Health Benefits and Cost – Effectiveness of Screening Mammography for Women age 40 to 80: the Effect of Breast Density and other Risk Factors

Technical Report Supplement

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This technical report explains the structure of the Markov cost-utility models and the derivations of the parameters that populate those models. The technical report is broken down into model structures, transition probabilities, direct costs, disutilities attributable to breast cancer and mammography, and sensitivity analyses.

Model Structure

We developed two Markov models that compared the cost effectiveness of several mammography screening strategies. One model was developed to allow comparison of mammography done once yearly, mammography every 2 years, and mammography once every 3 to 4 years (**figure 1a**), with the proportions of invasive breast carcinoma at the time of diagnosis within each historical SEER stage (localized, regional, or distant) derived from Breast Cancer Surveillance Consortium data stratified by age, mammogram frequency, *and* Breast Imaging Reporting and Data System (Bi-Rads) breast density level. A second model was constructed that compared these three mammography strategies to no mammography. This model incorporated invasive breast cancer stage distributions stratified by age and mammogram frequency but not by breast density, since breast density cannot be known in the absence of mammography. The structure of all Markov processes are all similar, one of which is shown in **figure 1c.**

For all strategies in both models, six health states are possible; no breast cancer, in situ breast cancer, localized invasive breast cancer, regional breast cancer, and distant breast cancer. With Monte Carlo simulations of the models, all individuals start off in the "No Breast Cancer" state, and are assumed to have had one negative mammogram that indicates their level of breast density at that time. From the No Breast Cancer state, individuals can remain breast cancer free, can develop in situ or invasive breast cancer, or can die of causes other than breast cancer. Those who develop an in situ breast cancer can remain in this state, can develop an invasive breast cancer, or can die of causes other than breast cancer.

No breast cancer specific mortality from the in situ state is assumed; in situ breast cancer is assumed to cause eventual breast cancer mortality only by progressing to invasive breast cancer. For those who remain in the in situ breast cancer state, mammography is done yearly for the yearly mammography strategy, but is done every two years for those originally assigned to the mammography every 2 years, every 3 years, or the no mammography strategy. The invasive breast cancer state is actually a tunnel state, as these individuals are assigned within that state to either localized, regional, or distant breast cancer immediately, according to the probabilities of stage distribution associated with the particular mammographic strategy at the time of diagnosis. Individuals then transition to the localized breast cancer, regional breast cancer, or distant breast cancer state, or die of causes other than breast cancer. Those in the localized breast cancer, regional breast cancer, or distant breast cancer states can remain alive in that state, can die of breast cancer, or can die of causes unrelated to breast cancer.

We did not explicitly model progression from more localized to more advanced stages of breast cancer. However, these progressions are captured in the mortality rates, and direct medical costs for breast cancer care assigned to each of these health states according to SEER historical stage *at the time of diagnosis* (see further sections on costs of breast cancer, breast cancer mortality, and quality of life loss associated with breast cancer). Additionally, there was no regression from distant breast cancer to regional or local cancer. A lifetime horizon was employed (to age 100 or death), to capture all long-term survival benefits and costs, and all downstream medical care utilization costs and impaired quality of life.

All model runs was repeated for each category of breast density as detected from the initial mammogram. The American College of Radiology defines four Bi-Rads density categories: almost entirely fat (category 1), scattered fibroglandular tissue (category 2), heterogeneously dense (category 3) and extremely dense (Category 4).(1, 2) Both increasing age and breast density are strong risk factors for incident breast cancer.(3-5) In general, more frequent mammographic screening causes a shift towards a higher percentage of local compared to regional or distant cancer. It is well established that cancers diagnosed at a more distant stage

have worse outcomes, thus a mortality reduction is postulated to occur in those who have mammography more frequently.(6) Mortality rates from breast cancer are dependent on stage at the time of diagnosis and number of years since diagnosis (see section on mortality rates).

Models were run performing mammographic screening at the aforementioned intervals between ages of 40 to 49, 50 to 59, 60 to 69 or 70 to 79, using TreeAge Pro HealthCare 2008 software (Williamstown, MA). Costs and health benefits were each discounted at 3%.

Transition Probabilities

Incidence rates for breast cancer

To calculate probabilities of transition from a no breast cancer state to an in situ or invasive breast cancer state we utilized age dependent rates provided by the National Cancer Institute in their Surveillance, Epidemiology and End Results (SEER) Program (**Table 1**).(7, 8)

In Situ Breast Cancer

For in situ incidence rates we utilized a look up table within the models to directly use age-dependent incidence rates as reported by SEER, for the years 1975 to 2005. While the overall incidence of in situ breast cancer from 1975 to 2005 was 20.1 women per 100,000 per year, however, the incidence of *in situ* breast cancer has risen from 5.8 per 100,000 women in 1975 to 32.0 per 100,000 women in 2005, a 5.52 fold difference. In contrast, the incidence of invasive breast cancer has risen only 1.18 fold over that time period.(7) There was very little use of mammography prior to 1980,(9) and it appears likely that although ductal carcinoma in situ (DCIS) is a risk factor for invasive breast cancer, there remains no clear evidence that DCIS *itself* develops into invasive breast cancer.(10, 11) Therefore, it appears likely that the far majority of the in situ carcinomas currently discovered with mammography are lesions that themselves would not develop into invasive breast cancer, and would not be known to exist were it not for mammography.

Therefore, we assumed that the age-specific relative risk of in situ breast cancer in the absence of mammography to be 1.18*5.8/20.1 = 0.34 times that of the age-specific rates for 1975 to 2005 in the SEER database. For those receiving mammography, we assumed that of the change in DCIS between 1975 and 2005 (32-5.8, or 26.2), the *apparent* excess risk of DCIS compared to invasive breast cancer would be (26.2/1.18) or 22.2 per 100,000 women. Therefore, the age-specific relative risk of DCIS among those receiving mammography com would be (5.8 + 22.2)/20.1, or 1.393.

Invasive breast cancer

For invasive incidence rates we constructed an invasive breast cancer risk equation from the SEER data as a function of age, age^2, and age^3 in order to better reflect the decreasing incidence of breast cancer after age 85 (**figure 2**) since the termination criterion for the Markov models was death or age > 100 years.

$$Rate_{Invasive} = -0.0003717*age + 9.9*(10^{-6})*age^2 - 6.53*(10^{-8})*age^3 + 0.0041328$$

This equation faithfully reproduces the actual incidence in SEER as noted in **table 2** and **figure 2**. Use of the equation slightly improved the agreement of our model with estimated lifetime cumulative incidence rates from SEER, compared to using the SEER invasive breast cancer rates as a look-up table.

The relative risks of in situ and invasive breast cancer based on breast density, family history of breast cancer in first degree relatives, and personal history of breast biopsy were incorporated into our model by results published by Jeffrey Tice and colleagues.(12) Using a cohort of 1,095,484 women age 35 and older Tice was able to model breast cancer risk based on breast density level, and reported relative hazards for each breast density level category as compared to level 2 (**table 3**). These relative risks were adjusted for the age-specific prevalence

of each breast density category, to yield relative risks ($RR_{BreastDensity}$) for each breast density level as compared to the entire population of women within that age group (**table 4**).

We also assumed, based on data of Tice and all, relative risks of invasive breast cancer of 1.454 and 0.938, respectively, for the presence and absence of a family history of breast cancer in a first degree relative. Similarly, we assumed relative risks of invasive breast cancer 1.495 and 0.906, respectively, for a positive and negative history of prior breast biopsy.

Importantly, breast density can change with age, but over a 10 year period this will occur in only 10% of women. We run our models for four 10 year screening periods from age 40 to 79 years separately, so our results allow for re-assessment of breast density on updated mammograms every 10 years, so that if necessary recommended mammogram frequency can be changed accordingly.

DCIS is a risk factor for invasive breast cancer, but the risk of subsequent invasive breast cancer after a DCIS diagnosis discovered with mammography is less than when DCIS is initially discovered by clinical examination.(13, 14) Compared to the healthy state, we assumed that the risk of subsequent invasive breast cancer among those with DCIS diagnosed while receiving no mammography to be raised 3.4 fold, and the risk of subsequent invasive breast cancer among those with DCIS receiving mammography to be raised 1.9 fold.(13, 14) The invasive breast cancer rates from SEER are for populations that include women with and without a history of DCIS; therefore, the rates of invasive breast cancer from the health and DCIS states were adjusted for the prevalence of breast cancer as follows;

$$\text{Invasive Breast Cancer Rate}_{HEALTHY} = \text{Rate}_{OVERALL} /(1 + \text{Prev}_{DCIS} * (RR_{DCIS} - 1))$$

$$\text{Invasive Breast Cancer Rate}_{DCIS} = RR_{DCIS} * \text{Rate}_{OVERALL} /(1 + \text{Prev}_{DCIS} * (RR_{DCIS} - 1)),$$

Where RR_{DCIS} is the relative risk of invasive breast cancer for women with DCIS compared to those without DCIS, and $Prev_{DCIS}$ is the prevalence of DCIS in the screened population. The age-specific prevalence of DCIS was calculated from SEER data using the DEVCAN software provided by SEER.

Compared to all women, the age-adjusted relative risks of invasive breast cancer in those with no family history and no history of a breast biopsy respectively, is 0.938 and 0.906.(12) We also did secondary analyses for those with a family history of breast cancer, a history of a breast biopsy, or both. The age-adjusted relative risks for those with a family history of breast cancer or a personal history of requiring a breast biopsy are, respectively, 1.454 and 1.495.

For all base case analyses, mammography frequency is assumed NOT to influence the *incidence* of invasive breast cancer, but rather the stage distribution of invasive breast cancers at the time of diagnosis. We believe this assumption is true if mammography does not result in overdetection of invasive breast cancer, e.g. lead to detection of localized breast cancers which are indolent, non-progressive, pose no threat to the health of the individual, and whose presence would not be known in the absence of mammography. For the base case analyses, we assume an overdetection rate of zero, but also do a sensitivity analysis assuming that an overdetection rate of 10%, e.g. that 10% of all invasive breast cancers diagnosed while receiving regularly screened mammography are indolent and non-progressive.

Proportions of Invasive Breast Cancers in Local, Regional and Distant Stages

A mammographic strategy improves Quality Adjusted Life Years (QALYs) primarily by creating a shift in the stage at diagnosis of invasive breast cancers from distant and regional cancers to local tumors, which are more amenable to treatment and thus have better outcomes. For this reason it was important in our model to correctly determine the stage proportions of those diagnosed with breast cancer depending on elapsed time since last mammography. We used data for 10,279 women participants of the Breast Cancer Surveillance Consortium diagnosed with breast cancer between 2006 and June 2009 with known breast density (Bi-Rads-1, -2, -3, or -4)

to estimate stage proportions at the time of diagnosis. The staging from the BCSC was reported in terms of the American Joint Committee on Cancer 6th edition (stages 0,I, II, III and IV). The best estimates of direct medical costs and disutilities associated with invasive breast cancer, however, have been were reported in terms of the historical SEER stages (localized, regional and distant).

For the comparisons of mammography at various frequencies to no mammography, we used raw data from the BCSC to estimate AJCC-6 stage distributions as a function of screening age (age 40-49, 50-59, 60-69, and 70-79), and mammogram frequency, but without stratifying by breast density. Those whose last mammogram was 0.5 to 1.5 years (6,000 women), 1.5 to 2.5 years (2,846 women), and 2.5 to 5.5 years (mean time 3.5 years, 1,433 women) prior to the date of breast cancer detection were assigned to the "annual mammography" group, "mammography every 2 years" group, and "mammography every 3 to 4 years" group, respectively. Mammography frequency for those whose last mammogram was less than 0.5 years prior to detection of breast cancer was determined by the time difference between the two most recent mammograms.

Among women participating in BCSC for whom breast density was reported, 6000 had mammography yearly, 2,846 received mammography once every 2 years, and 1,433 received mammography every 3 to 4 years. Those Bi-Rads-2 and -3 breast density far outnumber those with Bi-Rads-1 or Bi-Rads-4 breast density, and hence there were only small numbers of women with Bi-Rads-1 or Bi-Rads-4 breast density in different cells broken down by age group and mammography frequency, particularly for those receiving mammography only every 3 to 4 years. Hence, we collapsed breast density into 2 levels, low breast density (Bi-Rads-1 or -2) and high breast density (Bi-Rads-3 or -4). The numbers of women in all subgroups broken down by age group, dichotomous breast density, and mammography frequency were then all 113 or higher (**table 5**).

We used the SEER database for women diagnosed with breast cancer from 2004 onward and who were staged with both the full AJCC categories and Historical Stage criteria to determine the correspondence between each AJCC-6 stage and each Historical Stage (**table 6a**). We used this convergence table to convert the AJCC-6 stage distribution for those whose last negative mammogram was 1 year ago, 2 years ago, and 3 to 4 years ago to the SEER historical stages (**table 6a**). To determine the expected proportion of breast cancer stages in the absence of mammography we utilized SEER data from 1975 to 1979 (**table 6b**).

For scenarios where mammography once every 3 to 4 years appeared to be cost-effective (cost less than $100,000 per QALY gained) we compared mammography once every one and every two years to mammography once every three to four years with stage distributions were further stratified according to two levels of breast density (low breast density equal to Bi-Rads-1 or -2 and high breast density equal to Bi-Rads-3 or -4). This was important to do, because the BCSC data appears to indicate that the stage distribution is more favorable at any particular frequency of mammography among those with low breast density compared to those with high breast density. Even after collapsing breast density to a 2-level variable, however, the distributions among the five categories of AJCC-6 categories of breast cancer have some imprecision to them for those receiving mammography only every 3 to 4 years, such that the raw distributions of AJCC-6 categories do not make sense across all age groups and mammography frequencies. For example, using the raw data among women with low breast density age 70 to 79, those receiving mammography only every 3 to 4 years have a more favorable stage distribution than those receiving mammography once every 2 years. We believe that this is due to the relatively smaller numbers of women in these separate cells, leading to imprecision in the raw estimates. For this reason, in order to "smooth" the data, we used a generalized ordinal logit regression model using all 10,279 women to estimate AJCC-6 stage distribution as a function of age category at the time of diagnosis, 2-level breast density, and mammogram frequency. We assigned predicted probabilities for all five AJCC-6 stages for all 10,279 women from the regression model. The AJCC-6 estimated stage probabilities for all subsets defined by age

category (age 40 to 49, 50 to 59, 60 to 69, or 70-79), breast density, and mammogram frequency were estimated by the mean predicted probabilities for all women in each subset (**table 6c**).

However, we also report in this technical supplement results comparing mammography of different frequencies with stage distributions stratified by age and mammography frequency only, and with stage distributions stratified by breast density and mammography frequency only.

Mortality

A background all-cause power mortality risk function was created from 2003 death rates for all U.S. females up to age 100 (**figure 3**);(15)

All Cause Mortality = $0.0012229+3.09*(10^{-17})*(Age^{8})$

However, since the models separate breast cancer mortality from mortality due to other causes, the *overall population* breast cancer mortality has to be subtracted from the all cause mortality function in order to yield a mortality function for causes other than breast cancer. The overall population breast cancer mortality is in the model in the form of a look-up table created from SEER table IV-8 (**table 1**).Mortality from invasive breast cancer was calculated using SEER data for 1973 through 2005 for each year following a diagnosis of invasive breast cancer as the relative survival in the previous year minus the relative survival in that year, according to age group at the time of diagnosis (example for those age 50 to 59 shown in **table 7**). We assumed no mortality due to breast cancer more than 20 years after diagnosis.

Mortality rates were converted to transition probabilities by use of the following equation.

1-e^(-"Mortality Rates").

Notably, we did not adjust breast cancer mortality for breast density, since there is no clear data that suggests that breast density affects breast cancer mortality in any way other than affecting stage distribution at diagnosis. However, we did do a sensitivity analysis around this issue.

Proportion of Mammograms that Yield False Positive Results (Table 8)

The proportions of mammograms that yield false positive results within each subset defined by age and breast density were calculated using data of Carney and colleagues and Tice and colleagues, From BCSC data, Carney et, al, estimated the incidence of all breast cancers diagnosed (including all of those with either true positive and false negative mammography results) as a function of age. We used the relative risks of invasive breast cancer as a function of breast density derived from Tice and colleagues to adjust the incidence of invasive breast cancers. The proportion of those who do *not* have invasive breast cancer (including all of those with true negative and false positive mammography results) is equal to 1 minus the proportion of those who do have invasive breast cancer. Carney and colleagues also calculated the specificity of mammography for invasive breast cancer in all subsets of women defined by age and breast density. We can then calculate the proportion of mammograms that are false positive using the following equations;

Proportion with invasive breast cancer = True Pos + False Neg

Proportion *without* invasive breast cancer (True Neg + False Pos) = 1- (True Pos + False Neg)_

Specificity = True Neg / (True Neg + False Pos); True Neg = Specificity*(TrueNeg + FalsePos)

Therefore False Pos =(Proportion with invasive breast cancer) – Specificity*(Proportion with invasive breast cancer)

Therefore False Pos = (1 – Specificity)*(1 – (TruePos + FalseNeg)
= (1-Specificity)*(Proportion *without* invasive breast cancer)

Direct Costs

Cost of Screening Mammography

The cost of an individual screening mammography exam was assumed to be $108, the median Medicare reimbursement rate for film mammography for 2008.(16)

False positive mammograms in our model is defined as any mammogram not definitively negative, such that follow-up images, additional diagnostic tests such as ultrasound, fine-needle aspiration, or biopsy need to be performed to establish that a cancer is not present. The mean cost of follow up after receiving a false positive mammogram was reported to be $330 (2004 U.S. dollars) by Tosteson and colleagues.(17) Using medical service inflation rates from the Consumer Price Index we adjusted this to 2008 U.S. dollars ($396).

To calculate the actual direct cost of screening mammography we added the cost of an individual screening mammography to the cost of a false positive times the proportion of mammograms that are false positives;

Overall Mammography Cost = [Cost of Individual Mammography + (Cost of False Positive)* (Proportion of Mammograms that are False Positive)]

It is important to note that the proportion of mammograms that are false positive is associated with breast density. Carney and colleagues reported the proportions of true positive and false negative mammograms as well as sensitivity, and specificity data of mammography for invasive breast cancer according to level of breast density.(18) From this data, we were able to calculate false positive rates for each of the four breast density groups that we utilize within our study (**table 8**).

Cost of Breast Cancer Treatment

A review of cost of care for breast cancer in the United States yields a number of studies utilizing several different methods for calculating breast cancer costs.(19-23) However, only two give costs of care based on cancer stage at diagnosis in addition to data in a phase of care approach which stratify costs into clinically relevant periods: initial period (first year) following diagnosis, continuing period (subsequent years until the last year of life), and the terminal period (last year of life) (**table 9**).(20, 24) We chose to base our estimated direct medical costs of breast cancer on the latest of these two,(24) out of concern that the older study may not reflect current breast cancer treatment practices as well as the current one.

Yabroff and colleagues supply cost estimates for initial, continuing, and terminal direct medical costs of invasive breast cancer based on stage at diagnosis (local, regional, or distant) whereas the initial costs of carcinoma in situ (DCIS) are from the older study by Taplin and colleagues. We estimated the initial costs for DCIS by multiplying the estimated cost for localized breast cancer reported by Yabroff by the ratio of In Situ breast cancer costs to local breast cancer costs reported by Taplin (1992 U.S. dollars) with the ratio of Taplin's costs for local breast cancer to Yabroff's cost for local breast cancer.

Estimated 2004 In Situ Costs = 2004 Local Costs*(1992 In Situ Costs/ 1992 Local Costs)

Yabroff and colleagues did not report the cost of continuing care for each stage at diagnosis. They did, however, report an annual cost of continuing care for all those with breast cancer regardless of stage. We estimated the costs of continuing care for breast cancer according to stage at diagnosis using this overall value ($1201) and the relative continuing costs for local, regional, and distant breast cancer with respect to each other reported by Taplin and colleagues(**table 9**).

All of these costs were adjusted to 2008 U.S. dollars using the Consumer Price Index for medical services.(25)

Health Utilities

Disutilities of the Healthy, In Situ Breast Cancer, and Invasive Breast Cancer States

The disutility of in situ and invasive breast cancers was estimated by Lidgren and colleagues in a sample of 361 Swedish women with localized, recurrent, or metastatic breast cancer, according to time since diagnosis (first year versus subsequent years).(26) In the case of primary and recurrent cancers, quality adjusted life year (QALY) values were estimated separately for those receiving systemic chemotherapy and for those not receiving chemotherapy. QALY estimates were estimated both indirectly with the EQ-5D and directly with a time trade-off (TTO) method, with the TTO values being higher (indicating less quality of life loss). We based our estimates on the values obtained from the EQ-5D in this study. We believe this study yields the most robust estimates to date of the quality of life loss associated with breast cancer. Other studies have generally used expert opinion to supply quality of life loss estimates associated with breast cancer, have provided estimates that cannot be mapped to specific historical SEER breast cancer stages, or are derived from individuals who are representative of neither the population at large nor women who have breast cancer.(27)

We assumed the QALY value for the first year after a diagnosis of localized breast cancer to be 0.696, the value for those with primary breast cancer in the first year among the Lidgren study population (**table 10**). For those with in situ breast cancer, we assumed the QALY value for the first year following diagnosis to be that of those with primary breast cancer not receiving chemotherapy (0.744). For the first year following a diagnosis of regional and distant breast cancer, respectively, we assumed the QALY value to be that of those with primary breast cancer receiving chemotherapy (0.620). Beyond the first year of diagnosis, we assumed no loss of quality of life from in situ breast cancer. For those with localized breast cancer, we assumed that 22% would be treated with chemotherapy, based on the estimated proportions from SEER of those with localized breast cancer with either primary tumors > 3 cm in diameter (6.4%) or those with 1 to 3 cm in diameter that are estrogen receptor negative (15.6%).(28) We assumed a QALY value of 0.745 for the 22% receiving chemotherapy and no loss of quality of life beyond the first year after diagnosis for the 78% not receiving chemotherapy, yielding a weighted average QALY value of 0.807 for all years beyond the first year after a diagnosis of localized breast cancer. For those with regional breast cancer, we assumed a QALY value for all with primary or recurrent breast cancer receiving chemotherapy (0.745), whereas for those with distant breast cancer we assumed the QALY value for those with metastatic breast cancer (0.685) beyond the first year of diagnosis.

Quality of life in general declines with age, however, as reflected in preference-weighted quality of life estimates using the EQ-5D of the American, British, and Swedish populations.(29-31) Therefore, the quality of life loss specifically attributable to breast cancer is lower than the QALY estimates stated above imply. For women of the overall Swedish population at the mean age of the Lidgren study population (age 57), we estimated the QALY value from the EQ-5D to be 0.823 by linear interpolation between values for Swedish women age 50 and age 60.(30) Therefore, the *proportion* of expected quality of life for any given age for all of the aforementioned breast cancer health states compared to perfect health (QALY = 1.0) are the previously stated values for each state divided by 0.823. The final QALY values for each breast cancer state for each age group is therefore these proportions multiplied by the health state QALY value for that age group (**table 10**).

We have used the study of disutility of Swedish women with breast cancer at various stages, because no comparable study of American women with breast cancer has been published. The mean age-specific QALY weights of American and Swedish women are similar (**table 11**)

Secondary and Sensitivity Analyses

Univariate sensitivity analyses were done varying the following variables individually over the ranges indicated in **table 11**; direct medical costs of breast cancer, costs of mammography, incidence rates of breast cancer, disutility of breast cancer states, and mortality from breast cancer. We also did a sensitivity analysis assuming overdetection of breast cancer by 10% with each mammography test. A modest proportion of invasive breast cancers may represent lesions

that do not progress and pose no threat to the health or life of the individual. While there remains substantial controversy what proportion of breast cancers detected by mammography are in fact harmless, an estimate of 10% is at the lower end of published estimates.

We also did a sensitivity analysis assuming disutility from false positive mammograms. While there is no consistent evidence that mammography per se is associated with any quality of life loss, there is evidence that those who have a false positive mammogram (e.g., one with equivocal or suspicious results that require additional diagnostic testing) can have their anxiety raised significantly from this.(32) Initial equivocal mammographic findings may mandate only that the individual be called back for additional mammographic views to be taken, or that additional diagnostic tests such as ultrasound or biopsy be done. The proportion of those who suffer significantly raised anxiety from this process has been estimated to be about 50%, lasting a short period of time for some but as long as a year for others.(32) In this sensitivity analysis, assumed that 50% of those with a false positive would have anxiety sufficient to increase the mood subscale from a 0 to 1, lasting a total of 2 months. According to U.S. EQ-5D tariffs, such a change for an entire year would decrease the estimated QALY value for that year by 0.156.(29) Therefore, the average annualized loss of quality of life loss for those with a false positive mammogram was estimated to be 0.156/12, or 0.013.

An additional sensitivity analysis was done assuming an overdetection rate of invasive breast cancer with screening mammography of 10%. A significant proportion of invasive breast cancers detected by screening mammography may be indolent, non-progressive lesions that pose no threat to the life of health of the individual. The size of this proportion is quite controversial, with some contending the overdetection rate is close to zero and others claiming it is as high as 35%. If overdetection is a real phenomenon, there is no data as to whether or not the rate of overdetection would differ according to frequency of mammography.

If a significant proportion of invasive breast cancers among those having regular screening mammography are non-progressive, however, then analyses that do not account for this will overestimate the cost-effectiveness of mammography compared to no mammography. Comparisons between mammography performed at regular intervals and no mammography require that the stage shift among only those cancers that are clinically relevant in the absence of mammography be captured. Therefore, if there is a 10% excess of invasive breast cancers that would not be clinically relevant in the absence of mammography, the apparent stage distribution of breast cancer among women having mammography needs to be re-calculated after subtracting 0.10 from the proportion of localized breast cancers diagnosed among women having mammography at regular intervals (**table 12**). The following example for women receiving mammography once every 2 years shows this.

Apparent stage distribution assuming no overdetection: 0.726 local, 0.259 regional, 0.015 distant

If 10% of invasive breast cancers are instances of overdetection and all of these overdetected breast cancers are local, then we subtract 0.1 from the local stage above (0.726 – 0.1 = 0.626).

Therefore, apparent stage distribution assuming 10% overdetection among the remaining 90%; local = 0.626/0.9 = 0.695; regional = 0.259/0.9 = 0.288; distant = 0.015/0.9 = 0.017.

The stage shift between no mammography and different frequencies is clearly less if a 10% overdetection rate is assumed. In a sensitivity analysis, we assumed that the 10% excess localized invasive breast cancers would incur the same direct medical costs and quality of life loss as in situ breast cancers. This was achieved by adding 0.10*(invasive breast cancer rate) to the in situ breast cancer rate for those undergoing regular mammography.

Secondary analyses assuming a more restrictive willingness to pay threshold of $50,000 per QALY gained show, for women with Bi-Rads-3 or -4 that mammography, once every 2 years

is still the preferred strategy between ages 50 to 79 regardless of other risk factors and between the ages of 40-49 with a prior breast biopsy or a family history of breast cancer (**figure 3**). For women with Bi-Rads-2 breast density, mammography every 2 years is the preferred strategy between the ages of 50 to 79 with either a breast biopsy or a family history of breast cancer, and between the ages of 40 to 49 with both a prior breast biopsy and a family history of breast cancer,

Mammography once every 3 to 4 years is the preferred strategy for women with Bi-Rads-2 breast density with neither a prior breast biopsy nor a family history of breast cancer between the ages of 50 and 79, for women with Bi-Rads-1 breast density and either a prior biopsy or a family history of breast cancer between the ages of 50 and 79, and for women with Bi-Rads-1 breast density and neither a prior biopsy nor a family history of breast cancer between the ages of 60 and 79.

For women with age 40, the preferred strategy is to repeat mammography at age 50 for those Bi-Rads-1 or -2 breast density and only one or no additional risk factor, and for those with Bi-Rads-3 or -4 breast density and no additional risk factors. Similarly, for women age 50 with Bi-Rads-1 breast density and no additional risk factors, the preferred strategy is to repeat mammography at age 60.

Probabilistic sensitivity analyses were also comparing mammography at different intervals for those scenarios where the cost per QALY gained was between $100,000 and $200,000 per QALY gained. This included mammography once every 2 years compared to every 3 to 4 years for women age 50 to 79 with low (BI-RADS-1) breast density and women age 70 to 79 with average (BI-RADS-2) breast density, and no additional breast cancer risk factors, and also mammography every 3 to 4 years versus no mammography for women age 40 to 49 with Bi-Rads-3 or -4 breast density, with or without additional breast cancer risk factors. In all of these analyses, the parameters allowed to vary over the distributions shown in **table 13**. We chose to show this comparison because in a few of the scenarios there is extended dominance of mammography once every 2 years over once every 3 years. As expected, mammography once every 2 years for women age 70 to 79 with Bi-Rads-2 breast density has a 23% probability of being cost-effective, whereas for women age 50 to 79 and Bi-Rads-1 breast density, the probability of cost-effectiveness drops to 11% or less (**figure 4a**)

Among women age 40 to 49 with no additional breast cancer risk factors, the probability that mammography every 3 to 4 years compared to no mammography costs less than $100,000 per QALY gained is <1% and 5.2%, respectively, for those with Bi-Rads-1, and -2 breast density (**figure 4b**).

Model Validation

This model has been validated in four ways; first, comparing how it predicts breast cancer mortality compared to SEER in the absence of mammography; second, the estimated costs per QALY gained compared to other published cost-effectiveness studies using two of the CISNET models; third, how the predicted cumulative incidence of incident breast cancer at different levels of breast density compared to published relative risks from the BCSC data; and fourth how the estimated breast cancer deaths averted with mammography once every two years compares to other published data. The model predicted lifetime breast cancer incidence and mortality are shown in **table 14**, compared to SEER, showing a close concordance between our model and SEER.

To compare our model to the CISNET model of Stout of colleagues, we ran our model comparing mammography over the same age intervals and converted our model cost inputs to 2000 U.S. dollars, assumed unknown breast density (and therefore no adjustment of breast cancer incidence for breast density), but otherwise left our model inputs the same as for our base case analyses. We took the same steps to compare our model to that of Ahern and colleagues, except that our model cost inputs were converted to 2004 U.S. dollars. The estimated cost per QALY gained of mammography once every two years compared to no mammography between the ages of 45 and 75 for all levels of breast density by our model ($27,028 in 2000 U.S. dollars) is modestly lower than that of Stout and colleagues ($34,000 in 2000 U.S. dollars).(33) The cost

of mammography once every 2 years compared to no mammography between the ages of 40 to 80, was lower in our model ($35,288 in 2000 U.S. dollars) compared to Stout et. al. ($47,000 in 2000 U.S. dollars) but is very close ($39,833 in 2004 U.S. dollars) compared to Ahern and colleagues ($35,000 in 2004 U.S. dollars).(34)

The number of women who need to be screened once every 3 to 4 years over a 10 year period to prevent one breast cancer death (NNS) varied from 337 for women age 70 to769 with very high (BI-RADS-4) breast density up to 8,475 women age 40 to 49 with low (BI-RADS-1) breast density. These results are quite compatible with the range of estimates (665 to 2,564) reported from randomized trials of mammography by Humphrey and colleagues.(35) Our model predicted NNS with mammography once every 2 years compared to no mammography (1634 for women age 40 to 49, 989 for women age 50 to 59, 343 for women age 60 to 69, and 326 for women age 70 to 70). The USPSTF estimated that the number needed to be invited to be screened were 1904 women age 40 to 49 (95% C.I. 929 to 6378); 1339 women age 50 to 59 (95% C.I. 322 to 7455); and 377 women age 60 to 69 (95% C.I. 230 to 1050). Our estimates are well within the confidence intervals of the USPSTF estimates, and would be expected to be slightly lower since some invited for breast cancer screening may not come in to actually have the test.

The proportions estimated by our model of breast cancer deaths occurring between age 40 and 100 prevented for mammography screening between ages 40 and 69, 40 and 79, and 50 and 75, respectively, were 15.0%, 23.4%, and 17.4%. These estimates are the same whether the raw BCSC stage distributions for those receiving mammography or the gologit stage distributions (stratified by age category and mammography frequency) are used. These are close to recently published values of 16%, 25%, and 20% from the Stanford CISNET model.

Within each of the four age groups, the cumulative incidence rate ratio of invasive breast cancer for those each of the four ages in for those with low (Bi-Rads-1) or high (Bi-Rads-3, or -4) breast density compared to those with average (Bi-Rads-2) breast density are very close to the empiric estimates of Tice and colleagues (**table 15**).

Finally, the predicted number of false positive mammograms for women screened biennially between the ages of 40 and 69 and between ages of 50 and 74, respectively, were 940and 725 (compared to 1250 and 940 predicted by CISNET models).(36)

Limitations

Unfortunately, we could think of no valid way to estimate stage distribution stratified by breast density in the absence of mammography. A reasonable question is whether or not there is significant, meaningful bias present in our cost-effectiveness estimations for mammography performed every 3 to 4 years compared to no mammography by not stratifying stage distributions by breast density. The estimated costs per QALY gained of mammography every 2 years compared to every 3 to 4 years shows that when stage distribution is stratified by age, mammography frequency, and breast density, the estimated costs per QALY gained for Bi-Rads-1 and -2 are higher and for Bi-Rads-3 and -4 are lower compared to estimated costs per QALY gained when stage distribution is not stratified by breast density (**table 14**). If the direction of bias comparing mammography every 3 to 4 years to no mammography is the same, then our conclusions regarding use mammography every 3 to 4 years in women age 40 to 49 with Bi-Rads-1 or -2 breast density are robust, because our base case estimates for these two scenarios are over $100,000 per QALY gained. We believe that it is highly likely that our conclusions are also robust for women age 60 to 79 with Bi-Rads-1 or -2 breast density regardless of the presence or absence of additional risk factors and for women age 50 to 59 with either a family history of breast cancer or a prior breast biopsy, since the base case estimated costs per QALY gained for these scenarios are so far below $100,000 per QALY gained. However, for women age 50 to 59 with Bi-Rads-1 breast density and no additional risk factors and for women age 40 to 49 with both a family history of breast cancer and a prior breast biopsy and Bi-Rads-1 or -2 breast density, the estimated base case costs per QALY gained are below but close enough to $100,000

that there is some uncertainty as to whether or not mammography is cost-effective for these individuals.

We did not model the cost-effectiveness of digital mammography. However, a previously published cost-effectiveness study found that digital mammography to be highly cost-ineffective relative to film mammography. Hence, we believe our analysis is still applicable to current technologies.

Figure 1a – Overall Markov Model Structures Comparing No Mammography with Mammography and Different Frequencies of Mammography with Each Other

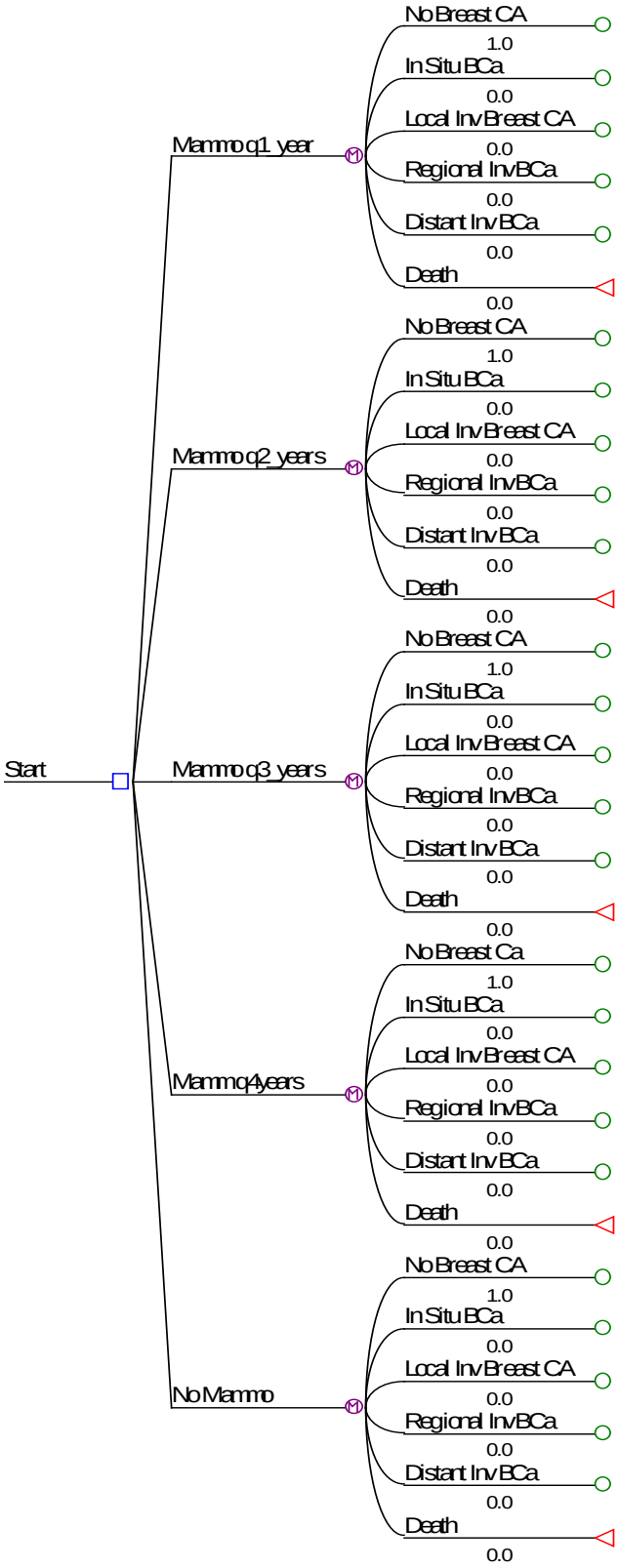


Figure 1b – Structure of Each Markov Process

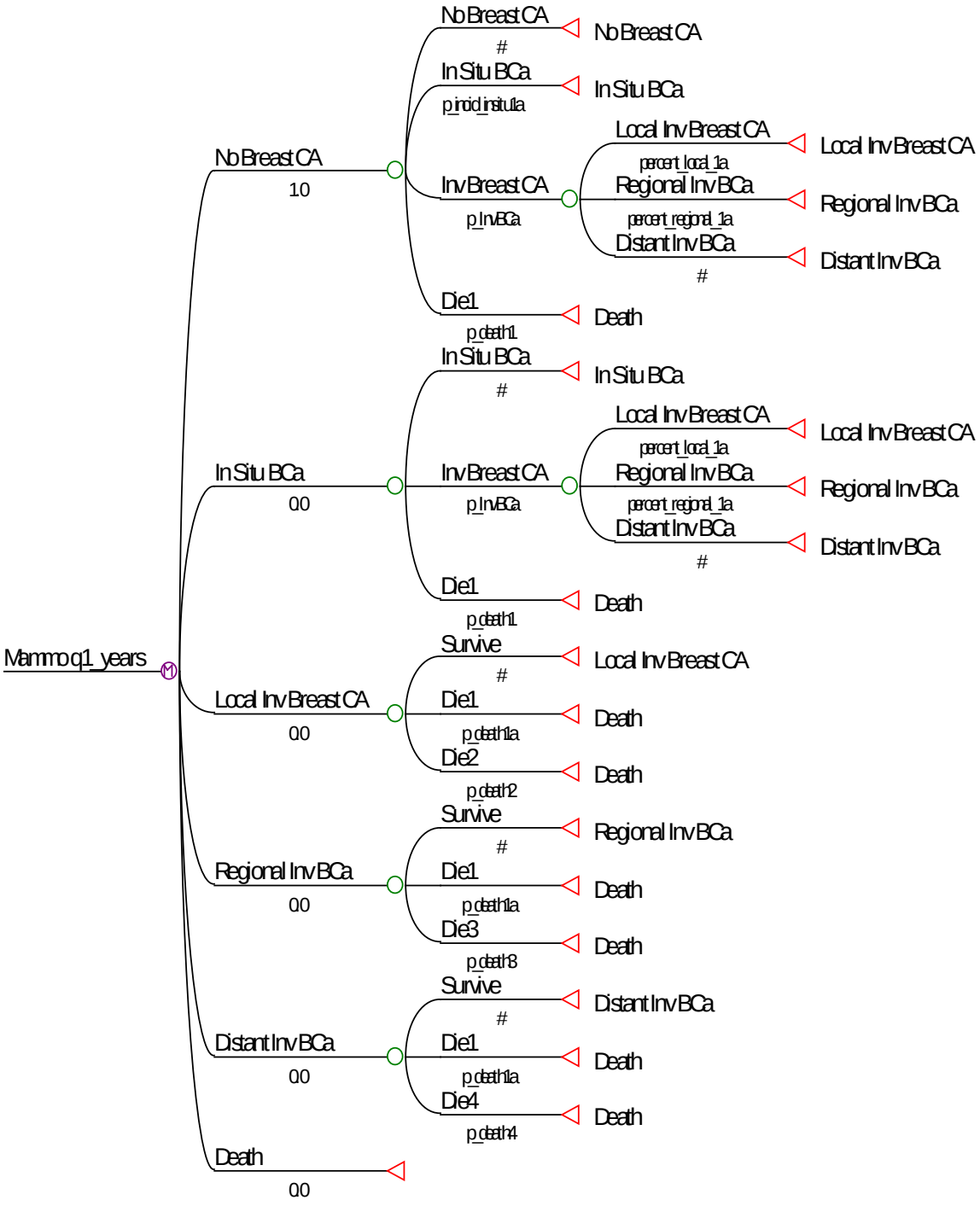


Table 1 – Age Dependent In Situ and Invasive Breast Cancer Incidence Rates

Age at Diagnosis	In Situ Incidence Rate[a]	Invasive Incidence Rate[b]	U.S. Female Population Breast Cancer Mortality[b]
10-14	-	-	-
15-19	-	0.2	-
20-24	0.2	1.4	0.1
25-29	0.8	7.8	0.7
30-34	2.5	26.1	3.3
35-39	9.9	58.9	8.2
40-44	34.1	117.6	15.3
45-49	54.8	185.3	24.5
40-54	67.1	234.4	37.2
55-59	80.0	299.7	50.6
60-64	87.6	359.9	63.4
65-69	96.7	402.3	74.7
70-74	91.8	423.9	91.4
75-79	87.4	453.1	111.5
80-84	66.7	435.9	137.0
85+	34.6	352.8	185.3

[a] Per 100,000 women (Table IV-9 SEER)
[b] Per 100,000 women (Table IV-8 SEER)

Table 2 – Regression of Incidence of Invasive Breast Cancer using age age2 and age3 as Predictors.

```
. regress incid_invas age age2 age3

      Source |       SS       df       MS              Number of obs =      14
-------------+------------------------------           F(  3,    10) = 1986.51
       Model |  .000038138     3  .000012713           Prob > F      =  0.0000
    Residual |  6.3994e-08    10  6.3994e-09           R-squared     =  0.9983
-------------+------------------------------           Adj R-squared =  0.9978
       Total |  .000038202    13  2.9386e-06           Root MSE      =  8.0e-05

------------------------------------------------------------------------------
 incid_invas |      Coef.   Std. Err.      t    P>|t|     [95% Conf. Interval]
-------------+----------------------------------------------------------------
         age |  -.0003717   .0000278   -13.36   0.000    -.0004337   -.0003097
        age2 |   9.90e-06   5.40e-07    18.34   0.000     8.70e-06    .0000111
        age3 |  -6.53e-08   3.26e-09   -20.04   0.000    -7.26e-08   -5.81e-08
       _cons |   .0041328    .000438     9.43   0.000     .0031567    .0051088
------------------------------------------------------------------------------
```

Figure 2: Actual versus predicted yearly incidence of invasive breast cancer as a function of age for females (all races)

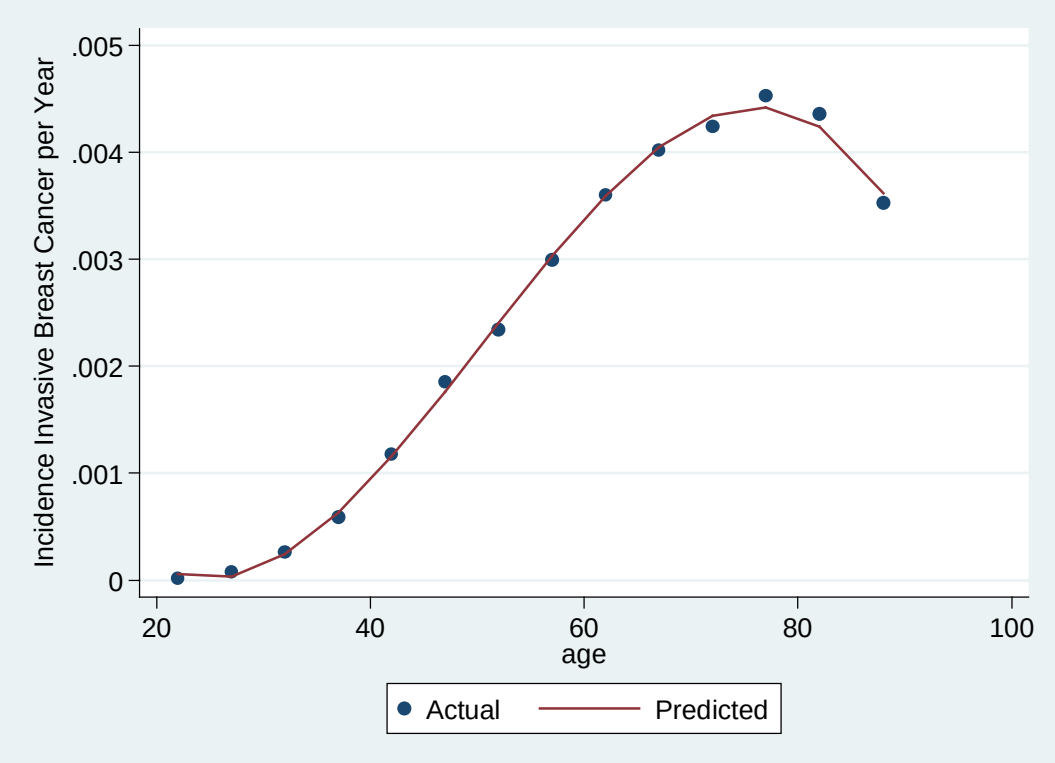


Table 3 – Relative Hazard Risk of Incidence of Breast Cancer Based on Breast Density Level (from the Breast Cancer Surveillance Consortium)

Breast Density Level	Relative Hazard	
	Age < 65 Years	**Age ≥ 65 Years**
1 (Fatty)	0.481	0.657
2 (Scattered Density)	1.000	1.000
3 (Heterogeneously Dense)	1.551	1.388
4 (Extremely Dense)	2.012	1.450

Table 4 – Relative Risk of Breast Cancer based on Age and Breast Density (from the Breast Cancer Surveillance Consortium)*

Breast Density	40 - 49 years	50 - 59 years	60 - 64 years	65 to 69 years	70 - 79 years
Level 1	0.351	0.388	0.400	0.581	0.600
Level 2	0.730	0.807	0.832	0.885	0.914
Level 3	1.131	1.251	1.291	1.228	1.268
Level 4	1.468	1.623	1.675	1.283	1.325

***Reference group for each relative risk is all women of that age group, (adapted data of Tice et.al.(12))

Table 5 – Numbers of Women Diagnosed with Breast Cancer in Subsets defined by age at diagnosis, breast density, and number of years since last mammogram (from the Breast Cancer Surveillance Consortium [BCSC])

Age at Diagnosis	Breast Density	Mammography Frequency		
		Every Year	Every 2 Years	Every 3 to 4 Years
40-49	Low*	232	146	113
	High**	686	403	241
50-59	Low	806	315	195
	High	1203	530	251
60-69	Low	904	395	194
	High	845	371	134
70-79	Low	780	398	189
	High	544	288	116

*Low breast density: Bi-Rads-1 or -2
**High breast density: Bi-Rads-3 or -4

Table 6a – Proportions of Those in AJCC-6 Stages within each Historical SEER Stage

AJCC-6 Stage	Historical SEER Stage			
	In Situ	Localized	Regional	Distant
0	0.9946	0.0054	0	0
I	0	0.9878	0.0122	0
II	0	0.3906	0.6094	0
III	0	0	0.9219	0.0781
IV	0	0	0	1

Table 6b – Historical SEER Stages for No Mammography and Mammography once every 1, 2, 3 to 4 Years, NO stratification by breast density*

Age Category	Historical SEER Stage	Mammogram Frequency			
		None	Every 3 to 4 Years	Every 2 Years	Every Year
40-49	Local	0.515	0.643	0.642	0.674
	Regional	0.431	0.327	0.338	0.300
	Distant	0.054	0.030	0.020	0.026
50-59	Local	0.484	0.660	0.700	0.706
	Regional	0.443	0.323	0.285	0.275
	Distant	0.073	0.016	0.015	0.019
60-69	Local	0.496	0.695	0.762	0.742
	Regional	0.407	0.273	0.224	0.236
	Distant	0.097	0.033	0.014	0.021
70-79	Local	0.533	0.764	0.782	0.773
	Regional	0.378	0.219	0.207	0.209
	Distant	0.090	0.017	0.012	0.017

***Derived from raw BCSC data

Table 6c - Stage Distributions According to Age, Mammographic Frequency, and Two-Level Breast Density (from the Breast Cancer Surveillance Consortium)*

Breast Density		**Low (Bi-Rads-1 or -2)**			**High (Bi-Rads-3 or -4)**		
Mammography Frequency		**Yearly**	**Every 2 Years**	**Every 3 to 4 Years**	**Yearly**	**Every 2 Years**	**Every 3 to 4 Years**
Age 40-49	Local	0.709	0.713	0.676	0.652	0.657	0.617
	Regional	0.267	0.269	0.296	0.321	0.323	0.353
	Distant	0.025	0.018	0.028	0.028	0.020	0.031
Age 50-59	Local	0.733	0.737	0.703	0.681	0.685	0.647
	Regional	0.248	0.249	0.276	0.299	0.299	0.330
	Distant	0.019	0.014	0.021	0.021	0.015	0.023
Age 60-69	Local	0.768	0.771	0.740	0.720	0.724	0.689
	Regional	0.209	0.213	0.234	0.254	0.258	0.283
	Distant	0.023	0.016	0.026	0.025	0.018	0.028
Age 70-79	Local	0.800	0.803	0.775	0.759	0.762	0.731
	Regional	0.186	0.187	0.209	0.226	0.227	0.252
	Distant	0.014	0.010	0.015	0.015	0.011	0.017

***Proportions are the mean predicted values from a generalized ordinal logit model of BCSC data with AJCC-6 stage regressed on age category, mammography frequency, and two-level breast density

Table 7 – Probability of Invasive Breast Cancer Death for those Diagnosed with Breast Cancer According to Years Since Diagnosis and Stage at Time of Diagnosis (U.S. Women Age 50 to 59); From SEER

Years Since Diagnosis	Local		Regional		Distant	
	Relative Survival[a]	Mortality Rate[b]	Relative Survival[a]	Mortality Rate[b]	Relative Survival[a]	Mortality Rate[b]
1	99.90%	0.001	98.20%	0.018	70.70%	0.293
2	99.10%	0.008	92.90%	0.053	50.60%	0.201
3	97.90%	0.012	87.20%	0.057	37.10%	0.135
4	96.50%	0.014	82.00%	0.052	29.00%	0.081
5	95.10%	0.014	77.60%	0.044	23.10%	0.059
6	93.90%	0.012	73.70%	0.039	19.20%	0.039
7	92.80%	0.011	70.10%	0.036	17.00%	0.022
8	91.80%	0.010	67.20%	0.029	15.40%	0.016
9	90.90%	0.009	64.70%	0.025	13.40%	0.020
10	90.10%	0.008	62.60%	0.021	12.50%	0.009
11	89.20%	0.009	60.40%	0.022	11.60%	0.009
12	88.40%	0.008	58.50%	0.019	10.60%	0.010
13	87.70%	0.007	56.90%	0.016	10.10%	0.005
14	87.10%	0.006	55.30%	0.016	9.90%	0.002
15	86.20%	0.009	54.10%	0.012	9.10%	0.008
16	85.50%	0.007	52.90%	0.012	8.60%	0.005
17	84.70%	0.008	51.60%	0.013	8.60%	0.000
18	84.00%	0.007	50.40%	0.012	8.60%	0.000
19	83.20%	0.008	49.20%	0.012	8.60%	0.000
20	82.60%	0.006	48.30%	0.009	8.60%	0.000

[a] From SEER data 1973 through 2004, calculated from observed and expected (in Breast cancer free age- and sex-matched women)
[b] Equal to relative survival of previous year minus relative survival of current year

Table 8 – Rate of False Positives by Breast Density (derived from the Breast Cancer Surveillance Consortium)

Age	Breast Density	Specificity*	Proportion with Invasive Breast Cancer**	RR Breast Density^	Proportion with Invasive Breast Cancer (adjusted)^^	False Pos[#]
40-49	Bi-Rads-1	0.962	0.235%	0.351	0.082%	3.80%
	Bi-Rads-2	0.919	0.235%	0.73	0.172%	8.09%
	Bi-Rads-3	0.901	0.235%	1.131	0.266%	9.87%
	Bi-Rads-4	0.901	0.235%	1.468	0.345%	9.87%
50-59	Bi-Rads-1	0.965	0.435%	0.388	0.169%	3.49%
	Bi-Rads-2	0.928	0.435%	0.807	0.351%	7.17%
	Bi-Rads-3	0.906	0.435%	1.251	0.544%	9.35%
	Bi-Rads-4	0.908	0.435%	1.623	0.706%	9.14%
60-69	Bi-Rads-1	0.968	0.590%	0.488	0.288%	3.19%
	Bi-Rads-2	0.935	0.590%	0.858	0.506%	6.47%
	Bi-Rads-3	0.912	0.590%	1.26	0.743%	8.73%
	Bi-Rads-4	0.914	0.590%	1.485	0.876%	8.52%
70-79	Bi-Rads-1	0.969	0.710%	0.6	0.426%	3.09%
	Bi-Rads-2	0.939	0.710%	0.914	0.649%	6.06%
	Bi-Rads-3	0.924	0.710%	1.268	0.900%	7.53%
	Bi-Rads-4	0.932	0.710%	1.325	0.941%	6.74%

*Specificity of Mammography (from table 5, Carney et. al.)
** From table 3, Carney et. al.(Equal to True Positives plus false negatives)
^ Derived from Tice et. al.
^^ Proportion of those with invasive breast cancer (True Positives plus False Negatives) adjusted for relative risks of breast cancer attributable to breast density [column 4 times column 5]
[#]Proportion *without* invasive breast cancer = 1- Proportion with invasive breast cancer
False Positives = $[(1 - (\text{Proportion with invasive breast cancer})_{\text{Adjusted}}]*(1 - \text{Specificity})$

Table 9 – Direct Medical Costs of Breast Cancer (2008 U.S. $)

Historical SEER Stage	Initial Phase[1]	Continuing Phase	Terminal Phase[2]
In Situ	$8,879	$776	n/a
Localized	$11,690	$553	$31,642
Regional	$22,102	$3,204	$37,453
Distant	$34,135	$10,044	$52,532

[1] Costs during first year after diagnosis
[2] Costs during last year of life *applicable only to those dying of breast cancer; not applied to those dying of other causes*

Table 10 – QALY values associated with Health states

Age	Healthy	In Situ 1st Year	In Situ Later Years	Local 1st Year	Local Later Years	Regional 1st Year	Regional Later Years	Distant 1st Year	Distant Later Years
40	0.859	0.777	0.859	0.727	0.842	0.647	0.777	0.647	0.715
50	0.845	0.764	0.845	0.715	0.828	0.636	0.765	0.636	0.703
60	0.812	0.734	0.812	0.687	0.796	0.611	0.735	0.611	0.676
70	0.788	0.712	0.788	0.667	0.772	0.593	0.713	0.593	0.656
80	0.762	0.689	0.762	0.645	0.747	0.574	0.690	0.574	0.634

Table 11 – Mean General Population QALY Values for General American and Swedish Female Populations(30, 37)

Age	US Women	Swedish Women
40-49	0.863	0.858
50-59	0.837	0.833
60-69	0.811	0.784
70-79	0.771	0.792

Table 12 – Stage Shifts for Secondary Analyses Assuming a 10% excess of Invasive Non-Progressive Breast Cancers Due to Mammography

Mammo Frequency	Proportions in Stages					
	Localized		Regional		Distant	
	No Excess	10% Excess	No Excess	10% Excess	No Excess	10% Excess
No Mammo	0.507	0.507	0.414	0.414	0.079	0.079
Every 3 to 4 Years	0.688	0.653	0.288	0.320	0.024	0.026
Every 2 Years	0.726	0.695	0.259	0.288	0.015	0.017
Every Year	0.728	0.698	0.252	0.280	0.020	0.023

Table 13 – Ranges for Univariate and Probabilistic Sensitivity Analyses

Parameter	Distribution	Standard Deviation	Minimum	Maximum
Breast Cancer Treatment Costs	Normal	25% of mean	50% of mean	150% of mean
Invasive Breast Cancer Incidence Rates	Normal	15% of mean	70% of mean	130% of mean
Breast Cancer Disutility	Uniform	n/a	50% of base case	150% of base case
Invasive Breast Cancer Mortality	Normal	15% of mean	70% of mean	130% of mean
Cost of Mammography[a]	n/a	n/a	$78	$138
DCIS Incidence	Uniform	n/a	50% of base case	150% of base case
Stage Shift with Mammography	Uniform	n/a	Local: ↓ 0.05 Regional ↑0.05	Local ↑0.05 Regional ↓0.05
Disutility False Positive Mammograms	Uniform	n/a	0.00	0.013[b]
Overdetection of breast cancer	Uniform	n/a	0%	10%

[a] Cost of mammography not varied in probabilistic sensitivity analyses

Table 13 – Model and SEER Predicted Lifetime Breast Cancer Incidence and Mortality, According to Starting Age

Starting Age	Lifetime Cumulative Breast Cancer Incidence		Lifetime Cumulative Breast Cancer Mortality	
	Our Model	SEER	Our Model	SEER
40	12.35%	11.92%	2.99%	2.89%
50	11.12%	10.84%	2.90%	2.75%
60	8.84%	8.99%	2.55%	2.45%
70	5.99%	6.44%	1.94%	2.02%

Table 14 – Model Predicted Relative Cumulative Incidence of Incident Breast Cancers Compared to Tice et. al.

Breast Density	Age 40-65		Age 65 and older	
	Tice et. al.	Our Model	Tice et. al.	Our Model
Bi-Rads-1	0.48	0.49	0.66	0.67
Bi-Rads-2*	1.0	1.0	1.0	1.0
Bi-Rads-3	1.55	1.53	1.39	1.37
Bi-Rads-4	2.01	1.97	1.45	1.43

*Reference Group

Figure 3 - Cost-Effective Mammography Screening Strategies from Age 40 through 79 for by Age and Breast Density (Assuming Willingness to Pay Threshold of $50,000 per QALY Gained)

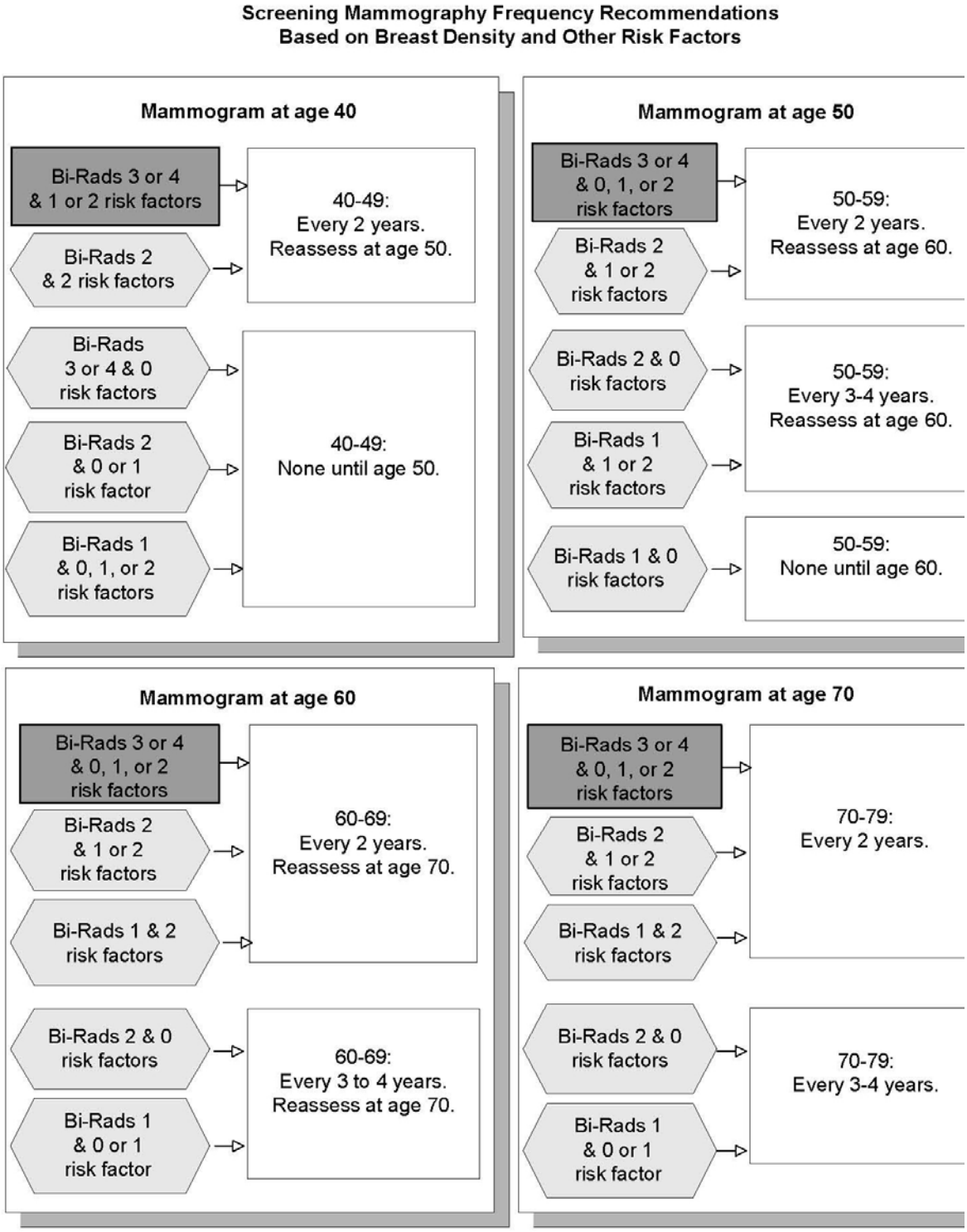


Figure 4a – Probabilistic Sensitivity Analyses comparing Mammography once every 2 years to every 3 to 4 years for Women age 59 to 79; Bi-Rads-1 or -2 Breast Density, NO Added Breast Cancer Risks

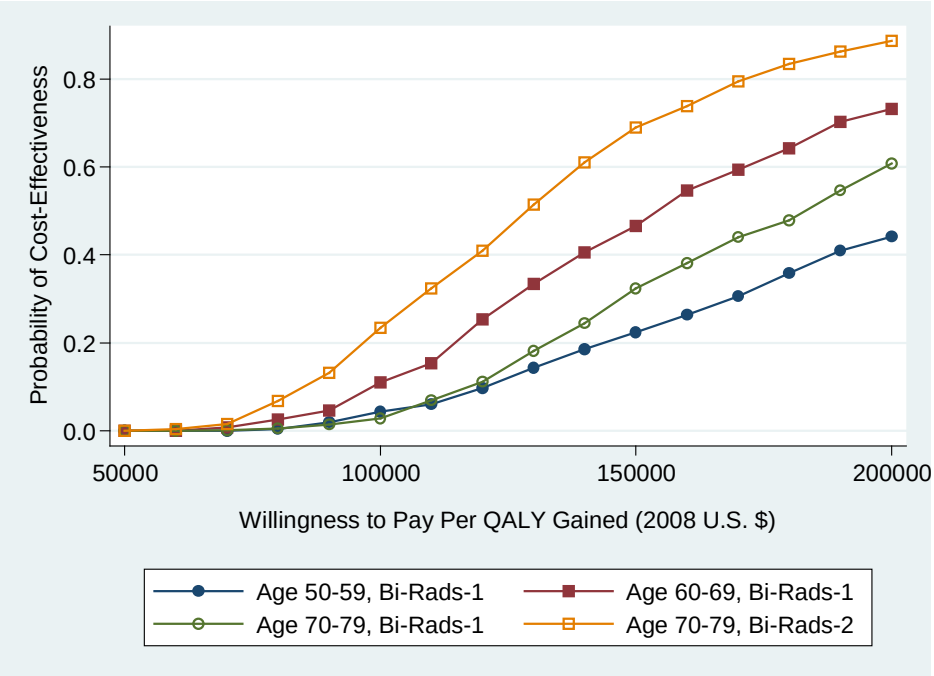
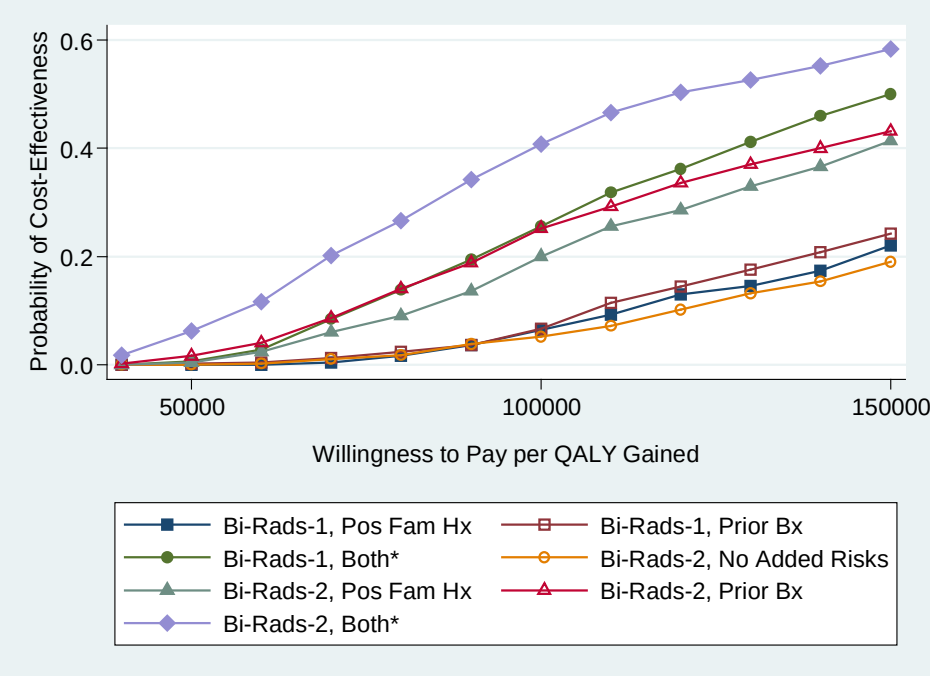


Figure 4b – Probabilistic Sensitivity Analyses: Mammography Age 40 to 49 with Low Breast Density



***Both positive family history of breast cancer and prior breast biopsy

References

1. **Liberman L, Menell JH.** Breast imaging reporting and data system (BI-RADS). *Radiol Clin North Am*. 2002;40(3):409-30, v.
2. **Berg WA, Campassi C, Langenberg P, Sexton MJ.** Breast Imaging Reporting and Data System: inter- and intraobserver variability in feature analysis and final assessment. *AJR Am J Roentgenol*. 2000;174(6):1769-77.
3. **Boyd NF, Guo H, Martin LJ, et al.** Mammographic density and the risk and detection of breast cancer. *N Engl J Med*. 2007;356(3):227-36.
4. **Boyd NF, Rommens JM, Vogt K, et al.** Mammographic breast density as an intermediate phenotype for breast cancer. *Lancet Oncol*. 2005;6(10):798-808.
5. **McCormack VA, dos Santos Silva I.** Breast density and parenchymal patterns as markers of breast cancer risk: a meta-analysis. *Cancer Epidemiol Biomarkers Prev*. 2006;15(6):1159-69.
6. **White E, Miglioretti DL, Yankaskas BC, et al.** Biennial versus annual mammography and the risk of late-stage breast cancer. *Journal of the National Cancer Institute*. 2004;96(24):1832-1839.
7. **Ries L.** Melbert D, Krapcho M, Stinchcomb DG, Howlader N, Horner MJ, Mariotto A, Miller BA, Feuer EJ, Altekruse SF, Lewis DR, Clegg L, Eisner MP, Reichman M, Edwards BK (eds). SEER Cancer Statistics Review, 1975-2005, National Cancer Institute. Bethesda, MD, http://seer.cancer.gov/csr/1975_2005/, based on November 2007 SEER data submission, posted to the SEER web site, 2008.
8. Surveillance, Epidemiology, and End Results (SEER) Program (www.seer.cancer.gov) Limited-Use Data (1973-2005), National Cancer Institute, DCCPS, Surveillance Research Program, Cancer Statistics Branch, released April 2008, based on the November 2007 submission. program]; 2007.
9. **Plevritis SK, Salzman P, Sigal BM, Glynn PW.** A natural history model of stage progression applied to breast cancer. *Stat Med*. 2007;26(3):581-95.
10. **Ernster VL, Ballard-Barbash R, Barlow WE, et al.** Detection of ductal carcinoma in situ in women undergoing screening mammography. *J Natl Cancer Inst*. 2002;94(20):1546-54.
11. **Erbas B, Provenzano E, Armes J, Gertig D.** The natural history of ductal carcinoma in situ of the breast: a review. *Breast Cancer Res Treat*. 2006;97(2):135-44.
12. **Tice JA, Cummings SR, Smith-Bindman R, Ichikawa L, Barlow WE, Kerlikowske K.** Using clinical factors and mammographic breast density to estimate breast cancer risk: development and validation of a new predictive model. *Ann Intern Med*. 2008;148(5):337-47.
13. **Ernster VL, Barclay J, Kerlikowske K, Wilkie H, Ballard-Barbash R.** Mortality among women with ductal carcinoma in situ of the breast in the population-based surveillance, epidemiology and end results program. *Arch Intern Med*. 2000;160(7):953-8.
14. **Kerlikowske K, Molinaro A, Cha I, et al.** Characteristics associated with recurrence among women with ductal carcinoma in situ treated by lumpectomy. *J Natl Cancer Inst*. 2003;95(22):1692-702.

15. **Arias E.** United States Life Tables, 2003. *National Vital Statistics Report*. 2007;54(14):1-40.
16. **Centers fMaMS.** Physician Fee Schedule Vol. 2009: Centers for Medicare and Medicaid Services; 2009.
17. **Tosteson AN, Stout NK, Fryback DG, et al.** Cost-effectiveness of digital mammography breast cancer screening. *Ann Intern Med*. 2008;148(1):1-10.
18. **Carney PA, Miglioretti DL, Yankaskas BC, et al.** Individual and combined effects of age, breast density, and hormone replacement therapy use on the accuracy of screening mammography. *Ann Intern Med*. 2003;138(3):168-75.
19. **Barron JJ, Quimbo R, Nikam PT, Amonkar MM.** Assessing the economic burden of breast cancer in a US managed care population. *Breast Cancer Res Treat*. 2008;109(2):367-77.
20. **Taplin SH, Barlow W, Urban N, et al.** Stage, age, comorbidity, and direct costs of colon, prostate, and breast cancer care. *J Natl Cancer Inst*. 1995;87(6):417-26.
21. **Tollestrup K, Frost FJ, Stidley CA, et al.** The excess costs of breast cancer health care in Hispanic and non-Hispanic female members of a managed care organization. *Breast Cancer Res Treat*. 2001;66(1):25-31.
22. **Warren JL, Yabroff KR, Meekins A, Topor M, Lamont EB, Brown ML.** Evaluation of trends in the cost of initial cancer treatment. *J Natl Cancer Inst*. 2008;100(12):888-97.
23. **Pelletier EM, Shim B, Goodman S, Amonkar MM.** Epidemiology and economic burden of brain metastases among patients with primary breast cancer: results from a US claims data analysis. *Breast Cancer Res Treat*. 2008;108(2):297-305.
24. **Yabroff KR, Lamont EB, Mariotto A, et al.** Cost of care for elderly cancer patients in the United States. *J Natl Cancer Inst*. 2008;100(9):630-41.
25. **Bureau oLS.** Consumer Price Index Detailed Reports. Vol. 2009: United States Department of Labor; 2009.
26. **Lidgren M, Wilking N, Jonsson B, Rehnberg C.** Health related quality of life in different states of breast cancer. *Qual Life Res*. 2007;16(6):1073-81.
27. **Earle CC, Chapman RH, Baker CS, et al.** Systematic overview of cost-utility assessments in oncology. *J Clin Oncol*. 2000;18(18):3302-17.
28. **Harlan LC, Abrams J, Warren JL, Clegg L, Stevens J, Ballard-Barbash R.** Adjuvant therapy for breast cancer: practice patterns of community physicians. *J Clin Oncol*. 2002;20(7):1809-17.
29. **Shaw JW, Johnson JA, Coons SJ.** US valuation of the EQ-5D health states: development and testing of the D1 valuation model. *Med Care*. 2005;43(3):203-20.
30. **Burstrom K, Johannesson M, Diderichsen F.** A comparison of individual and social time trade-off values for health states in the general population. *Health Policy*. 2006;76(3):359-70.
31. **Macran S, Weatherly H, Kind P.** Measuring population health: a comparison of three generic health status measures. *Med Care*. 2003;41(2):218-31.
32. **Brett J, Bankhead C, Henderson B, Watson E, Austoker J.** The psychological impact of mammographic screening. A systematic review. *Psychooncology*. 2005;14(11):917-38.

33. **Stout NK, Rosenberg MA, Trentham-Dietz A, Smith MA, Robinson SM, Fryback DG.** Retrospective cost-effectiveness analysis of screening mammography. *J Natl Cancer Inst*. 2006;98(11):774-82.
34. **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):718-25.
35. **Humphrey LL, Helfand M, Chan BK, Woolf SH.** Breast cancer screening: a summary of the evidence for the U.S. Preventive Services Task Force. *Ann Intern Med*. 2002;137(5 Part 1):347-60.
36. **Mandelblatt JS, Cronin KA, Bailey S, et al.** Effects of mammography screening under different screening schedules: model estimates of potential benefits and harms. *Ann Intern Med*. 2009;151(10):738-47.
37. **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):1162-70.