggests that not including the healthcare expenditures of competing risks would favor the interventions that extend life over the interventions that improve the quality of life. The impact is greater when the interventions extend life expectancy more than when they improve the quality of life. In the U.S., there are no clearly defined thresholds to define whether an intervention is cost effective or not,[46] but thresholds of $50,000 and $100,000 are common. For the interventions with the ICERs close to the threshold used, these updates could make a substantial impact on the cost-

Table 2. The Impact of Including Competing Risks on the Cost-Effectiveness of Cancer Screening Programs (Selection of Results)

Screening strategy (reference)	Screening started and ended at age, years	ΔCosts (in U.S. $ year), original study	ΔQALY, original study	ICER, original study[a]	Updated ICER[b]	Updated ICER[c]	Updated ICER[d]
FS/FIT every 3 years[36]	From 50 to 80	139 (2010)	0.078 3	Cost saving	Cost saving	9,555	11,779
Sigmoidoscopy/FOBT[38]	From 50 to 80	44 (2010)	0.079 1	602	788	11,961	14,302
mSEPT9-3well[38]	From 50 to 80	520 (2010)	0.061 9	9,088	11,900	23,605	22,788
Vaginal HPV DNA screening with cytology triage, triennial[40]	From 18 to 85	Not available	Not available	11,546	14,438	Not available	21,802
Stool DNA[39]	From 50 to 80	1,423 (2014)	0.090 3	15,935	20,864	25,885	29,634
Pap, triennial[42]	From 20 to 75	1,815 (2000)	0.153 4	17,349	21,795	18,003	27,606
Digital mammography, biennial[44]	From 40 to 74	1,720 (2012)	0.042	42,523	55,665	42,554	55,229
MM/2 &CBE/1, interval between examinations 2[45]	From 40	3,400 (assumed 2003)	0.069	65,582	85,850	84,243	78,288

[a]Inflated to 2015 U.S. $ ($ per QALY gained).
[b]Only quality of life losses included using the formula ICER $= \Delta\frac{cost}{\Delta}\ QALY \times \frac{LE_{screened}}{QALE_{screened}}$.
[c]Only costs of competing risks included using the formula
ICER $= \Delta\frac{cost}{\Delta}\ QALY + \Delta healthcare\ expenditures\ of\ competing_{\frac{risks}{\Delta QALY}}$.
[d]Quality of life losses and HCE of competing risks included using the formula: ICER $= \Delta\frac{cost}{\Delta}\ QALY + \Delta healthcare\ expenditures\ of\ competing_{\frac{risks}{\Delta QALE}}$.
CBE, clinical breast examination; FOBT, fecal occult blood testing; FS/FIT, flexible sigmoidoscopy/fecal immunochemical testing; HPV, human papilloma virus; ICER, incremental cost–effectiveness ratio; LE, life expectancy; MM, mammography; mSEPT9-3well, methylated Septin 9 DNA plasma assay; QALE, quality-adjusted life expectancy; QALY, quality-adjusted life year.

effectiveness of these interventions. Furthermore, some interventions that were considered cost saving were no longer cost saving after the inclusion of medical expenditures of competing risks. It should be noted that also in Europe, the standard seems to be to exclude both costs and quality of life losses of competing risks in the life years gained when evaluating cancer screening.

With regard to costs, the findings were consistent with previous studies showing that not considering healthcare expenditures for competing risks underestimated the lifetime healthcare costs.[16–18] De Kok et al.[19] showed that the ICER of cancer screening increased by approximately €4,000 per life year gained when the healthcare costs for competing risks were taken into account. To compare their results with the current findings, healthcare expenditures for competing risks per life year gained are calculated based on Table 1, which ranged from $7,600 to $10,000. The difference could be explained by methodologic differences, such as different discount rates, and by the fact that U.S. healthcare expenditures are generally higher than those in the Netherlands. With regard to the quality of life, the findings by age and sex were also consistent with previous studies.[47–49]

Limitations

The study has some limitations. One is that the quality of life and costs were regressed on age, whereas previous studies suggest that the quality of life and healthcare costs depend on age and time to death.[50–53] These studies found that modeling the costs and quality of life exclusively conditional on age results in an overestimation of the incremental healthcare costs and quality of life losses. With the MEPS data set, it was not possible to estimate the impact of the time to death on health spending and quality of life. At the same time, the MEPS data do not fully represent the costs and quality of life related to the end of life because individuals in institutions (for example, in hospices) are excluded from the survey. In a sensitivity analysis, cost estimates from Lassman and colleagues[33] were used, who also used other data sources in addition to the MEPS to reflect the spending of the institutionalized population. Consequently, the impact on the ICER is also about double. The impact of competing risk might still be underestimated in this study, because competing risks were assumed to be equal to those of the general population. However, cancer survivors might run higher risks on some disease. Another limitation is that the quality of life and healthcare expenditures were estimated by simultaneously excluding respondents with breast, cervical, and colorectal cancer. Therefore, the final estimates of the healthcare expenditures and quality of life are unrelated to breast, cervical, and colorectal cancer. However, it is expected that the results would not change much, because the healthcare expenditure and quality of life losses for competing diseases depend on the prevalence of these competing diseases in the general population, which would not be changed dramatically when all the cancers were excluded simultaneously or separately for each cancer. The validity of the updating framework crucially depends on the age pattern at which mortality is impacted by screening. It was assumed that the impact at which the screening affects mortality follows the same pattern as the cause-specific cancer mortality. If this assumption does not hold, it indicates that the impact on the ICER is overestimated if mortality is impacted at a lower age because of screening. If the screening impacts mortality at a higher age than assumed, the impact is underestimated.

CONCLUSIONS

Despite the limitations, these findings have important practical and policy implications. The values of the quality of life losses and healthcare expenditures of competing risks that were estimated could be used in economic evaluations of interventions targeted at breast, cervical, and colorectal cancer in the U.S. In addition, it was shown how these estimates can be readily included in economic evaluations of such programs. The ideal way to include them in economic evaluations is to use appropriately developed tools to facilitate standardized inclusion.[54]

This study demonstrated the importance of including quality of life losses for competing diseases and the healthcare expenditures of competing risks in economic evaluations of life-extending interventions to support better medical decision making. The updates increased the ICERs in absolute terms and changed the relative ordering of the alternatives. In jurisdictions where interventions are accepted based on their cost per QALY, the inclusion of quality of life losses and healthcare expenditures for competing diseases may affect the decision about the acceptability of a given intervention. Decisions based on underestimated ICERs could translate into inefficient allocation of healthcare resources.

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SUPPLEMENTAL MATERIAL

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REFERENCES

1. Lansdorp-Vogelaar I, Knudsen AB, Brenner H. Cost-effectiveness of colorectal cancer screening. *Epidemiol Rev.* 2011;33(1):88–100. https://doi.org/10.1093/epirev/mxr004.
2. Esselen KM, Feldman S. Cost-effectiveness of cervical cancer prevention. *Clin Obstet Gynaecol.* 2013;56(1):55–64. https://doi.org/10.1097/GRF.0b013e3182823797.
3. Feig S. Cost-effectiveness of mammography, MRI, and ultrasonography for breast cancer screening. *Radiol Clin North Am.* 2010;48(5):879–891. https://doi.org/10.1016/j.rcl.2010.06.002.
4. Ahern CH, Shen Y. Cost-effectiveness analysis of mammography and clinical breast examination strategies: a comparison with current guidelines. *Cancer Epidemiol Biomarkers Prev.* 2009;18(3):718–725. https://doi.org/10.1158/1055-9965.EPI-08-0918.
5. O'Donoghue C, Eklund M, Ozanne EM, Esserman LJ. Aggregate cost of mammography screening in the United States: comparison of current practice and advocated guidelines. *Ann Intern Med.* 2014;160(3):145. https://doi.org/10.7326/M13-1217.
6. Konijeti GG, Shrime MG, Ananthakrishnan AN, Chan AT. Cost-effectiveness analysis of chromoendoscopy for colorectal cancer surveillance in patients with ulcerative colitis. *Gastrointest Endosc.* 2014;79(3):455–465. https://doi.org/10.1016/j.gie.2013.10.026.
7. Lieberman D. Colon cancer screening and surveillance controversies. *Curr Opin Gastroenterol.* 2009;25(5):422–427. https://doi.org/10.1097/MOG.0b013e32832d1e2a.
8. Sharek D. Screening mammography: a continued debate over the appropriate guidelines. *Int J Womens Health Wellness.* 2016;2(3):4–5. https://doi.org/10.23937/2474-1353/1510028.
9. Van Der Steen A, Knudsen AB, van Hees F, et al. Optimal colorectal cancer screening in states' low-income, uninsured populations - the case of South Carolina. *Health Serv Res.* 2015;50(3):768–789. https://doi.org/10.1111/1475-6773.12246.
10. Zauber AG. Cost-effectiveness of colonoscopy. *Gastrointest Endosc Clin N Am.* 2010;20(4):751–770. https://doi.org/10.1016/j.giec.2010.07.008.
11. Sanders GD, Neumann PJ, Basu A, et al. Recommendations for conduct, methodological practices, and reporting of cost-effectiveness analyses: Second Panel on Cost-Effectiveness in Health and Medicine. *JAMA.* 2016;316(10):1093–1103. https://doi.org/10.1001/jama.2016.12195.
12. Drummond M, Brixner D, Gold M, et al. Toward a consensus on the QALY. *Value Health.* 2009;12(suppl 1):S31–S35. https://doi.org/10.1111/j.1524-4733.2009.00522.x.
13. Garber AM, Phelps CE. Future costs and the future of cost-effectiveness analysis. *J Health Econ.* 2008;27(4):819–821. https://doi.org/10.1016/j.jhealeco.2008.05.002.
14. Meltzer DO. Accounting for future costs in medical cost-effectiveness analysis. *J Health Econ.* 1997;16(1):33–64. https://doi.org/10.1016/s0167-6296(96)00507-3.
15. Nyman JA. Should the consumption of survivors be included as a cost in cost-utility analysis? *Health Econ.* 2004;13(5):417–427. https://doi.org/10.1002/hec.850.
16. van Baal PH, Feenstra TL, Hoogenveen RT, De Wit GA, Brouwer WBF. Unrelated medical care in life years gained and the cost utility of primary prevention: in search of a 'perfect' cost−utility ratio. *Health Econ.* 2007;16(4):421–433. https://doi.org/10.1002/hec.1181.
17. van Baal P, Meltzer DO, Brouwer WBF. Future costs, fixed healthcare budgets, and the decision rules of cost-effectiveness analysis. *Health Econ.* 2016;25(2):237–248. https://doi.org/10.1002/hec.3138.
18. de Vries LM, van Baal PHM, Brouwer WBF. Future costs in cost-effectiveness analyses: past, present, future. *Pharmacoeconomics.* 2019;37(2):119–130. https://doi.org/10.1007/s40273-018-0749-8.
19. De Kok IMCM, Polder JJ, Habbema JD, et al. The impact of healthcare costs in the last year of life and in all life years gained on the cost-effectiveness of cancer screening. *Br J Cancer.* 2009;100(8):1240–1244. https://doi.org/10.1038/sj.bjc.6605018.
20. Fryback DG, Lawrence WF. Dollars may not buy as many QALYs as we think: a problem with defining quality-of-life adjustments. *Med Decis Mak.* 1997;17(3):276–284. https://doi.org/10.1177/0272989X9701700303.
21. Cohen JW.Design and methods of the Medical Expenditure Panel survey household component. https://meps.ahrq.gov/mepsweb/survey_comp/household.jsp. Updated June 25, 2019. Accessed July 30, 2019.
22. Brazier JE, Roberts J. The estimation of a preference-based measure of health from the SF-12. *Med Care.* 2004;42(9):851–859. https://doi.org/10.1097/01.mlr.0000135827.18610.0d.
23. Dunn A, Grosse SD, Zuvekas SH. Adjusting health expenditures for inflation: a review of measures for health services research in the United States. *Health Serv Res.* 2018;53(1):175–196. https://doi.org/10.1111/1475-6773.12612.
24. Basu A, Manca A. Regression estimators for generic health-related quality of life and quality-adjusted life years. *Med Decis Making.* 2012;32(1):56–69. https://doi.org/10.1177/0272989X11416988.
25. Mihaylova B, Briggs A, O'Hagan A, Thompson SG. Review of statistical methods for analysing healthcare resources and costs. *Health Econ.* 2011;20(8):897–916. https://doi.org/10.1002/hec.1653.
26. Bonneux L, Barendregt JJ, Nusselder WJ, der Maas PJ. Preventing fatal diseases increases healthcare costs: cause elimination life table approach. *BMJ.* 1998;316(7124):26–29. https://doi.org/10.1136/bmj.316.7124.26.
27. Grootjans-van Kampen I, Engelfriet PM, van Baal PHM. Disease prevention: saving lives or reducing health care costs? *PLOS ONE.* 2014;9(8):e104469. https://doi.org/10.1371/journal.pone.0104469.
28. Briggs A, Claxton K, Sculpher M. *Decision Modelling for Health Economic Evaluation*. Oxford, UK: Oxford University Press, 2006.
29. CDC. WONDER. Multiple cause of death data. https://wonder.cdc.gov/mcd.html. Accessed July 30, 2019.
30. Human mortality database. www.mortality.org/. Accessed July 30, 2019.
31. Manns B, Meltzer D, Taub K, Donaldson C. Illustrating the impact of including future costs in economic evaluations: an application to end−stage renal disease care. *Health Econ.* 2003;12(11):949–958. https://doi.org/10.1002/hec.790.
32. Meltzer D, Egleston B, Stoffel D, Dasbach E. Effect of future costs on cost-effectiveness of medical interventions among young adults: the example of intensive therapy for type 1 diabetes mellitus. *Med Care.* 2000;38(6):679–685. https://doi.org/10.1097/00005650-200006000-00009.
33. Lassman D, Hartman M, Washington B, Andrews K, Catlin A. US health spending trends by age and gender: selected years 2002–10. *Health Aff (Millwood).* 2014;33(5):815–822. https://doi.org/10.1377/hlthaff.2013.1224.
34. Heijink R, van Baal P, Oppe M, Koolman X, Westert G. Decomposing cross-country differences in quality adjusted life expectancy: the impact of value sets. *Popul Health Metr.* 2011;9(1):17. https://doi.org/10.1186/1478-7954-9-17.
35. Berger BM, Schroy PC 3rd, Dinh TA. Screening for colorectal cancer using a multitarget stool DNA test: modeling the effect of the intertest interval on clinical effectiveness. *Clin Colorectal Cancer.* 2016;15(3):e65–e74. https://doi.org/10.1016/j.clcc.2015.12.003.
36. Sharaf RN, Ladabaum U. Comparative effectiveness and cost-effectiveness of screening colonoscopy vs. sigmoidoscopy and alternative strategies. *Am J Gastroenterol.* 2013;108(1):120–132. https://doi.org/10.1038/ajg.2012.380.
37. Ladabaum U, Mannalithara A. Comparative effectiveness and cost effectiveness of a multitarget stool DNA test to screen for colorectal neoplasia. *Gastroenterology.* 2016;151(3). 427−439.e6 https://doi.org/10.1053/j.gastro.2016.06.003.
38. Ladabaum U, Allen J, Wandell M, Ramsey S. Colorectal cancer screening with blood-based biomarkers: cost-effectiveness of methylated septin 9 DNA versus current strategies. *Cancer Epidemiol Biomarkers Prev.* 2013;22(9):1567–1576. https://doi.org/10.1158/1055-9965.EPI-13-0204.

39. Kingsley J, Karanth S, Revere FL, Agrawal D. Cost effectiveness of screening colonoscopy depends on adequate bowel preparation rates – a modeling study. *PLOS ONE.* 2016;11(12):e0167452. https://doi.org/10.1371/journal.pone.0167452.
40. Balasubramanian A, Kulasingam SL, Baer A, et al. Accuracy and cost-effectiveness of cervical cancer screening by high-risk human papillomavirus DNA testing of self-collected vaginal samples. *J Low Genit Tract Dis.* 2010;14(3):185–195. https://doi.org/10.1097/LGT.0b013e3181cd6d36.
41. Kim JJ, Campos NG, Sy S, et al. Inefficiencies and high-value improvements in U.S. cervical cancer screening practice: a cost-effectiveness analysis. *Ann Intern Med.* 2015;163(8):589–597. https://doi.org/10.7326/M15-0420.
42. Mandelblatt JS, Lawrence WF, Womack SM, et al. Benefits and costs of using HPV testing to screen for cervical cancer. *JAMA.* 2002;287(18):2372–2381. https://doi.org/10.1001/jama.287.18.2372.
43. Vijayaraghavan A, Efrusy MB, Goodman KA, Santas CC, Huh WK. Cost-effectiveness of using human papillomavirus 16/18 genotype triage in cervical cancer screening. *Gynecol Oncol.* 2010;119(2):237–242. https://doi.org/10.1016/j.ygyno.2010.07.004.
44. Stout NK, Lee SJ, Schechter CB, et al. Benefits, harms, and costs for breast cancer screening after US implementation of digital mammography. *J Natl Cancer Inst.* 2014;106(6). dju092 https://doi.org/10.1093/jnci/dju092.
45. Shen Y, Parmigiani G. A model-based comparison of breast cancer screening strategies: mammograms and clinical breast examinations. *Cancer Epidemiol Biomarkers Prev.* 2005;14(2):529–532. https://doi.org/10.1158/1055-9965.EPI-04-0499.
46. Neumann PJ. *Using Cost-Effectiveness Analysis to Improve Health Care: Opportunities and Barriers.* New York, NY: Oxford University Press, 2005.
47. Fryback DG, Dunham NC, Palta M, et al. US norms for six generic health-related quality-of-life indexes from the National Health Measurement Study. *Med Care.* 2007;45(12):1162–1170. https://doi.org/10.1097/MLR.0b013e31814848f1.
48. Gheorghe M, Brouwer WBF, van Baal PHM. Did the health of the Dutch population improve between 2001 and 2008? Investigating age- and gender-specific trends in quality of life. *Eur J Health Econ.* 2015;16(8):801–811. https://doi.org/10.1007/s10198-014-0630-4.
49. Hanmer J, Lawrence WF, Anderson JP, Kaplan RM, Fryback DG. Report of nationally representative values for the noninstitutionalized US adult population for 7 health-related quality-of-life scores. *Med Decis Mak.* 2006;26(4):391–400. https://doi.org/10.1177/0272989X06290497.
50. van Baal PHM, Feenstra TL, Polder JJ, Hoogenveen RT, Brouwer WBF. Economic evaluation and the postponement of health care costs. *Health Econ.* 2011;20(4):432–445. https://doi.org/10.1002/hec.1599.
51. Gheorghe M, Brouwer WBF, van Baal PHM. Quality of life and time to death: have the health gains of preventive interventions been underestimated? *Med Decis Making.* 2015;35(3):316–327. https://doi.org/10.1177/0272989X14555771.
52. Stearns SC, Norton EC. Time to include time to death? The future of health care expenditure predictions. *Health Econ.* 2004;13(4):315–327. https://doi.org/10.1002/hec.831.
53. Zweifel P, Felder S, Meiers M. Ageing of population and health care expenditure: a red herring? *Health Econ.* 1999;8(6):485–496. https://doi.org/10.1002/(sici)1099-1050(199909)8:6<485::aid-hec461>3.0.co;2-4.
54. van Baal PHM, Wong A, Slobbe LC, Polder JJ, Brouwer WB, de Wit GA. Standardizing the inclusion of indirect medical costs in economic evaluations. *Pharmacoeconomics.* 2011;29(3):175–187. https://doi.org/10.2165/11586130-000000000-00000.