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Model of Cost-Effectiveness of MRI for Women of Average Lifetime Risk of Breast Cancer

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Abstract

Background: Mammography is the current standard for breast cancer detection however magnetic resonance imaging (MRI) is a more sensitive method of breast imaging. Despite MRI's increased sensitivity, MRI has more false positives and higher costs. The purpose of this study was to determine if MRI or MRI in conjunction with mammography was a cost-effective solution for breast cancer detection in women with average lifetime risk of breast cancer.

Methods: A mathematical model was used to compare annual mammography, annual MRI, and mammography and MRI on alternate years. The model included the natural history of breast cancer, screening by mammography and MRI, screening and treatment costs, and health state utilities. The Surveillance, Epidemiology, and End Results project provided data for the natural history model. Data from the Breast Cancer Surveillance Consortium and from the literature was used to model screening. Costs were taken from the Physician Fee Schedule for Medicare and Medicaid Services (CMS) and from the literature. In particular, mammograms were priced at $81.35 each and MRIs were priced at $787.23 each. Utilities for stages of breast cancer were found using Tuft University Cost Effectiveness Analysis Registry

Results: The difference between MRI only and mammography only was $842,297/QALY at the standard cost of screening found from the CMS. The difference between MRI plus mammography and mammography only was $749,131/QALY at standard CMS screening costs.

Discussion: Although MRI may have health benefits, at current prices, MRI screening is not a cost-effective alternative to annual mammography in women age 40 to 80 with average risk of breast cancer. MRI's would cost effective at a $50,000 per QALY level if the cost of MRI screening were comparable to that of mammography.

Background

The most common cancer affecting women in the western world is breast cancer [1]. Because of the volume of women affected by this cancer, certain methods must be developed to detect and prevent the spread of breast cancer. Methods for the latter include surgical operations such as bilateral mastectomy or chemoprevention with the use of tamoxifen and related drugs. Methods for the detection include clinical surveillance, ultrasound, mammography and magnetic resonance imaging (MRI). The tests developed to detect breast cancer are rated by sensitivity and specificity. Sensitivity relates to the tests ability to identify positive results (cancers). Specificity relates to the ability of the test to identify negative results (non-cancers). Mammography, with a relatively high sensitivity level, has been proven to reduce mortality rate in women with breast cancer [2].

Although breast cancer is usually considered a sporadic disease, women with familial or hereditary breast cancer may carry a breast cancer susceptibility gene BRCA mutation which can give them up to 60-80% lifetime risk of breast cancer[1]. Prophylactic bilateral mastectomy appears to be the most effective way to prevent breast cancer in women who have a high risk of breast cancer[1]. Even for women with a BRCA gene mutation, the decision for a mastectomy is difficult because of the emotional and mutilating effects. Current national guidelines do not recommend mastectomy as a standard procedure for all women with BRCA gene mutation[2]. Current aggressive surveillance practices for high risk women consist of mammogram and physical examination every 6 to 12 months beginning at age 25[3].

Magnetic Resonance Imaging (MRI) is an option for women at high risk of breast cancer. MRI's have a higher biopsy rate but help to detect more cancers than mammography[4]. HIBCRIT'**s** study on Italian women concluded that the addition of magnetic resonance imaging to current screening regimen for women in the high risk category may enable the detection of breast cancers that may have otherwise been missed[5]. MRI's are also beneficial because mammography is affected by breast density causing mammography tests to be less effective on young women with denser breasts. Another advantage of MRI screening is unlike mammography, the MRI test does not use ionizing radiation. MRI screening for breast cancer has been deemed to be impractical for use on the general population (women without high hereditary risk or BRCA gene mutations) because of its high cost and limited availability[5]. MRI also has a low specificity rate leading to further tests and more money being spent.

Studies have been conducted to determine whether regular MRI screening has been effective in high risk women. In a study by Moore et al, research found that although there may be health benefits to using MRI's, it does not appear to be cost effective at a willingness to pay thresholds greater than 120,000/quality-adjusted life years (QALY) [6]. A similar study was conducted by Plevritis et al. in BRCA1/2 carriers. Plevritis et al. found that in that population, MRI along with mammography is cost-effective compared to mammography alone. However, the results vary greatly with age [7].

It is now current scientific consensus that woman with a BRCA1 or BRCA2 mutation undergo MRI in addition to mammography[8]. However, little is known about the cost effectiveness of using MRI surveillance in women without an extremely elevated risk (45-65% lifetime risk) [6]. It is this segment of the population with an average risk of developing breast cancer that on which we conducted our research.

Methods

We created a mathematical model in an effort to determine the cost-effectiveness of magnetic resonance imaging (MRI) versus mammography. In order to create a computer simulation capable of determining this cost-effectiveness, we researched many factors about breast cancer natural history and screening. Key factors include survivability, tumor size, sensitivity and specificity of screening methods, utility weights based on quality of life years (QALY), and cost of treatment.

Sensitivity and Specificity of Mammography and MRI Screening

To determine sensitivity and specificity, three studies were chosen because they were split into first and subsequent MRI tests that were rated on the same BIRAD scale of 3+. These three studies were conducted by Dr. Martin Leach and the MARBIS study group in 2005, Dr. Mike Kriege in 2004, and Dr. Ellen Warner in 2004[2, 8, 9].Table 1 below gives a description of these findings.

Table 1

Study	Kreige		Warner		Leach	
	First	*Subsequent*	*First*	*Subsequent*	*First*	*Subsequent*
Sens MRI	.79	.62	.83	.67	.75	.67
Sensmamm	.38	.43	.38	.43	.40	.40
Spec MRI	.87	.92	.93	.98	.82	.81
Spec mamm	.94	.95	.100	.100	.94	.95
# of MRI screens	1909	2260	236	221	649	1232
# of mamm screens	1909	2260	236	221	649	1232
Total # of cancers	24	21	13	9	20	15
True positives MRI	19	13	11	6	15	12
True positive mamm	9	9	5	3	8	6
False negative MRI	5	8	2	3	5	3
False negative mamm	15	12	8	6	12	9
False positive MRI	245	179	15	5	113	231
False positive mamm	113	112	1	0	4	73
True negative MRI	1640	2059	208	207	516	986
True negative mamm	1772	2127	222	222	585	1144
Found on both	22	19	4	2	427	35
Found in interval	2	3	1	2	1	1

Table 2 consolidates this data by taking the sums and weighted averages of the information in Table 1.

Table 2

	First	*Subsequent*
Sens MRI	.79	.67
Sensmamm	.39	.40
Spec MRI	.86	.88
Spec mamm	.94	.95
# of screens	2794	3713
Total # of cancers	57	45
True positives MRI	22	18
True positive mamm	9	9
False negative MRI	12	14
False negative mamm	35	27
False positive MRI	373	415
False positive mamm	113	112
True negative MRI	1640	2059
True negative mamm	158	185
Found on both	453	56
Found in interval	4	6
False pos rate MRI	0.134	0.112
False pos rate mamm	0.057	0.049

Incidence

Surveillance Epidemiology and End Results, SEER[10], allowed us to see the ages, races and ethnicities that were most prone to developing breast cancer. We used the equation:

$$y = \exp\left(ax^2 + bx + c\right)$$

where x represented age t and y represented incidence per 100,000 people. We fit the parameters a, b and c to the SEER data stratified by age and ethnicity.

Growth of Breast Tumors

We used a modified exponential growth model to describe tumor growth. Growth was modeled by the equation $V = V_0 \times \exp^{(\mathrm{k}\times\mathrm{t})}$, where k represented the growth parameter that was ln(2)/doubling time and $V_0$was the volume at the time of detection by symptoms. In this modified version of the exponential growth model, the median doubling time increased with age, according to the equation $y = (0.021 \times -2.3)$, where x was age (in years) and y represented doubling time (in years)[11]. Each woman has their own doubling time curve based off of a random number drawn from a lognormal distribution. The growth parameters were chosen to match detection rates from the Breast Cancer surveillance Consortium[12]. The distribution of tumor sizes at the time of detection by symptoms came from SEER, year 1983[10]. We then assigned a random number to each woman to determine her tumor size at the time of detection. Within the model tumors may also be detected at a smaller size by screening using either a mammogram or MRI.

Detection of Breast Cancer

By Symptoms - The probability of getting breast cancer by age t was given by the equation $P(t) = 1 - \exp\left(-\int_0^t \frac{h(x)}{100\,000}\right)$, where h(x) is the incidence by age curve. Based on the model each woman was given a random number r ranging from 0 to 1, representing her susceptibility of acquiring breast cancer. Her age of diagnosis of breast cancer by symptoms was represented by the age t at which P (t) = r. A woman with a random number closer to 0 would mean that she would acquire breast cancer at a much earlier age. However, a woman with a random number closer to 1 acquired breast cancer later on in age or not at all.

By Mammograms– The model assumes the probability of detecting a tumor on a mammogram depends on the tumor size and the mammographic density of the breast. We use the equation $P(s) = 1 - \exp(-a1 \times s^2)$, to represent the probability of detecting a tumor on a mammogram. The variable s represents the tumors diameter in millimeters (mm), P(s) represents the probability of detecting the tumor on a mammogram and a1 represents a parameter of women with dense breasts; based on women in their 40's[13]. Women in this age group have an average breast density of 40% dense tissue[13]. We then used a separate parameter a2 based of BCSC data for women in their 60's, which have an average breast density of 25% dense tissue[12]. To calculate probability of women from other age groups, we took the average breast densities for the ages of these women and linearly interpolated between the two probability equations.

MRI's– Similarly to mammograms, we assumed that the probability of detection increases with tumor size and used the equation $P(s) = 1 - \exp(-a3 \times s^2)$. We fit this parameter to sensitivity data from three analysis that reported on data incidence and prevalence in high risk women undergoing mammograms and MRI's[5, 8, 14].Details about the sensitivity and specificity analysis can be seen in Table 1 and Table 2.

Survival

We assumed that the probability of survival from breast cancer decreased with increasing tumor size. The rate that survival decreased depended on the time since detection and varied by race and ethnicity. R Studio used to carry out a proportional hazard analysis; stratified by both race and ethnicity, with the natural log of the tumor diameter [15]. We obtained information on tumor size from SEER; data set 18 from years 1988 – 2003[10]. For tumors of average size we modeled survival with the equation$y = \exp\left(\frac{ax+b}{cx+1}\right)$, where x is the time since diagnosis and y is the probability of survival. The relative risk of dying as a function of tumor size was given by the equation rr = exp(beta*(ln(diameter) – mu)), where mu was the average of ln(diameter) at detection, and beta represents the coefficient from the proportional hazards model. The final equation for survival was P = exp((a*x + b)/(c*x + 1))^exp (beta*(ln(diameter) – mu)).

Mortality

We went to the Centers for Disease Control (CDC) website and selected data from 2001 – 2010, using 5 year age groups, stratified by gender, race[16]. Using Excel and R Studio we graphed the mortality and fit the equation: $y = ae^{bx}$; where x represented age and y represented mortalities per 100,000.

A similar process was used to determine mortality from other causes. We fit an exponential curve to the CDC data for breast cancer mortality for women, stratified by race. The data set that we obtained this information from was CDC years 2001 – 2010[16]. The equation that we set the information to was $y = a \times \exp(bx)$ with age represented byx and breast cancer deaths per 100,000 women represented by y. Parameters a and b depended on gender, race and origin. Mortality from other causes besides breast cancer is the difference between mortality from all causes and mortality from breast cancer.

Utility Weights

To determine an accurate set of utility weights we went to the Tuft University Cost Effectiveness Analysis (CEA) Registry[17]and used the basic search with the search term "breast cancer" with the utility weights clicked. Over 20 pages of utility weights matched our search. Each utility weight from 2003 onward was analyzed and ranked according to how relevant it was to how we wanted our model to be set up, which was by stages of breast cancer or by the time since diagnosis. The article by Dr. Schousoe which divided up the cancers into stages and first year vs. subsequent years seemed to be most conducive to the goals of our simulation because these factors significantly affected the cost of treatment [18]. Schousboe's article referenced another article, "Health related Quality of Life in Different States of Breast Cancer", by Dr.

Lidgren[19]. Ledgren's article surveyed individuals in a time trade off scenario as well as an EQ-5D model. We chose our utilities for our simulation to be the means from the EQ-5D model. The means for first year after primary breast cancer, subsequent years of primary breast cancer and metastatic diseases were .686, .776, and .689 respectively [19].

Cost of Treating Breast Cancer

To find the cost of treating breast cancer we did a Google Scholar search with the term 'Cost of treating breast cancer in the United States'[20]. The most promising result was a review article by Dr. Campbell titled, "The costs of treating breast cancer in the US: a synthesis of published evidence"[21]. This article yielded Table 3. Campbell's article reviewed and compiled 8 different studies based on cost of treating breast cancer in the initial 6 months, continued treatment and terminal 6 months of breast cancer. Because many of these studies are dated and the currency is not equivalent each section was put into the perspective of 2012 United States dollars (USD) by using "Tom's Inflation Calculator"[22]which is based on the Consumer Price Index [23]. To find each value in 2012 USD, the cost at the base line year, the base line year, and 2012 were entered in the calculator along with highlighting the option of 'U.S Medical Inflation (1935-2012)'. Each value was recorded in Table 2. The medians for the cost of initial 6 months of treatment was were $20,821.31, the cost of continued treatment per 6 months was $4,445.72 and the cost of 6 months prior to termination was $63,202.45. In this simulation, the cost of continued treatment was applied for 5 years after initial year of treatment.

Table 3

Study	Year	Initial	Subsequent	Final
Baker	1984	6,663.98		33,583.70
Tplin	1989	25,965.56	1,504.68	
Legorreta	1989	20,821.31		
Riley	1990	22,700.96	3,993.61	128,488.50
Fireman	1992	32,151.08	4,897.82	76,973.22
McDonough	1995	17,099.24	9,130.88	69,683.64
Barnett	1997			151,767.69
Barlow	1998	14,561.92		56,721.26
Warren	1998	12,175.48		40,293.69
Lamerato	2003	57,237.53		33,070.72
Median		20,821.31	4,445.72	63,202.45

***Note: Initial refers to cost in USD for the first 6 months of diagnosis, Subsequent refers to cost of continuing treatment in USD for 6 month intervals and Final is the cost of treating the last 6 months on life in USD.*

Cost of Mammography and MRI screening

To determine the cost of mammography and MRI screening, the Physician Fee Schedule Search from the Centers of Medicare and Medicaid Services (CMS) was employed[24]. In the Physician Fee Schedule Search the criteria we used was 2012A year, pricing information, single Healthcare Common Procedure Coding System (HCPCS) or Current Procedural Terminology (CPT) code, all carriers, the corresponding HCPCS code for the individual test and all modifiers. The search yielded a cost for a digital mammography screening test $81.35 and the cost for MRI screening to be $787.23. The corresponding HCPCS/CPT numbers were 77057 and 7705 respectively.

Using the R-Studio simulation

To create a computer simulation able to run clinical trials on groups of 100,000 women the computer software R Studio was used [15]. Into the input 3 arms were created each running simulated cohorts of 100,000 women. In these arms future cost and QALYs were discounted by a factor of 0.03. In the first arm the simulation gave women a mammogram every year from age 40 to 80 which is the current recommendation for women that have an average risk of developing breast cancer in their lifetime [3]. The second arm is using MRI screening only from age 40 to age 80. Arm 3 alternates between mammography and MRI every year from age 40 to 80. These arms were simulated using the actual cost of mammography and MRI and then used adjusted costs to determine the price for MRI screening that would make it cost-effective compared to mammography in terms of cost per QALY. All other variables remained the same throughout the tests

Results

Each clinical trial consisted of three arms. Arm 1 is mammography only from 40 to 80 yearly, arm 2 is MRI only from 40 to 80 yearly, and arm 3 is mammography and MRI alternating years from 40 to 80. "Number" on the y-axis refers to the difference in the number of QALYs and "Time" refers to years. MRI screening was able to preserve QALYs however it proved to be more costly as seen in Figure 1 and Figure 2.

Figure 1

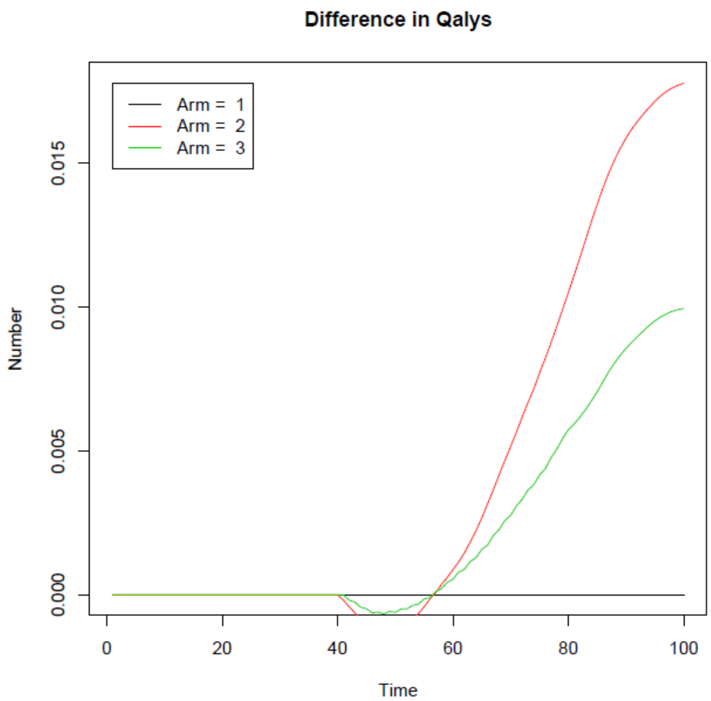
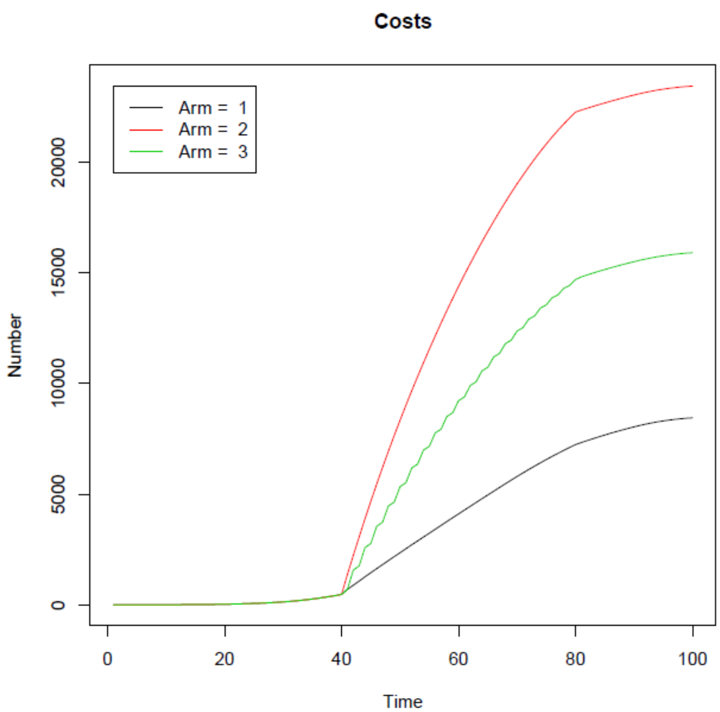


Figure 1 shows how when screening begins at age 40, the trials with MRI (Arm 2) only and MRI and mammogram (Arm 3) drop lower than the QALYs of the trial of mammography only (Arm 1). This can be explained by MRI's detecting more cancers in younger women, and when these women discover they have cancer their QALYs lower form 1to what was discovered in our utility weights for first year after primary breast cancer to be .686 [19].However, as time goes on and more breast cancers are being discovered by the mammogram only trial and less metastatic cases are present in the MRI and MRI and mammogram trial, these QALY's end up being higher when being compared to the mammography only arm. The MRI only arm reaches .018 more than the mammogram arm and the MRI and mammogram arm reaches .010 (Table 4).

Figure 2



The costs in Figure 2 demonstrate how MRI only (Arm 2) is more expensive than MRI and mammography (Arm 3) and mammography only (Arm 1). The costs begin to differentiate themselves at age 40 when the screening begins and stay steadily different until age 80 when screening ends.

We used the incremental cost-effectiveness ratio (ICER) in an effort to compare screening strategies of MRI and mammogram. Our ICER was the difference between costs divided by the difference of QALY. The comparison of ICER values for differing prices of MRI screens are shown in Table 4.

Table 4

Sample*	MRI only vs. mammography only			MRI and mammogram vs. mammography only		
	Cost	*QALY*	*ICER*	*Cost*	*QALY*	*ICER*
Standard Costs**	14984	0.018	842,297	7458	0.010	749,131
MRI 2x cost of mamm	2018	0.018	113,452	1094	0.010	109,863
MRI 1.5x cost of mamm	1174	0.018	65,990	679	0.010	68,234
MRI same cost as mamm	329	0.018	18,515	265	0.010	26,593

**Sample consists of 100,000 individuals each arm*
***Standard costs are $81.35 per mammogram and $787.23 per MRI*

The ICER value decreases as the cost of MRIs decreases. This is logical because as the difference in cost of MRIs decreases, the total breast cancer cost decreases and the difference in QALYs is not affected by cost.

Table 5

	BC* diagnosed	BC deaths	False Positives
Mammography only	0.116	0.018	2.80
Mammography and MRI	0.117	0.016	3.58
MRI only	0.118	0.015	3.83

**breast cancer*
***Result per person*
****Sample consists of 100,000 individuals in each arm*

The use of MRI screening allows for more diagnoses of breast cancer and less deaths by breast cancer. However, the number of false positives in the mammogram only trial is less that the false positive rate in the Mammography and MRI and the MRI only trial.

Table 6

	Screening cost ($)/% of total	*False Positive Cost ($)/% of total*	*Cost of treatment ($)/% of total*	*Death cost ($)/% of total*	*Total Cost ($)*
Mammogram only Standard Cost**	1693/ 20	900 / 11	3985 / 47	1868 / 22	8447
Mammogram only Same Cost***	1693 / 20	900 / 11	3985 / 47	1868 / 22	8447
MRI and Mammogram Standard Cost	8897 / 56	1108 / 7	4028 / 25	1872 / 12	15904
MRI and Mammogram Same Cost	1705 / 20	1108 / 13	4028 / 46	1872 / 21	8711
MRI only Standard Cost	16344 / 70	1161 / 5	4053 / 17	1873 / 8	23431
MRI only Same Cost	1689 / 19	1160 / 13	4053 / 46	1874 / 21	8777

**data based on dollars per person of 100,000 sample*
*** Standard screening costs are $81.35 per mammogram and $787.23 per MRI*
****Same cost were $81.35 per mammogram and $81.35 per MRI*

For the use of mammography screening only, the primary cost involved is the cost of treatment. However, when MRI is used alone or with mammography screening the major cost is the screening. The cost of MRI screening is causing a large cost difference between mammography screening and MRI plus mammography and MRI alone. Note that even when MRIs cost the same as mammograms, the MRI arm has higher total costs than the mammogram arm. This is primarily due to the increased number of false positives that are associated with MRI's and partially due to MRI's ability to detect more breast cancers earlier and therefore increasing the treatment costs.

Discussion

Although MRI may have health benefits, based on a $100,000/QALY cost effectiveness ratio, current prices of MRI do not support that MRI screening for women yearly from ages 40 to 80 or alternating between mammography and MRI yearly for women of the same ages as cost effective. However, if the costs of MRI were able to come down to twice the current price of mammography, the ICER value suggests that at a $100,000/QALY threshold, alternating MRI and mammography screening would be cost effective. With MRI prices equal to mammography prices, MRI alone as well as MRI with mammography screening would be cost effective even at a $50,000/QALY ratio.

Our findings are similar to those of Susan G Moore in her 2009 study which found that MRI screening is not cost effective at current MRI price. However, our study does not deal with a young age population or with individuals of pre-determined high risk. Other studies such as Pleuvertis 2006 and Lee 2010, also dealing with high risk categories, however, found the practice of MRI screening to be cost effective in specific cases.

Weaknesses in our analysis could include that the specificity and sensitivity of our screening techniques were determined by studies of women of high risk. The sensitivity and specificity of these tests for women on the typical population could be different. Another weakness in our model could be the utility weights. The current utility weights indicate that the first year of being diagnosed with breast cancer is nearly equal to the metastatic stage which does not seem intuitive.

Future directions of study include what level of risk makes MRI cost-effective. Since MRI is not cost-effective for the entire population it may be useful to know what category of 5-year risk would make MRI's cost effective. Sensitivity analysis could be conducted to see the impact of specific elements.

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