Systematic Review of the Cost Effectiveness of Breast Cancer Prevention, Screening, and Treatment Interventions

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INTRODUCTION

It has been nearly 5 decades since Congress passed the 1971 National Cancer Act to strengthen the National Cancer Institute's ability to eliminate the suffering from cancer.¹ Most early efforts of the National Cancer Institute focused on development of cancer therapeutics. Later, Congress passed the 21st Century Cancer Access to Life-Saving Early Detection, Research and Treatment Act to increase the national research focus on prevention and early detection.²

Data from this period in US health care history suggest that the investments in prevention, screening, and treatment have together reduced cancer mortality by 27% over the past quarter of a century.³ The present era holds the promise to further reduce mortality with an explosion of scientific discoveries and new technologies based on knowledge about personal, lifestyle, genetic, and molecular disease factors.⁴⁻⁹ Although these recent advances have the potential to avoid cancer incidence,¹⁰ detect cancer earlier, and/or improve cancer survival, it has become increasingly complex to determine which intervention has the best value or the greatest improvement in health outcomes for the US population at the most reasonable and affordable costs.^{11,12}

Economic evaluation provides data on several aspects of cancer care that can be used to address discussions about value and inform policies and guidelines.^{13,14} Cost-effectiveness analysis is the most common economic evaluation tool currently used to inform public health policy decisions, resource allocation, and investment decisions (eg, purchase of equipment or coverage of a specific drug). Although cost effectiveness does not capture all aspects of value to the system, payers, or consumers, it can be useful to assess whether investments in a new technology or drug extend life and at what added cost compared with current standard of care.

In this study, we review modern breast cancer prevention, screening, and treatment cost-effectiveness analyses. We focus on breast cancer because it is a common cancer, accounts for the largest proportion of

cancer economic analyses,¹⁵ has seen major advances in technology and shifts in treatment paradigms, and has cost-effectiveness analyses research spanning prevention through treatment. The results of the review are intended to determine whether new technology and therapies have improved population breast cancer outcomes at reasonable ranges of economic value, highlight gaps in the field, and inform the design of future economic analyses conducted to inform decisions about the value and prioritization of investments in breast cancer prevention and control.

METHODS

This study used study-level results and was exempt from institutional review board approval at Georgetown University. The review followed the guidelines included in the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA),¹⁶ and is registered in the International Prospective Register of Systematic Reviews (PROSPERO, ID CRD42019149014).¹⁷

Search Strategy

We conducted a PubMed search using the following Medical Subject Headings terms individually using the National Library of Medicine controlled vocabulary thesaurus used for indexing articles: "cost-effectiveness analysis" or "economic model" or "cost utility analysis" or "cost benefit" or "economic analysis" and "breast cancer." We included English-language original research articles published from January 1, 2015, to August 12, 2019, that included costs and life-years saved or quality-adjusted life-years (QALYs) saved with breast cancer primary prevention, screening, or systemic treatment in the United States, Europe, and Canada as a result of similarities in rates of disease and populations. We excluded reviews, articles that only included costs or effects alone, article on other topics (eg, mammography reading methods, ancillary services to get women to screening facilities, radiation and surgical techniques, and tertiary prevention and follow-up care), or duplicate publications of the same analysis. Two authors reviewed the articles for final eligibility; any disagreements were resolved via conferencing. We chose the earlier date of 2015 to represent current screening

Author affiliations and support information (if applicable) appear at the end of this article.

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and treatment; earlier studies have been reviewed previously.¹⁵ We also provided an overall summary of the median QALYs per person across studies within phases of cancer control.

Finally, we assessed the quality of each reviewed study using the International Society for Pharmacoeconomics and Outcomes Research (ISPOR) Consolidated Health Economic Evaluation Reporting Standards (CHEERS) checklist.¹⁸ This checklist is composed of 24 items suggested for inclusion when reporting economic evaluations of health care interventions. For each item, the studies received a score of 0 (item is absent), 0.5 (item is partially fulfilled), or 1 (item is present). We separately assessed the number of studies that have conducted model validation according to the recommendations of the ISPOR–Society for Medical Decision Making Modeling Good Research Practices Task Force.¹⁹

RESULTS

We identified 390 potentially eligible studies. After removal of ineligible or duplicate articles, a total of 64 articles were included in the review (Fig 1); 13% evaluated primary prevention ($n = 8$), 30% evaluated screening ($n = 19$), and 58% evaluated treatment ($n = 37$). The characteristics and results of the studies are listed in Table 1. None of the studies simultaneously evaluated the relative cost effectiveness of all phases of breast cancer control.

Prevention

There were 8 cost-effectiveness analyses on primary prevention²⁰⁻²⁷; one used observational data, and the remainder were model based.²² None of the studies included prevention via tamoxifen, elimination of carcinogenic environmental exposures, or lifestyle change, despite some evidence of effectiveness. The economic analyses for prevention

FIG 1. Selection of cost-effectiveness analysis (CEA) studies in breast cancer published from 2015 to 2019. The PRISMA diagram depicts the flow of studies through the phases of the systematic review from study identification to data synthesis. A priori reasons for exclusion are presented at each stage.

TABLE 1. Cost Effectiveness of Cancer Prevention, Screening, and Treatment Interventions

Study	Methods	Population	Intervention	Incremental Costs (per woman)	Incremental QALY (per woman)	ICER	Conflicts of Interest Reported
Prevention							
Manchanda et al, ²⁰ 2015	Model; discount rate 3.5%; 2014 US dollars; UK National Health Service	UK or US non-Jewish women	Population <i>BRCA1/BRCA2/RAD51C/RAD51D/BRIP1/PALB2</i> mutation testing v testing with > 10% prior probability; includes surveillance and preventive surgery	\$412	0.0075	\$49,300/QALY	Yes
Li et al, ²¹ 2017	Model; discount rate 3%; 2015 US dollars; payer perspective	Hypothetical cohort of 40-year-old women eligible for testing using NCCN criteria, United States	Genetic testing for <i>BRCA</i> and intermediate-risk mutations and preventive surgery v <i>BRCA</i>	\$280	0.006	\$48,300/QALY for 7-gene test variants in <i>BRCA1</i> , <i>BRCA2</i> , <i>TP53</i> , <i>PTEN</i> , <i>CDH1</i> , <i>STK11</i> , and <i>PALB2</i> v <i>BRCA1/2</i>	Yes
Schrauder et al, ²² 2017	Observed data; discount rate not reported; unknown year for euros; German health care system	University clinic, Germany	Mastectomy and oophorectomy in unaffected women with known <i>BRCA</i> mutations (no test costs)	NE: Previously published data	NE: Previously published data	Undiscounted €1,695-€39,100/LYS for risk-reducing surgery	Yes
Manchanda et al, ²³ 2018	Model; discount rate 3.5%; 2010 US dollars; health care system/payer's perspective	UK Ashkenazi Jewish women	Population <i>BRCA</i> mutation testing v testing with > 10% prior probability; includes surveillance and preventive surgery	Saves £34	0.031	Cost and QALY saving	Yes
Norum et al, ²⁴ 2018	Model; discount rate 3%; 2015 US dollars; societal perspective	Oslo, Norway	Genetic testing for <i>BRCA</i> mutations in all breast cancer patients v patients with FH; no preventive surgery considered	\$631	0.1113 LYG	€5,669/LYG	Yes
Patel et al, ²⁵ 2018	Model; discount rate 3.5%; 2015 US dollars; health system/payer perspective	US or UK Sephardic Jewish women	Genetic testing for <i>BRCA</i> mutations, surveillance, and preventive surgery in Sephardic Jewish women v general population testing	Saves £67.08 Saves \$308.52	Fewer 1.0016 Fewer 1.0005	£67.04/QALY \$308.42/QALY	Yes
Asphaug and Melberg, ²⁶ 2019	Model; discount rate 4%; 2016 US dollars; health care sector perspective	Norway, 55-year-old women	7-gene panel v genetic testing for <i>BRCA</i> only 14-gene panel v genetic testing for <i>BRCA</i> only	\$510.70 \$71.20	0.0096 0.0006	\$53,300/QALY \$127,071/QALY	Yes

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TABLE 1. Cost Effectiveness of Cancer Prevention, Screening, and Treatment Interventions (continued)

Study	Methods	Population	Intervention	Incremental Costs (per woman)	Incremental QALY (per woman)	ICER	Conflicts of Interest Reported
Müller et al, ²⁷ 2019	Model; discount rate 3%; year of dollars not reported; German statutory health insurance perspective	Germany	BRCA testing, surveillance, and preventive surgery in women with > 10% probability of mutations v no testing	€29,434	0.43	€17,027/QALY	Yes
Screening							
Gocgun et al, ²⁸ 2015	Model; discount rate 3%; converted to present value but year not reported; health system perspective	Canada	Various screening policies to study the impact of mammography screening for age-based subpopulations v no screening	\$3,391,056-\$20,555,085 (per 10,000 women)	6.3-18.5 deaths averted (per 10,000 women)	\$537,410-\$1,109,886 per death averted	Yes
Sprague et al, ²⁹ 2015	Collaborative CISNET modeling; discount rate 3%; 2013 US dollars; payer perspective	US population	Biennial mammography and ultrasound for women age 50-74 years; heterogeneously or extremely dense breasts	\$560	0.0017	\$329,000/QALY for ultrasound plus biennial mammography v biennial mammography for women age 50-74 years	Yes
Sankatsing et al, ³⁰ 2015	Single CISNET model; discount rate 3.5%; unknown year for euros; health care payer perspective	Netherlands	Biennial mammography screening at age 49-74 v 50-74 years	€475	0.07 LYS	€18,800/LYS	Yes
Lee et al, ³¹ 2015	Single CISNET model; 1980 birth cohort; discount rate 3%; 2013 US dollars; federal payer perspective	United States	Digital mammography plus 3D mammography v digital alone, dense breasts, biennial, age 50-74 years	\$349	0.007	\$53,900/QALY	Yes
Arrospe et al, ³² 2016	Adapted CISNET single model; discount rate 3%; unknown year for euros; Basque National Health Service perspective	Spain	Organized population screening program v no screening; 50,000 women	€728	0.17	€4,214/QALY	Yes
Trentham-Dietz et al, ³³ 2016	Collaborative CISNET modeling; discount rate 3%; 2014 US dollars; Medicare perspective	US population	Digital mammography schedules by risk	Not provided	Not provided	~\$269,000/QALY for annual screening in low risk to \$26,000/QALY in 2× average risk	Yes
Rafia et al, ³⁴ 2016	Model; discounted rate 3.5%; 2008-2009 UK pounds; NHS perspective	England and Wales	Triennial screening ages 50-70 v 50-73 to 90 years (selected: age 78 v 75)	£34.81	0.00231	£15,000/QALY	Yes
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TABLE 1. Cost Effectiveness of Cancer Prevention, Screening, and Treatment Interventions (continued)

Study	Methods	Population	Intervention	Incremental Costs (per woman)	Incremental QALY (per woman)	ICER	Conflicts of Interest Reported
Obdeijn et al, ³⁵ 2016	Single CISNET model; 1980 birth cohort; discount rate 3.5%; unknown year for euros; health care payer perspective	Netherlands	Starting ages for mammography screening: age 30 v 40 years in <i>BRCA</i> carriers; all have MRI	Saves €545.8	0.002 fewer LYS	€272,900/LYS	Yes
Mittman et al, ³⁶ 2015	Single CISNET model; discount rate 5%; 2012 US dollars; Canadian societal perspective	Canadian population	Plain film mammogram screening intervals and start and end ages; 11 strategies	\$1,388-\$6,943	14.06-14.09	\$94,762-\$262,828/QALY	Yes
Schiller-Fruehwirth et al, ³⁷ 2017	Model; discount rate 3%; 2012 euros; health care payer perspective	Austria	Organized v opportunistic screening	Saves euro 10.90	0.009 LYS	Dominant	Yes
Van Luijt et al, ³⁸ 2017	Single CISNET model; discount rate 3.5%; unknown year of dollars; societal perspective	Norway	Screening invitations age ≥ 50 years v no screening	2,848 kroner	0.0254	112,200 kroner/QALY	Yes
Morton et al, ³⁹ 2017	Model; discount rate 3.5%; 2008-2009 pounds; UK NHS perspective	UK	Biennial screening age 50-74 years v no screening	NE	NE	£11,546/QALY	Yes
Gray et al, ⁴⁰ 2017	Model; discount rate 3.5%; 2015 US dollars; UK NHS perspective	UK	Risk- and/or density-tailored screening v age-based screening	NE	NE	£16,689/QALY and £23,924/ QALY for risk-based screening v usual program	Yes
Koleva-Kolarov et al, ⁴¹ 2018	Model; discount rate 3%; unknown year for euros; Dutch payer perspective	Netherlands	Biennial screening at age 46-74 v 50-74 years	€145	0.01182 LYS	€126,000/LYS for 46-74 v 48-74	Yes
Kalra et al, ⁴² 2016	Model; discount rate 3%; 2015 US dollars; federal payer perspective	US	Digital v3D (tomosynthesis), age 40-79 years	\$812	0.04	\$20,300/QALY	No
Pashayan et al, ⁴³ 2018	Model; discount rate 3.5%; unknown year of pounds; UK NHS perspective	UK	Polygenic risk-based (70th percentile) v age-based triennial screening, age 50-69 years	Saves £537	0.0443	Dominant	Yes
Phi et al, ⁴⁴ 2019	Single CISNET model; discount rate 3%; 2017 US dollars; payer perspective	Netherlands	Annual MRI and mammography v mammography alone, age 60-74 years, <i>BRCA</i> mutation carriers	€68.2	0.00132 LYS	€156,000/LYS	Yes

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TABLE 1. Cost Effectiveness of Cancer Prevention, Screening, and Treatment Interventions (continued)

Study	Methods	Population	Intervention	Incremental Costs (per woman)	Incremental QALY (per woman)	ICER	Conflicts of Interest Reported
Tina Shih et al, ⁴⁵ 2019	Model; discount rate 3%; 2017 US dollars; societal perspective	US population	Different digital screening strategies; each compared with no screening	\$1,016	0.026	\$40,000/QALY for annual age 45-54 years, biennial age 55-74 years v no screening	NE
Rim et al, ⁴⁶ 2019	Model; discount rate 3%; 2018 US dollars; societal perspective	United States; CDC Early Breast and Cervical Cancer Screening Program, 1.8 million women	Mammography v no screening	\$3,533	0.071	\$49,800/QALY v no screening	Yes
Treatment, neoadjuvant/ adjuvant							
Lairson et al, ⁴⁷ 2015	Observational data: SEER- Medicare; discount rate at 3%; 2009 US dollars; US payer perspective	United States	Anthracycline v no chemotherapy	\$32,672	4.24	\$7,688/QALY	Yes
			Non-anthracycline based v anthracycline	\$3,736	Fewer 2.49	Dominated	
Attard et al, ⁴⁸ 2015	Model; discount rate 5%; 2014 Canadian dollars; Canadian health care payer perspective	Canada	Pertuzumab, trastuzumab, and docetaxel v trastuzumab and docetaxel	\$7,879	0.310	\$25,388/QALY	Yes
			Pertuzumab, docetaxel, carboplatin, and trastuzumab v docetaxel, carboplatin, and trastuzumab	\$14,337	0.310	\$46,196/QALY	
Kwon et al, ⁴⁹ 2017	Model; discount rate 3%; 2016 US dollars; societal perspective	Canada	Extended tamoxifen v no further treatment	\$2,476	0.62 LYG	\$4,042/LYG	Yes
			Ovarian ablation and aromatase inhibitor v extended tamoxifen	\$10,762	Fewer 0.25 LYG	Dominated	
Seferina et al, ⁵⁰ 2017	Model; discount rate 4% for cost, 1.5% health effects; 2012 euros; Dutch health care perspective	Netherlands	Trastuzumab v no trastuzumab (real-world scenario)	€3,560	0.827	€4,304/QALY	Yes
Clarke et al, ⁵¹ 2017	Model; discount rate 3.5%; 2013-2014 pounds; UK NHS payer perspective	UK	9-week adjuvant trastuzumab duration v no trastuzumab	£3,110	1.4	£2,221/QALY	Yes
			12-month v 9-week adjuvant trastuzumab duration	£23,197	Fewer 0.8	Dominated	
Garrison et al, ⁵² 2019	Model, trial based; discount rate 3%; 2017 US dollars; US payer perspective	United States	Pertuzumab, trastuzumab, and chemotherapy v trastuzumab and chemotherapy	\$74,420	0.45	\$167,185/QALY	Yes

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TABLE 1. Cost Effectiveness of Cancer Prevention, Screening, and Treatment Interventions (continued)

Study	Methods	Population	Intervention	Incremental Costs (per woman)	Incremental QALY (per woman)	ICER	Conflicts of Interest Reported
Hajjar et al, ⁵³ 2019	Model; discount rate 3%; 2016 US dollars; societal perspective	United States (age 40-49 years)	Adjuvant paclitaxel and trastuzumab v no adjuvant trastuzumab	\$69,829	6.6	\$10,584/QALY	Yes
Treatment, metastatic or advanced breast cancer			Doxorubicin, cyclophosphamide, paclitaxel, and trastuzumab v adjuvant paclitaxel and trastuzumab	\$43,324	Fewer 0.71	Dominated	
			Docetaxel, carboplatin, and trastuzumab v adjuvant paclitaxel and trastuzumab	\$19,823	Fewer 1.15	Dominated	
Xie et al, ⁵⁴ 2015	Model; discount rate 3%; 2014 US dollars; US payer perspective	United States	Everolimus and exemestane v exemestane	\$55,224	0.39	\$139,740/QALY	Yes
Kourlaba et al, ⁵⁵ 2015	Model; discount rate 3.5%; 2014 euros; third-party payer perspective	Greece	Everolimus and exemestane v fulvestrant	\$26,191	0.17	\$157,749/QALY	Yes
			Everolimus and exemestane v tamoxifen	\$34,630	0.30	\$115,624/QALY	
			Everolimus and exemestane v bevacizumab and paclitaxel	Savings €12,958	0.035	Dominant	
Le et al, ⁵⁶ 2016	Model; discount rate 3%; 2015 US dollars; societal perspective;	United States	Everolimus and exemestane v bevacizumab and capecitabine	Savings €7,800	0.004	Dominant	Yes
			Trastuzumab emtansine v lapatinib plus capecitabine	\$61,906	0.336	\$183,828/QALY	
			Trastuzumab emtansine v monotherapy with capecitabine	\$114,581	0.909	\$126,001/QALY	
Beauchemin et al, ⁵⁷ 2016	Model; discount rate 5%; 2015 Canadian dollars; Canadian health care system perspective	Canada	Lapatinib and letrozole v letrozole alone	\$49,559	0.38	\$131,811/QALY	Yes
			Lapatinib and letrozole v trastuzumab and anastrozole	\$11,643	0.21	\$56,211/QALY	
			Lapatinib and letrozole v anastrozole alone	\$49,736	0.49	\$102,477/QALY	
Diaby et al, ⁵⁸ 2016	Model; discount rate 3.5%; 2015 US dollars; US Centers for Medicaid and Medicare Services perspective	United States	Different treatment strategies that can be used for patients with newly diagnosed HER2- positive metastatic breast cancer	\$25,991-\$159,991	0.13-0.40	\$197,012-\$398,444/QALY	Yes
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TABLE 1. Cost Effectiveness of Cancer Prevention, Screening, and Treatment Interventions (continued)

Study	Methods	Population	Intervention	Incremental Costs (per woman)	Incremental QALY (per woman)	ICER	Conflicts of Interest Reported
Durkee et al, ⁵⁹ 2016	Model; discount rate of 3%; 2014 US dollars; societal perspective	United States	Docetaxel, trastuzumab, and pertuzumab v docetaxel and trastuzumab	\$294,747	0.62	\$472,668/QALY	Yes
Raphael et al, ⁶⁰ 2017	Model; discount rate 5%; unknown year of dollars; Canadian health care payer perspective	Canada	Letrozole and palbociclib v letrozole	\$161,508	1.22 (14.7 QALM)	\$131,989/QALY (\$10,999/ QALM)	Yes
Sabale et al, ⁶¹ 2017	Model; discount rate 3%; 2015/2016 euros; Swedish national payer perspective	Sweden	Fulvestrant v letrozole	€14,986	0.442	€33,883/QALY	Yes
			Fulvestrant v anastrozole	€13,283	0.393	€33,808/QALY	
			Fulvestrant v exemestane	€13,862	0.282	€49,225/QALY	
Shapiro et al, ⁶² 2017	Model; incremental costs per mean SRE avoided; discount rate of 3%; 2015 US dollars; US payer perspective	United States	Denosumab v monthly zoledronic acid	\$47,910	0.57 SREs/0.01- 0.02 fewer QALYs	Dominated	Yes
			Zoledronic acid every 3 months v monthly zoledronic acid	Savings \$3,622	0.01 fewer SREs/ 0-0.01 QALY gained	Dominant	
Mamiya et al, ⁶³ 2017	Model; discount rate 3%; 2015 US dollars; societal perspective	United States	Palbociclib and letrozole v letrozole	\$244,326	0.32	\$768,498/QALY	Yes
			Palbociclib and fulvestrant v fulvestrant	\$114,591	0.12	\$918,166/QALY	
Matter-Walstra et al, ^{64,65} 2017	Model; discount rate 3%; CHF value for updated results was not provided; Swiss health care system perspective	Switzerland	Palbociclib and letrozole v letrozole	Updated value not available	1.00	CHF 143,585/QALY	Yes
van Kampen et al, ⁶⁶ 2017	Model; discount rate for costs and effects, 4% and 1.5%, respectively; 2012 euros; Dutch health care perspective	Netherlands	Bevacizumab and taxane v taxane alone (real world)	€56,213	0.362 (undiscounted)	€155,261/QALY	Yes
Mistry et al, ⁶⁷ 2018	Model; discount rate 3%; 2016 US dollars; US private third-party payer perspective	United States	Ribociclib and letrozole v palbociclib and letrozole	Savings \$43,037	0.086	Dominant	Yes
			Ribociclib and letrozole v letrozole alone	\$144,915	0.689	\$210,369/QALY	
Galve-Calvo et al, ⁶⁸ 2018	Model; discount rate 3%; 2017 euros; Spanish National Health System perspective	Spain	Ribociclib and letrozole v Palbociclib and letrozole	€439.86	0.285	€1544/QALY	Yes

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TABLE 1. Cost Effectiveness of Cancer Prevention, Screening, and Treatment Interventions (continued)

Study	Methods	Population	Intervention	Incremental Costs (per woman)	Incremental QALY (per woman)	ICER	Conflicts of Interest Reported
Petitjean et al, ⁶⁹ 2019	Model; discount rate 4%; 2016 euros; third-party payer perspective	France	Bevacizumab and paclitaxel v paclitaxel alone (overall population)	€27,390	0.48	\$56,721/QALY	Yes
Telford et al, ⁷⁰ 2019	Model; discount rate 3.5%; 2016 British pounds sterling; UK NHS payer and personal social services perspective	UK	Fulvestrant v anastrozole	£18,867	0.55	£34,109/QALY	Yes
			Fulvestrant v letrozole	£23,097	0.77	£29,827/QALY	
			Fulvestrant v tamoxifen	£17,131	0.76	£22,532/QALY	
Zhang et al, ⁷¹ 2019	Model; discount rate 3%; 2018 US dollars; US payer perspective	United States	Palbociclib and fulvestrant v fulvestrant	\$277,504	0.568	\$488,854/QALY	Yes
Zhang and Long, ⁷² 2019	Model; discount rate 3%; 2016 US dollars; US health care system perspective	United States	Palbociclib and letrozole v letrozole	\$304,510	0.48	\$634,000/QALY	Yes
			Ribociclib and letrozole v letrozole	\$378,335	0.86	\$440,000/QALY	
Treatment selection							
Blank et al, ⁷³ 2015	Model; discount rate 3%; 2010 euros; German third-party payer perspective	Austria	EndoPredict (Myriad, Salt Lake City, UT) alone v German-S3 guideline alone to decide on chemotherapy use	Savings €2,712	0.004	Dominant	Yes
Katz et al, ⁷⁴ 2015	Model; discount rate 4%; 2013 euros; societal perspective	France	Oncotype DX (Genomic Health, Redwood City, CA) v standard care	Savings €601.97	0.17	Dominant	Yes
Kip et al, ⁷⁵ 2015	Model; discount rate for costs and effects, 4% and 1.5%, respectively; 2012 euros; Dutch health care payer's perspective	Netherlands	Oncotype DX testing to support adjuvant chemotherapy recommendations v current clinical practice	€1,236	0.11	€11,236/QALY	Yes
Miquel-Cases et al, ⁷⁶ 2015	Model; discount rate for costs and effects, 4% and 1.5%, respectively; 2013 euros; Dutch societal perspective	Netherlands	Targeted treatment with high-dose alkylating chemotherapy (ie, <i>BRCA1</i> -like strategy) v no testing with standard (anthracycline-based) chemotherapy treatment	€76,369	0.93	€81,981/QALY	Yes
Raldow et al, ⁷⁷ 2016	Model; discount rate 3%; 2013 US dollars; Medicare perspective	United States; 60-year-old women	Five treatment strategies based on Oncotype DX DCIS testing, Oncotype DX DCIS score, and/or grade with or without radiation	\$1,553-\$4,526	0-0.01	No strategy incorporating the Oncotype DX DCIS score was cost effective	Yes
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TABLE 1. Cost Effectiveness of Cancer Prevention, Screening, and Treatment Interventions (continued)

Study	Methods	Population	Intervention	Incremental Costs (per woman)	Incremental QALY (per woman)	ICER	Conflicts of Interest Reported
Marguet et al, ⁷⁸ 2016	Model; both costs and benefits were discounted according to guidelines in the 3 countries; 2013 euros; perspective of the health care system of each country	France Germany Netherlands	Urokinase plasminogen activator (uPA)/plasminogen activator inhibitor-1 (PAI-1)	Savings €4,179	Fewer 0.04	€104,475/QALY	Yes
			chemotherapy decisions v chemotherapy to all patients (age 50-75 years)	Savings €7,245	Fewer 0.07	€103,500/QALY	
				Savings €8,052	Fewer 0.12	€67,100/QALY	
Jahn et al, ⁷⁹ 2017	Model; discount rate by 5%; unknown year of euros; health care system perspective	Austria/Canada	Omission of adjuvant chemotherapy v adjuvant chemotherapy in risk groups based on Adjuvant! Online and Oncotype DX for 12 scenarios in Austria and Canada	Austria: €12,236-€2,687 in savings; Canada: €6,375-€578 in savings	Austria: 3.98 fewer to 0.39 gains; Canada: 0.91 fewer to 3.96 gains	Omission of chemotherapy was dominant in women with low Oncotype DX risk independent of Adjuvant! Online risk and in women with low Adjuvant! Online risk and intermediate risk Oncotype DX risk	Yes
Chandler et al, ⁸⁰ 2018	Model; discount rate 3%; 2015 US dollars; societal perspective	United States	Community Oncotype DX use v usual care	\$301	0.0016	\$188,125/QALY	Yes
Ibarrondo et al, ⁸¹ 2018	Model; discount rate 3%; unknown year of euros; societal perspective	Spain	Oncotype DX v standard of treatment based on clinical and pathologic criteria	Savings €849	0.09	Dominant	Yes
Wang et al, ⁸² 2019	Model; 3 clinical risk groups according to the PREDICT model; discount rate 3%; 2015 US dollars; US payer perspective	United States	In PREDICT low-risk group, chemotherapy to women with Oncotype DX recurrence score ≥ 31 v no testing, no chemotherapy	\$3,600	0.03	\$124,600/QALY	Yes
			In PREDICT intermediate-risk group, chemotherapy to women with Oncotype DX recurrence score ≥ 31 v no testing, no chemotherapy	\$5,000	0.18	\$28,700/QALY	
			In PREDICT high-risk group, chemotherapy to women with Oncotype DX recurrence score ≥ 31 v no testing, no chemotherapy	\$5,200	0.33	\$15,700/QALY	
Ozmen et al, ⁸³ 2019	Model; discount rate and year of dollar values not reported; national insurance perspective	Turkey	Oncotype DX v usual care	\$4,919.3	0.68	\$7,207.9/QALY	Yes

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TABLE 1. Cost Effectiveness of Cancer Prevention, Screening, and Treatment Interventions (continued)

Study	Methods	Population	Intervention	Incremental Costs (per woman)	Incremental QALY (per woman)	ICER	Conflicts of Interest Reported
Hannouf et al, ⁸⁴ 2019	Model; discount rate 1.5%; 2017 Canadian dollars; Canadian public health care system	Canada	12-gene RS assay (EndoPredict) plus clinicopathologic predictors v clinicopathologic predictors alone	NE	NE	\$36,274/QALY	Yes
			58-gene RS assay (Prosigna; NanoString Technologies, Seattle, WA) plus clinicopathologic predictors v clinicopathologic predictors alone	NE	NE	\$48,525/QALY	
			21-gene RS assay (Oncotype DX) plus clinicopathologic predictors v clinicopathologic predictors alone	NE	NE	\$74,911/QALY	

Abbreviations: 3D, 3-dimensional; CDC, Centers for Disease Control and Prevention; CHF, Swiss franc; CISNET, Cancer Intervention and Surveillance Modeling Network; DCIS, ductal carcinoma in situ; FH, family history; HER2, human epidermal growth factor receptor 2; ICER, incremental cost-effectiveness ratio; LY, life-year; LYG, life-years gained; LYS, life-years saved; MRI, magnetic resonance imaging; NCCN, National Comprehensive Cancer Network; NE, not estimable from data presented; NHS, National Health Service; QALM, quality-adjusted life-month; QALY, quality-adjusted life years; RS, recurrence score; SRE, skeletal-related event; UK, United Kingdom.

evaluated the cost effectiveness of testing for cancer-predisposing genes (breast and ovarian cancer) followed by prophylactic surgery. *BRCA* mutation testing for unaffected and affected women with a 10% or greater prior probability of having a mutation and cascade testing of relatives of affected women with mutations were cost-effective strategies when accompanied by prophylactic bilateral mastectomy and oophorectomy, with the lowest costs when preventive surgery occurred at younger versus older ages.^{21-25,27} *BRCA* testing in the general population was not cost effective unless it was targeted to Ashkenazi or Sephardic Jewish women.^{20,25} Testing for intermediate-risk and *BRCA* mutations was also cost effective among high-risk populations.^{21,23,26} Overall, these analyses demonstrated that cost effectiveness of mutation testing depends on the expected population prevalence and optimistic assumptions about the uptake of surgery among carriers.

Screening

Nineteen articles examined breast cancer screening, comparing different screening schedules, newer versus older technology, and/or targeting screening schedules by risk of breast cancer.²⁸⁻⁴⁶ All of the screening analyses relied on modeling. Two of the studies used multiple models sharing common input analyses.^{29,33}

Most of the analyses examining population screening strategies examined the ages of initiation or cessation and intervals of screening (from annual to triennial).^{28-31,34-36,38-45} The results were consistent in finding that biennial screening from ages 50-69 or 50-74 years was the most efficient (ie, there were no other strategies that saved more QALYs for the same costs). Results of several analyses suggested that annual screening from ages 40-49 or 45-54, followed by biennial screening, was also efficient and resulted in costs per QALY that are within current willingness-to-pay (WTP) thresholds of \$100,000 per QALY (eg, Tina Shih et al⁴⁵). There was also a consistent finding that annual screening had unfavorable cost-effectiveness ratios compared with biennial strategies as a result of the higher costs of the increased number of mammograms and evaluation of false-positive tests relative to a small gain in life-years.

The major new technology evaluated for general population screening was tomosynthesis. Two analyses^{31,42} found a minimal improvement in QALYs and a wide range of costs using observational data for test performance and based on a variety of assumptions about uncertain data. At least one of these analyses had industry-relevant conflicts of interest that could potentially lead to bias in the methods, findings, and interpretation of findings.

Several publications examined risk-based screening, with risk determined from polygenic testing, epidemiologic risk calculators, breast density, or a combination of these factors.^{29,31,33,35,40,43,44} Uniformly, these analyses found that risk-based screening was more cost effective than standard age-based guidelines, with larger gains in QALYs than those seen using new technologies.

Systemic Treatment

Cost-effectiveness analyses of drug treatments are relatively common. A total of 70 interventions were evaluated in the 37 studies. There was heterogeneity in the evidence concerning the cost effectiveness of treatment and treatment selection for breast cancer as a result of variability in choice of comparators, context, whether therapy was being used in the adjuvant or metastatic setting, subtype of the patient population, and perspective.

Neoadjuvant and adjuvant therapy. A total of 7 articles estimated the cost effectiveness of chemotherapy (n = 2), hormone receptor–targeted therapy (n = 1), and human epidermal growth factor receptor 2 (HER2)–targeted therapy (n = 4) in the neoadjuvant and adjuvant settings.⁴⁷⁻⁵³ Adjuvant treatment with anthracyclines⁴⁷ had favorable incremental cost-effectiveness ratios (ICERs) compared with non-anthracycline-based chemotherapy regimens (dominated) or no chemotherapy (\$7,688 per QALY) considering a WTP threshold of \$100,000 per QALY among elderly women diagnosed with hormone receptor–positive, stage I, II, or IIIA breast cancer. Among women with hormone receptor–positive tumors, extended tamoxifen was more cost effective compared with ovarian ablation plus aromatase inhibitors (dominated) or no further treatment (\$4,042 per life-year).⁴⁹ In women with HER2-positive cancers, trastuzumab was cost effective compared with no trastuzumab according to analyses conducted in the Netherlands (€4,304 per QALY)⁵⁰ and the United Kingdom (£2,221 per QALY),⁵¹ considering a WTP threshold of €80,000 per QALY in the Netherlands and £30,000 per QALY in the United Kingdom, respectively. In the United States, the addition of pertuzumab to trastuzumab plus chemotherapy had higher costs and smaller QALY gains, resulting in an unfavorable ICER of \$167,185 per QALY at a WTP threshold of \$100,000 per QALY.⁵²

Metastatic or advanced breast cancer. Eighteen articles estimated the cost effectiveness of therapies in the metastatic setting, including chemotherapy (n = 8), hormone receptor–targeted treatment (n = 2), HER2-targeted treatment (n = 2), and targeted (biologic) therapy (n = 6).⁵⁴⁻⁷² Eight articles estimated the cost effectiveness of chemotherapeutic agents.^{54,55,57,60,63,65,71,72} Four studies showed that the addition of palbociclib, a chemotherapy agent used for the treatment of hormone receptor–positive and HER2-negative breast cancer, had cost-effectiveness ratios that exceeded the US WTP threshold of \$100,000 per QALY.^{60,63,71,72} Everolimus with exemestane was not cost effective compared with exemestane alone, fulvestrant alone, or tamoxifen alone, at a US WTP of \$100,000 per QALY.⁵⁴ However, the combination was found to be cost saving compared with bevacizumab plus paclitaxel or capecitabine from a third-party payer perspective in Greece.⁵⁵

Two articles estimated the cost effectiveness of fulvestrant, a hormonal treatment of advanced breast cancer, and

each article found it to be cost effective in comparison with exemestane (aromatase inhibitor), letrozole (aromatase inhibitor), or tamoxifen at WTP thresholds in Sweden and the United Kingdom.^{61,70}

The cost effectiveness of HER2-targeted interventions for metastatic treatment exceeded the US WTP threshold of \$100,000.^{56,59} For example, the ICERs of trastuzumab emtansine were \$183,828 per QALY compared with lapatinib plus capecitabine and \$126,001 per QALY compared with capecitabine alone.⁵⁶ The addition of pertuzumab to trastuzumab plus docetaxel cost \$472,668 per QALY.⁵⁹

Five articles estimated the cost effectiveness of targeted therapy and one bone-modifying agent.^{57,62,66-69} The ICERs widely varied depending on the comparators, perspective, and study setting. For example, the ICER for ribociclib plus letrozole ranged from cost saving (v palbociclib plus letrozole) to €1544 per QALY (v palbociclib plus letrozole) and \$210,369-\$440,000 per QALY (v letrozole alone).

Treatment selection. Twelve articles evaluated the use of new diagnostic technology, such as gene expression profile testing to guide adjuvant treatment selection.⁷³⁻⁸⁴ The majority of the studies (n = 9) evaluated the cost effectiveness of the 21-gene recurrence score assay (Oncotype DX; Genomic Health, Redwood City, CA) to select treatment.^{74,75,77,79-84} Seven of these 9 studies reported cost savings or cost-effective results for Oncotype DX testing or the incorporation of Oncotype DX test results with clinical features to guide treatment decisions in patient subgroups.^{74,75,81,83,84} For example, Kip et al⁷⁵ found costs of €11,236 per QALY for using Oncotype DX testing to support adjuvant chemotherapy recommendations, compared with current clinical practice, in the Netherlands. However, Chandler et al⁸⁰ reported \$188,125 per QALY for Oncotype DX testing (v usual care) based on observed community testing patterns and actual test properties in the United States. The study also reports that the ICER could be as low as \$28,947 per QALY based on the most favorable assumptions about test accuracy for prediction of distant recurrences, 100% use of Oncotype DX, and 100% adherence to Oncotype DX score-concordant treatment.⁸⁰

Overall, of the 70 interventions evaluated across the 37 therapeutic studies, nearly half found that the intervention of interest did not have reasonable costs per QALY for the country of analysis, although the threshold for being considered cost effective varied by setting and country. In general, the ICERs in the metastatic phase were relatively unfavorable compared with those in the adjuvant phase of care because of higher drug costs and small QALY gains. However, several industry-sponsored cost-effectiveness analyses of metastatic regimens showed favorable results.^{48,52,54,55,61,67-70,73-75}

Overall Summary

We compared the QALYs per person across the 3 phases of cancer care. The median QALYs gained per person for prevention, screening, and treatment were 0.007, 0.033, and 0.315, respectively. However, these values are not directly comparable because they were not generated from one model that included all phases of breast cancer prevention, screening, and control. There is variability in underlying natural history assumptions and sources of population utilities. Costs per person cannot be compared across studies because of differences in units, perspective, years of currency, and settings.

Quality Assessment

The results of the reporting quality assessment based on the ISPOR CHEERS checklist¹⁸ are listed in Table 2. The overall quality was good, but there were some gaps in completeness of reporting. Almost all of the studies sufficiently described the broad context for the study and its relevance for policy or practice and clearly justified why the comparisons were chosen for analysis (96.9%). Utility weights were described in 97.6% of all relevant studies.

There were gaps in provision of the justification for the discount rate selected (78.1%). Several studies did not report the dates of the estimated resource quantities and unit costs (11%), describe the analytic methods supporting the evaluation (12%), or provide the assumptions underpinning the model (9.5%). Only 72.7% of the articles described the extent of funder involvement in the studies. Almost all of the studies reported conflicts of interest (96.9%). More than half of the studies did not provide any information on model validation (57.1%).

DISCUSSION

This systematic review highlights findings from modern analyses of the cost effectiveness of breast cancer care. We found that targeting general populations for cancer control interventions has reasonable costs per QALY saved compared with doing nothing but that risk-targeted approaches lowered costs without major trade-offs in lives saved. The cost effectiveness of new technology and drugs can be more difficult to evaluate than established care because of high initial pricing, limited data on efficacy or long-term effects, and potential for bias in the methods and findings as a result of industry-related conflicts of interest. There were no modern analyses of primary prevention, such as lowering environmental risks or using chemoprevention, and there were no analyses that simultaneously assessed prevention, screening, and treatment.

Delivery of breast cancer interventions to subgroups of women who are most likely to benefit from an intervention based on age or demographic or clinical characteristics generally decreases costs and yields favorable cost-effectiveness ratios compared with the use of the intervention by all women in the general

TABLE 2. CHEERS¹⁸ Checklist Quality Assessment

Item No.	Section or Item	Recommendation	Score, %*
1	Title	Identify the study as an economic evaluation or use more specific terms such as cost-effectiveness analysis, and describe the interventions compared.	92.2
2	Abstract	Provide a structured summary of objectives, perspective, setting, methods (including study design and inputs), results (including base case and uncertainty analyses), and conclusions.	100
Introduction			
3	Background and objectives	Provide an explicit statement of the broader context for the study. Present the study question and its relevance for health policy or practice decisions.	100
Methods			
4	Target population and subgroups	Describe characteristics of the base case population and subgroups analyzed, including why they were chosen.	98.4
5	Setting and location	State relevant aspects of the system(s) in which the decision(s) need(s) to be made.	88.3
6	Study perspective	Describe the perspective of the study, and relate this to the costs being evaluated.	95.3
7	Comparators	Describe the interventions or strategies being compared, and state why they were chosen.	96.9
8	Time horizon	State the time horizon(s) over which costs and consequences are being evaluated and say why appropriate.	90.6
9	Discount rate	Report the choice of discount rate(s) used for costs and outcomes and say why appropriate.	78.1
10	Choice of health outcomes	Describe what outcomes were used as the measure(s) of benefit in the evaluation and their relevance for the type of analysis performed.	99.2
11a	Measurement of effectiveness	Single study-based estimates: Describe fully the design features of the single effectiveness study and why the single study was a sufficient source of clinical effectiveness data.	96.8
11b		Synthesis-based estimates: Describe fully the methods used for identification of included studies and synthesis of clinical effectiveness data.	
12	Measurement and valuation of preference-based outcomes	If applicable, describe the population and methods used to elicit preferences for outcomes.	97.6
13a	Estimating resources and costs	Single study-based economic evaluation: Describe approaches used to estimate resource use associated with the alternative interventions. Describe primary or secondary research methods for valuing each resource item in terms of its unit cost. Describe any adjustments made to approximate to opportunity costs.	97.6
13b		Model-based economic evaluation: Describe approaches and data sources used to estimate resource use associated with model health states. Describe primary or secondary research methods for valuing each resource item in terms of its unit cost. Describe any adjustments made to approximate to opportunity costs.	
14	Currency, price date, and conversion	Report the dates of the estimated resource quantities and unit costs. Describe methods for adjusting estimated unit costs to the year of reported costs if necessary. Describe methods for converting costs into a common currency base and the exchange rate.	89.8
15	Choice of model	Describe and give reasons for the specific type of decision analytical model used. Providing a figure to show model structure is strongly recommended.	93.7
16	Assumptions	Describe all structural or other assumptions underpinning the decision-analytical model.	91.3
(continued on following page)			

TABLE 2. CHEERS¹⁸ Checklist Quality Assessment (continued)

Item No.	Section or Item	Recommendation	Score, %*
17	Analytical methods	Describe all analytical methods supporting the evaluation. This could include methods for dealing with skewed, missing, or censored data; extrapolation methods; methods for pooling data; approaches to validate or make adjustments (eg, half-cycle corrections) to a model; and methods for handling population heterogeneity and uncertainty.	89.0
Results			
18	Study parameters	Report the values, ranges, references, and, if used, probability distributions for all parameters. Report reasons or sources for distributions used to represent uncertainty where appropriate. Providing a table to show the input values is strongly recommended.	93.7
19	Incremental costs and outcomes	For each intervention, report mean values for the main categories of estimated costs and outcomes of interest, as well as mean differences between the comparator groups. If applicable, report incremental cost-effectiveness ratios.	93.0
20a	Characterizing uncertainty	Single study-based economic evaluation: Describe the effects of sampling uncertainty for the estimated incremental cost and incremental effectiveness parameters, together with the impact of methodologic assumptions (eg, discount rate, study perspective).	94.5
20b		Model-based economic evaluation: Describe the effects on the results of uncertainty for all input parameters and uncertainty related to the structure of the model and assumptions.	
21	Characterizing heterogeneity	If applicable, report differences in costs, outcomes, or cost effectiveness that can be explained by variations between subgroups of patients with different baseline characteristics or other observed variability in effects that are not reducible by more information.	98.0
Discussion			
22	Study findings, limitations, generalizability, and current knowledge	Summarize key study findings and describe how they support the conclusions reached. Discuss limitations and the generalizability of the findings and how the findings fit with current knowledge.	98.4
Other			
23	Source of funding	Describe how the study was funded and the role of the funder in the identification, design, conduct, and reporting of the analysis. Describe other nonmonetary sources of support.	72.7
24	Conflicts of interest	Describe any potential for conflict of interest of study contributors in accordance with journal policy. In the absence of a journal policy, we recommend authors comply with International Committee of Medical Journal Editors recommendations.	96.9
Model validation	Model transparency and validation according to ISPOR-SMDM Modeling Good Research Practices Task Force ¹⁹	Assess face validity, verification or internal validity, cross-validity, external validity, or predictive validity.	42.9

Abbreviations: CHEERS, Consolidated Health Economic Evaluation Reporting Standards; ISPOR-SMDM, International Society for Pharmacoeconomics and Outcomes Research–Society for Medical Decision Making.

*Percent score = (Group score/Total group score for the item) × 100.

population. This was seen in cost-effectiveness analyses of prevention strategies for breast (and ovarian) cancer through genetic testing and preventive surgery among high-risk populations (eg, relatives of affected women, Ashkenazi or Sephardic Jewish women),²⁰⁻²⁷ screening schedules tailored to breast cancer risk,^{30-32,34,39-41,43,45} and targeting chemotherapy to women at highest risk

of distant recurrence based on genomic test results.^{74,75,79,81-84} However, health care systems would require an investment of resources, training and time of providers to identify women meeting criteria for intervention, and time for counseling of women regarding the need for the intervention. None of the targeted cancer control interventions we reviewed included these types of

costs, making it difficult to fully evaluate the economic value of implementing targeted care.

Many of the studies we reviewed focused on new technology or drugs designed to decrease breast cancer mortality. Early in the evolution of a new approach, there are limited data on effectiveness, especially long-term effectiveness, and studies may involve financial support or data from the manufacturer. We observed that analyses with industry relationships or sponsorship were more likely to show favorable cost-effectiveness ratios compared with similar studies without industry relationships. This trend could bias assessments of value and affect adoption ahead of full data.

In a prior review of cost-effectiveness analyses included in the Tufts database through 2013, Winn et al¹⁵ found that, of 208 articles reporting cost effectiveness in breast cancer, only 7.7% were on primary prevention. Our finding of 12% of studies on the cost effectiveness of prevention in the period from 2015 to 2019 indicates a continuing gap in economic studies of breast cancer control. Prevention might be costly given the need to invest in programs (and infrastructure) for large populations because most women will never develop breast cancer or will develop it many years into the future.⁸⁵ It is also difficult to implement all recommended breast cancer prevention strategies in busy primary care practices,⁸⁶ resulting in lower effectiveness than seen originally in efficacy trials. In addition, it is difficult to change individual behavior, diminishing the actual impact of proven efficacious strategies. Given the continuing interest in prevention, including interactions between the environment and health, this is an important area for future economic research.

Consistent with previous studies,^{15,87-89} there were significant increases in societal and/or payer costs and QALY or life-year gains associated with new treatments (v older regimens). Although the newer therapies increased health benefits, they generally had higher treatment costs relative to benefits, so that costs exceeded the US \$100,000 per QALY WTP threshold. This is often a result of high initial drug prices. Although prices come down over time and would likely result in lower cost-effectiveness ratios, analyses are primarily done at the time of introduction of new treatments.

This review also highlights several challenges in the metastatic breast cancer setting. First, the paradigm for metastatic care has focused on quality of life, with short survival, making it difficult for most therapies to be cost effective, despite important potential benefits in patients' day-to-day lives. At the same time, many of these therapies have substantial toxicity, reducing cost effectiveness. Second, only a few studies demonstrated cost effectiveness at levels that would facilitate coverage under private insurance plans or single-payer national health care systems. Overall, new metastatic treatments have high

opportunity costs, where dollars allocated to drugs that show minimal benefit are not being spent on gains elsewhere. Third, industry-sponsored studies resulted more often in cost-effectiveness ratios below the US WTP threshold than non-industry-sponsored studies, raising concerns about the potential for bias in the methods and findings of industry-sponsored studies.

There are several limitations of our analysis that should be considered in evaluating our results. First, there were some important aspects of breast cancer prevention and control cost effectiveness that we did not review, such as radiation and surgical techniques for reconstruction and interventions to improve well-being after active therapy. These can have a meaningful impact on QALYs and should be investigated. Second, it is not possible to conduct a quantitative meta-analysis because of the heterogeneity of model assumptions, outcomes, and other study features. Using collaborative modeling, where a group shares common inputs and research questions, could facilitate such data synthesis. Another limitation of reviewing studies is that they were conducted in various countries with different health care systems, pricing structures, WTP thresholds, and coverage approval processes, potentially limiting conclusions for the United States.

The specific examples of cost effectiveness discussed earlier consider the costs and effects of breast cancer prevention, screening, or treatment separately. The overall summary of results suggests that primary systemic treatment could provide the highest value in terms of QALYs gained. However, the costs of prevention, screening, and treatment relative to each other in reducing breast cancer mortality are less clear. We are unaware of any studies that directly address the question of the relative costs and effects of breast cancer prevention, screening, and treatment in one analysis. Models that are designed to consider all phases of cancer prevention and control, such as the Cancer Intervention and Surveillance Modeling Network (CISNET) models, would be ideally suited for these purposes.⁹⁰⁻⁹² For example, in a CISNET study simultaneously evaluating prevention, screening, and treatment of breast cancer, screening could have averted 10.2%-10.6% of the deaths, systemic treatment (with no screening change) could have avoided 22.8%-25.3% of deaths, and eliminating obesity could have averted 6.6%-9.9% of deaths versus continuation of current obesity levels.⁹¹ It will be important to consider the costs of care in such future population analyses.

In conclusion, decisions about the cost effectiveness of methods to reduce breast cancer mortality will remain difficult without comprehensive analyses across the full spectrum from prevention to screening and treatment, including consideration of implementation costs. Confidence in results might also be facilitated by evaluating the potential for bias in methods, findings, and interpretation of findings.

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AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST AND DATA AVAILABILITY STATEMENT

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AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

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