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Computer Simulation Estimation of the Benefits and Costs of Breast Cancer Chemoprevention

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ABSTRACT

Background: While screening and chemoprevention offer the potential for reducing the rate of breast cancer death before the appearance of disease, critical questions concern the actual saving in life and morbidity that can be expected from these interventions, their cost, interaction, and best mix. ***Method****s*: A computer simulation model of breast cancer growth, spread, and detection, which calculates the savings in life and cost/benefit ratios expected from various usages of mammography screening and chemoprevention. ***Results***: Women age 50 to 75 can expect to gain ~4-5 days of life for every year of screening, slightly less than 1 day of life for every year of tamoxifen chemoprevention, and slightly more than 1 day of life for every year of Letrozole chemoprevention. A group of women beginning screening and chemoprevention at age 40 who live until age 85 can expect to gain of ~7 months of life for annual screening. In contrast, women may be expected to gain about ~7 days of life for 5 years of tamoxifen chemoprevention and ~10 days of life for 5 years of Letrazole chemoprevention. Screening's markedly lower cost and greater potential for reducing death makes it a far more economical way to save life than chemoprevention; for women in their fifties, screening costs ~$7000/year of life saved, while tamoxifen chemoprevention costs ~$200,00/year of life saved, and Letrozole chemoprevention costs ~$1,00,000/year of life saved. Identifying women at high risk has little impact on these values. ***Conclusions***: Chemoprevention can be expected to yield a modest saving in life, although at considerable cost, while mammographic screening should lead to a considerable savings in life, at modest cost. The small benefit of breast cancer chemoprevention may justify its high cost once widespread use of prompt annual screening has been achieved.

INTRODUCTION

Options for reducing the rate of breast cancer death before the occurrence of disease include screening and chemoprevention. Screening's principal mechanism for reducing breast cancer death lies in its capacity to bring breast carcinomas to medical attention at smaller and thus less lethal sizes,[19-27] while chemoprevention's principal mechanism for reducing breast cancer death lies in its capacity to reduce the incidence of breast carcinoma. The reduction of cancer death by mammographic screening has been demonstrated in randomized trials.[1] However, a similar reduction of cancer death by chemoprevention has not been demonstrated in randomized trials, although a reduction in the incidence of breast cancer has been found.[2-14]

Since the trials of chemoprevention were designed to measure a reduction in the incidence of breast cancer, but not survival, the effectiveness and cost of chemoprevention, in terms of survival and years of life saved, could only be examined by modeling.[15-18] Generally, these studies have revealed that chemoprevention may have a small potential for reducing breast cancer death, although at high cost. However, no previous studies have quantified how chemoprevention compares with screening, how the two interventions interact, and which might be the best combinations of chemoprevention and screening for achieving the maximal possible reductions in death. Here we use a computer simulation model of breast cancer growth, spread, and detection,[19,20,21-23] based on actual data[24] on the rate of breast cancer growth,[25] the sizes at which breast cancers become detectable on mammographic and clinical grounds,[26] the relationship between tumor size and survival,[21,27] cancer incidence by age, population age structure, life expectancy by age, and the costs of screening to estimate the costs and benefits that may be expected from breast cancer chemoprevention and screening..[282930]

METHODS

The simulation:

The core of the simulation is based upon the day-to-day increase in tumor cell number (*N*), expected for exponential growth (Equation #1 below) and the relationship between tumor size (*N*) and the fraction (*L*) of women with lethal metastatic disease (Equation #2 below):

(1) $$N_{today} = N_{yesterday} + (g * N_{yesterday})$$

where *g*, is the fraction of live cells today that will be replaced by two live cells tomorrow (see Equation #4 below), and the lethality of breast cancer is captured by the expression:

(2) $$L = 1 - e^{-Np}$$

where *p* is the probability, per cell, of an event of spread of breast cancer from the primary site in the breast to the periphery leading to death, which we have found[27] can be calculated with the expression:

(3) $$p = 0.00005017 * N^{0.5575}$$

The value of *g* in Equation #1 is related to the tumor doubling time by the expression:

(4) $$g = (2 \wedge (1 / \textit{doubling time})) - 1$$

Unless otherwise stated, the *doubling time* used is the empirically based value of 130 days, based upon a variety of sources of information, as outlined in the accompanying paper.[19]

Details of the implementation of the simulation can be found in the accompanying paper.[31]

Here we have estimated the cost of screening at $100 per mammogram (see accompanying paper[19] for other cost considerations). We have estimated the cost of Letrozole = $315/week,[32] and the cost of tamoxifen at $415/year,[33] the same value used by Melnikow et al.[15]

Here we examine the consequences that would occur should tamoxifen reduce ~~in~~ the incidence of breast cancer by 50%, as was found in the P1 trial,[67] and should Letrozole reduce the incidence of breast cancer by an additional 40%, as taken from the P4 study proposal.[35]

Results were calculated in terms of both "days/weeks/months/years of life saved", that is, the benefit of prevention of years lost to premature death caused by cancer, and "cancer free days/weeks/months/years of life saved", that is, the benefit of prevention of years lost to both premature death caused by cancer and to metastatic disease. These values were estimated assuming a mean time from diagnosis to death of 5.74 years, as found from the patients seen at this institution before 1990; this mean time period remained roughly constant from age 30 to about age 70, only in the 80's does this time period decline markedly (30's: 6.8 years; 40's: 5.4 years; 50's: 6.2 years; 60's: 6.0 years; 70's: 5.3 years; 80's: 3.6 years).

The simulation was written in Visual Basic 6, and can be found at the end of this Technical Report.

RESULTS

The simulation

The impact of chemoprevention and screening on the breast cancer death rate could be estimated with a computer simulation model that makes simultaneous calculations of two biological aspects of cancer lethality: FIRST, the change in tumor size that occurs over time, and SECOND, the change in the risk of death that occurs as tumors increase in size.[19,22,23,31] Both processes have been characterized by simple equations (#1 and #2, Materials and Methods), which have been amply substantiated empirically.[21,27] Screening acts by finding tumors at smaller sizes than would otherwise be the case, while chemoprevention reduces the number of women with breast carcinoma, and the simulation calculates the impact of these effects on the survival rate and years of life lost to cancer.

The yearly benefits of screening and chemoprevention

The simulation revealed that women between age 50 and 75 can expect to gain approximately 4-5 days of life for every year of mammographic screening, about 1 day of life for every year of tamoxifen treatment, and slightly more than 1 day of life for every year of Letrozole treatment (FIGURE 1). Lower benefits are reached for women younger than 50, principally because of the lower cancer incidence at these ages, and for women older than 75, principally because they have fewer years of life remaining. The declines before 50 and after 75 are gradual, with no obvious cut-off.

The accumulated benefits of screening and chemoprevention

The simulation results reveal that a group of women who begin screening at age 40 and who live until age 85 can expect to gain 7.32 months of life for annual screening (TABLES I and II). In contrast, women in the 50's and 60's (the age at which they will receive the greatest benefit from preventative therapy: FIGURE 1) who utilize 5 years tamoxifen therapy can expect to gain ~7 extra days of life, while women who utilize 5 years of Letrozole therapy can expect to gain about ~10 extra days of life (TABLES I and II).

The costs of screening and chemoprevention

The simulation revealed that for women in their 50's and 60's, mammographic screening costs about $7,000 for each year of life saved. In contrast, tamoxifen prevention costs about $200,000 for each year of life saved, while Letrozole costs slightly more than $1,000,000 for each year of life saved (FIGURE 2).

Screening and chemoprevention in high-risk women

One strategy for increasing the effectiveness of chemoprevention is to identify patients at higher risk for breast cancer than is seen in the population as a whole. However, the simulation reveals that the relatively low power of the current predictive methods for finding women at markedly higher risk than the population as whole limits the practical effectiveness of such an approach. For example, limiting treatment to patients with at least a 1.66% 5-year risk of breast cancer, as assessed by the Gail score, will only have a very small impact on the cost/benefit ratio of screening and chemoprevention for women younger than 50, and only have a significant impact for women younger than 40, few of whom would be eligible for such treatment (FIGURE 3). A more stringent method for selection of patients at high risk is the model of Rosner and Colditz.[34] However, even if preventative chemotherapy were limited to the 10% of patients they have identified by this model with the highest risk of breast cancer,[34] the impact on cost/benefit would be minimal, reducing the cost/benefit ratio of tamoxifen treatment from approximately $90,000/year of life saved to approximately $50,000/year of life saved, and reducing the cost/benefit ratio of Letrozole treatment from approximately $600,000/year of life saved to approximately $300,000/year of life saved (data not shown).

The interaction of screening and chemoprevention

The simulation revealed that chemoprevention has less of an impact in populations of women who attend screening regularly than in populations of women who never attend screening (FIGURE 4).

However, mammography always achieves a greater impact on survival, at a lower cost, than chemoprevention. This means that chemoprevention can never be a rational substitute for screening, and only makes sense once the maximal possible level of screening has been achieved.

DISCUSSION

The simulation results indicate that chemoprevention can be expected to result in a modest saving in life, although at considerable cost. In comparison, mammographic screening would appear capable of leading to considerable savings in life at modest cost. While women can expect to gain, on average, about 7 months of life for a lifetime of annual mammographic screening, even given the best assumptions of the efficacy of chemoprevention, and without including any assumptions of negative consequences of such treatment, these women can expect to gain only about 7 days of life for 5 years of tamoxifen treatment and only about 10 days of life for 5 years of Letrazole treatment. The simulation also revealed that the greater potential of mammographic screening for savings years of life, as well as mammography's considerably lower cost makes screening a far more economical way to save life than chemoprevention. For example, for women in their 50's and 60's, mammographic screening costs about $7,000 for each year of life saved, while tamoxifen prevention costs about $200,000 for each year of life saved, and Letrozole costs slightly more than $1,000,000 for each year of life saved. Identifying women at high risk yields little improvement in these values.

As we have found in the studies reported in the accompanying paper,[19] a population of women who follow the recommendation of prompt annual screening from age 40 can expect almost a 90% breast carcinoma survival rate. This means that in such a well-screened population, ten cancers must be prevented for each life saved. This low effectiveness of chemoprevention in the context of effective screening, combined with its high cost, accounts for much of its poor cost/benefit ratio.

It has been suggested, based on the P-1 trial of chemoprevention, that tamoxifen can reduce the incidence of these cancers by approximately 50%,[6,7] and that Letrozole will lead to a 40% reduction in the incidence of the remaining cancers,[35] "based on the effects seen for the reduction of contralateral breast cancer in several treatment trials."[36,37,38] We have used these values in the simulation results reported here. However, other trials have found smaller reductions in cancer incidence,[5-13] and it could well be that the actual benefits of chemoprevention will be lower than even the low values we are reporting here. We have also not taken into account the lethal non-breast cancer consequences of chemoprevention. Substantial increases in the rates of endometrial cancer and thromboembolic events have been found to occur in the trials.[2-13] The analysis of the four prevention trials estimated that while 176 cases of invasive breast cancer where prevented, there were almost as many cases, 166, of serious side effects.[2] Since, as we have noted above, our simulation results suggest that a population of women who follow the recommendation of prompt annual screening from age 40 can expect almost a 90% breast carcinoma survival rate, then it can be expected that if these serious side effects have as much as a 10% case fatality rate, then the life-sparing potential of chemoprevention would have been wiped out. Our simulation model can measure the impact of such non-breast cancer lethalities on the benefit of chemoprevention, but data are lacking for estimating the magnitude of these lethal consequences, and all of the trials have been underpowered for measuring their magnitude. Indeed, it might be wondered how one can make any sort of recommendation, when information on the magnitude of these negative consequences are unknown.[39,40,41,42,43,44]

Our values for costs and benefits of chemoprevention are generally in line with estimates of others.[15-18] For example, for tamoxifen prevention, our simulation, which did not take into account the potential lethal non-breast cancer consequences of treatment, has yielded a cost about $200,000 for each year of life saved, while Melnikow et al,[15] using a Markov model that did take into account the potential lethal non-breast cancer consequences of treatment, found a cost of about $1,300,000 for each year of life saved.

The randomized trials have found that the cancers prevented by Tamoxifen or Aromitase Inhibitors are principally ER+, while the cancers that occur are likely to be ER-.[2-14] This has a number of

interesting considerations, such as the fact that the ER- tumors that are not prevented are less amenable to adjuvant therapy, and this may also degrade the potential benefit of chemoprevention.

The simulation offers the potential to determine how to use specific amounts of financial resources for achieving the maximal possible reductions in death. In the accompanying manuscript,[19] we use this approach to identify the optimal screening interval, and patient selection, for minimizing the risk of death. The simulation results shown here reveal that no mix of screening and chemoprevention will yield such a maximal reduction in death for a given level of financial resources. Even at its most intensive screening interval (every six months) and patient selection (starting at age 30), mammography provides a cheaper source of years of life saved per dollar than chemoprevention at any age and with any agent. Thus, in the context of a finite level of financial resources, any re-deployment of expenditure away from screening to chemoprevention will actually result in a population-wide increase in the breast cancer death rate. It is only at the point in time when mammographic screening is fully utilized that expenditures in chemoprevention make sense.

The simulation recapitulates the simultaneous increase in tumor size,[26] tumor detectability,[26] and lethality[27] of breast carcinoma that occurs over time, and then uses this information, together with data on incidence of breast cancer[45] and life expectancy by age,[46] to calculate the breast cancer death rate, and years of life lost to breast cancer, that occur in the context of various usages of screening and chemoprevention. As such, it provides what Gazelle and his colleagues have called a "biologically based deep model."[47] Therefore, the results generated by our simulation can be considered the direct, if perhaps unobvious, consequences of what we now know about breast cancer incidence, growth, spread, and detectability. One of the appealing qualities of this simulation method,[21,22,23] and the mathematics used to build it,[21,24-31] is that they provide an integrated toolkit for examining how we might choose among the many options for both prevention and treatment. In the accompanying paper,[19] we have seen how the simulation can identify the survival consequences for various choices of screening interval and age of screening initiation. Here, we have seen how the simulation can quantify the impact of screening and chemoprevention. There is no reason why the simulation cannot also be used to make such assessments for the impact of other screening methods,[48] such as clinical breast exam, MRI, or ultrasound, or for predicting the magnitude of the life-sparing impact of screening for other types of cancer.[49,50,51] The mathematical tools involved can also be used to examine the impact of the various treatment choices that present themselves after cancer is detected, including adjuvant chemotherapy and radiation therapy options. Indeed, we have been able to use this mathematics to create web-calculators that carry out such calculations (see http://www.cancer-math.net/ for examples.) We would suggest that such an integrated consideration of the optimal choice of preventative and treatment choices offers the potential for learning how to most effectively use the resources available to us to reach the highest possible level of breast carcinoma survival.

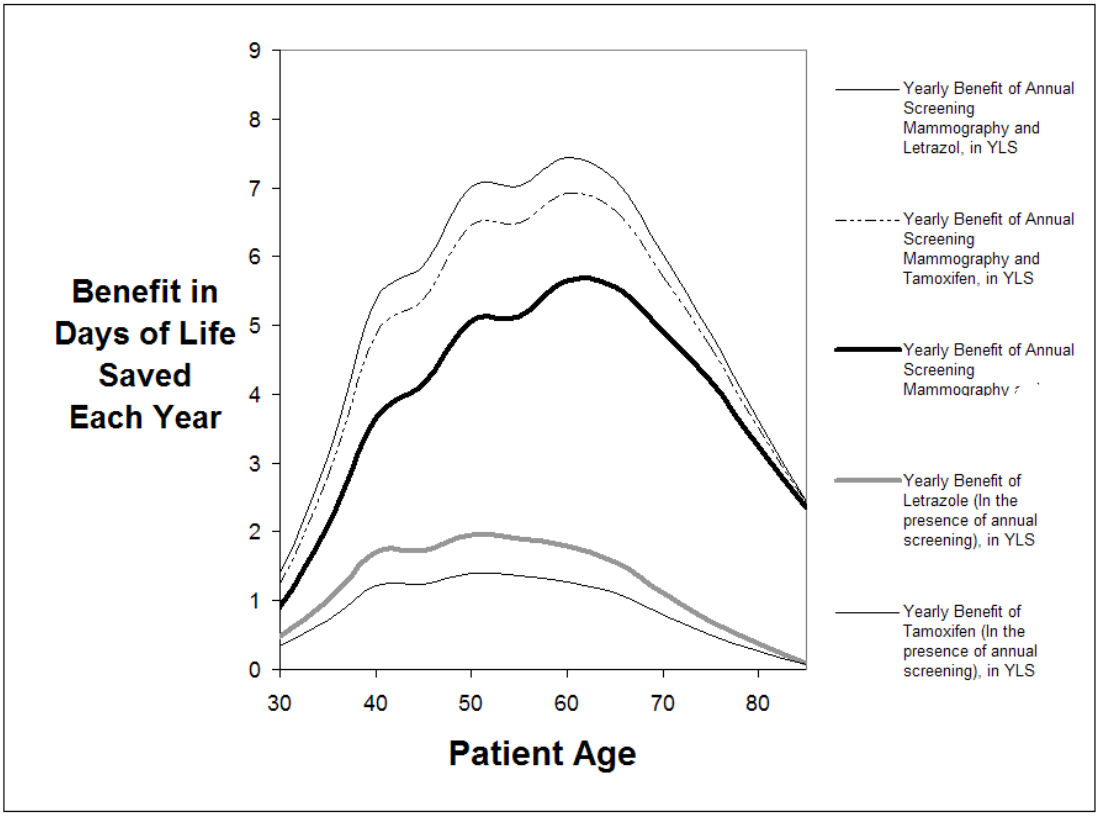

FIGURE 1

Yearly Benefit of Breast Cancer Chemoprevention and Screening

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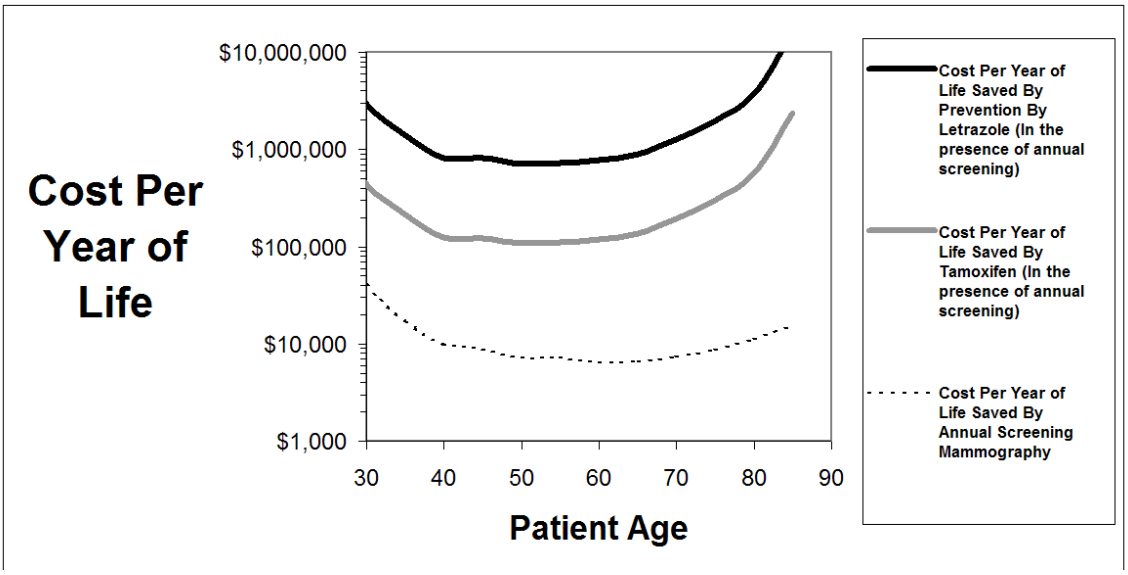

FIGURE 2

Yearly Cost of Breast Cancer Chemoprevention and Screening, per Year of Life Saved

C:\Triple modified april25\code to send out modifed for Prevention 4 07 #4 YYL Maybe 5th try\Raw Data From My Dump 2nd Try May 15 YLS 543 \ [All three YLS.xls]CostBenfitOfScreeningNochemoFIG'!$AV$60

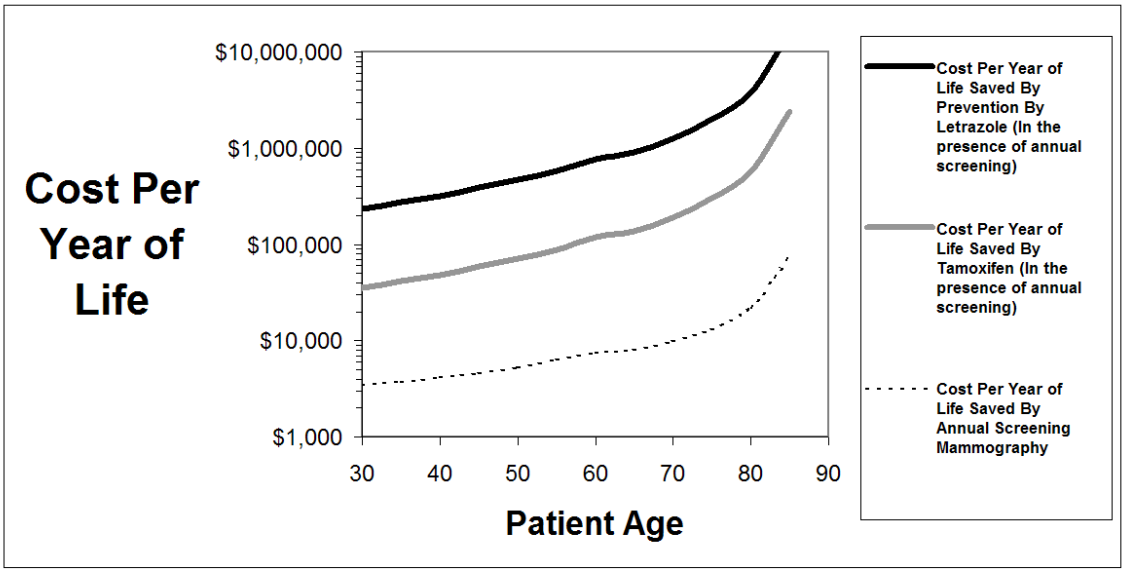

FIGURE 3

Yearly Cost of Breast Cancer Chemoprevention and Screening, per Year of Life Saved For Populations of Women Selected to be at High Risk, as Defined by the Gail Score

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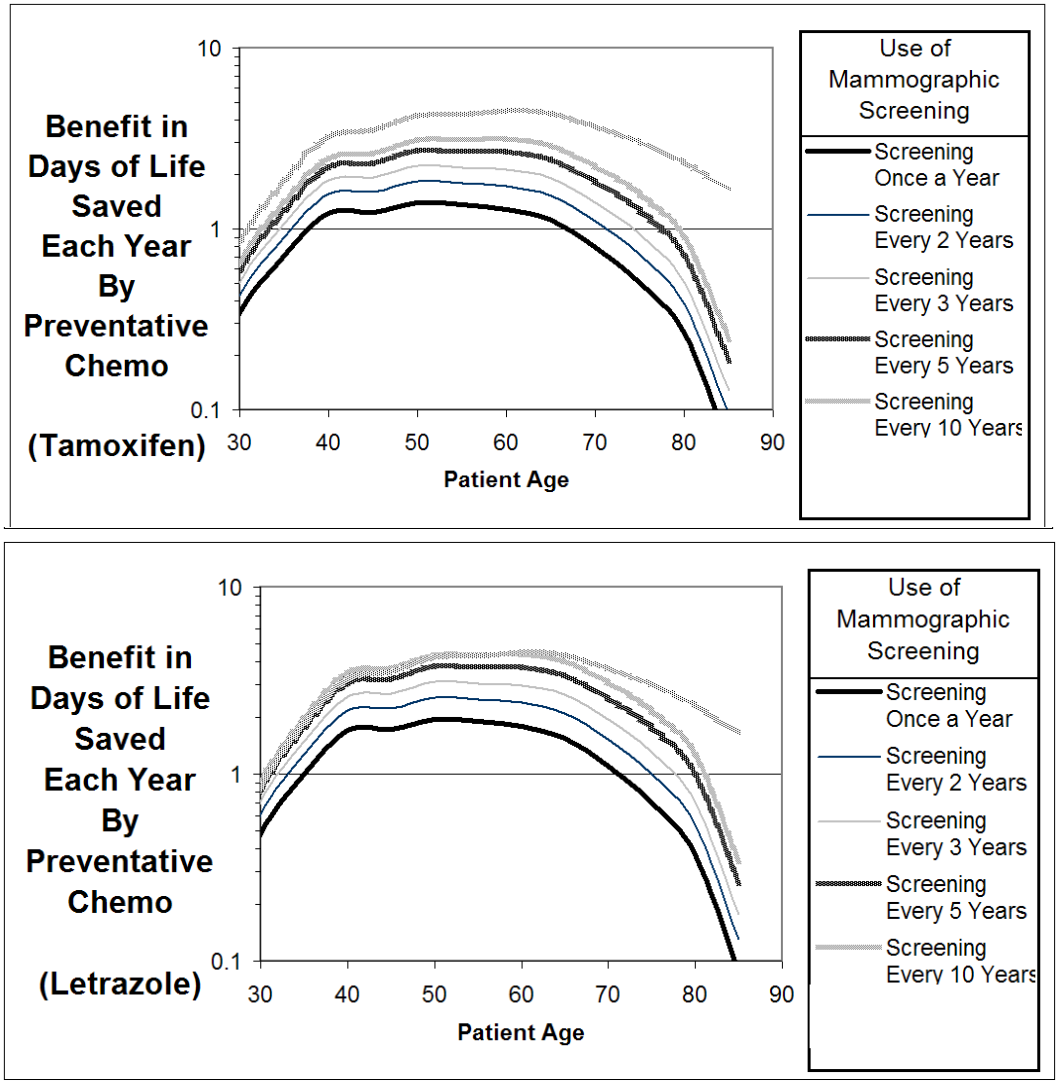

FIGURE 4

Interaction of Breast Cancer Chemoprevention and Screening

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TABLE I
Cumulative Benefits and Costs of Screening and Chemoprevention, in Terms of Years of Life Saved, for Women who Live to Age 85

Cumulative Benefit of Annual Screening	Savings in Months of Cancer Free Life	Cost
beginning at age 30	7.82 months of life	$5,500
beginning at age 40	7.32 months of life	$4,500
beginning at age 50	6.02 months of life	$3,500
Cumulative Benefit of Preventative tamoxifen (in the context of annual screening)		
age 30-84	1.74 months of life	$22,825
age 40-84	1.71 months of life	$18,675
age 50-84	1.54 months of life	$14,525
age 30-34	0.06 months of life	$2,075
age 35-39	0.12 months of life	$2,075
age 40-44	0.2 months of life	$2,075
age 45-49	0.21 months of life	$2,075
age 50-54	0.23 months of life	$2,075
age 55-59	0.23 months of life	$2,075
age 60-64	0.21 months of life	$2,075
age 65-69	0.19 months of life	$2,075
age 70-74	0.13 months of life	$2,075
age 75-79	0.08 months of life	$2,075
age 80-84	0.04 months of life	$2,075
Cumulative Benefit of Preventative Letrozole (in the context of annual screening)		
age 30-84	2.4 months of life	$210,760
age 40-84	2.15 months of life	$172,440
age 50-84	1.58 months of life	$134,120
age 30-34	0.08 months of life	$19,160
age 35-39	0.17 months of life	$19,160
age 40-44	0.29 months of life	$19,160
age 45-49	0.29 months of life	$19,160
age 50-54	0.33 months of life	$19,160
age 55-59	0.32 months of life	$19,160
age 60-64	0.3 months of life	$19,160
age 65-69	0.26 months of life	$19,160
age 70-74	0.18 months of life	$19,160
age 75-79	0.12 months of life	$19,160
age 80-84	0.06 months of life	$19,160

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TABLE II
Cumulative Benefits and Costs of Screening and Chemoprevention, in Terms of Cancer free Years of Life Saved, for Women who Live to Age 85

Cumulative Benefit of Annual Screening	Savings in Months of Cancer Free Life	Cost
beginning at age 30	9.21 months of cancer free life	$5,500
beginning at age 40	8.67 months of cancer free life	$4,500
beginning at age 50	7.26 months of cancer free life	$3,500
Cumulative Benefit of Preventative tamoxifen (in the context of annual screening)		
age 30-84	2.4 months of cancer free life	$22,825
age 40-84	2.37 months of cancer free life	$18,675
age 50-84	2.17 months of cancer free life	$14,525
age 30-34	0.09 months of cancer free life	$2,075
age 35-39	0.19 months of cancer free life	$2,075
age 40-44	0.33 months of cancer free life	$2,075
age 45-49	0.34 months of cancer free life	$2,075
age 50-54	0.4 months of cancer free life	$2,075
age 55-59	0.4 months of cancer free life	$2,075
age 60-64	0.4 months of cancer free life	$2,075
age 65-69	0.37 months of cancer free life	$2,075
age 70-74	0.29 months of cancer free life	$2,075
age 75-79	0.22 months of cancer free life	$2,075
age 80-84	0.17 months of cancer free life	$2,075
Cumulative Benefit of Preventative Letrozole (in the context of annual screening)		
age 30-84	3.32 months of cancer free life	$210,760
age 40-84	3.04 months of cancer free life	$172,440
age 50-84	2.37 months of cancer free life	$134,120
age 30-34	0.06 months of cancer free life	$19,160
age 35-39	0.14 months of cancer free life	$19,160
age 40-44	0.24 months of cancer free life	$19,160
age 45-49	0.24 months of cancer free life	$19,160
age 50-54	0.29 months of cancer free life	$19,160
age 55-59	0.29 months of cancer free life	$19,160
age 60-64	0.28 months of cancer free life	$19,160
age 65-69	0.26 months of cancer free life	$19,160
age 70-74	0.21 months of cancer free life	$19,160
age 75-79	0.16 months of cancer free life	$19,160
age 80-84	0.12 months of cancer free life	$19,160

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BenfitOfScreeningNochemFIG'!$CE$22

CODE

```
Attribute VB_Name = "Module1"
Sub main()
'  James Michaelson      michaelj@helix.mgh.harvard.edu
'  Modified May 12 07 to examine effect of Prevention, in terms of years of life saved;
'    In the previous (April 21 07) version of this code, we estimated the benefit in terms of cancer free years of life saved.
'   Here we shall make a modification, so that we can also estimated the benefit in terms of years of life saved.
     'Where such changes have been made:
        ""Modified May 12 07 to examine effect of Prevention in terms of years of life saved" has been pasted in
'  Modified April 21 07 to examine effect of Prevention;
     'Where such changes have been made "'Modified April 21 07 to examine effect of Prevention" has been pasted in
'  '  Personal Communication: please do not pass along without permission
'  Modified May 20 07 to examine effect of Prevention, in the context of a gail score,
'    which requires a 5-year 1.66% risk of breast cancer
'      (If ((INCIDENCE(Age) * 5)) < GailLimit Then INCIDENCE(Age) = (GailLimit / 5))

'  A program to give:
'          The curves of:
'               :"death rate" versus "screening interval"(by age)
'               :"reduction in death rate" vs. "screening interval"(by age)
'               : cost and marginal costs
'               : tables of optimal screening strategies
' in order to interpret the results of the latest data collection from the MGH database
'_____________

'FIRST, we'll dimension the array variables, and define the important constants

'Modified April 21 07 to examine effect of Prevention"
' YLLost(2200, 90) will calculate the Years of Life Lost to Cancer (Screening Interval, Age)
' YLLost(2200, 90) = DEATHFRACTION(Screening Interval,Age)*INCIDENCE(Age)*YLL(Age) [calculated just before making files]
Dim YLLost(3651, 90) As Single

'  Modified May 20 07 to examine effect of Prevention, in the context of a gail score,
'    which requires a 5-year 1.66% risk of breast cancer (0r whichever GailLimit we choose
'  See:  (If ((INCIDENCE(Age) * 5)) < GailLimit Then INCIDENCE(Age) = (GailLimit / 5))
Dim GailLimit As Single
'  GailLimit = 0.0166
GailLimit = 0.0166

""Modified May 12 07 to examine effect of Prevention in terms of years of life saved"
'  when TimeTillDeath is set =1 below, this gives us the results in terms of cancer free years of life save
'  when TimeTillDeath is set =1.8424 below, this gives us the results in terms of cancer free years of life save
'  Since the mean time from diagnosis to death (as found from the Van Nuys Population) is 1.8424 years
'  when TimeTillDeath is set =5.043 below, this gives us the results in terms of cancer free years of life save
'  Since the mean time from diagnosis to death (as found from the Parters Patients seen before 1990) is 5.74years
Dim TimeTillDeath As Single
TimeTillDeath = 0
'TimeTillDeath = 1.8424
' TimeTillDeath = 5.74
```

```
' INCIDENCEREDUCTION is the reduction caused by prevevtative chemotherapy: It's 1 if no treatment is used.
' I set it by hand for each run
Dim INCIDENCEREDUCTION As Single
INCIDENCEREDUCTION = 0.3

' THE NEXT 2 lines CALCULATE THE TOTAL NUMBER OF MAMMO'S GIVEN TO THE POPULATION
Dim MammoTotal(2200) As Single
Dim AgeAjustedMammoTotal(2200) As Single

' We'll need the next three variables to make calculations for common, but inefficient,
'         patterns of screening such as the ACS recomendation, UK pattern, etc.
Dim Pattern As Integer
Dim PatternName(2200) As String
Dim IndicatedInterval(2200, 90) As Integer

' x is s simple marker to keep track of the screening interval that
'            corresponds to marginal cost, zeta lets us keep track of "none's"
Dim x As Integer
Dim zeta As Integer
Dim zeta2 As Integer
'  the "UnAgeAdustedOverallAVERAGECOST"  is the average cost for a group of 65 women,
'                  each of a different age, from age 20 to age 85, for each marginal cost.
'  the "USAAgeAdustedOverallAVERAGECOST" is the average cost for a population of women
'                  with the age structure of the USA, for each marginal cost
Dim UnAgeAdustedOverallAVERAGECOST(2200) As Single
Dim USAAgeAdustedOverallAVERAGECOST(2200) As Single

' MinAGE and MaxAGE are the youngest and oldest ages that we will make calulations for
Dim MinAGE As Integer
Dim MaxAGE As Integer
MinAGE = 20
MaxAGE = 85

'AgeStructureAdjustemnt allows us to calculate effect on USA population of women
Dim AgeStructureAdjustemnt(99)

' below are the (Cancer Free) years of life saved for woman as a whole,
'               and for the womenwho will get breast cancer
Dim PopulationWideYLS(2200) As Single
Dim CancerPatientsYLS(2200) As Single

'the following string allows me to put a label at the top of every file
Dim title As String
title = "all ages 20-85, for doubling time 130"
'  , density 4"
"'Duffy-Tabar growth rate estimates"
"'Simulation for All Women"

'doublingtime is the tumor doubling time, discovered through anlysis of the MGH data
doublingtime = 130


'testcost is the cost for each mammography exam (in $)
testcost = 100

'the next three variables are for:
```

```
'   "INCIDENCE", the cancer indence, and
'   "YLL", (Years of Life Left)=years of life saved by preventing a death from breast cancer, and
'   "AGEfraction", for the fraction of women of this age in the population,
'     all by age.        They are derrived from standard references, as noted below
Dim INCIDENCE(90) As Single
Dim YLL(90) As Single
Dim AGEfraction(90) As Single

'Modified April 21 07 to examine effect of Prevention"
' Below is the original Incidence data
' Below that, is the Incidence data expected for women how have passed the Gail test,
            'and thus will receive preventative treatment


' INCIDENCE data from the SEER national datbase, as quoted in Kopans "Breast Imaging", 2nd Edition
For Age = MinAGE To MaxAGE
If Age >= 20 Then INCIDENCE(Age) = (5 / 100000) + ((1 / 5) * (Age - 20) * ((7.2 - 5) / 100000))
If Age >= 25 Then INCIDENCE(Age) = (7.2 / 100000) + ((1 / 5) * (Age - 25) * ((27 - 7.2) / 100000))
If Age >= 30 Then INCIDENCE(Age) = (27 / 100000) + ((1 / 5) * (Age - 30) * ((66 - 27) / 100000))
If Age >= 35 Then INCIDENCE(Age) = (66 / 100000) + ((1 / 5) * (Age - 35) * ((129 - 66) / 100000))
If Age >= 40 Then INCIDENCE(Age) = (129 / 100000) + ((1 / 5) * (Age - 40) * ((159 - 129) / 100000))
If Age >= 45 Then INCIDENCE(Age) = (159 / 100000) + ((1 / 5) * (Age - 45) * ((220 - 159) / 100000))
If Age >= 50 Then INCIDENCE(Age) = (220 / 100000) + ((1 / 5) * (Age - 50) * ((261 - 220) / 100000))
If Age >= 55 Then INCIDENCE(Age) = (261 / 100000) + ((1 / 5) * (Age - 55) * ((330 - 261) / 100000))
If Age >= 60 Then INCIDENCE(Age) = (330 / 100000) + ((1 / 5) * (Age - 60) * ((390 - 330) / 100000))
If Age >= 65 Then INCIDENCE(Age) = (390 / 100000) + ((1 / 5) * (Age - 65) * ((421 - 390) / 100000))
If Age >= 70 Then INCIDENCE(Age) = (421 / 100000) + ((1 / 5) * (Age - 70) * ((461 - 421) / 100000))
If Age >= 75 Then INCIDENCE(Age) = (461 / 100000) + ((1 / 5) * (Age - 75) * ((461 - 421) / 100000))

'Modified May 20 07 to examine effect of Prevention, in the context of a gail score,
' which requires a 5-year 1.66% risk of breast cancer
If ((INCIDENCE(Age) * 5)) < GailLimit Then INCIDENCE(Age) = (GailLimit / 5)


' Below, the simulation estinates the reduction in incidence caused by preventative cheotheraoy
INCIDENCE(Age) = INCIDENCE(Age) * INCIDENCEREDUCTION

'  YLL data from "National Vital Statistics Reports Vol 47 #28  December 13 1999"
'  YLL = Years of Life Left
If Age >= 20 Then YLL(Age) = 60.2 - ((1 / 5) * (Age - 20) * ((60.2 - 55.4)))
If Age >= 25 Then YLL(Age) = 55.4 - ((1 / 5) * (Age - 25) * ((55.4 - 50.5)))
If Age >= 30 Then YLL(Age) = 50.5 - ((1 / 5) * (Age - 30) * ((50.5 - 45.7)))
If Age >= 35 Then YLL(Age) = 45.7 - ((1 / 5) * (Age - 35) * ((45.7 - 40.9)))
If Age >= 40 Then YLL(Age) = 40.9 - ((1 / 5) * (Age - 40) * ((40.9 - 36.6)))
If Age >= 45 Then YLL(Age) = 36.3 - ((1 / 5) * (Age - 45) * ((36.6 - 31.7)))
If Age >= 50 Then YLL(Age) = 31.7 - ((1 / 5) * (Age - 50) * ((31.7 - 27.3)))
If Age >= 55 Then YLL(Age) = 27.3 - ((1 / 5) * (Age - 55) * ((27.3 - 23.1)))
If Age >= 60 Then YLL(Age) = 23.1 - ((1 / 5) * (Age - 60) * ((23.1 - 19.2)))
If Age >= 65 Then YLL(Age) = 19.2 - ((1 / 5) * (Age - 65) * ((19.2 - 15.5)))
If Age >= 70 Then YLL(Age) = 15.5 - ((1 / 5) * (Age - 70) * ((15.5 - 12.1)))
If Age >= 75 Then YLL(Age) = 12.1 - ((1 / 5) * (Age - 75) * ((12.1 - 9.1)))
If Age >= 80 Then YLL(Age) = 9.1 - ((1 / 5) * (Age - 80) * ((9.1 - 6.6)))
If Age >= 85 Then YLL(Age) = 6.6 - ((1 / 5) * (Age - 85) * ((6.6 - 4.7)))
If Age >= 90 Then YLL(Age) = 4.7 - ((1 / 5) * (Age - 90) * ((4.7 - 3.4)))
If Age >= 95 Then YLL(Age) = 3.4 - ((1 / 5) * (Age - 95) * ((3.4 - 2.5)))
```

```
' "AGEfraction" data from "Statistical Abstracts of the United Staes 1998": values over 85 are rough guestimates
If Age >= 20 Then AGEfraction(Age) = 0.062 / 5
If Age >= 25 Then AGEfraction(Age) = 0.069 / 5
If Age >= 30 Then AGEfraction(Age) = 0.076 / 5
If Age >= 35 Then AGEfraction(Age) = 0.083 / 5
If Age >= 40 Then AGEfraction(Age) = 0.079 / 5
If Age >= 45 Then AGEfraction(Age) = 0.069 / 5
If Age >= 50 Then AGEfraction(Age) = 0.057 / 5
If Age >= 55 Then AGEfraction(Age) = 0.045 / 5
If Age >= 60 Then AGEfraction(Age) = 0.039 / 5
If Age >= 65 Then AGEfraction(Age) = 0.075 / 10
If Age >= 70 Then AGEfraction(Age) = 0.075 / 10
If Age >= 75 Then AGEfraction(Age) = 0.052 / 10
If Age >= 80 Then AGEfraction(Age) = 0.052 / 10
If Age >= 85 Then AGEfraction(Age) = 0.001 / 10
If Age >= 90 Then AGEfraction(Age) = 0.001 / 10
If Age >= 95 Then AGEfraction(Age) = 0.0001 / 10

Next Age

' Now, we 'll create a way to adjust the values for the population as a whole for the
'  age structure (ie AGEfraction above) of the population
AgeFractionDENOMINATOR = 0
For Age = MinAGE To MaxAGE Step 1
AgeFractionDENOMINATOR = AgeFractionDENOMINATOR + AGEfraction(Age)
Next Age
'
For Age = MinAGE To MaxAGE Step 1
AgeStructureAdjustemnt(Age) = ((AGEfraction(Age) / AgeFractionDENOMINATOR) _
/ (1 / (MaxAGE - MinAGE)))
Next Age


'The following variables describe the death rate, and reduction in death rate, for all the whole population of women,
'  by screening interval and age  [(3651, 90)]
Dim DEATHFRACTION(3651, 90) As Single
Dim DEATHREDUCTION(3651, 90) As Single

'below , we 'll use these to calculate how much death would occur without mammography
Dim tempMAXDEATH(5, 5) As Single
Dim MAXDEATH(90) As Single

'Since we'll be treating the breast cancers within a population of women as the sum of a
'  variety of slightly different tumors
' [specifically differing at the size at which they'll be detected by mammography (Sm)  and by palpation (Sp)],
' we'll need temporary values (tempDEATHFRACTION and tempDEATHREDUCTION), from which to later make
' the overall estimate of DEATHFRACTION and DEATHREDUCTION  for the whole population by
' summing tempDEATHFRACTION and tempDEATHREDUCTION.

Dim tempDEATHFRACTION(7, 7, 3651) As Single
Dim tempDEATHREDUCTION(7, 7, 3651) As Single

' The following variable are used to calculate cost and marginal cost.
Dim AVERAGECOST(3651, 90) As Single
Dim MARGINALCOST(3651, 90) As Single
```

```
'the following are for making tables of marginal cost etc
Dim INTERVALforEACHmarginalAMOUNT(2200, 90) As Variant
Dim CorrespondingReduction(2200, 90) As Single
Dim PopulationWideCorrespondingReduction(2200) As Single
Dim UnAgeAdjustedPopulationWideCorrespondingReduction(2200) As Single
Dim AVERAGEPopulationWideCorrespondingReduction(2200) As Single

'by defining the next variable, we can keep track of what the marginal cost ("ammount")
'   is for each each line that we will make in a table of marginal amounts
'  above 2000, we'll use it to keep track of various types of screening recomendations
Dim amountFOReachAmountMarker(2200) As Single


'HERE'S THE BODY OF THE BREAST CANCER GROWTH/SPREAD SIMULATION:
'                IT GOES DOWN TO ABOUT LINE 310

' (note, below we'll be examining woman of various ages.

For Age = MinAGE To MaxAGE

' next we shall consider each of the various levels of mammographic and palpable
'   detectability, by considering that there are a variety of classes of tumors differing
'     with respect to the minimal sizes detectable by mammography (Sm) and palpation(Sp).
For SmClass = 1 To 5
For SpClass = 1 To 5

' note:
'  for women as a whole,        the median   (SmClass 3) ~ .7, modifier = 1


'  FIRST OPTION : IF WE DON'T KNOW DENSITY, LET AGE SET the value of "Sm"
'  for women less than 50,      the median   (SmClass 3) ~ .95, modifier = 1.357
'  for women more than 50,      the median   (SmClass 3) ~ .7, modifier = 1
' assuming linear extrapolation:
'
modifier = 2.16025 - (Age * 0.01785)

'  SECOND OPTION : IF WE DO KNOW DENSITY
'  for women of density 1,2,3,  the median   (SmClass 3) ~ .60, modifier = .857
'  for women of density 4       the median   (SmClass 3) ~ 1.0, modifier = 1.43
'  for women of density 5,6,7   the median   (SmClass 3) ~ 1.2, modifier = 2
' so:
' if density =123 then modifier = 0.857
' if density =4 then modifier = 1.43
' if density =567 then modifier = 2

If SmClass = 1 Then SmDiameter = 0.35 * modifier
If SmClass = 2 Then SmDiameter = 0.55 * modifier
If SmClass = 3 Then SmDiameter = 0.7 * modifier
If SmClass = 4 Then SmDiameter = 0.925 * modifier
If SmClass = 5 Then SmDiameter = 1.17 * modifier

' estimate from MGH
'If SpClass = 1 Then SpDiameter = 0.8
'If SpClass = 2 Then SpDiameter = 1.2
'If SpClass = 3 Then SpDiameter = 1.7
```

```
'If SpClass = 4 Then SpDiameter = 2.2
'If SpClass = 5 Then SpDiameter = 5.9

' rough guestimate from Tabar (ADJUSTED to give a median value of 2 cm)
If SpClass = 1 Then SpDiameter = 0.8 * 1.176
If SpClass = 2 Then SpDiameter = 1.2 * 1.176
If SpClass = 3 Then SpDiameter = 1.7 * 1.176
If SpClass = 4 Then SpDiameter = 2.2 * 1.176
If SpClass = 5 Then SpDiameter = 5.9 * 1.176


'@ the following line can be used to examine not screening below a certain age
' If Age < 40 Then SmDiameter = SpDiameter + 0.000001


 '"screenlimit" is the minimal tumor size detectable by a mammogram.
screenlimit = (4 / 3) * 3.14 * (SmDiameter / 2) ^ 3 * 100000000#

'"naturallimit" is the minimal tumor size detectable by palpation.
naturallimit = (4 / 3) * 3.14 * (SpDiameter / 2) ^ 3 * 100000000#

' tempMAXDEATH (SmClass, SpClass) is the amount of death that would occur in
'   the absence of screening.
Nx = ((4 / 3) * 3.14 * (SpDiameter / 2) ^ 3) * 100000000#
Px = (Nx ^ (0.4425 - 1)) * 0.00005017
tempMAXDEATH(SmClass, SpClass) = 1 - (1 / (Exp((Nx * Px))))


'"If_Im_1_thenMammo_Saw_CA" is used as a sign that the tumor is detectable by
'  mammography.
' "If_Im_1_thenMammo_Saw_CA" starts out as =0, but when the screenlimit
'  has been reached, {i.e when the cell number (n) comes to exceed the screenlimit,}
'  (after line 220), "If_Im_1_thenMammo_Saw_CA" is reset to "If_Im_1_thenMammo_Saw_CA=0".
'  Every time the program goes to examine women of a different age, it gets set on
'  the next line back to "If_Im_1_thenMammo_Saw_CA=0.
If_Im_1_thenMammo_Saw_CA = 0


'"Today" will be used as a reset-able day-counter, to be reset twice:
'       1)-Today gets reset on line 110, at the time when the tumor first starts to
'             grow from 1 cell (n=1 line 120)
'        and
'       2)-Today gets reset to 1 (after line 220), after the tumor first becomes detectable by
'             mammography,  that is, when the screenlimit (Sm) is reached.
110 Today = 1

' n is the number of cells in the tumor; obviously it starts with one cell (n=1).
'  However, at some very slow growth rates,growth never gets beyond a single cell,
'   so, from a practical stanpoint, we shall start at n=100
'  (This has a negigable effect on the probability of spread estimates)

'  Growth occurs just below line 301.
' ######  march 30   changed below to higher number to shorten runtime
120 N = Int(screenlimit) - 100

' "prob" is the probability of the tumor as a whole forming one or more distant
```

```
'     metastases; it is derived from the Poisson distribution, prob = 1 - (1 / (Exp((n * p)))), line 227 below
' "LastCumprob" is used to estimate below how much additional
'   benefit is gained with the loss of each additional day between exams,
'   i.e. in the calculation of the marginal cost of screening, (LastCumprob = cumprob), line 302 below
' Below, we'll need to reset the these two values each time we examine women
'   of a different group.
cumprob = 0
prob = 0

'the breast cancer doubling time is from our analysis of screening data.
'  "g" is the growth fraction, that is, the fraction of cells that must
'  be dividing to achieve such a tumor doubling time (which was set above),
'  assuming a cell cycle time of 24 hours.  g = ln(2)/ doublingtime

' below is the estimate of tumor growth from duffy/Tabar
'doublingtime = (6.954 * Age) - 106.19
' below is the calulation of g, the fraction of cells dividing
g = (2 ^ (1 / doublingtime)) - 1

'In the next two lines, we'll be checking whether the tumor has reached
' mammographically detectable size (the "screenlimit"), and modifying the simulation
' to determine the consequences  of this event.
220  If If_Im_1_thenMammo_Saw_CA = 1 Then GoTo 221
If N > screenlimit Then If_Im_1_thenMammo_Saw_CA = 1: Today = 0: cumprob = 0
221 Today = Today + 1
' If Today > 3650 And If_Im_1_thenMammo_Saw_CA = 1 Then GoTo 410
If Today > 3650 Then GoTo 410

301 If prob = 1 Or N > naturallimit Then GoTo 302

' next is the equation that makes the tumor grow.
223 N = N + (g * N)

' "p" is the probability of each cell in the tumor forming a distant metastasis.
225 p = (N ^ (0.4425 - 1)) * 0.00005017
'  GRIFFIN'S QUOTE BELOW
'and where you divided by ((10000000000#) ^ 0.4841), which occurs both in the calculation
'of "p" and in the tempMAXDEATH calculation, I now multiply by 1.424E-5.
'Note that 1/1E10^0.4841 = 1.442E-5. So, your approximation actually was very close.


' again, "prob" is the probability of the tumor as a whole forming one or more distant
'     metastases; it is derived from the Poisson distribution.
227 prob = 1 - (1 / (Exp((N * p))))

' next, we're going to need "LastCumprob" , which, as we noted above, is used to estimate below how
'  much additional  benefit is gained with the loss of each additional day between exams,
'   i.e. in the calculation of the marginal cost of screening.
302 LastCumprob = cumprob

'"cumprob" is the PROBABILITY of distant metastasis in the SUM all women who
' are examined. Randomness in the time when these tumors arise means that
' the tumor in a woman is equally likely to have reached mammographically
' detectable size the day after her last negative exam as on the day before
' her following positive exam, or any day in between. Thus, cumprob is the
' SUM of all probabilities of spread ("probs") from the day after that negative
```

```
' exam, to today, (i.e. the "Today"). Note, in our calculations below, we'll need
' to divide "cumprob" by the "Today" to get the average probability of all women in
' such a group.
cumprob = cumprob + prob

'Since no detection can occur when tumors are smaller that the screenlimit,
' (i.e If_Im_1_thenMammo_Saw_CA has been made to be If_Im_1_thenMammo_Saw_CA=0), we'll
' run up the tumor size by returning to the growth step till the screenlimit is reached.
'If, however, the screenlimit has been reached (i.e if n>screenlimit),
'  thus making If_Im_1_thenMammo_Saw_CA= 1, below line 22 above), then the program can pass on from
'  here to put these results into an array, and then do further work.
310 If If_Im_1_thenMammo_Saw_CA = 0 Then GoTo 220

tempDEATHFRACTION(SmClass, SpClass, Today) = (cumprob / Today)

tempDEATHREDUCTION(SmClass, SpClass, Today) = 1 - ((cumprob / Today) / tempMAXDEATH(SmClass,
SpClass))


'In the following loop, we shall make our daily return to the point where the
'  cell number increases:
GoTo 220

410
Next SpClass
Next SmClass

' below, before finishing the age loop by going to the next age in line 411, we'll do
'     a couple of small loops to calculate MAXDEATH, DEATHFRACTION, and DEATHREDUCTION
For SpClass = 1 To 5
For SmClass = 1 To 5
MAXDEATH(Age) = MAXDEATH(Age) + (tempMAXDEATH(SmClass, SpClass) * (1 / 25))
Next SmClass
Next SpClass

For Today = 1 To 3650
For SpClass = 1 To 5
For SmClass = 1 To 5
DEATHFRACTION(Today, Age) = _
DEATHFRACTION(Today, Age) + (tempDEATHFRACTION(SmClass, SpClass, Today) * (1 / 25))
Next SmClass
Next SpClass
DEATHREDUCTION(Today, Age) = 1 - (DEATHFRACTION(Today, Age) / MAXDEATH(Age))
Next Today

411 Next Age

' next, we'll calculate the total costs per year of life saved,& place it into an array
'     AVERAGECOST = [testcost *(365/Today)] / (INCIDENCE)* (DEATHREDUCTION)*(YLL)
For Age = MinAGE To MaxAGE
For Today = 1 To 3650
AVERAGECOST(Today, Age) = (testcost) * (365 / Today) / _
((INCIDENCE(Age)) * MAXDEATH(Age) * (DEATHREDUCTION(Today, Age)) * YLL(Age))
Next Today
Next Age
```

```
' Next we'll calculate the marginal cost
'NOTE: we do NOT calculate MARGINALCOST for Today=1
For Age = MinAGE To MaxAGE Step 1
For Today = 2 To 3650

' @  "If (DEATHREDUCTION(Today - 1, Age) <> DEATHREDUCTION(Today, Age)) Then"  added below
If (DEATHREDUCTION(Today - 1, Age) <> DEATHREDUCTION(Today, Age)) Then
MARGINALCOST(Today, Age) = (testcost) * ((365 / (Today - 1)) - (365 / Today)) / _
((((DEATHREDUCTION(Today - 1, Age)) - DEATHREDUCTION(Today, Age)) * MAXDEATH(Age) * _
(INCIDENCE(Age)) * YLL(Age)))

Next Today
Next Age

'next, we'll set the marginal costs that we will list in our array,& place in the file:
'     $0 to $10,000 by 400 $25 intervals then
'     $10,000 to $100,000 by 360 $250 intervals then
'     $100,000 to $1,00,00 by 360 $2500 intervals
'     $100,0000 to $29,00,000 by 1120 $2500 intervals
For AmountMarker = 1 To 2000
If amount < 9999 Then amount = amount + 25
If amount >= 9999 And amount < 99999 Then amount = amount + 250
If amount >= 99999 And amount < 999999 Then amount = amount + 2500
If amount >= 999999 And amount Then amount = amount + 25000
' below, we 'll use "(amountFOReachAmountMarker(AmountMarker)" to index the lines
'          in our table of marginal costs
amountFOReachAmountMarker(AmountMarker) = amount
Next AmountMarker


'NOW we'll construct the table of marginal cost vs. interval (by age)
450 For Age = MinAGE To MaxAGE
500 For AmountMarker = 1 To 2000
510 Today = 3650
511 Today = Today - 1
If Today <= 0 Then GoTo 520
If MARGINALCOST(Today, Age) < amountFOReachAmountMarker(AmountMarker) Then GoTo 511
If MARGINALCOST(Today, Age) > amountFOReachAmountMarker(AmountMarker) Then:
   If Today >= (3650 - 1) Then INTERVALforEACHmarginalAMOUNT((AmountMarker), Age) = "none"
   If Today < (3650 - 1) Then INTERVALforEACHmarginalAMOUNT((AmountMarker), Age) = Today / 30
   If Today >= (3650 - 1) Then CorrespondingReduction((AmountMarker), Age) = 0
   If Today < (3650 - 1) Then CorrespondingReduction((AmountMarker), Age) = DEATHREDUCTION(Today,
Age)
      GoTo 520
520 Next AmountMarker
Next Age



'Modified April 21 07 to examine effect of Prevention
'  Now We'll calculate the Years of Life Lost (YLLost)

650 For Age = MinAGE To MaxAGE

' YLLost(0, Age) will tell us the years of life lost in the absense of screening
```

```
'    "'Modified May 12 07 to examine effect of Prevention in terms of years of life saved"
'       Since the mean time from diagnosis to death (as found from the Van Nuys Population) is 1.8424 years,
'        we have added the value "TimeTillDeath"; when set =1, the simulation now gives us values in terms of
'        "cancer free years of life saved", while if TimeTillDeath = 1.8424, the simulation gives us values in terms of
'        "years of life saves".  The value of "TimeTillDeath" is set above at the very top of the code
YLLost(0, Age) = MAXDEATH(Age) * INCIDENCE(Age) * (YLL(Age) - TimeTillDeath)
If YLLost(0, Age) < 0 Then YLLost(0, Age) = 0

' YLLost(Today, Age), where Today is between 1 and 3650,
'will tell us the years of life lost among women who go for mammograms every "Today" days

700 For Today = 1 To 3651
YLLost(Today, Age) = DEATHFRACTION(Today, Age) * INCIDENCE(Age) * (YLL(Age) - TimeTillDeath)
If YLLost(Today, Age) < 0 Then YLLost(Today, Age) = 0
720 Next Today

Next Age



'We'll NOW put the data we've generated into files, so we can see them:

'  First: we'll dump into a file the curves of:
'   total amount of death ("DEATHFRACTION"),versus screening interval("Today")
'   reduction in death ("DEATHREDUCTION ") versus screening interval("Today"),
'   marginal cost ("MARGINALCOST") versus screening interval("Today"), and
'   total cost versus screening interval("Today"), each graph by age
999 Open "c:\My Dump\APRv3a.txt" For Output As #2

Write #2, title
Write #2, , 20, 25, 30, 35, 40, 45, 50, 55, 60, 65, 70, 75, 80, 85, , 20, 25, 30, 35, 40, 45, 50, 55, 60, 65, 70, 75, 80, 85,
, 20, 25, 30, 35, 40, 45, 50, 55, 60, 65, 70, 75, 80, 85, , 20, 25, 30, 35, 40, 45, 50, 55, 60, 65, 70, 75, 80, 85, ,

For Today = 1 To 3650

'Add the "If then" part of the next statement to make graphs with smaller datasets
If Today / 30 = Int(Today / 30) Then Write #2, Today, DEATHFRACTION(Today, 20),
DEATHFRACTION(Today, 25), DEATHFRACTION(Today, 30), DEATHFRACTION(Today, 35),
DEATHFRACTION(Today, 40), DEATHFRACTION(Today, 45), DEATHFRACTION(Today, 50),
DEATHFRACTION(Today, 55), DEATHFRACTION(Today, 60), DEATHFRACTION(Today, 65),
DEATHFRACTION(Today, 70), DEATHFRACTION(Today, 75), DEATHFRACTION(Today, 80);
DEATHFRACTION(Today, 85), _
Today, DEATHREDUCTION(Today, 20), DEATHREDUCTION(Today, 25), DEATHREDUCTION(Today, 30),
DEATHREDUCTION(Today, 35), DEATHREDUCTION(Today, 40), DEATHREDUCTION(Today, 45),
DEATHREDUCTION(Today, 50), DEATHREDUCTION(Today, 55), DEATHREDUCTION(Today, 60),
DEATHREDUCTION(Today, 65), DEATHREDUCTION(Today, 70), DEATHREDUCTION(Today, 75),
DEATHREDUCTION(Today, 80), DEATHREDUCTION(Today, 85), Today, MARGINALCOST(Today, 20),
MARGINALCOST(Today, 25), MARGINALCOST(Today, 30), MARGINALCOST(Today, 35),
MARGINALCOST(Today, 40), MARGINALCOST(Today, 45), MARGINALCOST(Today, 50),
MARGINALCOST(Today, 55), MARGINALCOST(Today, 60), MARGINALCOST(Today, 65),
MARGINALCOST(Today, 70), MARGINALCOST(Today, 75), MARGINALCOST(Today, 80),
MARGINALCOST(Today, 85), _
Today, AVERAGECOST(Today, 20), AVERAGECOST(Today, 25), AVERAGECOST(Today, 30),
AVERAGECOST(Today, 35), AVERAGECOST(Today, 40), AVERAGECOST(Today, 45),
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AVERAGECOST(Today, 50), AVERAGECOST(Today, 55), AVERAGECOST(Today, 60), AVERAGECOST(Today, 65), AVERAGECOST(Today, 70), AVERAGECOST(Today, 75), AVERAGECOST(Today, 80), AVERAGECOST(Today, 85)

Next Today

Close #2

'We'll NOW put the data on Years of Life Lost (YLLost) into a file, fir

1999 Open "c:\My Dump\APRv3b.txt" For Output As #3

Write #3, "Reduction Caused by Therapy (or its absence) with Gail Test", INCIDENCEREDUCTION, TimeTillDeath, "GailLimit", GailLimit
Write #3, , 20, 25, 30, 35, 40, 45, 50, 55, 60, 65, 70, 75, 80, 85

For Today = 0 To 3650

' Add the "If then" part of the next statement to make graphs with smaller datasets
If Today / 30 = Int(Today / 30) Or Today = 0 Then Write #3, Today, YLLost(Today, 20), YLLost(Today, 25), YLLost(Today, 30), YLLost(Today, 35), YLLost(Today, 40), YLLost(Today, 45), YLLost(Today, 50), YLLost(Today, 55), YLLost(Today, 60), YLLost(Today, 65), YLLost(Today, 70), YLLost(Today, 75), YLLost(Today, 80); YLLost(Today, 85)

Next Today

' Now, we'll Recorde the incidence by age
Write #3, Today, INCIDENCE(20), INCIDENCE(25), INCIDENCE(30), INCIDENCE(35), INCIDENCE(40), INCIDENCE(45), INCIDENCE(50), INCIDENCE(55), INCIDENCE(60), INCIDENCE(65), INCIDENCE(70), INCIDENCE(75), INCIDENCE(80); INCIDENCE(85)

Close #3


7000 End

End Sub
```

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