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Medical costs associated with metastatic breast cancer in younger, midlife, and older women

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Abstract

Background: This study estimated average medical costs due to metastatic breast cancer (mBC) in three different life stages -- younger (aged 18-44), midlife (aged 45-64), and older women (aged 65 and older)—and by phase of care: initial, continuing, and terminal.

Methods: We used 2003-2014 North Carolina cancer registry data linked with administrative claims from public and private payers. In addition to women with mBC at diagnosis, we developed a claims-based algorithm to identify breast cancer patients who progressed to metastatic disease. We matched breast cancer patients (mBC and earlier stage) to non-cancer patients on age group, county of residence, and insurance plan. Outcomes were average monthly medical expenditures and expected medical expenditures by phase. We used generalized estimating equation regression models to estimate excess costs attributed to mBC as the difference in mean payments between patients with mBC and patients with each earlier stage breast cancer (stage 1, stage 2, stage 3 and unknown stage) and non-cancer controls by treatment phase and age group. Regressions adjusted for age, insurance, months enrolled, Klabunde Comorbidity Index and year.

Results: We analyzed 4,805 women with mBC, 21,772 women with earlier stage breast cancer, and 109,631 matched non-cancer controls. Adjusted monthly costs for women with mBC were significantly higher than for women with earlier stage breast cancer and non-cancer controls for all

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age groups and treatment phases except the initial treatment among women with stage 3 breast cancer at diagnosis. Across all age groups, cancer stages and treatment phases, the largest expected total costs were for women aged 18-44 with mBC during the continuing phase ($209,961 95% Confidence Interval $165,736 – 254,186).

Conclusions: We found substantial excess costs for mBC among younger women and during the continuing and terminal phases of survivorship. It is important to ensure this care is high value for these women.

INTRODUCTION

Breast cancer is the most common non-skin cancer among females in the United States (US) and the second leading cause of cancer death in women.[1] Although less than 10% of all breast cancers are diagnosed among women younger than age 45, incidence in this age group has increased dramatically during the past 30 years.[2] Breast cancer in younger women is typically diagnosed at more advanced stages, is more aggressive, is less responsive to treatment, and results in poorer survival outcomes compared to breast cancer in older women.[3-9] Evidence suggests that the economic burden of non-metastatic breast cancer in younger women is substantial.[10,11] In prior research, direct medical expenditures during and right after treatment were higher, on a per-person basis, for younger women than for midlife women due to the aggressiveness of cancer and its treatment and differences in sources of insurance.[12,13] Thus, breast cancer creates significant economic burden for women at all stages of life.

In the US, 6-10% of breast cancers are metastatic at diagnosis and an additional 30% of women diagnosed at earlier stages will eventually progress to metastatic breast cancer (mBC).[14,15] Women with mBC have a more prolonged and costly treatment trajectory than those with earlier stage disease due to their need for continued therapy and end of life care; the five-year survival for mBC is only 26.3% compared to 98.8% for localized cancer.[16] The economic impact of mBC treatment in different life stages -- younger (aged 18-44), midlife (aged 45-64) and older (aged 65+) women -- is an understudied and important area for public health programs. Economic data on the medical costs of treating mBC would provide invaluable information to decision makers to allocate health resources.

In the past, several studies have provided substantial economic data on medical care costs of breast cancer treatment both in younger and older women.[10-13,17] However, less is known about the medical costs of treating mBC patients over the lifespan. The objective of this study was to estimate the average direct medical costs due to mBC in three different life stages -- younger (aged 18-44), midlife (aged 45-64), and older women (aged 65 and older) -- and by phases of care: initial, continuing, and terminal. These costs can be used to 1) identify targeted support to patients experiencing financial burden, 2) populate cost effectiveness models for new treatments and interventions for mBC and 3) further explore high-cost patient groups and phases of care to ensure the quality of care is commensurate with the costs (i.e., of high value).

METHODS

Data

We utilized linkages between the North Carolina Central Cancer Registry (NC CCR) and administrative claims data from Medicare, Medicaid, and commercial health plans in NC maintained by the Cancer Information & Population Health Resource (CIPHR) at the University of North Carolina, Lineberger Comprehensive Cancer Center. The NC CCR collects clinical information relevant to diagnosed cancers (e.g., date of diagnosis, primary site, American Joint Committee on Cancer [6th edition] stage, grade), selected treatments, vital status, and cause of death data for all individuals diagnosed with cancer in NC. CIPHR linked data from the NC CCR for individuals residing in NC who had both a primary cancer diagnosis and enrollment in one or more of the following insurers: Medicare (2003 through 2014), large commercial health plans (2003 through 2014) and Medicaid (2003 through 2012). Linkage to both public insurers and commercial health plans allowed assessment of complete claims for both full and partial dual enrollees.[18] CIPHR linked approximately 85% of the NC population diagnosed with cancer to claims. We also used claims from enrollees who did not have cancer in Medicaid, fee-for-service Medicare, and large commercial health plans to compare direct medical expenditures across cancer cases and non-cancer controls. The claims data provided details on healthcare utilization (such as visits to inpatient, outpatient, and emergency room departments, and prescription drug use).

Cancer Sample

We included women aged 18 and older diagnosed alive with first and only invasive primary breast cancer in the NC CCR (Figure 1). We included breast cancer patients who successfully linked to claims data and were continuously enrolled for at least three months prior to their diagnosis to identify comorbidities at the time of diagnosis. In the Medicaid program, some beneficiaries are enrolled for relatively short periods of time.[19] As a result, they were not required to have a full year of enrollment.[13] We included patient months after diagnosis in our analysis for as long as the woman was continuously enrolled in any of the insurance databases after diagnosis of breast cancer. We defined continuous enrollment as having at least one day of enrollment in either a fee-for-service only or a primary case management only (PCCM) plan in Medicaid in consecutive months. We included women with PCCM plans in Medicaid because, during our analysis time period, providers of PCCM patients were paid on a fee-for-service model.[20] For Medicare enrollees, we required Part D enrollment at the time of diagnosis forward so that we could include prescription expenditures comparably across insurance plans. We censored women at end of data window, disenrollment, enrollment in managed care (after which we would not see payments in claims) or death.

Progression algorithm

Cancer registries record stage at initial diagnosis, but do not capture progression of early stage to metastatic disease or other disease-specific outcomes. We therefore developed a claims-based algorithm, informed by existing algorithms intended to capture recurrence of breast cancer,[21] to identify treatment patterns indicating progression to distant metastatic disease (Figure 2). The mBC was defined as: 1) stage IV at initial diagnosis; or 2) two

claims for secondary malignant neoplasm (i.e., second cancer diagnosis) within 60 days at any time after diagnosis (Appendix Table 1); or 3) two claims for fulvestrant (an injected anti-estrogen only used in the metastatic setting) at any time after diagnosis; or 4) if no chemotherapy within 12 months of diagnosis, had at least one claim for chemotherapy after 12 months; or 5) if chemotherapy within 12 months of diagnosis, a 60 day chemo-free interval, defined as a 60 day period with no claims for chemotherapy, followed by resumption of chemotherapy AND had at least one chemotherapy claim after 12 months (Appendix Table 1). The last criterion was intended to capture women whose initial treatment for earlier stage disease was complete but who later resumed treatment.

Matching

We also included women aged 18 and older with no diagnosis of cancer for comparison. To maximize sample sizes for matching cancer (mBC and earlier stage breast cancer) and non-cancer patients, we did not require the non-cancer population to be continuously enrolled but rather adjusted for their length of enrollment in the statistical analysis. We used coarsened exact matching, a method for matching that 'coarsens' the data on a few select variables, to find exact matches between breast cancer patients and patients without cancer with the goal of improving balance between the two groups. We completed the match within in each group (18-44, 45-64, 65+) on county of residence and insurance plan (any Medicaid, any private insurance and no Medicaid, and Medicare only).[22] We assigned the non-cancer controls a pseudo-diagnosis date identical to that of her matched cancer patient (either at diagnosis or progression to mBC as appropriate).[13] We retained up to five matched non-cancer controls per cancer case and used weights to control for the varying number of non-cancer patients per cancer case.[23]

Treatment phases

For estimation of costs, we defined phases of care for each patient: initial, continuing and terminal.[24] The terminal phase was the final 12 months of life. Terminal stage includes costs in the last 12 months of life prior to death from any cause. The initial phase was the first 12 months after the (pseudo-) date of diagnosis. The continuing phase was the time spent between the initial and terminal phases. In cases in which the patient lived for less than 18 months and did not contribute to all three phases, the terminal phase took priority followed by the initial phase. For the non-cancer controls, costs during the phases (based on pseudo-diagnosis date) act as a counterfactual to represent what costs would have been for mBC patients if they did not have mBC.

Dates of death were available from the NC CCR, Medicare and Medicaid enrollment files. However, we did not know the vital status of non-cancer controls who disenrolled from private insurance. To avoid misclassification of (pseudo-) treatment phase for these patients, we excluded any possible terminal phase by censoring their observations 12 months prior to disenrollment.

A woman could contribute both non-mBC and mBC time if she was captured in our progression algorithm. For women who progressed, the time between initial diagnosis and progression was considered "non-mBC". The time after date of progression was considered

"mBC". In addition, the initial phase was reset for women who progressed to mBC (e.g., initial phase reset to capture first six months after mBC diagnosis).

Outcome

We collapsed the data to one observation per woman, cancer stage (i.e., none, mBC, unknown stage, stage 1, stage 2 and stage 3), and treatment phase. The outcome of interest was average monthly medical expenditures during that cancer stage/phase, defined as a continuous variable including spending for all points of service.

Unlike the Medicaid and Medicare claims, the large commercial health plans only included charged amounts for services, not payments. We constructed payment-to-charge ratios (PCR) by point of service for the private insurance plan in two steps. First, using public Medicare reports, we constructed PCRs *by point of service* (inpatient=0.255, outpatient=0.157, and physicians and other suppliers=0.339) as the ratio of total Medicare payments to total submitted charges.[25] For Medicare prescriptions, we used PCRs (=0.22) from an RTI International report.[26] Second, we scaled the Medicare PCRs to better reflect private insurance using the ratio of PCRs for inpatient stays for private insurance to Medicare reported in Smith et al. (=1.52).[27] The final PCRs we used for the private insurer were 0.388 for inpatient, 0.239 for outpatient, 0.516 for physicians and other suppliers and 0.335 for prescriptions. We hereafter refer to the outcome variable as costs.

Analysis

We conducted all analyses separately for women in three life stages: younger (aged 18-44), midlife (aged 45-64) and older (aged 65 and older). We estimated expected monthly costs using generalized estimating equation regression models to account for repeated observations (i.e., cancer stage and treatment phases) within women. We used a log link and gamma family with exchangeable covariance structure (Stata 14.2, College Station, TX).[28]

To control for residual observed differences not accounted for in matching, and improve precision of our estimates, regressions included interactions of cancer stage (none, mBC, unknown stage, stage 1, stage 2 and stage 3) and phase of care (initial, continuing and terminal). Regressions also included age (in years), insurance (any Medicaid, any private insurance and no Medicaid, and Medicare only), number of months enrolled during the treatment phase, Klabunde modification of Charlson Comorbidity Index (zero, greater than zero) and year indicators.[29] The Klabunde index was calculated using data from the three months prior to breast cancer diagnosis and excluded cancer from the index.[13] Because comorbidities were measured prior to mBC, any side effects from mBC treatment will be included in our cost estimates for mBC. We controlled for covariates so that the comparisons between women with and without mBC are not skewed by differences in demographics and health status apart from mBC.

We calculated excess costs (i.e., attributable to mBC) as the difference in mean payments between the patients with mBC and each other cancer stage (stage 1, stage 2, stage 3, and unknown stage) and non-cancer patients by treatment phase and age group. We calculated total medical payments for each cancer stage and treatment phase by multiplying the average number of months in the phase by the estimated per-month payment for that phase. We also

calculated 95% confidence intervals (CI). All costs were adjusted to 2018 dollars using the medical care component of the Consumer Price Index.[30] This study was approved by the University of North Carolina at Chapel Hill Institutional Review Board.

RESULTS

Our analysis sample included 4,805 women with mBC, 21,772 women with non-mBC, and 109,631 matched non-cancer controls (Figure 1). Among the women with mBC, 27% were stage IV at diagnosis, 61% were detected through diagnosis codes for secondary malignant neoplasms and the remaining 11% were detected through codes for treatment for mBC. Approximately 5% of women with mBC were aged 18-44 (Table 1). One third of women with mBC were covered by Medicaid. Women with mBC had shorter enrollment (25 months) relative to women with non-mBC (57 months) and women without breast cancer (55 months). This could be due to shorter life expectancy for women with mBC or because women identified through the progression algorithm had fewer months post-mBC in the study window.

After adjusting for observable characteristics, expected monthly costs for women with mBC were significantly higher than for earlier stage breast cancer and non-cancer controls for all age groups and treatment phases except during the initial treatment phase among women with stage 3 breast cancer at diagnosis (Table 2). For example, average monthly costs for women with mBC were $7,564 higher (95% confidence interval [CI]: $6,011 - $9,118) than for women without cancer in the initial treatment phase. Within each age group, the incremental average monthly costs of mBC during the initial treatment phase decreased as comparator stage increased. For example, among women aged 18-44, the incremental average monthly cost of mBC were $4,463 [95% CI: $2,760 - $6,167] compared to stage 1, $2,418 [95% CI: $813 - $4,022] compared to stage 2 and were not statistically significantly different from average monthly costs for stage 3 patients. Within each treatment phase, the incremental average monthly costs of mBC were not statistically significantly different across age groups. The full set of exponentiated regression coefficients are in Appendix Table 2.

When we predicted expected costs accounting for average monthly costs within treatment phase and the average number of months spent in each treatment phase, the differences in total expected costs between mBC and non-mBC during the initial treatment phase were smaller within each age group (Figure 3). For each age group, total expected costs for the continuing and terminal phases were higher for mBC than for earlier stage breast cancers and non-cancer controls. However, the differences between mBC continuing and terminal phases and earlier stage and non-cancer continuing and terminal phases were larger for younger and midlife women (Figure 3a and 3b). Across all age groups, cancer stages and treatment phases, the largest expected costs were for women aged 18-44 with mBC during the continuing phase ($209,961 [95% CI: $165,736 - $254,186], Figure 3a).

DISCUSSION

This study found that women with mBC had higher medical costs than comparable non-cancer patients and women with earlier-stage breast cancer at all ages, especially during continuing and terminal phases of care. These costs can be used to identify patients and phases of care that may need extra support (e.g., financial, psychological) and to further explore the value of care provided in these high-cost groups. Our findings were similar to an earlier study of younger and mid-life women with private insurance that also found that the costs of treating advanced-stage breast cancer were significantly higher than those for treating early-stage breast cancer.[31]

We found substantial excess costs for mBC relative to non-cancer controls among younger women. This finding follows a similar pattern to previous estimates of the excess medical cost of earlier-stage breast cancer among younger women.[12,13] Like our findings for mBC during the continuing phase for younger women, the other studies found that younger breast cancer patients had higher within-stage excess costs.

We also estimated costs by phase of treatment, which revealed new information about the timing of the excess medical cost for mBC relative to early-stage disease. Specifically, the largest incremental costs of mBC occurred during the continuing and terminal phases of survivorship. In the last year of life, the terminal costs for women with mBC are likely picking up women who died from their breast cancer. Alternatively, the terminal costs for women without breast cancer or earlier-stage breast cancer are likely capturing women who died from other causes.[32] Given that we examined a reasonably long terminal phase of 12 months, the larger end of life costs for mBC relative to non-cancer patients and survivors of earlier-stage disease (stages one through three) could be due to more aggressive cancer-focused treatment during the last year life or higher unit costs for cancer-related treatment. The price escalation resulting from entry of multiple new drug treatments into the oncology market is well described.[33] For younger and middle-age women with mBC, more aggressive treatment, even toward the end of life, could be economically justified (i.e., younger women's willingness-to-pay for additional months of life may be higher than for older women), and may reflect younger women's preferences to continue aggressive treatment into end of life. These preferences would consider the effects of the disease and treatment on health-related quality of life. However, it may also result from breakdowns in shared decision-making that lead to treatments with minimal economic or patient health benefits.

Cost of treatment and continued care is also a substantial issue for young women living with mBC and their families. These young women are often dealing with issues related to job loss and difficulty caring for families. For example, The Education and Awareness Requires Learning Young (EARLY) Act authorized the Centers for Disease Control and Prevention (CDC) to conduct research and develop initiatives to advance understanding and awareness of breast cancer among younger women.[34] CDC has a variety of initiatives, such as the *Multiple Approaches to Support Young Breast Cancer Survivors and Metastatic Breast Cancer Patients* cooperative agreement which aids national organizations, state health departments, and other institutions to increase supportive services for young breast cancer survivors, including those living with mBC, and their caregivers and families.[35]

Our results should be interpreted in the context of several limitations. First, our data come from North Carolina and may not generalize to other populations. However, North Carolina is a populous and racially/ethnically and socioeconomically diverse state that allowed us to access claims from multiple payers to include women of all ages. Second, detecting breast cancers that progress from earlier stages to metastatic in claims data is difficult. For example, our algorithm may capture the costs of diagnostic workup for mBC in the continuing phase of earlier stage disease. In this case, any misclassification of costs would bias our estimates of costs attributable to mBC toward the null. Future research could validate the mBC progression algorithm to establish its sensitivity and specificity. Third, we relied on PCRs to represent medical expenditures in the private insurance claims. Fourth, it is possible our non-cancer controls may have had differential enrollment patterns that were correlated with their monthly costs. Finally, our estimates of excess medical costs represent total payments and do not separate patients' responsibilities (e.g., out-of-pocket costs). Patient out-of-pocket costs for metastatic disease, which can be high, can create significant economic burden not captured in this study.[36]

The economic data presented here highlights key cost drivers in mBC by age group and provides cost information enabling additional research and investments to improve mBC treatment, including appropriate de-escalation of treatment, and supportive services. For example, our estimates could populate cost effectiveness models for new treatments and interventions for mBC. We hope that this study will motivate further research to explore high-cost patient groups and phases of care to ensure the care provided is of high value (i.e., benefits in extended life and increase quality of life are worth the cost) for each patient.

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Disclaimer: The findings and conclusions in this report are those of the authors and do not necessarily represent the official position of the Centers for Disease Control and Prevention.

Appendix

Appendix Table 1:

International Classification of Diseases (9th edition) and National Drug Codes used in progression to metastatic breast cancer algorithm

Event	Codes
International Classification of Diseases (9th edition; ICD-9)	
Secondary malignant neoplasm	197
	1970
	1971
	1972
	1973
	1974
	1975

Event	Codes
	1976
	1977
	1978
	198
	1980
	1981
	1983
	1984
	1985
	1986
	1987
	1988
	19882
	19889
National Drug Codes (NDC)	
Bevacizumab	50242006001
	50242006002
	50242006101
	70360000102
Capecitabine	00004110020
	00004110051
	00004110116
	00004110150
	00004110175
	00054027121
	00054027223
	00093747306
	00093747489
	00378251191
	00378251278
	16714046701
	16714046801
	16729007212
	16729007329
	42291019060
	42291019112
	51079051001
	51079051005
	54569571700
	54868414300
	54868414301
	54868414302

Event	Codes
	54868526000
	54868526001
	54868526002
	54868526003
	54868526004
	54868526005
	54868526006
	54868526007
	54868526008
	54868526009
	60687014911
	60687014994
	68258903601
Doxorubicin, peg-liposomal	17314960001
	17314960002
	47335004940
	47335005040
	47335008250
	47335008350
	59676096001
	59676096002
	61471029512
Eribulin	62856038901
Fulvestrant	00310072010
	00310072050
	00310072025
Gemcitabine	00002750101
	00002750201
	00069385710
	00069385810
	00069385910
	00409018101
	00409018125
	00409018201
	00409018225
	00409018301
	00409018325
	00409018501
	00409018601
	00409018701
	00591356279
	00591356355

Event	Codes
	00703577501
	00703577801
	00781328275
	00781328379
	16729009203
	16729011711
	16729011838
	23155021331
	23155021431
	23155048331
	23155048431
	23155052831
	23155052931
	25021020810
	25021020950
	25021023410
	25021023550
	45963061257
	45963061959
	45963062060
	45963062357
	45963062458
	45963063660
	47335015340
	47335015440
	55111068607
	55111068725
	55390039110
	55390039150
	63323010210
	63323010213
	63323010294
	63323012550
	63323012553
	63323012594
	63323012600
	67457046201
	67457046302
	67457046420
	68001028222
	68001028223
	68001028224

Event	Codes
	68001028225
	68001028226
	68001028227
Ixabepilone	00015191012
	00015191113
	70020191001
	70020191101
Lapatinib	00078067119
	00173075200
Vinorelbine	00069009901
	00069010303
	00069020510
	00069020550
	00081065601
	00081065644
	00173065601
	00173065644
	00703418201
	00703418281
	00703418291
	00703418301
	00703418381
	00703418391
	10019097001
	10019097002
	25021020401
	25021020405
	45963060755
	45963060756
	55390006901
	55390007001
	55390026701
	55390026801
	59911595801
	59911595901
	60831308601
	60831308602
	61703034106
	61703034109
	63323014801
	63323014805
	64370021001

Event	Codes
	64370025001
	64370053201
	64370053202
	64370308601
	64370308602
	66758004501
	66758004502
	67457043111
	67457047953
	67457048101

Appendix Table 2.

Exponentiated regression coefficients from generalized estimating equations with log link and gamma family [95% confidence interval]

	Age 18-44	Age 45-64	Age 65+
No cancer	0.287*** [0.245,0.336]	0.210*** [0.197,0.224]	0.187*** [0.178,0.196]
mBC[1]	1	1	1
Unknown stage	0.781* [0.623,0.978]	0.577*** [0.524,0.635]	0.678*** [0.634,0.726]
Stage 1	0.579*** [0.480,0.699]	0.560*** [0.525,0.598]	0.516*** [0.490,0.542]
Stage 2	0.772** [0.660,0.903]	0.808*** [0.756,0.863]	0.688*** [0.650,0.727]
Stage 3	0.889 [0.748,1.057]	0.984 [0.916,1.056]	0.956 [0.900,1.016]
Initial	1	1	1
Continuing	0.602*** [0.503,0.722]	0.569*** [0.518,0.624]	0.590*** [0.553,0.630]
Terminal	1.354*** [1.136,1.614]	1.431*** [1.291,1.587]	1.566*** [1.481,1.657]
No cancer * Initial	1	1	1
No cancer * Continuing	1.345** [1.109,1.631]	1.576*** [1.434,1.733]	1.771*** [1.656,1.894]
No cancer * Terminal	1.899*** [1.546,2.333]	2.080*** [1.846,2.344]	2.107*** [1.984,2.239]
mBC * Initial	1	1	1
mBC * Continuing	1	1	1
mBC * Terminal	1	1	1
Unknown stage * Initial	1	1	1
Unknown stage * Continuing	0.353*** [0.258,0.483]	0.624*** [0.534,0.730]	0.716*** [0.656,0.782]
Unknown stage * Terminal	0.713 [0.397,1.282]	0.824 [0.648,1.046]	0.771*** [0.701,0.848]
Stage 1 * Initial	1	1	1

	Age 18-44	Age 45-64	Age 65+
Stage 1 * Continuing	0.514*** [0.379,0.697]	0.469*** [0.420,0.525]	0.731*** [0.681,0.786]
Stage 1 * Terminal	0.668 [0.365,1.222]	0.766* [0.590,0.995]	0.891** [0.818,0.970]
Stage 2 * Initial	1	1	1
Stage 2 * Continuing	0.368*** [0.289,0.468]	0.393*** [0.350,0.440]	0.599*** [0.554,0.647]
Stage 2 * Terminal	0.566* [0.354,0.906]	0.499*** [0.394,0.631]	0.664*** [0.611,0.723]
Stage 3 * Initial	1	1	1
Stage 3 * Continuing	0.373*** [0.269,0.517]	0.415*** [0.363,0.475]	0.524*** [0.464,0.592]
Stage 3 * Terminal	0.706* [0.498,0.999]	0.477*** [0.391,0.583]	0.575*** [0.516,0.640]
Medicaid	1	1	1
Any private (no Medicaid)	1.337*** [1.202,1.487]	0.709*** [0.686,0.734]	0.845*** [0.813,0.878]
Medicare only	1.319* [1.018,1.708]	0.882*** [0.839,0.927]	0.774*** [0.761,0.788]
Age	1.000 [0.991,1.008]	0.975*** [0.972,0.978]	0.999 [0.998,1.001]
Months in phase	1.001 [0.999,1.003]	0.999 [0.999,1.000]	0.999*** [0.999,0.999]
Klabunde index > 0	1.748*** [1.543,1.981]	1.655*** [1.595,1.717]	1.504*** [1.479,1.529]
2003	1	1	1
2004	1.480*** [1.187,1.846]	1.013 [0.846,1.213]	1.119*** [1.056,1.185]
2005	1.261* [1.002,1.587]	0.918 [0.772,1.092]	1.195*** [1.122,1.273]
2006	1.424** [1.153,1.758]	1.016 [0.854,1.209]	1.209*** [1.146,1.275]
2007	1.654*** [1.349, 2.028]	1.210* [1.013,1.446]	1.252*** [1.187,1.322]
2008	1.597*** [1.307,1.951]	1.169 [0.985,1.387]	1.275*** [1.209,1.345]
2009	1.799*** [1.482, 2.183]	1.188* [1.001,1.411]	1.271*** [1.207,1.339]
2010	1.824*** [1.494, 2.226]	1.195* [1.006,1.418]	1.250*** [1.187,1.317]
2011	1.659*** [1.361,2.023]	1.232* [1.037,1.463]	1.247*** [1.185,1.312]
2012	2.398*** [1.925,2.987]	1.164 [0.979,1.384]	1.156*** [1.098,1.217]
2013	1.794*** [1.420, 2.266]	1.184 [0.991,1.414]	1.065* [1.007,1.127]
2014	1.420 [0.938, 2.150]	1.256* [1.013,1.558]	0.735* [0.574,0.942]
N	6,217	62,104	190,690

mBC, metastatic breast cancer

*, **, and *** represent statistical significance at the 90%, 95% and 99% confidence level, respectively.

1. Variables with exp(coefficient) = 1 represent omitted reference categories.

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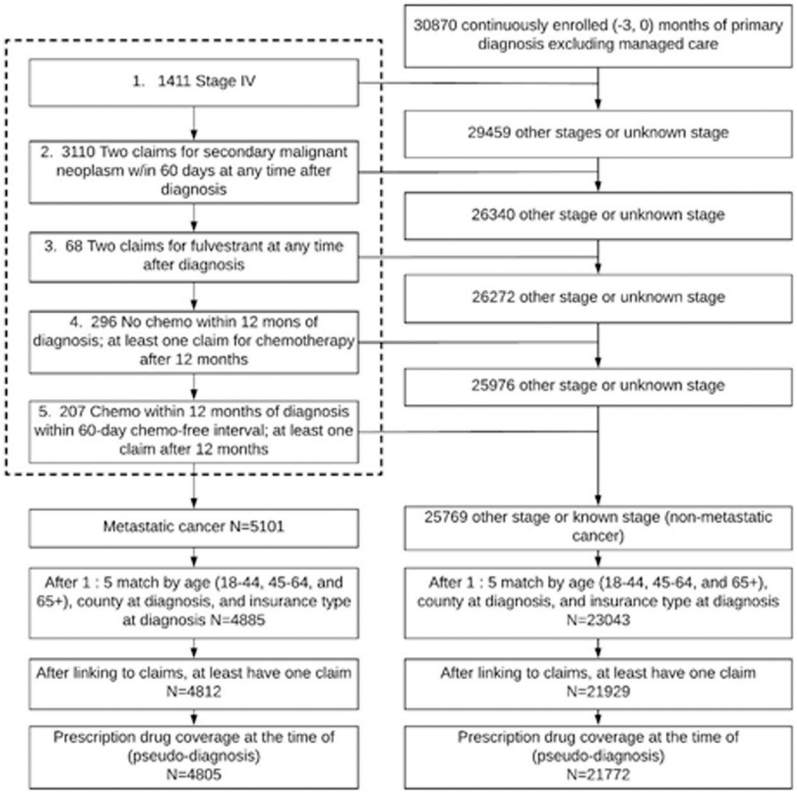

Figure 1.
CONSORT diagram used to illustrate select cancer cohort

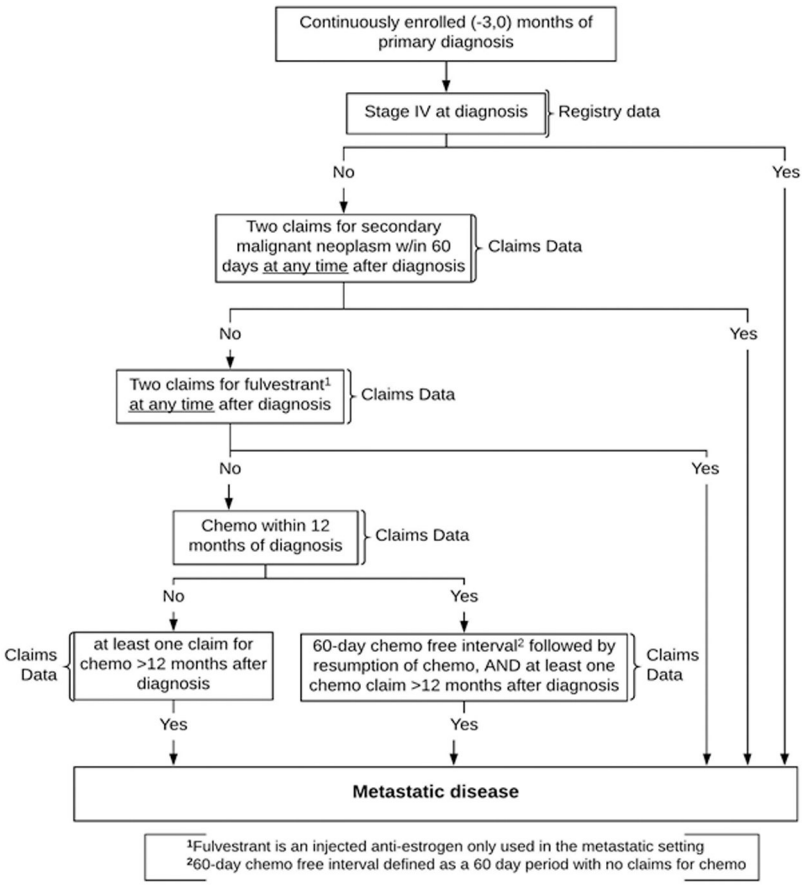

Figure 2.

Metastatic progression algorithm used to identify metastatic breast cancer disease

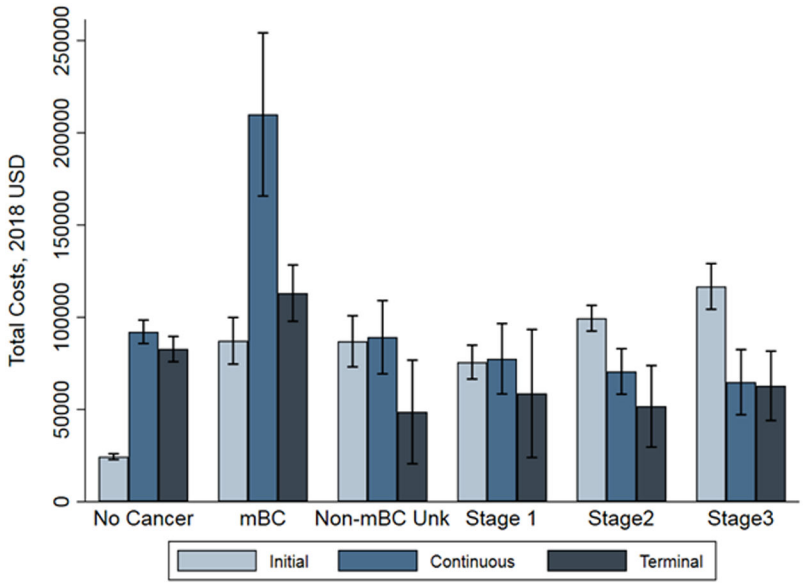

Figure 3a.

Total expected costs, by cancer stage, phase of care and age group: Age 18-44

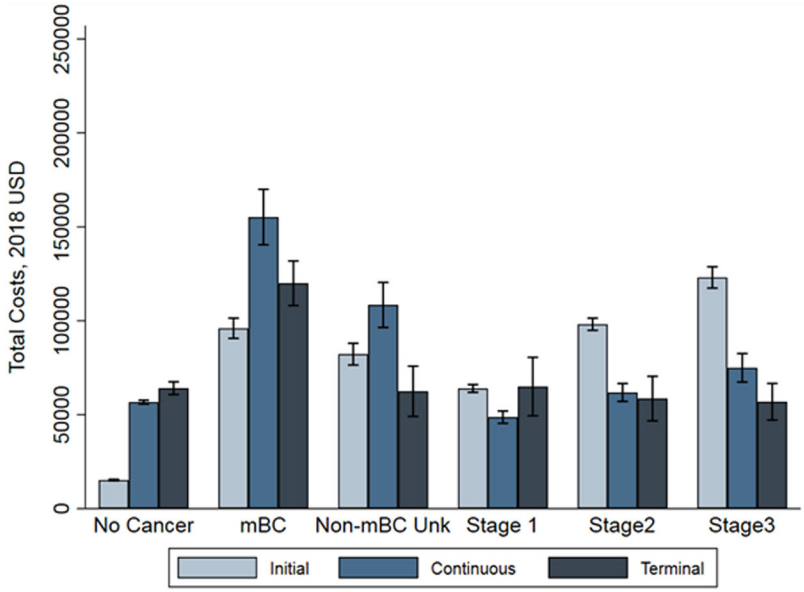

Figure 3b.

Total expected costs, by cancer stage, phase of care and age group: Age 45-64

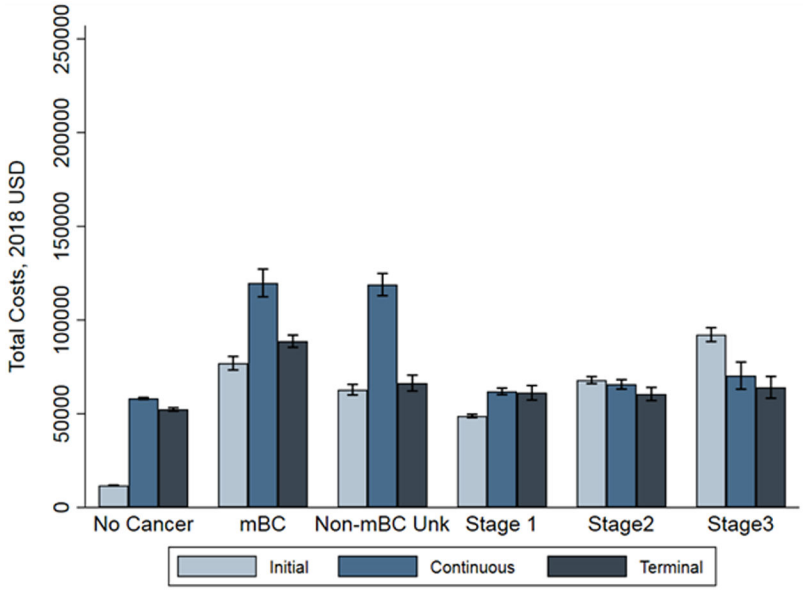

Figure 3c.

Total expected costs, by cancer stage, phase of care and age group: Age 65+

Table 1.

Characteristics of study population

Characteristics		Metastatic		Non metastatic		No cancer	
		n=4805	%	n=21772	%	n=109631	%
Age (mean, std)		67.8	12.6	68.35	12.1	69.5	10.6
	18-44 years	230	4.8	663	3.1	2544	2.3
	45-64 years	1268	26.4	6010	27.6	28664	26.2
	65+ years	3307	68.8	15099	69.4	78423	71.5
AJCC stage at diagnosis							
	I	719	15.0	10387	47.7		
	II	1066	22.2	6532	30.0		
	III	797	16.6	1670	7.7		
	IV	1298	27.0				
	Unknown	925	19.3	3183	14.6		
Insurance							
	Any Medicaid	1651	34.4	5135	23.6	26803	24.5
	Any Private (no Medicaid)	655	13.6	5188	23.8	22855	20.9
	Medicare	2499	52.0	11449	52.6	59973	54.7
Number of months of enrollment (mean, std)		24.69	27.2	56.75	34.4	54.64	37.8
Klabunde comorbidity index[1]							
	0	3783	78.7	16666	76.6	94620	86.3
	>=1	1022	21.3	5106	23.5	15011	13.7

AJCC, American Joint Committee on Cancer, 6th edition

1. Klabunde comorbidity index calculated in the three months prior to (pseudo) diagnosis.

Table 2.

Incremental average monthly cost of metastatic breast cancer by cancer stage, treatment phase and age[1]

Comparator	Age 18-44	Age 45-64	Age 65+
No Cancer			
Initial	7564*** (6011, 9118)	7048*** (6533, 7563)	6293*** (5926, 6659)
Continuing	3925*** (2573, 5277)	3394*** (2911, 3877)	3056*** (2774, 3338)
Terminal	6543*** (4486, 8599)	7193*** (5893, 8494)	7347*** (6894, 7801)
Unknown stage			
Initial	2325* (217, 4434)	3777*** (3144, 4411)	2491*** (2041, 2941)
Continuing	4628*** (3221, 6035)	3247*** (2725, 3769)	2349*** (2045, 2654)
Terminal	6365** (1565, 11165)	6705*** (4944, 8465)	5787*** (5171, 6403)
Stage 1			
Initial	4463*** (2760, 6167)	3921*** (3391, 4452)	3748*** (3377, 4119)
Continuing	4489*** (3060, 5918)	3738*** (3247, 4229)	2845*** (2560, 3130)
Terminal	8806*** (5397, 12215)	7284*** (5459, 9109)	6553*** (5986, 7121)
Stage 2			
Initial	2418** (813, 4022)	1714*** (1150, 2279)	2417*** (2019, 2816)
Continuing	4576*** (3195, 5958)	3463*** (2970, 3957)	2687*** (2396, 2977)
Terminal	8082*** (4666, 11498)	7622*** (5894, 9349)	6585*** (6035, 7135)
Stage 3			
Initial	1174 (−596, 2943)	147 (−482, 776)	337 (−124, 798)
Continuing	4268*** (2800, 5735)	3000*** (2482, 3518)	2277*** (1910, 2644)
Terminal	5351** (2098, 8603)	6775*** (5174, 8375)	5459*** (4720, 6198)
N	6,217	62,104	190,690

*, **, and *** represent statistical significance at the 90%, 95% and 99% confidence level, respectively.

1. Adjusted for age, insurance (any Medicaid, any private insurance and no Medicaid, and Medicare only), number of months enrolled during the treatment phase, Klabunde Comorbidity Index (zero, greater than zero) and year indicators.