Laboratory for Quantitative Medicine

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A NEW MATHEMATICS, AND NEW COMPARATIVE EFFECTIVENESS CALCULATORS (CancerMath.net), FOR PREDICTING MELANOMA DEATH

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Note: this technical report accompanies a research paper in the submission process but with the full complement of tables and other information that could not be accommodated within the space limitations of the journal

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ABSTRACT

BACKGROUND: Predicting the risk of melanoma death is both a challenge, and an essential step in indentifying the best treatment for each patient.

METHODS: The *binary-biological model of cancer metastasis* captures, in mathematical terms, the most common mechanism of cancer death: the lethal spread of cancer cells, and contains equations that can tease out the independent impact on mortality of primary tumor size, nodal status, and other prognostic factors (the *SizeAssessment* and *Prognostic Measurement* methods) as well as combining information on primary tumor size, nodal status, and other prognostic factors into estimates of the risk of cancer death (the *SizeOnly*, *Size+Nodes* and *Size+Nodes+PrognosticFactors* [*SNAP*] methods).

RESULTS: 13 prognostic factors were found to make marked independent contributions to melanoma lethality: thickness, nodal status, Clark's level II, Clark's level II, mixed epithelioid-spindle cell melanoma, desmoplastic melanoma, female, skin of upper limb & shoulder, Clark's level II, nodular melanoma, ulcerated, skin of scalp & neck, acral lentiginous melanoma. The *SNAP* method reveals that each millimeter of primary tumor thickness is associated with ~8% risk of death while each positive lymph node is associated ~23% extra risk of death. The accuracy of the *SNAP* method was confirmed with data on ~2700 melanoma patients seen at the MGH, and ~90,000 patients from the SEER national dataset.

CONCLUSIONS: The equations of the *binary-biological model* were found to make highly accurate estimates of the risk of melanoma death, and provided a basis for web-based comparative effectiveness calculators (http://www.CancerMath.net), for estimating the risk of death for each patient.

INTRODUCTION

Finding ways to accurately calculate patient survival, and then to communicate this information to physicians and patients, have been goals, embraced with various degrees of enthusiasm, by the comparative effectiveness movement, as a way to improve medical outcome.[1-6] Indeed, the collection of data, and development of methods for predicting the risk of melanoma death[7,8,9,10,11,12] and nodal involvement[13,14,15] has been an active area of research, with considerable success[16].

We have developed a new mathematical framework, the *binary-biological model of cancer metastasis*, which captures, in mathematical terms, the most common mechanism of cancer death: the spread of cancer cells from the primary site to the periphery leading to lethal distant metastatic disease.[17,18,19,20,21,] This approach takes advantage of the intrinsically binary, discrete, *either/or* quality of cells. For example, each cell in a tumor will *either* spread to the periphery, leading to death, *or* it will not, and from this *either/or* quality, we are able assign a probability of the spread of cancer cells, and from this, derive the equations of the *binary-biological model*. These equations include a series of expressions that can be used to tease out the independent impact on mortality of primary tumor size, nodal status, and other prognostic factors (*SizeOnly*, *SizeAssessment* and *PrognosticMeasurement* methods), and other expressions that provide ways to combine information on tumor size, nodal status, and other prognostic factors into estimates of the risk of cancer death (*Size+Nodes* and *Size+Nodes+PrognosticFactors* [*SNAP*] methods). The accuracy of these methods have been confirmed on three very large datasets of patients with breast carcinoma, as well as on a single dataset of ~2700 patients with melanoma. Here we extend this analysis to a second, much larger melanoma dataset (~90,000 patients). We also use this information to produce a set of web-calculators, at www.CancerMath.net, which clinicians can use to estimate survival and nodal status for individual melanoma patients.

METHODS

Mathematical Methods

The general theory behind the mathematical methods used here to capture the features of cancer lethality, and other manifestations of the spread of cancer cells, the *binary-biological model of cancer metastasis*, is based on a consideration of the spread of cancer cells, occurring with a definable probability per cell. A full description of the *binary-biological model of cancer metastasis* can be found in reference 22 and in Technical report #1 at http://cancer.lifemath.net/about/techreports/index.php, while the application of this framework to the analysis of breast carcinoma survival can be found in the other technical reports at this website. For consistency with previous publications, Equations #1-#4 are numbered in agreement with our previous publications[17, ,22] and thus will appear out of order when presented below.

Data

SEER: Data were available on 90,801 melanoma patients from the SEER (Survey Epidemiology and End Results) national dataset (between the years 1988 and 2003) for whom there was complete continuous tumor size and survival data. A subset of these patients (20,215) possessed complete tumor size and nodal status data. (The entire SEER dataset contains information on 251,083 melanoma patients from 17 data repositories throughout the United States between 1973-2005**)**

MGH: Data were available on 2,770 melanoma patients seen at the Massachusetts General Hospital from 1970 to 2002. Of these 2,770 patients, complete nodal information was known for 664. Preliminary analyses of these data can be found in references 18 .

Construction of the calculators

The calculators were written in JavaScript, PHP, and HTML, using XML/SWF Charts v5.07 package along with Adobe Flash to animate and display the graphs. The JavaScript code for the calculators, together with documentation, can be viewed in the browser by selecting "View→Source" in the browser menu, while a full technical report outlining how the code works can be found at http://www.lifemath.net/cancer/about/techreports/index.php [23]

RESULTS

Time-course of melanoma lethality

The mathematical framework that we shall use here for capturing the features of melanoma lethality, the *binary-biological model of cancer metastasis*, examines cancer death as the consequence of the lethal spread of cancer cells. For example, for a patient with a tumor of N cancer cells, which has a probability p, per cell, that a cell will spread to the periphery and give rise to lethal distant metastatic disease, the relationship the chance of death L and the size of a cancer, N, will be:

$$L \approx N * p \qquad \text{(a)}$$

Time-course of melanoma lethality

Before proceeding with such a treatment, we must first establish how many years of follow up are required before the value of L can be known. To address this question, we measured the risk of death over the long-term for the melanoma patients in the MGH and SEER datasets.

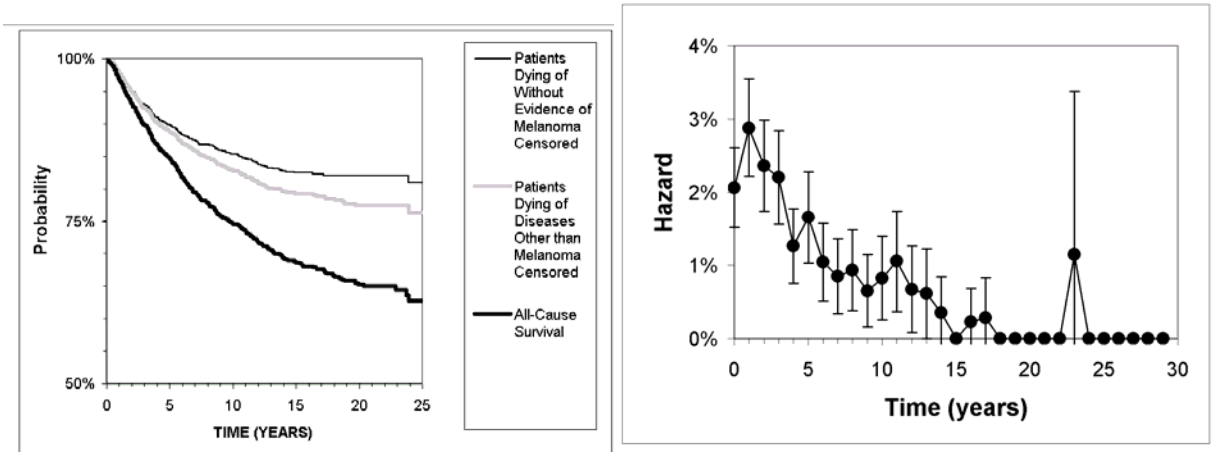

FIGURE 1A LEFT: Kaplan-Meier survival curves for the 2770 melanoma patients in the MGH dataset. *All-cause-survival,* in which patients were censored only for time of follow-up (thick black line), *disease-specific-survival,* in which patients dying without evidence of melanoma are censored (thin black line), and *modified-disease-specific-survival,* in which patients dying of diseases other than melanoma are censored (thin gray line).

RIGHT: Hazard function estimates for disease-specific-melanoma lethality among the the 2770 melanoma patients in the MGH dataset

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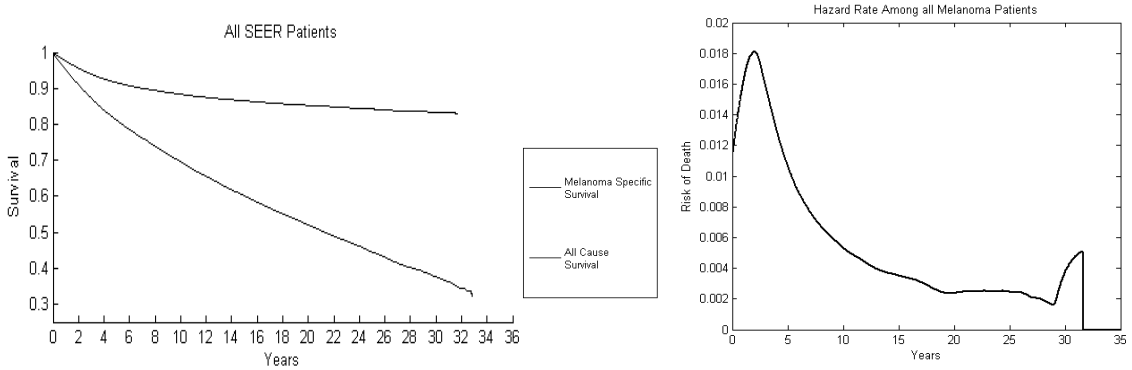

Figure 1D: Melanoma Lethality in the SEER Dataset

Overall Melanoma Hazard- The risk of death from Melanoma for the 90,801 patients in the SEER dataset. The risk of death maximizes around two years, and reaches a stable low level around 20 years. This illustrates the motivation in choosing15 years as the designation when most melanoma lethality has occurred.

There were 2770 melanoma patients in the MGH dataset, for which 1032 had 10+ years of follow up, 545 had 15+ years of follow up, and 236 had 20+ years. There were 353 melanoma deaths, 324 in the first 10 years, 26 between 10 to 15 years, 2 between 15 to 20 years, and 1 at 24 years. Hazard function calculations revealed a ~2% risk of melanoma death in year 1, a ~3% risk in year 2, a ~1% risk in years 6 to 11, becoming indistinguishable from 0% by year 15 (FIGURE 1).

There were 251,083 melanoma patients in the SEER dataset, for which 50,179 had 10+ years had follow-up, 24,786 had 15+ years of follow up, 11,999 had 20+ years of follow-up, and 1011 had 30+ years of follow-up. There were 18,499 melanoma deaths in the first 10 years, 1,034 melanoma deaths between year 10 and year 20, 764 melanoma deaths between years 15 and 20, and 128 melanoma deaths between years 25 and 30. Hazard function analysis revealed a ~1% risk of death in year 1, reaching a maximum ~1.6% risk of death in year 2, diminishing to a 0.3% chance of death by year 15, remains relatively low for the remainder of follow-up, despite a small rise to 0.4% around year 32. Note that the Kaplan-Meier disease-specific death curves reveal that at 10 years, the cumulative death rate had only achieved about 70% of the total death accumulated by 30 years, but that by 15 years, the cumulative death rate had achieved more than 90% of the total death accumulated by 30 years (FIGURE 1).

Thus, the 10-year point is not sufficient to capture the melanoma death rate, but that by 15 years at least 90% of the risk of death to melanoma has occurred. Indeed, the residual risk of death after 15 years is so low that it is difficult to know whether it is ascribable to the original melanomas, or to a subsequent melanoma, ad these patients have been found to be at elevated risk for second cancers.[24] But, whatever the origin of the small risk of death after 15 years, these data reveal that 15-year disease-specific death rate probably provides the best end-point for studying factors impacting melanoma lethality, *L*.

<u>The relationship between tumor size and cancer death is well captured by the *SizeOnly* Equation.</u>

Building from Equation #a, we have been able to derive[18,25] an expression, the *SizeOnly* Equation, for relating the risk of cancer death (*L*) to tumor size (*D*):

$$L = 1 - e^{-QD^Z} \qquad (1)$$

As we have reported previously, the *SizeOnly* Equation accurately captures the relationship between the 15-year Kaplan-Meier cancer-specific death rate, *L* , and thickness, *D*, for the melanoma patients in the MGH dataset, such *Z*=1 and *Q*=0.132. (The *SizeOnly* Equation has also been shown to accurately capture cancer lethality for breast and renal cell carcinoma, but with different values of *Q*[22].) As can be seen in Figure 2, this is also the case for the much larger dataset of patients in the SEER dataset (TABLE II) such that, such *Z*=1 and *Q*=0.1455. As can also be seen in Figure 2, that the slight difference in the values of *Q* derived for the MGH and SEER populations is essential trivial.

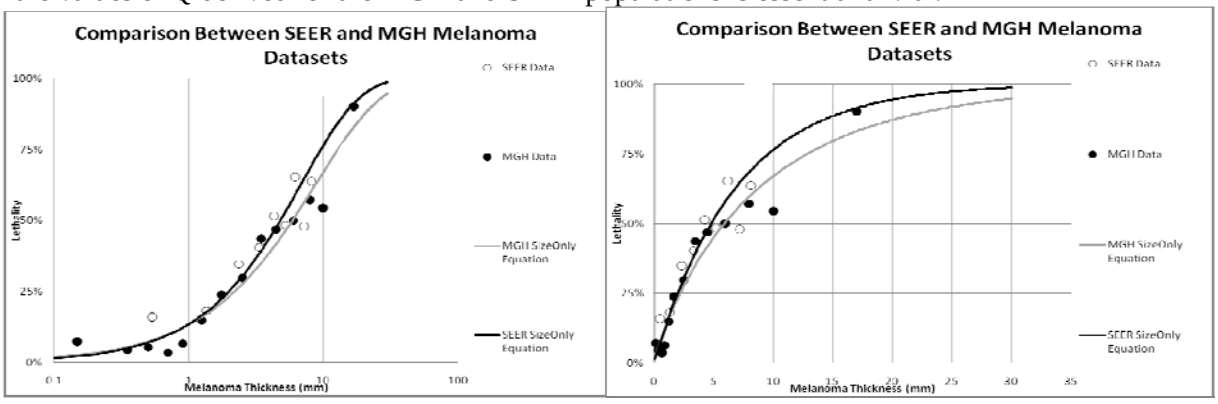

FIGURE 2

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TABLE II: Survival of Melanoma Patients by Tumor Thickness

Thickness Range (mm)	Patient Group	Nominal Median Thickness (mm)	# of Patients	Cancer-Specific Death (15-year Kaplan-Meier) (*L*)
0-.299	MGH All	0.15	209	7.21%
.3-.39	MGH All	0.35	232	4.51%
.4-.59	MGH All	0.5	424	5.47%
.6-.79	MGH All	0.7	294	3.50%
.8-.99	MGH All	0.9	227	6.45%
1-1.49	MGH All	1.25	381	14.75%
1.5-1.99	MGH All	1.75	272	23.67%
2-2.99	MGH All	2.5	314	29.61%
3-3.99	MGH All	3.5	164	43.71%
4-4.99	MGH All	4.5	91	46.92%
5-6.99	MGH All	6	87	49.98%
7-8.9	MGH All	8	36	57.21%
9-11.99	MGH All	10	23	54.26%
12 to 22	MGH All	17	14	90.08%
1-1.49	MGH Node -	1.25	112	8.95%
1.5-1.99	MGH Node -	1.75	106	19.64%
2-2.99	MGH Node -	2.5	107	22.78%
3-3.99	MGH Node -	3.5	56	27.27%
4-4.99	MGH Node -	4.5	25	35.06%
0-.299	SEER All	0.17	15731	5.66%
.3-.39	SEER All	0.33	10563	3.14%
.4-.59	SEER All	0.47	17718	4.45%
.6-.79	SEER All	0.67	11787	6.88%
.8-.99	SEER All	0.87	7026	10.25%
1-1.49	SEER All	1.18	10046	17.24%
1.5-1.99	SEER All	1.69	5237	25.69%
2-2.99	SEER All	2.35	5647	35.36%
3-3.99	SEER All	3.32	2903	43.72%
4-4.99	SEER All	4.27	1870	48.24%
5-6.99	SEER All	5.59	1905	52.08%
7-8.99	SEER All	7.55	898	52.82%
9-11.99	SEER All	9.12	243	57.36%
1-1.49	SEER Node -	1.19	4550	14.96%
1.5-1.99	SEER Node -	1.69	2659	22.78%
2-2.99	SEER Node -	2.36	2893	31.14%
3-3.99	SEER Node -	3.33	1446	38.72%
4-4.99	SEER Node -	4.29	873	48.48%
5-5.99	SEER Node -	5.24	507	53.28%
6-6.99	SEER Node -	6.22	335	49.06%
7-7.99	SEER Node -	7.18	225	73.20%
8-8.99	SEER Node -	8.14	144	54.73%
9-9.87	SEER Node -	9.12	90	69.85%

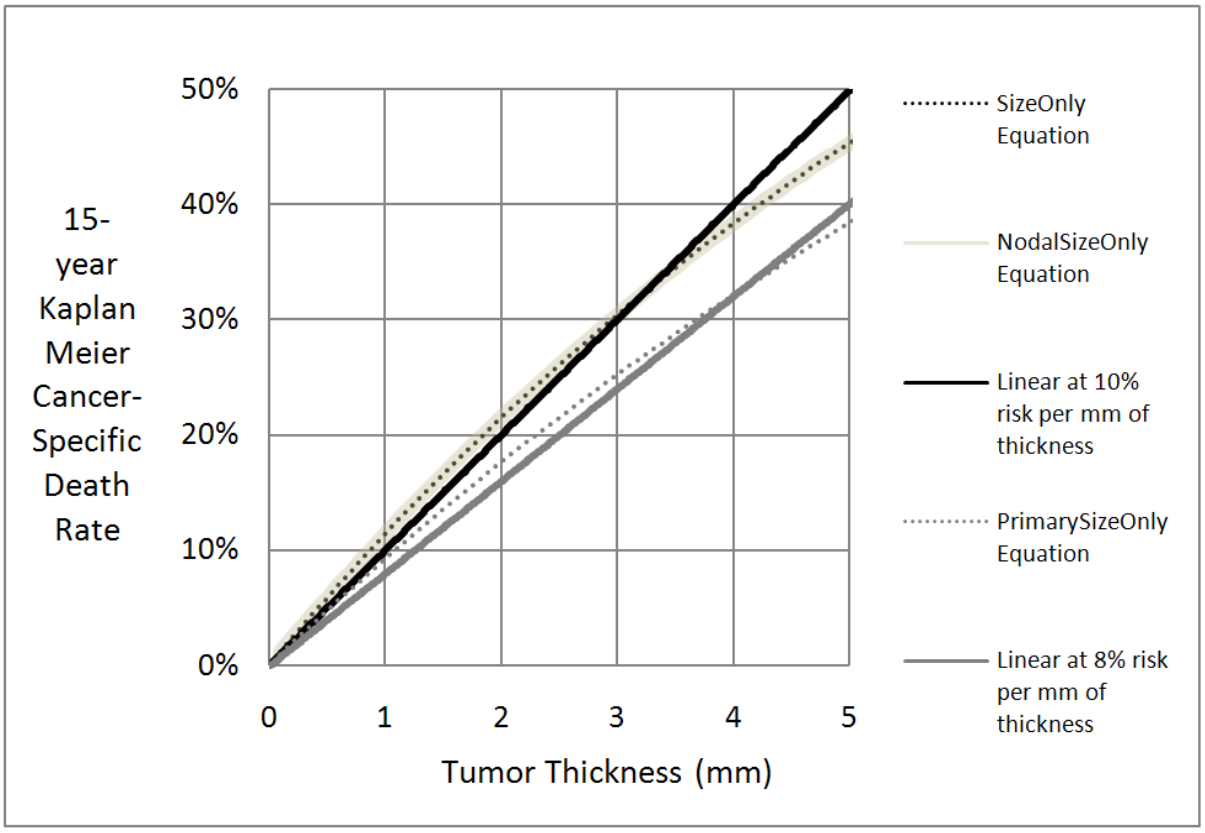

FIGURE 3. Approximate linearity of the relationship between the thickness of the primary mass and melanoma death rate captured by the *SizeOnly* equation (all patients), the *PrimarySizeOnly* equation (node-negative patients), and the *NodalSizeOnly* equation (all patients with nodal status information) derived from the SEER dataset.

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A simple mnemonic for capturing the lethal contribution of melanoma thickness

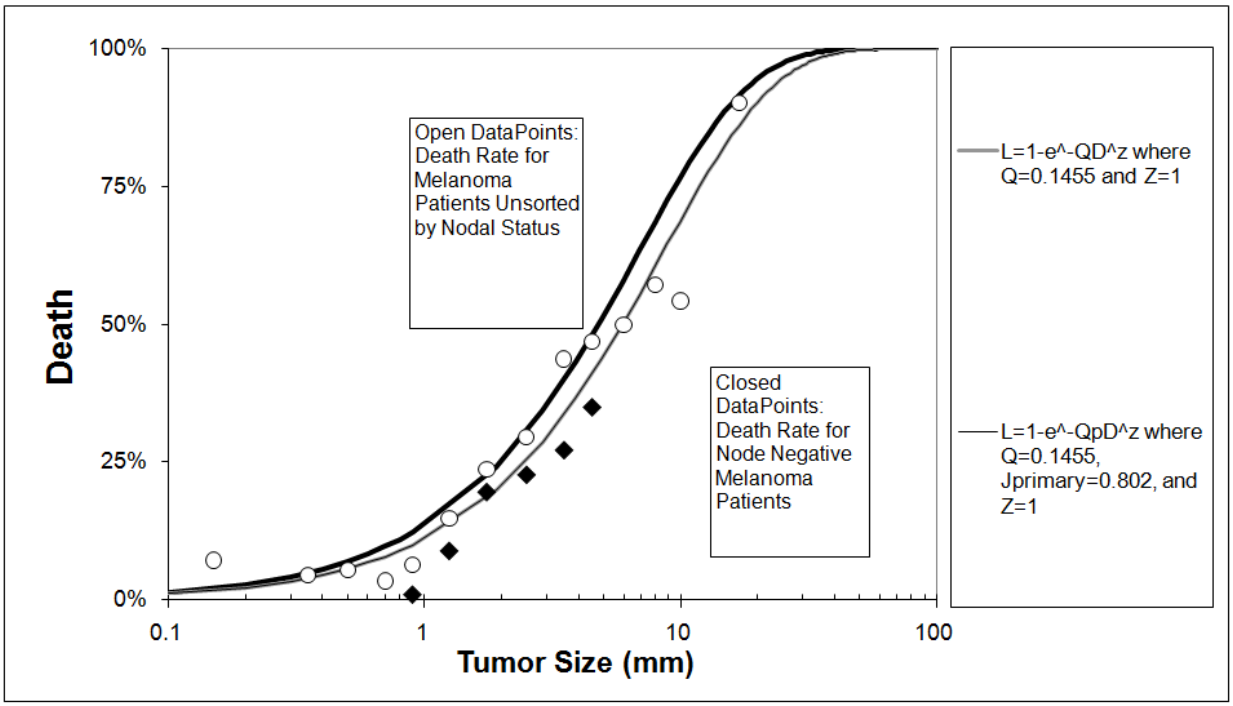
Fortuitously, the middle of the *SizeOnly* Equation (#1c) is quite linear, with a slope of roughly 0.1 (Figure 3). This provides a convenient mnemonic for the lethal impact of tumor thickness, such that each millimeter in tumor thickness is associated with about a 10% increase in lethality.

The relationship between tumor size and cancer death for node negative patients is well captured by the *PrimarySizeOnly* Equation

We have previously found for node negative melanoma patients in the MGH dataset, that the relationship between tumor thickness (D) and the risk of cancer death ($L_{primary}$) is well fit to a variant of the *SizeOnly* Equation, the *PrimarySizeOnly* Equation (#1c)

$$L_{primary} = 1 - e^{-(Q^* j_{primary}) D^Z} \quad (1c)$$

such that for the MGH dataset, $j_{primary}$= 0.801 (FIGURE 3).[18] From the data in TABLE II, we can see that the much larger dataset of patients in the SEER dataset yields precisely the same value of $j_{primary}$=0.801 (FIGURE 4).



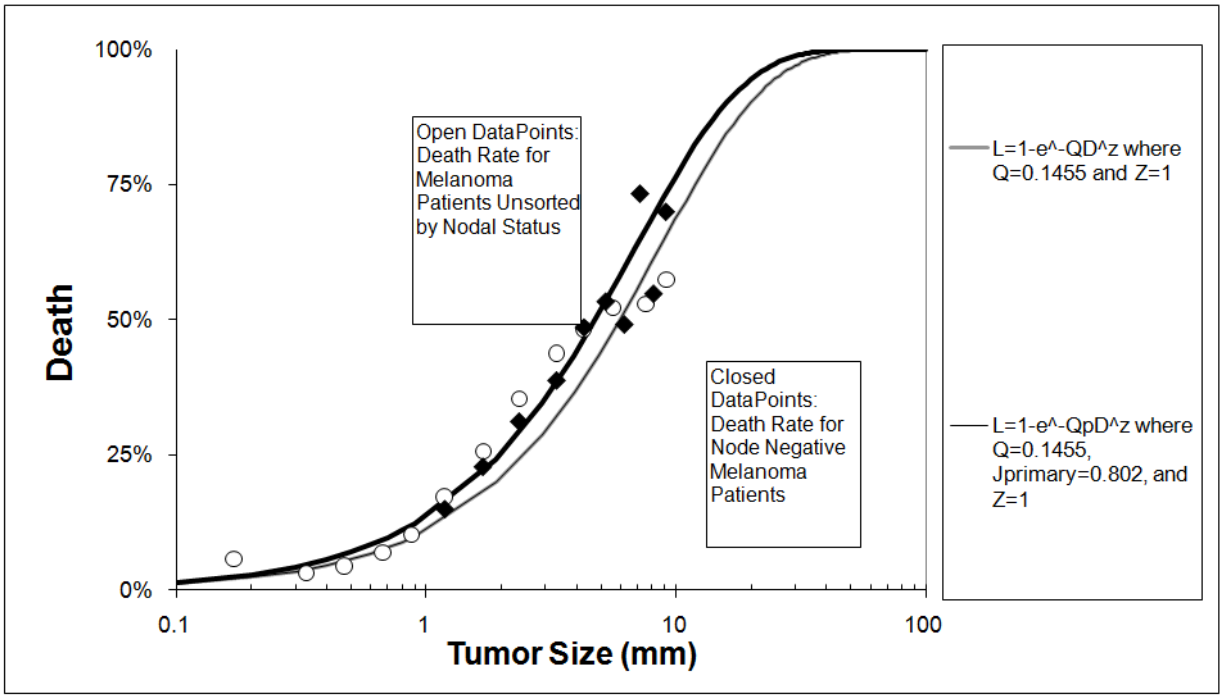


FIGURE 4 Relationship between tumor size and cancer death for all melanoma patients and node-negative melanoma patients**.** MGH (top) SERR (bottom)

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Each positive node is associated ~23% extra risk of lethality

The migration of melanoma to the local lymph nodes has long been known to contribute to the chance of death. Unfortunately, we cannot simply compare the survival of patients with various numbers of positive nodes, because tumor size and nodal status are conflated: as the tumor size increases, both the fraction of patients with positive nodes, and the average number of positive nodes, increase, while as the number of nodes increases so does the tumor size (Table III). However, we can use the *binary-biological* mathematics to quantify the lethal impact of cancer in the nodes, L_{nodes}, such that:

$$L = L_{primary} + L_{nodes} - \left(L_{primary} * L_{nodes}\right) \quad (4)$$

The product ($L_{primary}$ * L_{nodes}) on the right hand side of the equation is there because no matter how high the values of $L_{primary}$ and L_{nodes} are, no patient can die twice, even if cancer cells have spread to the periphery from both the primary site and from the nodes. That is, no patient can have greater than a 100% chance of death.

As we have previously reported, for the melanoma patients in the MGH population, each positive lymph node is associated about a 23% extra chance of death.[22] It follows that the lethal contribution from cancer in the nodes will be:

$$L_{nodes} = 1 - e^{-(M * L_{per-node})} \quad (2)$$

The exponential form of this equation takes into account the fact that no matter how many positive nodes there are, no patient can die twice, even if cancer cells had spread to the periphery from more than one positive node.

The combination of Equations #1c, #4, and #3 provides a technique, the *Size+Nodes* method, for integrating tumor size and nodal status into an estimate of the risk of death for each patient. Reversing these equations for subgroups of patients with various numbers of positive nodes (*M*) provides a way to measure the lethal contribution per node, $L_{per-node}$. Since this calculation means running the *Size+Nodes* method in reverse for each of a large number of patients, we execute these repetitive calculations by MatLab code: see "the iterative method" in Technical report #1 at http://cancer.lifemath.net/about/techreports/index.php. Using this iterative method, the lethal contribution per node in the MGH population was found to be 21% (for patients with 1 positive node), 24% (2 nodes), 24% (3 nodes), 23% (4 or 5 nodes), 24% (6 or 7 nodes), while for the SEER population the lethal contribution per node was 32% (for patients with 1 positive node), 15% (2 nodes), 25% (3 nodes), 19% (4 nodes), 24% (1 or more nodes), 19% (2 or more nodes), 20% (3 or more nodes), 18% (4 or more nodes), 17% (5 or more nodes) (TABLE III, FIGURE 4). Note that for all node positive patients, the lethal contribution per node is 0.22527 for MGH patients and 0.2253 for SEER patients, and this provides the most accurate measure of $L_{per-node}$. These data make clear that for patients in both the MGH and the SEER populations, no matter how many nodes are found to have cancer, the presence of each positive node is associated with about an extra 23% chance of death (+/- 8%) (TABLE III, FIGURE 5).

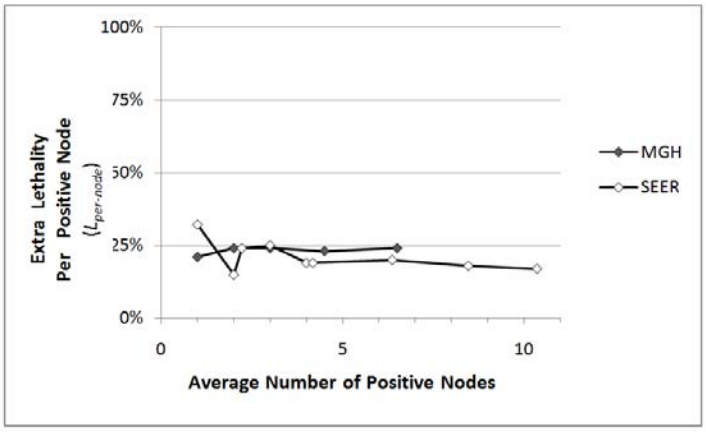

FIGURE 5

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TABLE III

Cancer death rates for groups of melanoma patients sorted by nodal status

Patient Group	Number of Patients	Nominal Average Number of Positive Nodes (*M*)	Mean Tumor Thickness (mm) (*D*)	Actual 15 year Disease Specific Death $L_{overall}$	The Level Of Death Expected for Node-negative Patients with Tumors of these Sizes $L_{primary} = 1-e^{-(Q^* j_{primary}) D^Z}$ (Eq. 1c)	Extra Death Ascribable To Positive Nodes, per node ($L_{per\text{-}node}$)
MGH Node Negative	487	0	2.35	21%	21%	-
MGH 1 positive node	92	1	3.24	40%	25%	21%
MGH 2 positive nodes	36	2	3.43	55%	27%	24%
MGH 3 positive nodes	21	3	4.14	67%	32%	24%
MGH 4&5 positive nodes	12	4.5	5.11	77%	34%	23%
MGH 6&7 positive nodes	10	6.5	3.64	86%	30%	24%
SEER Node Negative	16521	0	1.6545	18%	--	--
SEER 1 positive node	2278	1	2.4548	49%	23%	32%
SEER 2 positive nodes	709	2	2.8063	50%	26%	15%
SEER 3 positive nodes	271	3	3.031	70%	27%	25%
SEER 4 positive nodes	130	4	3.2784	71%	29%	19%
SEER 1 or more positive node	3694	2.2195	2.6652	55%	25%	24%
SEER 2 or more positive nodes	1416	4.1815	3.0036	76%	27%	19%
SEER 3 or more positive nodes	707	6.3692	3.2015	76%	28%	20%
SEER 4 or more positive nodes	436	8.4633	3.3075	80%	29%	18%
SEER 5 or more positive nodes	306	10.3595	3.3198	84%	29%	17%

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A simple mnemonic for estimating the risk of death from tumor thickness and number of positive nodes

Fortuitously, the middle of the *PrimarySizeOnly* Equation (#1c) is quite linear, such that each millimeter in tumor thickness is associated with about an 8% increase in lethality (Figure 3). When combined with the observation, noted above, that each positive lymph node is associated with about a 23% extra chance of death, this provides a convenient mnemonic for combining the lethal impact of tumor thickness and nodal status into a quick and rough estimate of the risk of melanoma lethality (TABLE V).

The relationship between tumor thickness and the chance of cancer in the nodes is well captured by the *NodalSizeOnly* Equation.

Of course, death is only one manifestation of the spread of cancer cells. Cancer cells may also spread from the primary site to the nodes. Following the same reasoning used above for the lethal spread of cancer cells, we should expect for the non-lethal spread of cancer cells that the relationship between tumor size and the chance of cancer in the nodes which results should also fit an equation of the form of the *SizeOnly* Equation, the *NodalSizeOnly* Equation:

$$L_{To-Nodes} = 1 - e^{-Q_n D^Z} \quad (1n)$$

As we have previously shown for the MGH patients[18], and here for the SEER patients, and as can be seen in FIGURE 6, this is the case, such that $Q_{to\text{-}nodes}$=0.1186, Z=1, as determined by the iterative method.

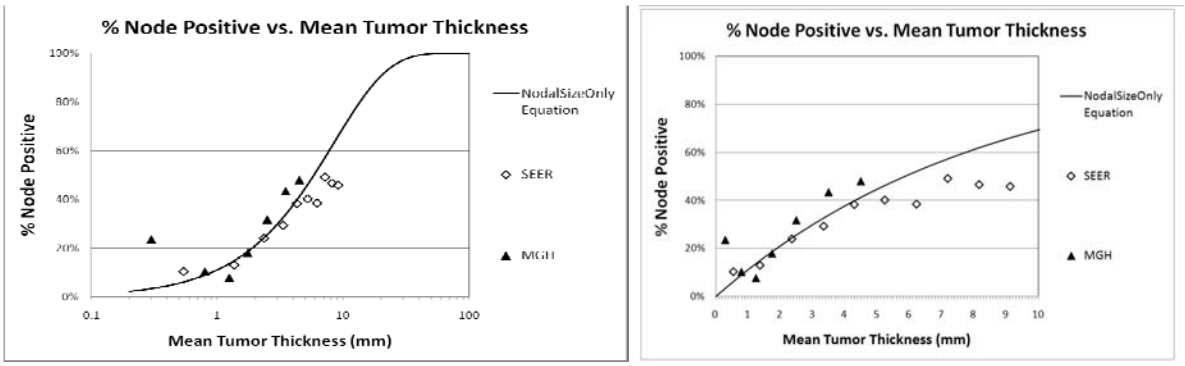

FIGURE 6. Relationship between primary tumor thickness and risk of node positivity, as captured by the *NodalSizeOnly* Equation (#1n), such that $Q_{to\text{-}nodes}$=0.1186 and Z=1.

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A simple mnemonic for the relationship between tumor thickness and the chance of cancer in the nodes

Fortuitously, the middle of the *NodalSizeOnly* Equation (#1c) is quite linear, with a slope of roughly 0.1 (Figure 3). This provides a convenient mnemonic for the relationship between tumor thickness and the chance of cancer in the nodes, such that each millimeter in tumor thickness is associated with about a 10% increase in the chance of a patient being node positive.

The impact of prognostic factors on melanoma lethality

There are an enormous number of additional prognostic factors that are suspected to contribute to melanoma lethality. Two methods of the *binary-biological model* give us the tools for analyzing such information: the *SizeAssessment* method provides a way to determine whether a prognostic factor truly contributes to lethality or is simply correlated with tumor size, while the *PrognosticMeasurement* method provides a way to measure the magnitude of each factor's contribution to the risk of death.[25]

In the *SizeAssessment* method, the actual 15-year cancer specific Kaplan-Meier death rate for a group of patients with a prognostic factor is compared with the death rate that would be expected by the *SizeOnly* equation. Such a test is necessary because some prognostic factors are correlated with tumor size, and it may not be clear whether the association of the prognostic factor with a different level of lethality is simply the result the correlation with tumor size, or whether the factor truly makes an impendent contribution to lethality of its own.

In the *PrognosticMeasurement* method, the magnitude of the lethal contribution of each prognostic factor is determined (by the iterative method, as outlined in reference* and in Technical report #1 at http://cancer.lifemath.net/about/techreports/index.php) by adding multipliers for each prognostic factor into the *SizeOnly* and *NodalSizeOnly* equations, which we call g and g_n parameters:

$$L = 1 - e^{-Q(g_1 * g_2 * g_3 * g_4 * ..) D^Z} \quad (1)$$

We used the *SizeAssessment* and *PrognosticMeasurement* tests to examine the lethal impact of fifty-one candidate prognostic factors in six categories: gender, ulceration, histological subtype, location of primary, Clark's level and ulceration. The values of their g parameters for all of these can be seen in TABLE IV; as rough guideline to distinguish between those prognostic factors that make an important impact on survival from those that make a trivial impact, we have chosen the somewhat arbitrary term "*marked*" to identify those prognostic factors that were statistically significant by *SizeAssessment* test and which increased or decreased the chance of death by roughly 25%, that is, those prognostic factors whose g parameters were found by the *PrognosticMeasurement* method to be either <0.74 or >1.33. There were not enough patients in the MGH dataset to determine with statistical certainty whether any prognostic factors examined made an impact on lethality, but using the SEER dataset, eleven factors were found to make marked contributions to lethality (plus size and nodal status, as indicated above). Factors associated with reduction in death included Clark's level I, Clark's level II, mixed epithelioid-spindle cell melanoma, desmoplastic melanoma, female, skin of upper limb & shoulder, Clark's level III), while factors associated with an increased chance of death included nodular melanoma, ulcerated, skin of scalp & neck, acral lentiginous melanoma. The factor found to have the strongest negative impact on lethality was Clark's Level I, g=0.36, which translates into patients with this factor having about 1/3rd of the risk of death when compared with patients chosen randomly from the population with tumors of the same thickness, while the factor found to have the strongest positive impact on lethality, Acral Lentiginous Melanoma, g=1.77, causes roughly a 75% greater chance of death.

TABLE IV

Category	g-parameter	n	% Difference	p-value
Male	1.19	50373	0.0212	p<0.001
Female	0.77	40398	-0.0251	p<0.001
Ulcerated	1.56	5071	0.1091	p<0.001
Nonulcerated	0.9	83446	-0.0107	p<0.001
Desmoplastic Melanoma	0.66	909	-0.0787	p<0.001
Nodular Melanoma	1.34	7185	0.0695	p<0.001
Acral Lentiginous Melanoma	1.77	1022	0.1148	p<0.001
Superficial Spreading Melanoma	0.84	35946	-0.0151	p<0.001
Mixed Epithelioid-Spindle Cell Melanoma	0.47	145	0.0238	0.024
Skin of Scalp & Neck	1.69	6078	0.0817	p<0.001
Skin of Trunk	1.09	31639	0.009	p<0.01
Skin of Upper Limb & Shoulder	0.78	22268	-0.0247	p<0.001
Skin of Lower Limb & Hip	0.89	18022	-0.0132	p<0.001
Clark's Level I	0.36	2360	-0.0348	p<0.001
Clark's Level II	0.41	33898	-0.0347	p<0.001
Clark's Level III	0.79	19469	-0.0236	p<0.001
Clark's Level IV	1.01	16446	0.0017	0.747
Clark's Level V	1.26	1733	0.0605	p<0.01

Category	g-parameter	n	% Difference	p-value
Clark's Level I	**0.36**	**2360**	**-0.0348**	**p<0.001**
Clark's Level II	**0.41**	**33898**	**-0.0347**	**p<0.001**
Mixed Epithelioid-Spindle Cell Melanoma	**0.47**	**145**	**0.0238**	**0.024**
Desmoplastic Melanoma	**0.66**	**909**	**-0.0787**	**p<0.001**
Female	**0.77**	**40398**	**-0.0251**	**p<0.001**
Skin of Upper Limb & Shoulder	**0.78**	**22268**	**-0.0247**	**p<0.001**
Clark's Level III	**0.79**	**19469**	**-0.0236**	**p<0.001**
Superficial Spreading Melanoma	0.84	35946	-0.0151	p<0.001
Skin of Lower Limb & Hip	0.89	18022	-0.0132	p<0.001
Nonulcerated	0.9	83446	-0.0107	p<0.001
Clark's Level IV	1.01	16446	0.0017	0.747
Skin of Trunk	1.09	31639	0.009	p<0.01
Male	1.19	50373	0.0212	p<0.001
Clark's Level V	1.26	1733	0.0605	p<0.01
Nodular Melanoma	**1.34**	**7185**	**0.0695**	**p<0.001**
Ulcerated	**1.56**	**5071**	**0.1091**	**p<0.001**
Skin of Scalp & Neck	**1.69**	**6078**	**0.0817**	**p<0.001**
Acral Lentiginous Melanoma	**1.77**	**1022**	**0.1148**	**p<0.001**

TABLE V

The *SNAP* (*Size+Nodes+PrognosticMarkers*) Method for Estimating the Risk of Cancer Death from Information on Tumor Size, Nodal Status, and Other Prognostic Factors

$$L = L_{primary} + L_{nodes} - (L_{primary} * L_{nodes})$$

(Eq. (3))

Source of Lethality	*Method of Estimation*	*Independent Variable*	*Parameters*	*Interpretation*
The lethal contribution from cancer at the primary site	$L_{primary} = 1 - e^{-(Q * j_{primary})*(g_1 * g_2 * g_3 * g_4 * ..)D^Z}$ Eq.(1)	D = Melanoma Thickness	Q= 0.1455 Z= 1 $j_{primary}$ =0.801 if nodal status is known $j_{primary}$ =1 if nodal status is unknown *Melanoma:* *g* parameters See Table III for values	*The lethal contribution of the primary mass increases gradually with tumor size, and the amount of that lethal contribution is influenced by prognostic factors, as captured by the g parameters*
The lethal contribution from cancer in the lymph nodes	$L_{nodes} = 1 - e^{-(M * Lper-node)}$ Eq. (2)	M = the Number of Positive Nodes	$L_{per\text{-}node}$ = 0.2253	*The presence of each positive lymph node contributes approximately 23% extra chance of death*

The *SNAP* (*Size+Nodes+PrognosticMarkers*) method reduces to:

- **the *Size+Nodes* method, when only size and nodal status are known.**
- **the *SizeOnly* method, when only size is known.**

A simple mnemonic for the *Size+Nodes* method

	Lethal contribution for each mm of primary tumor size		Lethal contribution for each positive lymph node
Risk of Melanoma Death ≈	~8% per mm	+	~23% per node

The *Size+Nodes+PrognosticFactors* (*SNAP*) method combines tumor size, nodal status, and other prognostic factors into estimates of the risk of death.

Once the value of each prognostic factor's *g* parameter is known, we are able to combine information on tumor size, nodal status, and other prognostic factors with three linked equations to estimate of the risk of death, *L* for each patient:

$$L = L_{primary} + L_{nodes} - \left(L_{primary} * L_{nodes}\right) \tag{2}$$

where

$$L_{primary} = 1 - e^{-(Q * j_{primary})(g_1 * g_2 * g_3 * g_4 * ..) D^Z} \tag{1cg}$$

and

$$L_{nodes} = 1 - e^{-(M * L_{per-node})} \tag{2}$$

where *M* is the number of local lymph nodes found to be positive for cancer, and $L_{per\text{-}node}$ is the lethal contribution for each positive node (Table V).

The validity of the *SNAP* method's predictions of melanoma lethality:

To test the accuracy of the *SNAP* calculations, individuals in the SEER and MGH datasets were sorted into groups of various types and the predicted survival value calculated by the *SNAP* method were compared with the actual 15-year cancer specific Kaplan-Meier death rates for each group. For example, the *SNAP* method was used to sort the patients for whom we have full information (20,215 from SEER, 2,770 from MGH) into groups of differing by a 10% risk of death (i.e. those patients expected to have 0%-9.9% risk of death, 10%-19% risk of death, 20%-29%, etc) (FIGURES 7, 9 and 10). Kaplan-Meier survival analysis for each of these group revealed that the expected and observed survival values agreed within 6.5% for all of the 10% groups in the MGH dataset, and all of the 10% risk groups in the SEER dataset with a risk of death up to 60%, which comprises 92% of all patients (FIGURES 9 and 10). Additionally, when patients in both the SEER and MGH populations were sorted by sex, ulceration, Clark Level, node postivity, site, thickness, or histological subtype, agreement between the expected and observed survival values proved to be excellent (FIGURE 10). Indeed, of the 87 groups of patients from the SEER and MGH datasets that are shown in FIGURES 7, 8, 9, and 10, ranging in lethality from one group with a 4.3% Kaplan-Meier death rate to another group with a 85% death rate, the average agreement between actual and expected values was better than 5%.

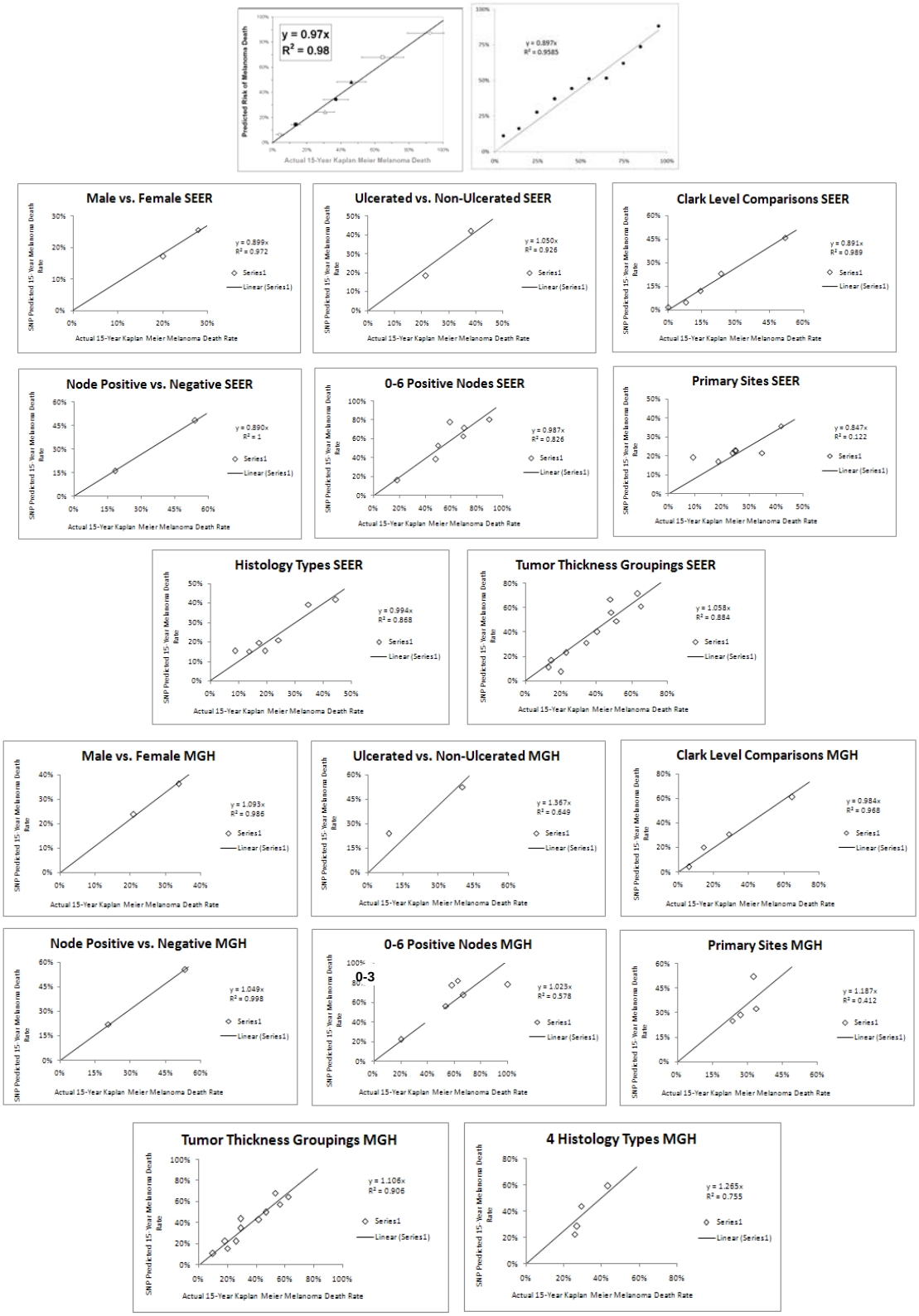


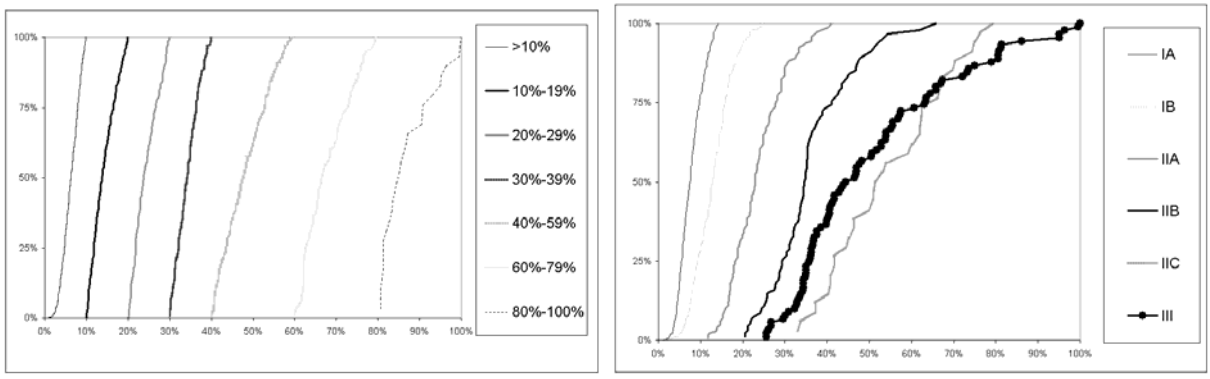
FIGURE 7. Confirmation of the accuracy of the *SNAP* method by examining melanoma patient subgroups with relevant prognostic factors from the SEER and MGH datasets. For full sized graphs and values, see the end of this Technical Report.

Comparison of the *SNAP* method and TNM staging in stratifying patients

The most widely used method for stratifying melanoma patients is by TNM stage (TABLE VI).[7] However, as we have found previously for breast carcinoma, TNM stage divides patients into groups of overlapping lethality[17]. Cumulative distributions of the risk of death estimated by the *SNAP* method for the groups of patients of each melanoma TNM stage also suggest the possibility that most TNM stage groups may contain considerable overall in the risk of death (FIGURE 8). Such a possibility was born out by comparing the actual 15-year Kaplan-Meier melanoma death rate of 1/3rd of stage II patients indicated by the *SNAP* method to have the worst chance of death with the actual 15-year melanoma death rate of 1/3rd of stage III patients indicated by the by the *SNAP* method to have the chance of death (FIGURE 9).

TABLE VI

STAGE	Number of Patients	*SNAP* Estimation of the Risk of Melanoma Death (15 year)	Actual 15 year disease specific (Kaplan-Meier)
IA	1433	7.27%	4.78%
IB	547	16.01%	18.75%
IIA	357	26.20%	30.79%
IIB	198	44.07%	45.29%
IIC	35	54.50%	48.05%
III	168	53.14%	52.89%



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C:\X_MelanomaAnalysisByExcell 1 1 04_SNP\Stage [Dataset For Excel #3 All SNP Stratified SmallerGrps STAGE.xls]Cum Dists'!$AH$2

FIGURE 8 Cumulative distributions of the *SNP* estimated risk of death of groups of melanoma patients sorted by the *SNP* method (left) and stage (right)

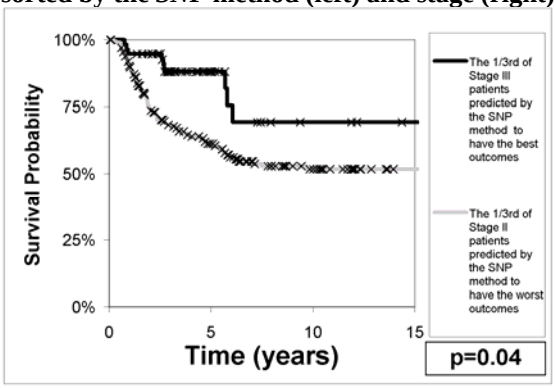

FIGURE 9 Kaplan-Meier Survival Curves revealing overlap in risk of death between groups of melanoma patients sorted by TNM stage.

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Web-based calculators based on the *SNAP* method (*CancerMath.net*)

Three types of breast carcinoma comparative effectiveness calculators are available at CancerMath.net website (Figure 10), based on the mathematics described above:

1) The *melanoma outcome* calculator uses the *SNAP* method executed in Javascript, to calculate survival information at the time of diagnosis that can expected from the current standard of care treatment;

2) The *melanoma conditional survival* calculator calculates survival information at various times after the time of diagnosis that can be expected from the current standard of care treatment;

3) The *melanoma nodal status* calculator uses the *NodalSizeOnly Equation* to calculate chance that cancer will be present in the nodes.

These CancerMath melanoma comparative effectiveness calculators provide information on the risk of death (to cancer, to causes other than cancer, and to all-causes combined) for each of the first 15-years after diagnosis, as well as the 15-year Kaplan Meier cancer specific death rate (FIGURE 12). The calculators also provide information on life expectancy, expressed in terms of both days of life and years of life, together with information on how life expectancy is shortened by the cancer diagnosis. The calculators also provide the patient's classification (T, N, and M) and stage.[7] The CancerMath *melanoma conditional survival* calculator provides updates of this information for patients who have survived without recurrence for each of the first 15 years after diagnosis.

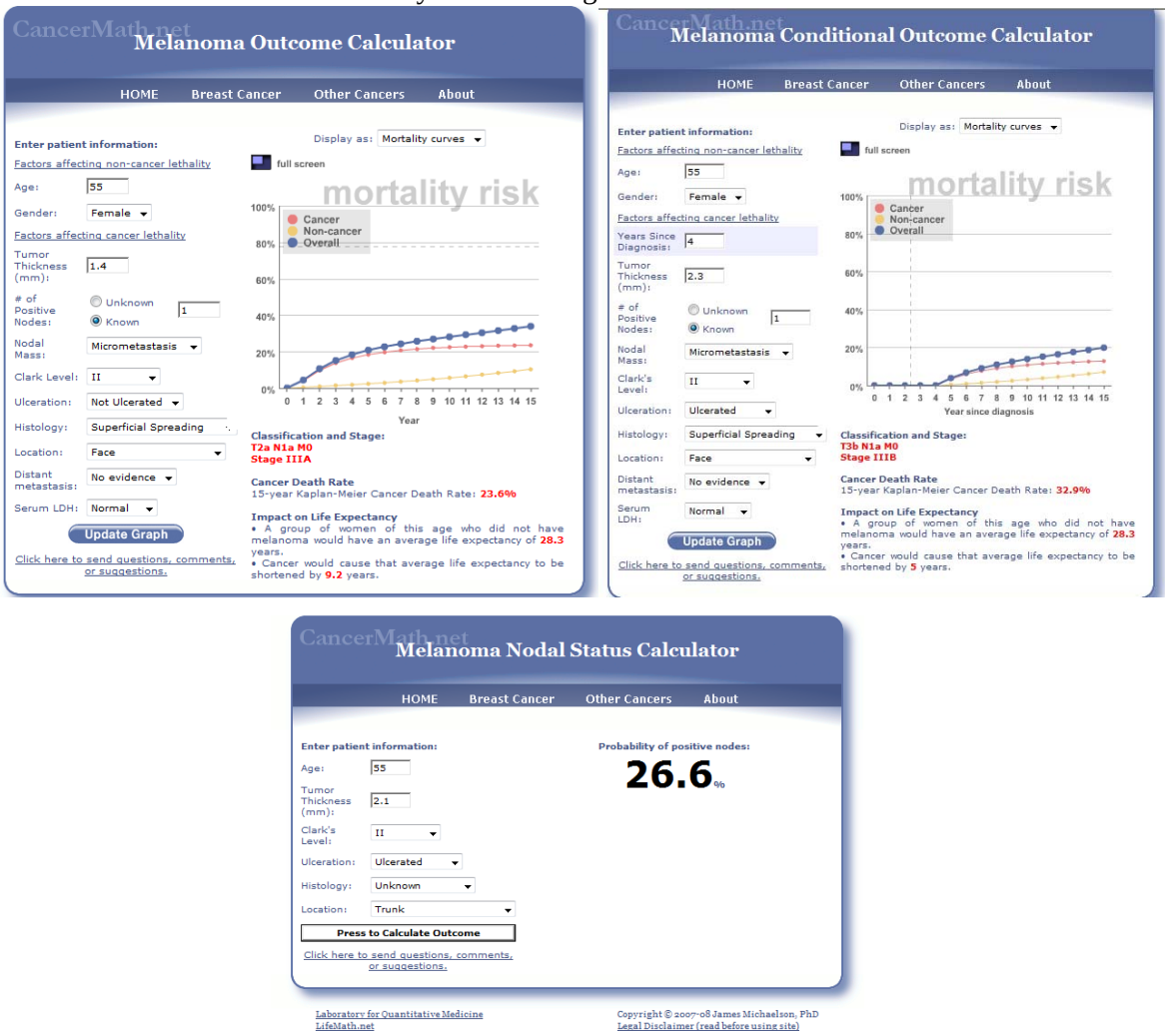


Figure10

The code behind the CancerMath calculators

The JavaScript code for the calculators, together with documentation, can be viewed in the browser by selecting "View→Source" in the browser menu. Here we outline the code for the *melanoma outcome calculator*, but the *conditional survival* calculator has a similar structure. The code begins by loading several lengthy arrays, such as the life expectancy tables, and proceeds through a series of sequential "Steps', which are numbered below. (STEPS 4 and 5 are not included below, as these tags are reserves for steps used in the CancerMath.net breast carcinoma treatment calculator). The various steps are also identified in the source code which is visible in the browser:

1. STEP 1 The program collects information that the user has entered into the web form:

1. Tumor thickness (in millimeters, to 2 decimal points)
2. Whether nodal status is known, and if so, the number of positive nodes (0, 1, 2, etc.)
3. Age
4. Tumor prognostic factors: Clark Level, Ulceration, Histology, and location (other factors entered into the web-form do not impact on outcome, but are used to specify stage (see STEP 7 below)

2. **STEP 2** The program calculates yearly and cumulative melanoma cancer, non-melanoma cancer, and total death rates for each of the 15 years after diagnosis, based on the entered user information:

1. The program loads information on the value of the parameters Q, Z, $j_{primaty}$ and $L_{per\text{-}node}$ (TABLE V), which are needed to execute the *SNAP* calculation (**STEP 2.b** below) for the probability of death to melanoma at 15 years.
2. The program loads information on whether nodal status is known
3. **STEP 2.a** The program loads the g parameters determined by the user input, and computes the product of all of them.
4. **STEP 2.b** The program calculates the 15-year Kaplan-Meier cancer death rate, L, using the *SNAP* method (TABLE V) from information on tumor size (**STEP 1** above), number of positive lymph nodes (**STEP 1** above), and other prognostic factors, as captured by the product of the g parameters (**STEP 2.a** above).
5. **STEP 2.c** The program calculates 15 values for the melanoma death rate in each of the 15 years after diagnosis. It accomplishes this for each year by multiplying the 15-year Kaplan-Meier cancer death rate, L, (calculated in **STEP 2.b** above) by the fraction of the total lethality which can be expected in each year. The total lethality expected in each year is a pre-computed 15-part step function derived from the melanoma hazard function, which we have derived from data on all of the melanoma patients in the SEER dataset for whom we have complete tumor thickness and nodal status information.
6. **STEP 2.d** The program calculates 15 values for the non-cancer death rate in each of the 15 years after diagnosis. It accomplishes this for each year by multiplying the fraction of patients not dying of cancer (=1 – (death rate calculated in **STEP 2.b**)) times the yearly risk of death due to non-cancer causes for the given age. The values for the yearly probability of death due to all non-cancer causes for ages 0 to 100 were taken from the National Vital Statistics Report (herein referred to as "NVSR")[26], while the values for ages 101 to 123 were extrapolated using the methodology described in the NVSR. Before creating the array values (nvsr_death_prob_yearly), we corrected them to account for the ~3% of deaths that can be ascribed to melanoma cancer. These values were loaded at the top of the program, before **STEP 1** as noted above.
7. **STEP 2.e** The program calculates 15 values for the overall death rate in each of the 15 years after diagnosis. It accomplishes this for each year by summing the cancer death rate (**STEP 2.c**) and the non-cancer death rate (**STEP 2.d**).

8. **STEP 2.f** The program calculates 15 values for cumulative melanoma cancer, non-melanoma cancer, and total death rates by summing the respective yearly values computed in the steps above.

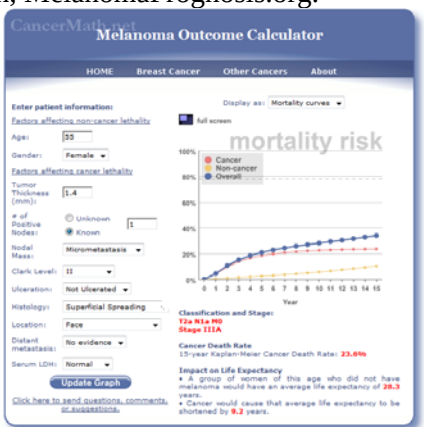
3. **STEP 3** The program calculates the mean number of years of life left that can be expected for the melanoma patient:
   1. **STEP 3.a** The program loads the value at year 0 for the number of people out of a group of 100,000 who survive to the user-specified age, based on yearly probabilities of death given by the NVSR.
   2. **STEP 3.b** For year 1 through year 15, the program multiplies the number of people out of the group of 100,000 who survive to the appropriate age (age+1 at year 1, age+2 at year 2, etc.) by the corresponding cumulative overall death rate (**STEP 2.f**). This applies the additional risk from cancer.
   3. **STEP 3.c** The program calculates the survival difference at year 15 by subtracting the calculated number of individuals surviving to year 15 from the NVSR-given value for the corresponding age (age+15).
   4. **STEP 3.d** The program then calculates 15 values for the total number of years lived by all surviving individuals in the group of 100,000 between each year, by taking the average of the number of individuals surviving to a given year and the number of individuals surviving to the following year.
   5. **STEP 3.e** The program calculates the total number of years lived by surviving individuals past each year, from year 0 to year 15. It begins at year 15, by taking the remaining years of life expected for the corresponding age (age+15), and subtracting away the total number of years that is expected to be lost because of cancer. The life expectancy in years for each age group is calculated as the number of people out of the group of 100,000 who survive to that age (from NVSR) multiplied by the residual life expectancy at that age (also from NVSR data). That expected number is the survival difference calculated in **STEP 3.c** multiplied by the additional number of years beyond the age at year 15 to reach age 101.
   6. **STEP 3.f** Then, working backwards from year 14 to year 0, the program calculates the total number of years lived by surviving individuals past each year by adding this value for the following year to the total number of years lived between that year and the following year (**STEP 3.d**). For example, the total number of years lived by surviving individuals past year 14 is the total number of years lived by surviving individuals past year 15 plus the total number of years lived between year 14 and year 15.
   7. **STEP 3.g** The program then calculates the mean life expectancy for the melanoma patient by dividing the new total number of years lived by individuals of the specified age (the value at year 0 from **STEP 3.f**) by the number of people out of the group of 100,000 who survive to that age (**STEP 3.f**).
   8. **STEP 3.h** The program calculates the expected years of life lost due to cancer, by subtracting the calculated life expectancy (**STEP 3.a**) from the NVSR-given life expectancy for the specified age.

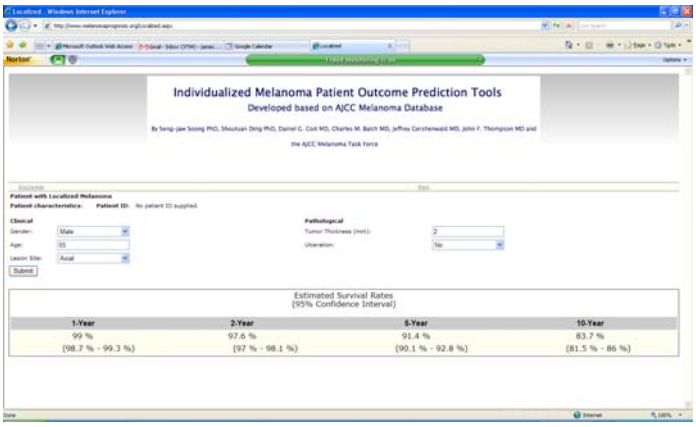
4. **STEP 6** The program graphs the risk curves for cancer (**STEP 2b)**, non-cancer (**STEP 1.a**), overall (**STEP 2.d**), in the user-specified mode, either as mortality curves, survival curves, a bar graph, a pie chart, or a pictogram. For the outcome calculator, the program displays the life expectancy (**STEP 3.a**), the life expectancy lost to cancer (**STEP 3.a**), and the 15-year Kaplan-Meier cancer-specific death rate (**STEP 1**).

5. **STEP 7** The program computes grade and stage, according to the AJCC criteria[7]

Comparison of CancerMath.net and MelanomaPrognosis.org Melanoma Calculators

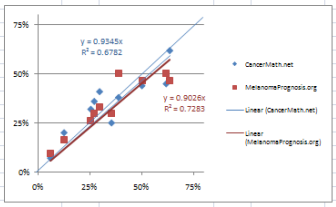
Balch et al. have recently produced a web-based calculator for estimating the risk of melanoma death, MelanomaPrognosis.org.





A comparison of the calculators reveals that for the few, rather large groups, into which the MelanomaPrognosis.org calculator sorts patients, the two calculators yield very similar values, and are about equally accurate, in terms of predicting outcome, as tested again the SEER dataset

# Postive Nodes	Age	Sex	Location	Tumor Size (mm)	SEER All-cause death	Error	Melanoma-specific death	Error	CancerMath.net All-cause death	Melanoma-specific death	MelanomaPrognosis.org Melanoma-specific death	CancerMath.net	CancerMath.net	MelanomaPrognosis.org	MelanomaPrognosis.org
0	65	Male	Axial/Trunk	0.5	23.04%	9.31%	6.13%	2.88%	41%	7%	9.50%	-0.87%	0.87%	-3.37%	3.37%
0	65	Male	Axial/Trunk	1.5	33.85%	8.12%	12.69%	5.20%	51%	20%	16.30%	-7.31%	7.31%	-3.61%	3.61%
0	65	Male	Axial/Trunk	2.5	39.65%	12.59%	25.57%	12.63%	59%	32%	26.20%	-6.43%	6.43%	-0.63%	0.63%
0	65	Male	Axial/Trunk	3.5	76.26%	23.74%	29.78%	14.79%	66%	41%	33.10%	-11.22%	11.22%	-3.32%	3.32%
1	65	Male	N/A	0.5	57.24%	17.06%	35.54%	13.71%	54%	25%	29.80%	10.54%	10.54%	5.74%	5.74%
1	65	Male	N/A	1.5	81.26%	18.74%	27.23%	9.87%	62%	36%	29.80%	-8.77%	8.77%	-2.57%	2.57%
1	65	Male	N/A	2.5	75.18%	21.01%	50.19%	24.35%	68%	44%	46.40%	6.19%	6.19%	3.79%	3.79%
1	65	Male	N/A	3.5	71.58%	16.34%	63.54%	19.59%	74%	62%	46.40%	1.54%	1.54%	17.14%	17.14%
2	50	Male	Axial/Trunk	0.5	38.89%	27.11%	38.89%	27.11%	44%	38%	50.10%	0.89%	0.89%	-11.21%	11.21%
2	50	Male	Axial/Trunk	1.5	68.06%	29.82%	61.84%	34.04%	50%	45%	50.10%	16.84%	16.84%	11.74%	11.74%
3	50	Male	Axial/Trunk	0.5					58%	50%	50.10%				
3	50	Male	Axial/Trunk	1.5					63%	57%	50.10%				
												0.14%	7.06%	1.37%	6.31%
												4.54%	7.46%	4.11%	8.70%



MP Survival
90.50%
83.70%
73.80%
66.90%
70.20%
70.20%
53.60%
53.60%
49.90%
49.90%
49.90%

Measures of Lethality:

- The MelanomaPrognosis.org calculator only provides a single value of melanoma lethality at 10 years.
- The CancerMath calculators provide information on the risk of death to cancer, non-cancer, and overall risk, for each of the first 15 years after diagnosis.

Our analysis of the time course of melanoma lethality (FIGURE 1) indicate that the 10-year value used by MelanomaPrognosis.org is not long enough to capture the full risk of death, but that the 15-year value used by CancerMath.net is sufficient for capturing the full risk of death.

- The CancerMath.net calculators provide a value (in days and years of life lost) for the impact of the melanoma on life expectancy.
- The CancerMath.net calculators provide the 15-year Kaplan-Meier Cancer-specific death rate.

Risk Groups:

- The MelanomaPrognosis.org calculator lumps patients into rather large groups of overlapping lethality. For example, patients with 2 or 3 nodes are considered as a single group, while the mathematics described above indicate that patients with 3 positive nodes will have about a 20% higher risk of death than patients with 2 positive nodes (FIGURE 5, TABLE II). Likewise, patients with 4 or more nodes are also considered as a single group.
- The CancerMath calculators provide results that are essentially continuous.

Risk Factors

- The MelanomaPrognosis.org calculator calculates its results from sex, age, thickness, ulceration, location (2 categories), and nodal status (0, 1, 2or3, 4ormore, +nodes, with tumor burden).
- The CancerMath.net calculator calculates its results from sex, age, thickness, ulceration, location (6 categories), and nodal status (all numbers of nodes, in single units), Clark Level, and Histology (10 categories).

Time Frame

- The MelanomaPrognosis.org calculator only provides a single value of melanoma lethality at 10 years, which is only valid at the time of diagnosis.
- The CancerMath melanoma conditional survival calculator provides survival information for patients who have remained disease free for up to 15 years after diagnosis.

Stage

- The CancerMath melanoma calculators provide Stage information.

Nodal Status

- The CancerMath melanoma nodal calculator provides estimates of the risk of cancer in the nodes.

Display:

- The MelanomaPrognosis.org calculator only provides a single value of melanoma lethality at 10 years.
- The survival information provided by the CancerMath calculators can be viewed in a variety of formats: in terms of death curves, survival curves, pie charts, or in terms of “smiley-face” charts, which have been provided to present the information is a fashion that may be more comprehensible to the lay person.

Code:

- An examination of the JavaScript that drives the MelanomaPrognosis.org calculator indicates that the calculations are carried out on a back-end server, so one can't see their formulas.
- The Cancer Math code is freely and fully visible in the browser, with full documentation.

DISCUSSION

Here we have seen that the lethal impact of melanoma thickness, nodal status, and other prognostic factors, is well captured by the mathematical framework of the of the *binary-biological model of cancer metastasis*. This framework has made it possible to determine that the relationship between tumor thickness and the risk of cancer death is well captured by a simple expression, the *SizeOnly* Equation. The *SizeOnly* Equation is quite linear at its center, such that each millimeter in tumor thickness is associated with about a 10% increase in lethality. The *binary-biological* framework also made it possible to determine that the relationship between tumor thickness and the risk of cancer death for node negative patients is well captured by a variant of the *SizeOnly* Equation, the *PrimarySizeOnly* Equation. The relationship between tumor thickness and the risk of cancer in the local nodes, another manifestation of the spread of cancer cells, was found to be well captured by another variant of the *SizeOnly* Equation, the *NodalSizeOnly* Equation. The *NodalSizeOnly* Equation is quite linear at its center, such that each millimeter in tumor thickness is associated with about a 10% increase in the chance of a patient being node positive. Other equations of the *binary-biological model* made it possible to determine that the each positive lymph node is associated with approximately an extra 23% extra chance of death. Since the *PrimarySizeOnly* Equation is quite linear at its center, such that each millimeter in tumor thickness is associated with about a 8% increase in lethality, and each positive lymph node add about a 23% extra chance of death, this provides a convenient, if somewhat inexact way to combine information on tumor size and nodal status into an estimate of the risk of death for each patient; a more precise estimation can be made by the linked equations that comprise the *Size+Nodes* method. Finally, the *SizeAssessment* and *PrognosticMeasurement* methods provided ways to measure the magnitude of the lethal contributions of prognostic factors to survival, while the *Size+Nodes+PrognosticFactors* (*SNAP*) method provided a way to generate accurate estimates the risk of death from information on a patient's prognostic factors, tumor size, and nodal status.

The mathematical basis of the *binary-biological model* is possible because it considers that each cell in a tumor will *either* spread to the periphery, thus leading to death, *or* it will not. This *either/or, binary*, quality allows us to assign a probability value, *p*, for the spread of cancer cell, from which we could derive our equations. In building our math from this intrinsically discrete, *either/or*, quality of cells, we take advantage of a fundamental feature of all microscopic entities, not only cells, but also the molecules, atoms, electrons, photons, and genes of which we are comprised (see: http://www.lifemath.net/binbio.html and reference 27). In fact, we have found this to be a useful starting point for building mathematical tools understanding a number of features of multicellullular systems, of which melanoma lethality is but a single example For example, by examining the events of molecular signaling that go on in the embryo as discrete, *either/or*, events, we have found that the growth of tissues, organs, and anatomical structures to predictable sizes, at predictable times, and to predictable shapes can arise as a natural consequence of such discreteness[27]. Similarly, by examining the molecular mitotic signaling events that go on within cells as discrete, *either/or*, single chemical events, we have found that growth of tissues to normal sizes is also the natural consequence of this discrete, *either/or*, nature of the events that occur among the oncogene and tumor suppressor gene products of the cell[27]. The same mathematics provided a way to see why mutations in some of these genes will lead to premalignant growth, while other combinations of mutations will lead to outright cancerous growth.[27] Thus, we would suggest that a mathematical consideration of the discrete, *either/or* events that go on among the cells, molecules, atoms, electrons, photons, and genes provides a versatile toolkit for understanding many aspects of normal and abnormal multicellularity, including cancer lethality, as we have seen here in capturing the lethal features of melanoma.

We have found that no matter how many lymph nodes are found to have melanoma, the presence of each positive node is associated with about an extra 23% chance of death. Some positive nodes are identified by elective nodal dissections, while others are identified by clinical evidence of cancer in the nodes, followed by node dissection. It is unfortunate that tumor registries do not distinguishing between these two categories. Logic would suggest that clinically evident nodes, with larger cancer masses, would

be associated with a greater than 23% lethal contribution, while elective nodal dissections, nodes, with smaller cancer masses, would be associated with less than a 23% lethal contribution. Indeed, there is evidence for such a possibility.[11] Clearly there would be much merit in collecting data to address this question.

One the advantages of the *binary biological* framework that drives the CancerMath melanoma calculators is that this mathematics can work with as little information as is at hand (the *SNAP* method can generate an estimate of a patient's 15-year death rate with just tumor thickness), as well as with as much information as is desired. An ongoing effort by our group is to collect such data on additional prognostic factors and to use the *SizeAssessment* and *PrognosticMeasurment* methods to quantify the impact of these factors and add this information to updates of the CancerMath calculators. Other prognostic factors, such as mitotic rate[8], or biochemical and molecular biological markers, such as gene expression array patterns, or genotype, can also readily be embraced by the mathematics.

The *binary biological* mathematical framework made it possible create a set of web-base comparative effectiveness calculators, located at www.CancerMath,net, which patients and physicians can use to estimate the chance of survival for individual melanoma patients. The same mathematics has made it possible for us to create analogous comparative effectiveness calculators for breast carcinoma[22] and renal cell carcinoma, and there is no reason why one could not use this framework to create calculators for other cancers. Even in the absence of such a biologically-motivated mathematical framework, comparative effectiveness calculators can be made on a strictly empirical basis. Indeed, we have created just such a calculator for providing individualized information on benefit, in terms of days of life, that may be expected from the various Class-A preventive interventions recommended by the U.S. Preventive Services Task Force (http://www.lifemath.net/preventive/). Thus, we would suggest that the CancerMath melanoma calculators provide an example of the sort of web-based tools which can be created to provide physicians and patients with the highly accurate, patient-specific information they need to reach the best treatment selection for each patient.

APPENDIX

TABLE A1
Stratification of Patients by Risk of Death Estimated by the *SNAP* Method, for the MGH dataset

Risk Group	SNAP Risk of Melanoma Death	Actual 15 Year Melanoma Death	Number of Patients
0%-10%	6.25%	4.30%	1215
10%-19%	14.18%	13.62%	734
20%-29%	24.32%	30.75%	332
30%-39%	34.28%	37.14%	194
40%-59%	48.15%	46.26%	183
60%-79%	67.96%	64.58%	77
80%-99%	87.21%	92.39%	29

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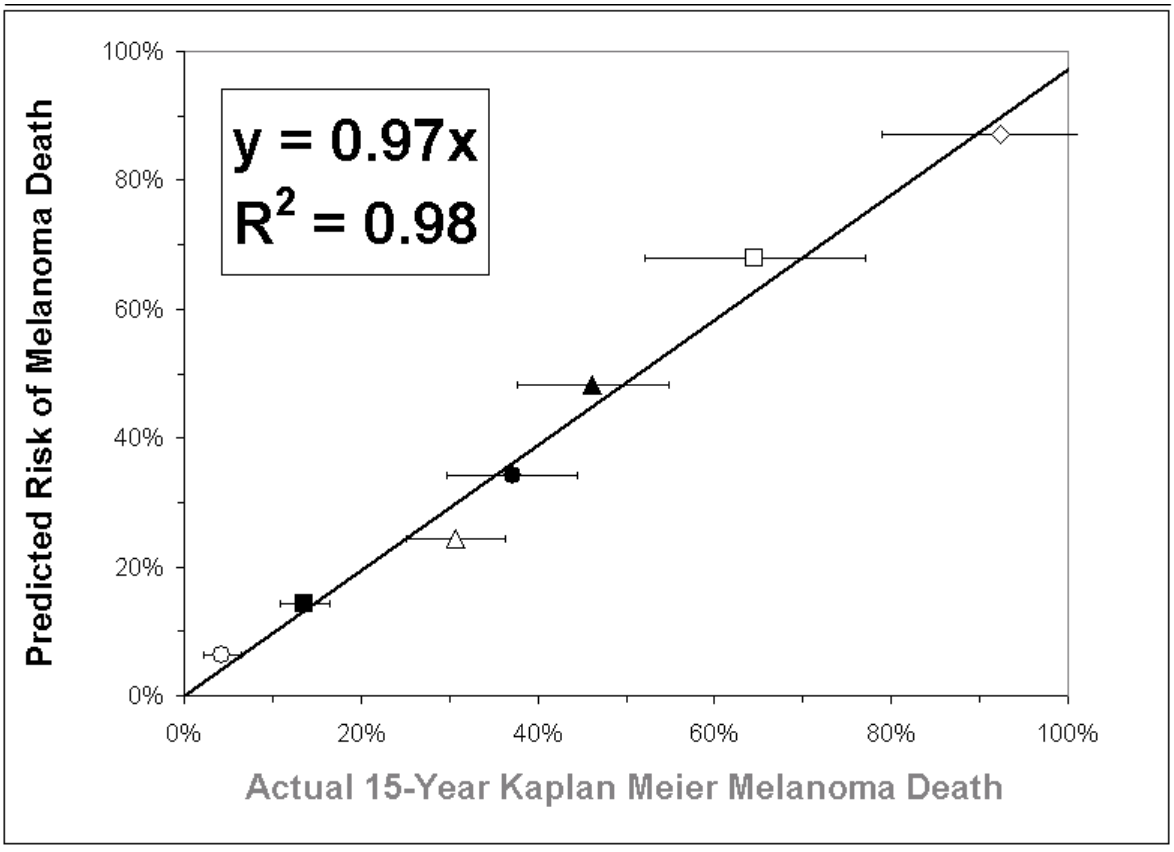

FIGURE A1
Stratification of MGH melanoma patients by risk of death estimated by the *SNAP* method.
TOP: Cumulative distribution of estimated risk of death and actual death rates.
BOTTOM: Comparison of estimated risk of death and actual death rates.
C:\X_MelanomaAnalysisByExcell 1 1 04_SNP \[Dataset For Excel #3 All SNP Stratified SmallerGrps.xls]Stratification FIG'!$DX$1

TABLE A2

Stratification of Patients by Risk of Death Estimated by the *SNAP* Method, for the SEER dataset

Risk Group	SNAP Risk of Melanoma Death	Actual 15 Year Melanoma Death	Number of Patients
0%-10%	11.050%	**5.045%**	7553
>10%-20%	16.105%	**14.120%**	4583
>20%-30%	27.684%	**24.530%**	2550
>30%-40%	37.082%	**34.866%**	1831
>40%-50%	44.249%	**44.766%**	1239
>50%-60%	51.197%	**54.774%**	902
>60%-70%	51.549%	**64.846%**	614
>70%-80%	62.052%	**74.733%**	441
>80%-90%	73.643%	**84.659%**	298
>90%-100%	88.243%	**95.129%**	204

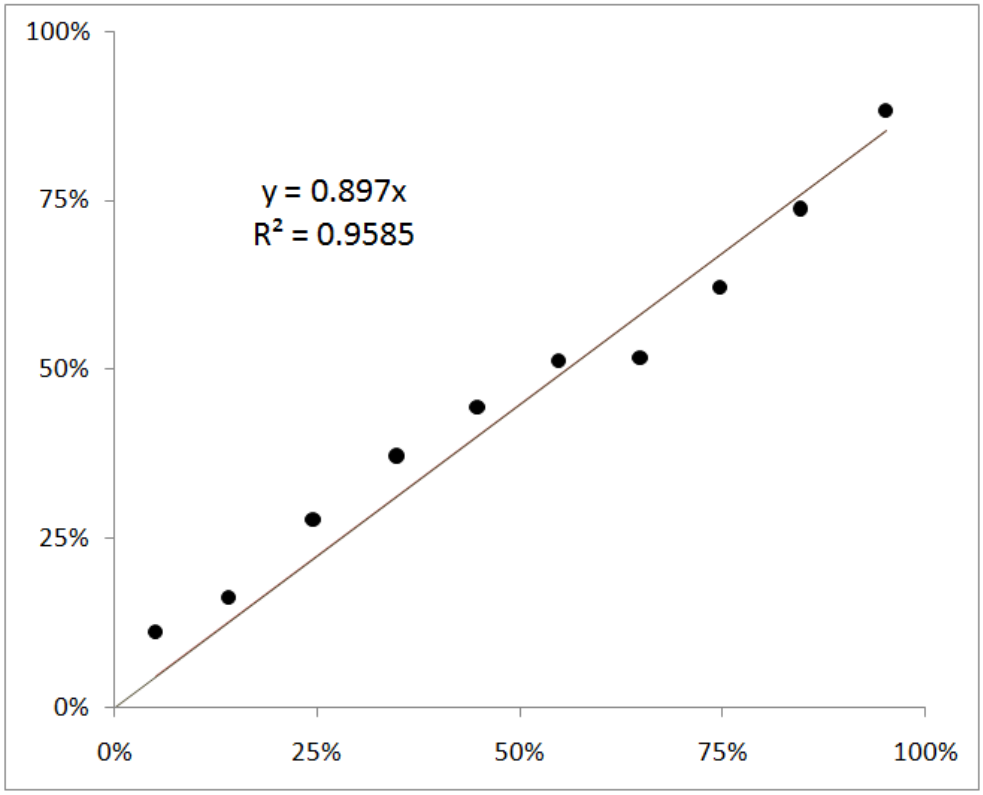

FIGURE A2

Stratification of SEER melanoma patients by risk of death estimated by the *SNAP* method.

Comparison of estimated risk of death and actual death rates.

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TABLE AND FIGURE A3

Risk of death estimated by the *SNAP* method among SEER melanoma patients grouped by sex.

Grouped by Sex	SNAP Risk of Melanoma Death	Actual 15 Year Melanoma Death	Number of Patients
Male	25.61%	27.83%	17203
Female	17.26%	20.07%	11713

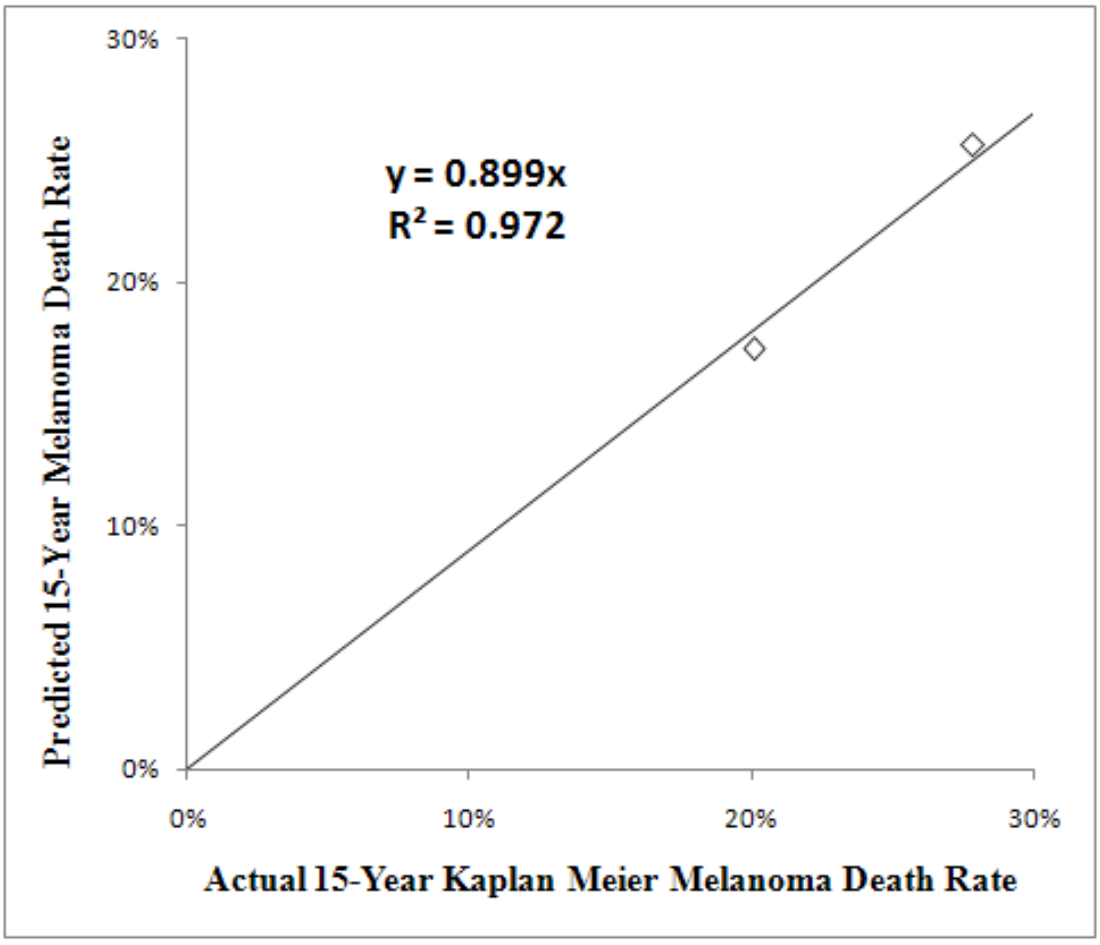


TABLE AND FIGURE A4

Risk of death estimated by the *SNAP* method among SEER melanoma patients grouped by ulceration.

Grouped by Ulceration	SNAP Risk of Melanoma Death	Actual 15 Year Melanoma Death	Number of Patients
Absent	18.44%	21.32%	16788
Present	42.13%	38.00%	2638

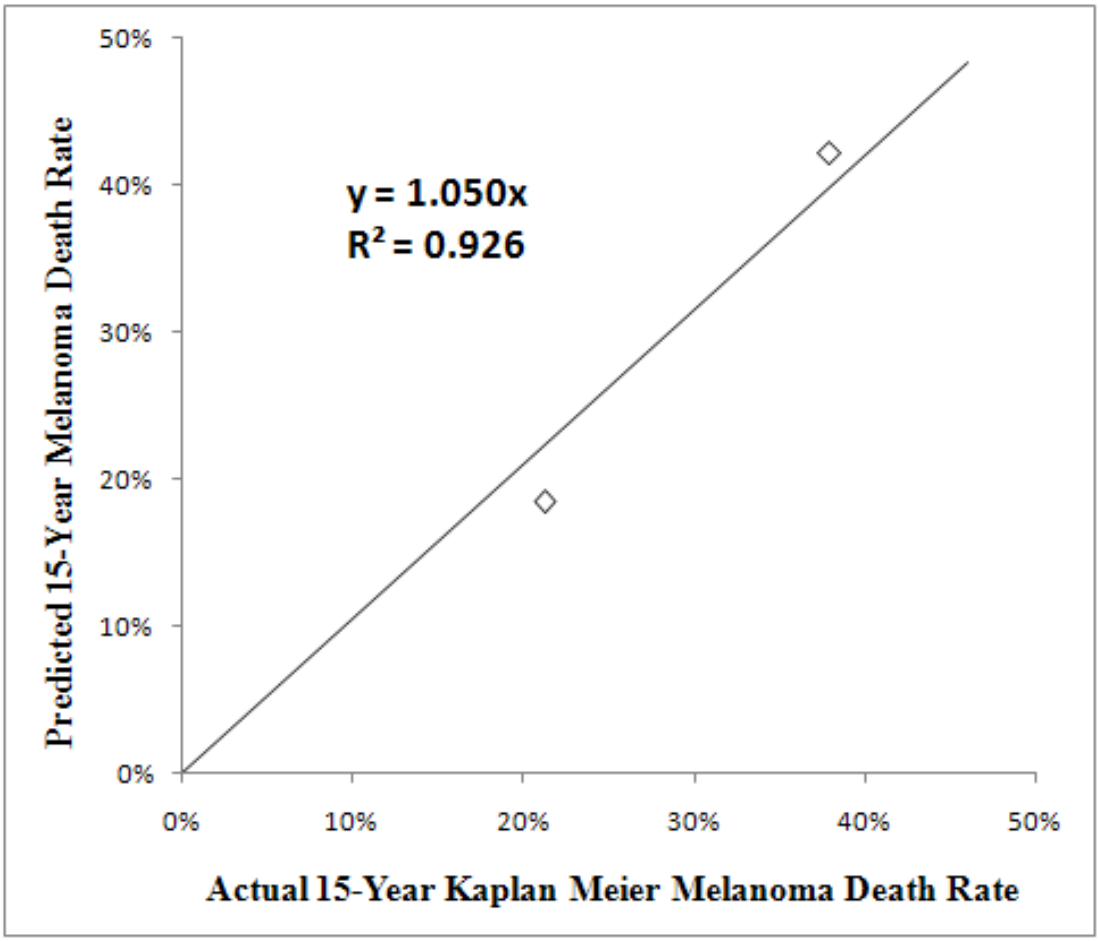


TABLE AND FIGURE A5

Risk of death estimated by the *SNAP* method among SEER melanoma patients grouped by Clark Level.

Grouped by Clark Level	SNAP Risk of Melanoma Death	Actual 15 Year Melanoma Death	Number of Patients
I	1.84%	0.00%	58
II	4.93%	7.86%	1698
III	12.18%	14.29%	4657
IV	23.10%	23.48%	7941
V	45.72%	51.86%	878

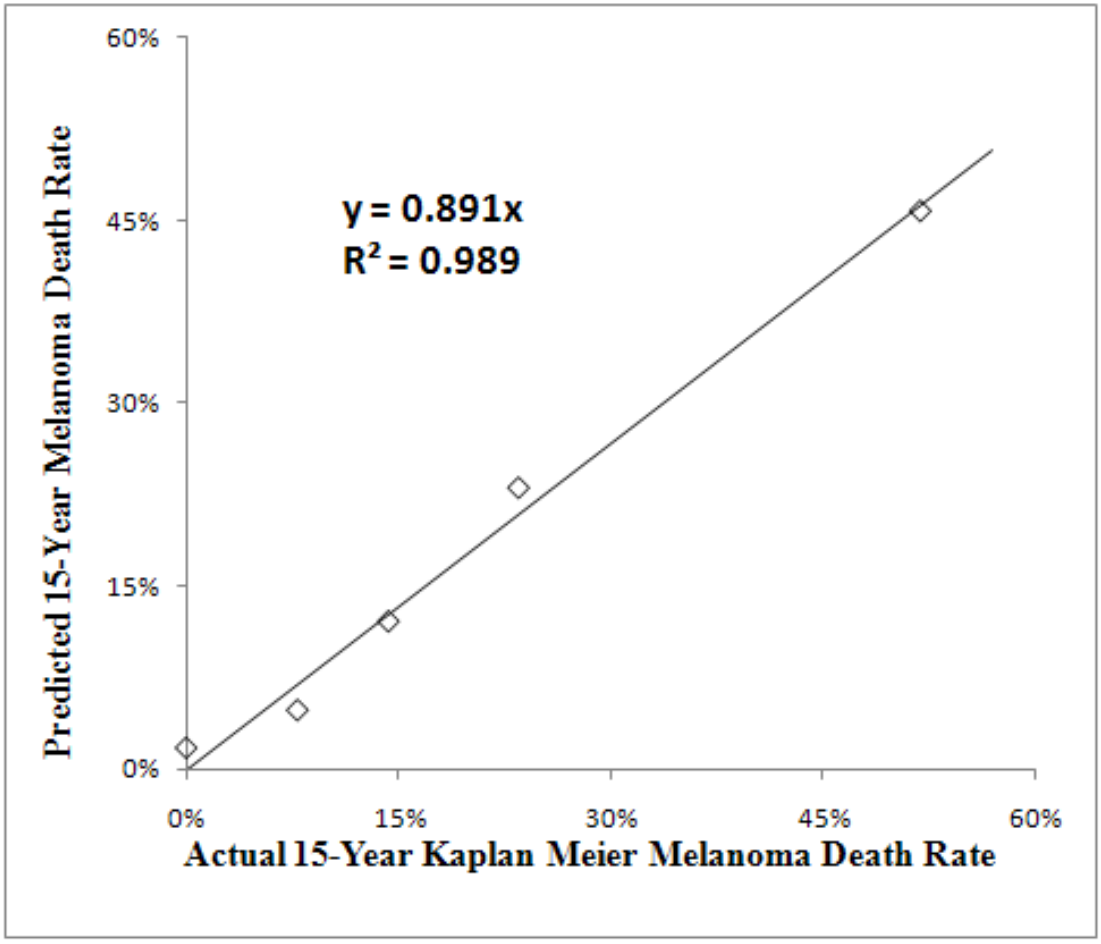


TABLE AND FIGURE A6

Risk of death estimated by the *SNAP* method among SEER melanoma patients grouped by nodal status.

Grouped by Nodal Status	SNAP Risk of Melanoma Death	Actual 15 Year Melanoma Death	Number of Patients
Node Negative	16.26%	18.29%	23726
Node Positive	48.19%	54.08%	5154

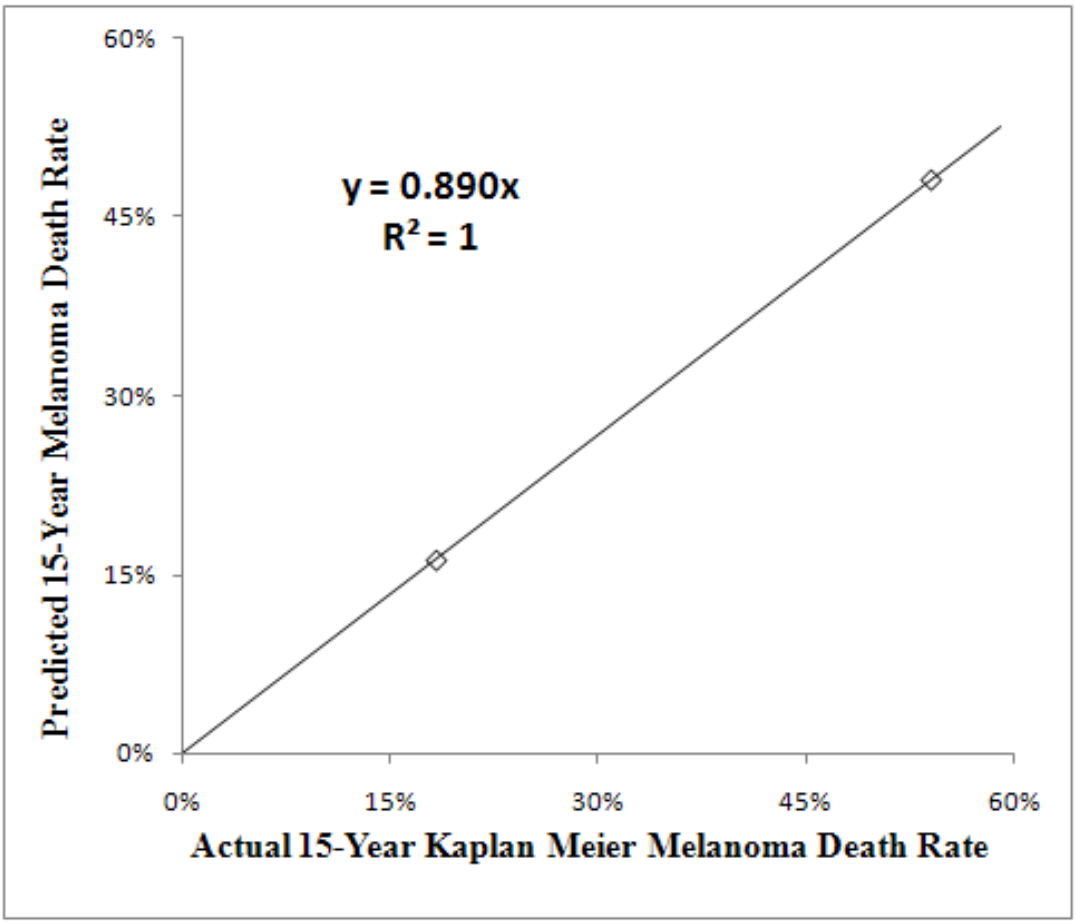


TABLE AND FIGURE A7

Risk of death estimated by the *SNAP* method among SEER melanoma patients grouped by number of positive nodes.

Grouped by Number of Positive Nodes	SNAP Risk of Melanoma Death	Actual 15 Year Melanoma Death	Number of Patients
0	16.26%	18.29%	23726
1	38.66%	48.14%	3194
2	53.15%	49.70%	1008
3	62.90%	69.21%	365
4	71.49%	70.27%	176
5	77.78%	59.04%	102
6	81.08%	89.62%	66

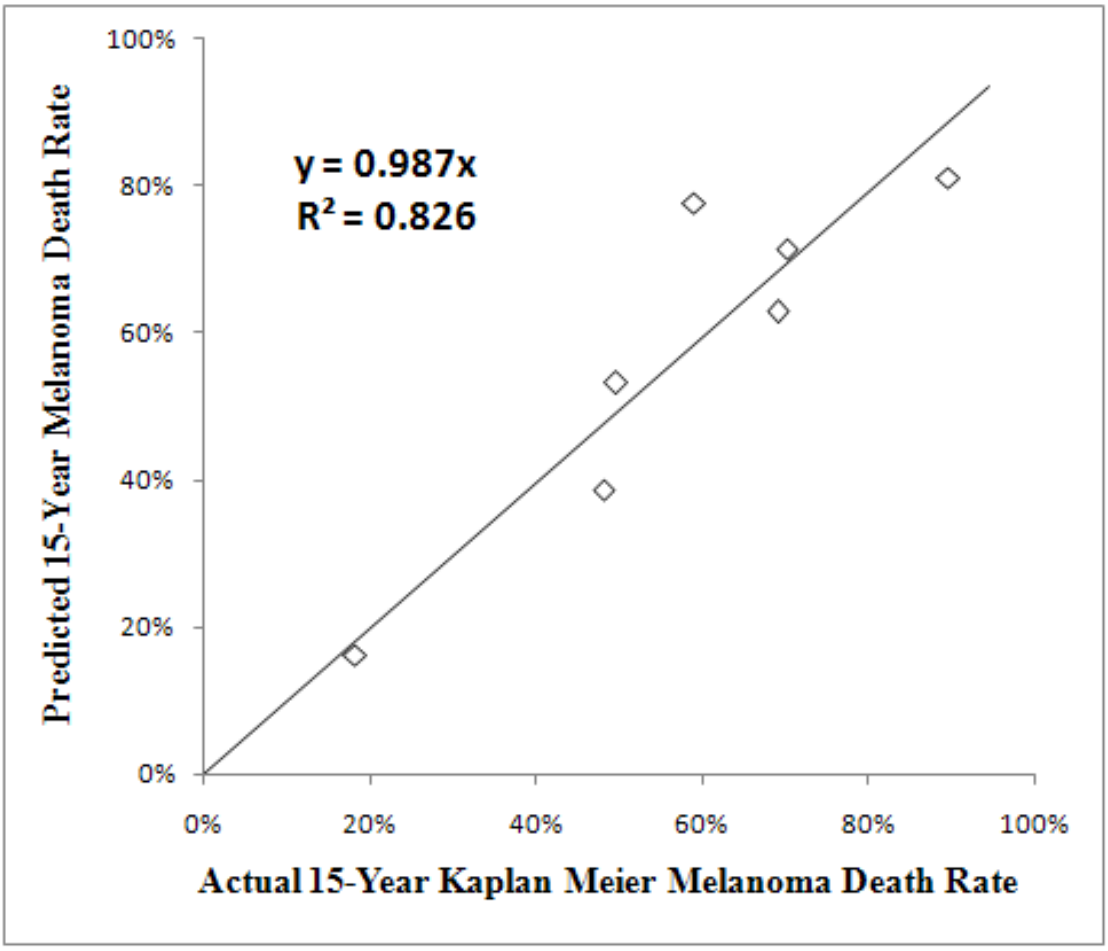
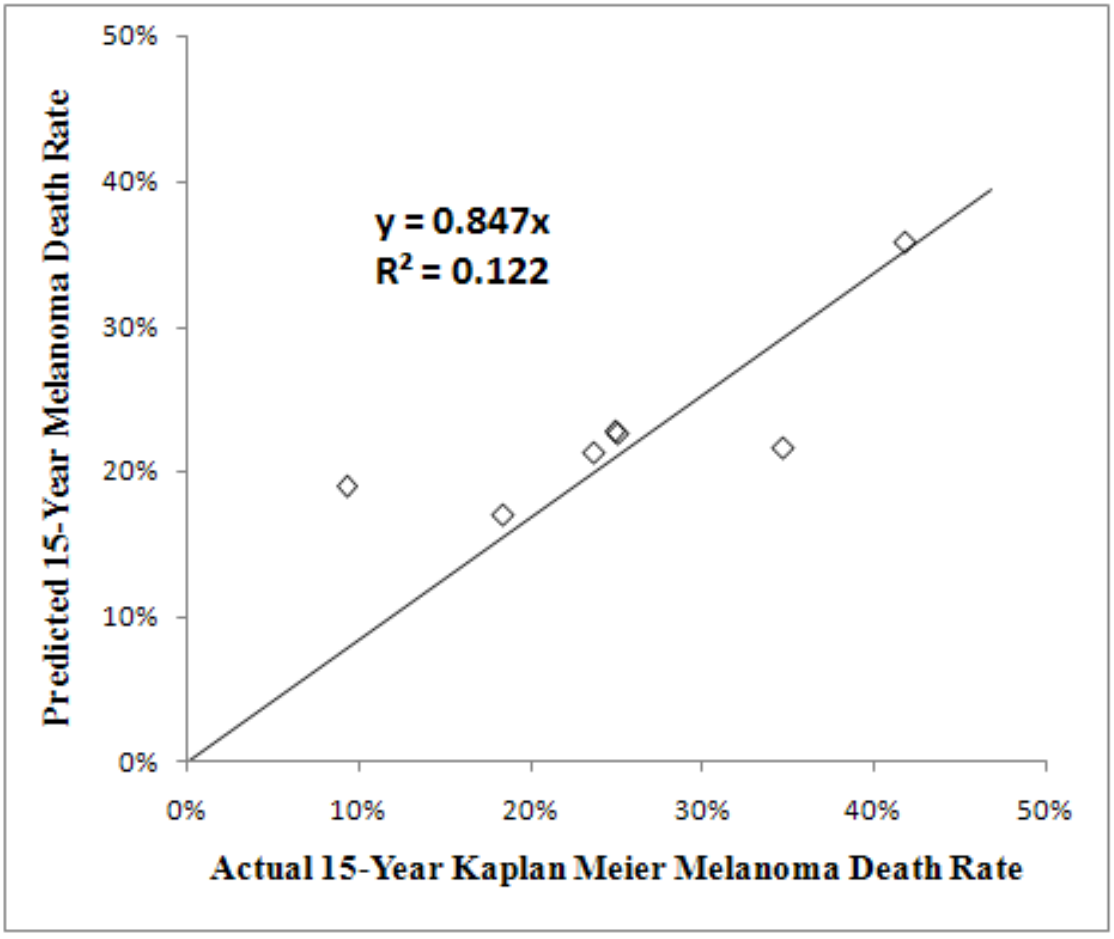
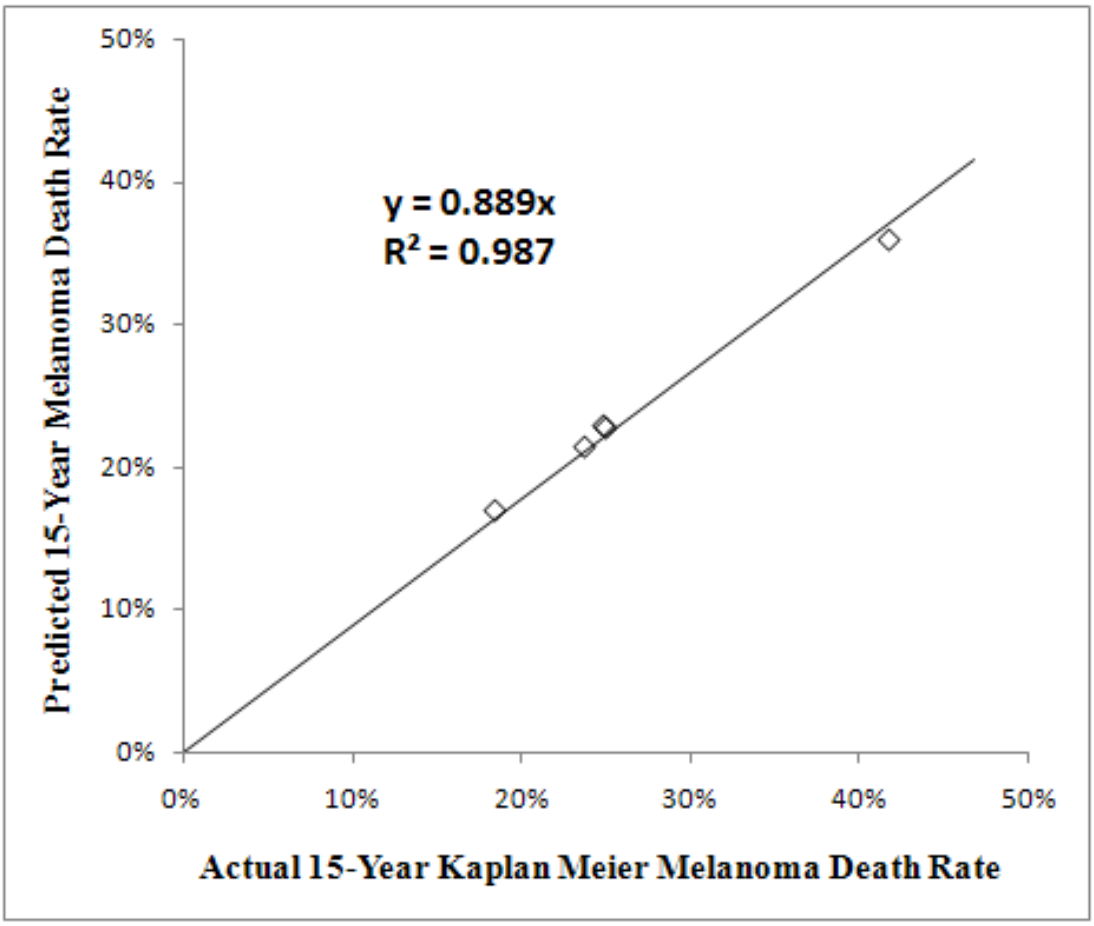


TABLE AND FIGURE A8

Risk of death estimated by the *SNAP* method among SEER melanoma patients grouped by primary site on skin.

Grouped by Primary Site on Skin	SNAP Risk of Melanoma Death	Actual 15 Year Melanoma Death	Number of Patients
Eyelid	19.10%	9.29%	46
External Ear	21.67%	34.69%	826
Face (unspecified)	22.84%	24.86%	1974
Scalp/Neck	35.93%	41.71%	2239
Trunk	22.71%	25.03%	9573
Upper Limb and Shoulder	17.03%	18.45%	7727
Lower Limb and Hip	21.41%	23.74%	6333



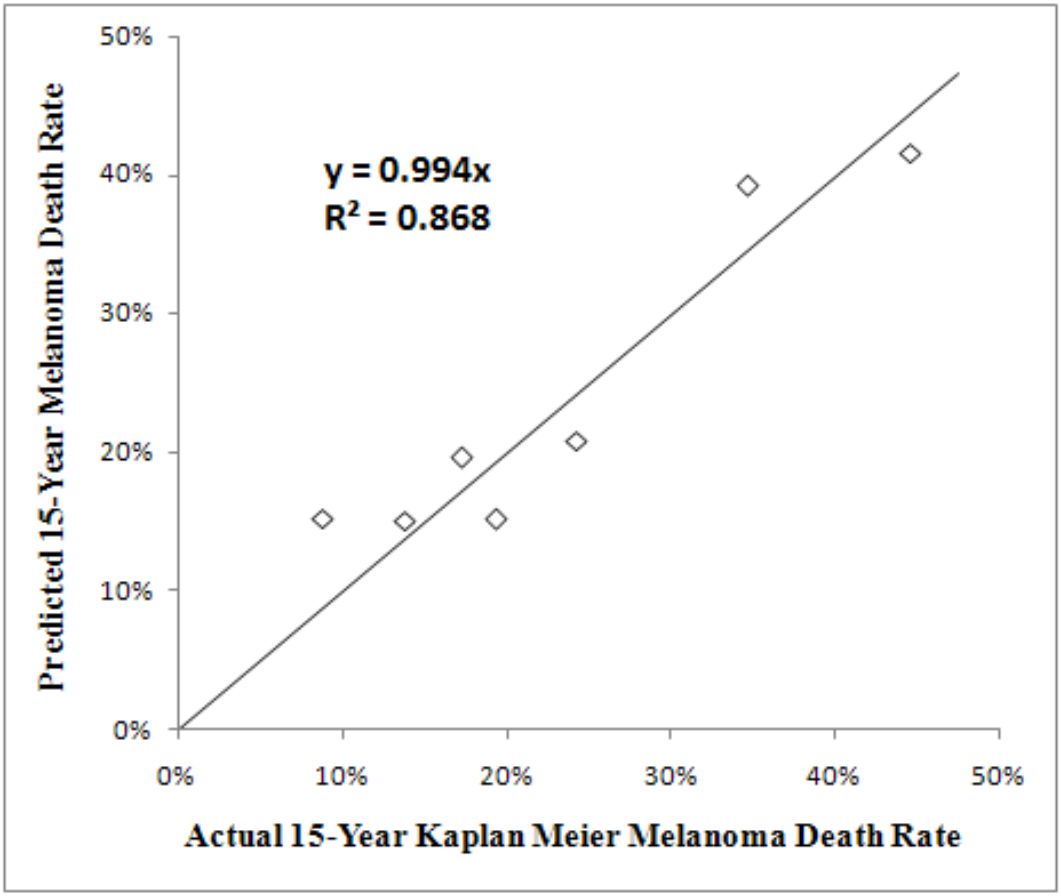


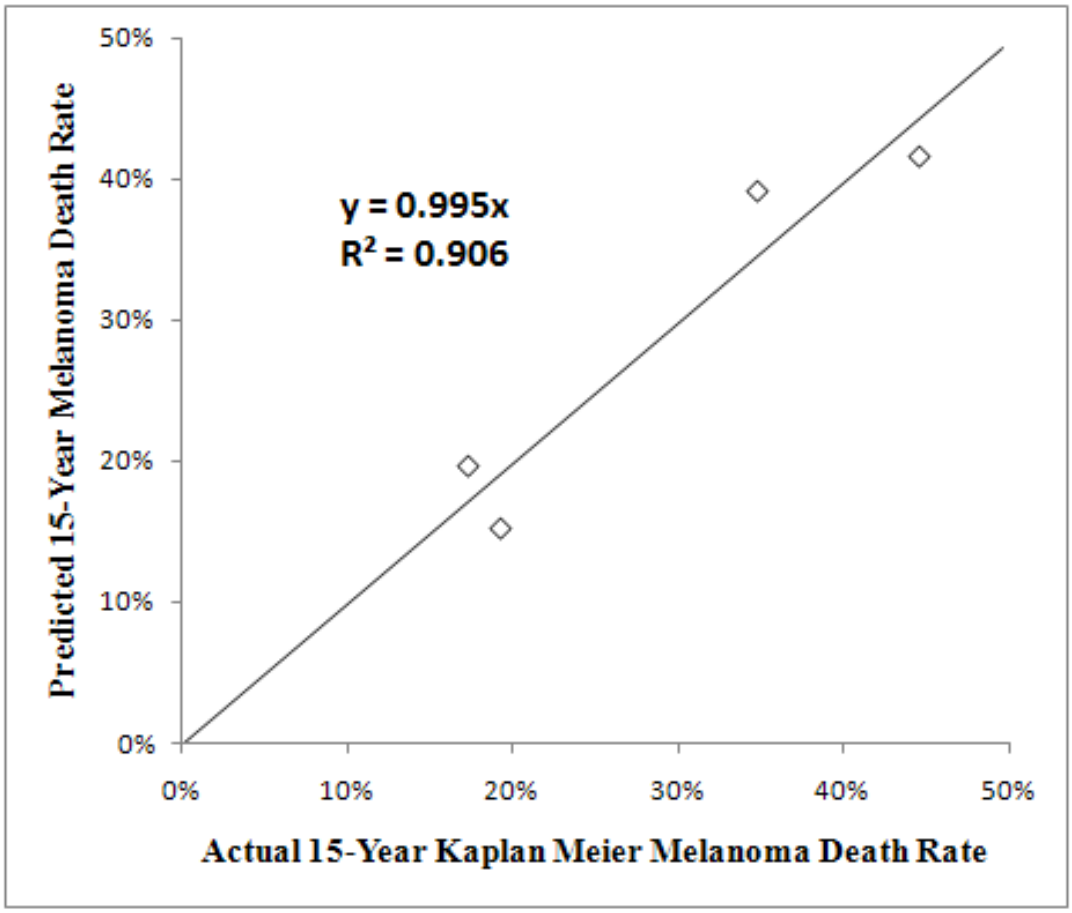
(Primary sites excluding eyelid, external ear, and face)

TABLE AND FIGURE A9

Risk of death estimated by the *SNAP* method among SEER melanoma patients grouped by histological type.

Grouped by Histological Type	SNAP Risk of Melanoma Death	Actual 15 Year Melanoma Death	Number of Patients
Malignant	20.88%	24.29%	12412
Nodular	39.16%	34.77%	4498
Lentigo Malignant	15.12%	13.81%	685
Superficial Spreading	15.27%	19.35%	8638
Acral Letiginous	41.60%	44.60%	613
Desmoplastic	19.68%	17.33%	577
Mixed Epithelioid-Spindle Cell	15.28%	8.85%	116





(Histological types excluding Malignant, Lentigo Malignant, and Mixed Epithelioid-Spindle Cell)

TABLE AND FIGURE A10

Risk of death estimated by the *SNAP* method among SEER melanoma patients grouped by tumor thickness.

Grouped by Tumor Thickness (mm)	SNAP Risk of Melanoma Death	Actual 15 Year Melanoma Death	Number of Patients
0.00 - 0.50	7.22%	19.71%	4205
0.51 - 1.00	11.00%	12.77%	6473
1.01 - 1.50	16.49%	14.57%	6214
1.51 - 2.00	22.97%	22.79%	3654
2.01 - 3.00	31.21%	34.22%	3808
3.01 - 4.00	40.37%	40.33%	1918
4.01 - 5.00	49.21%	51.16%	1140
5.01 - 6.00	56.16%	48.29%	620
6.01 - 7.00	61.32%	64.98%	419
7.01 - 8.00	66.86%	47.69%	267
8.01 - 9.00	71.38%	63.28%	164

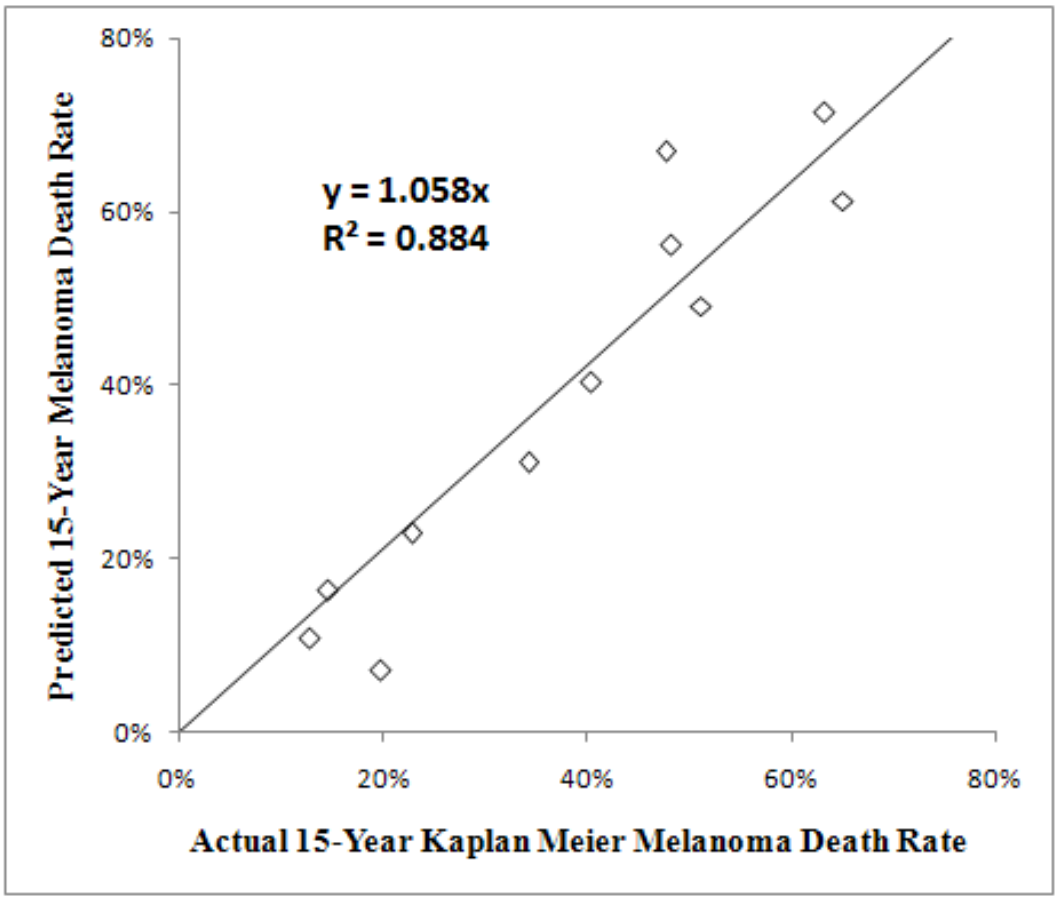


TABLE AND FIGURE A11

Risk of death estimated by the *SNAP* method among MGH melanoma patients grouped by sex.

Grouped by Sex	SNAP Risk of Melanoma Death	Actual 15 Year Melanoma Death	Number of Patients
Male	36.23%	33.64%	396
Female	23.64%	20.81%	288

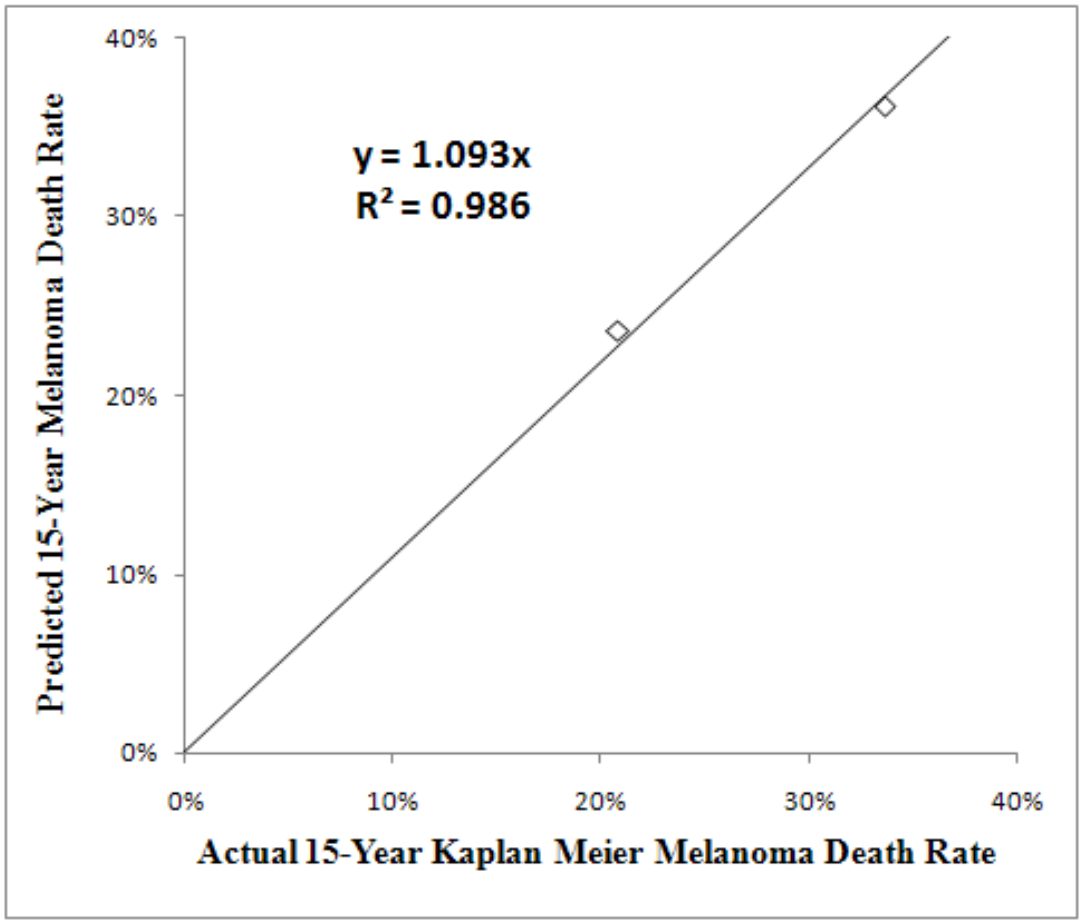


TABLE AND FIGURE A12

Risk of death estimated by the *SNAP* method among MGH melanoma patients grouped by ulceration.

Grouped by Ulceration	SNAP Risk of Melanoma Death	Actual 15 Year Melanoma Death	Number of Patients
Absent	23.69%	8.74%	263
Present	52.38%	40.16%	94

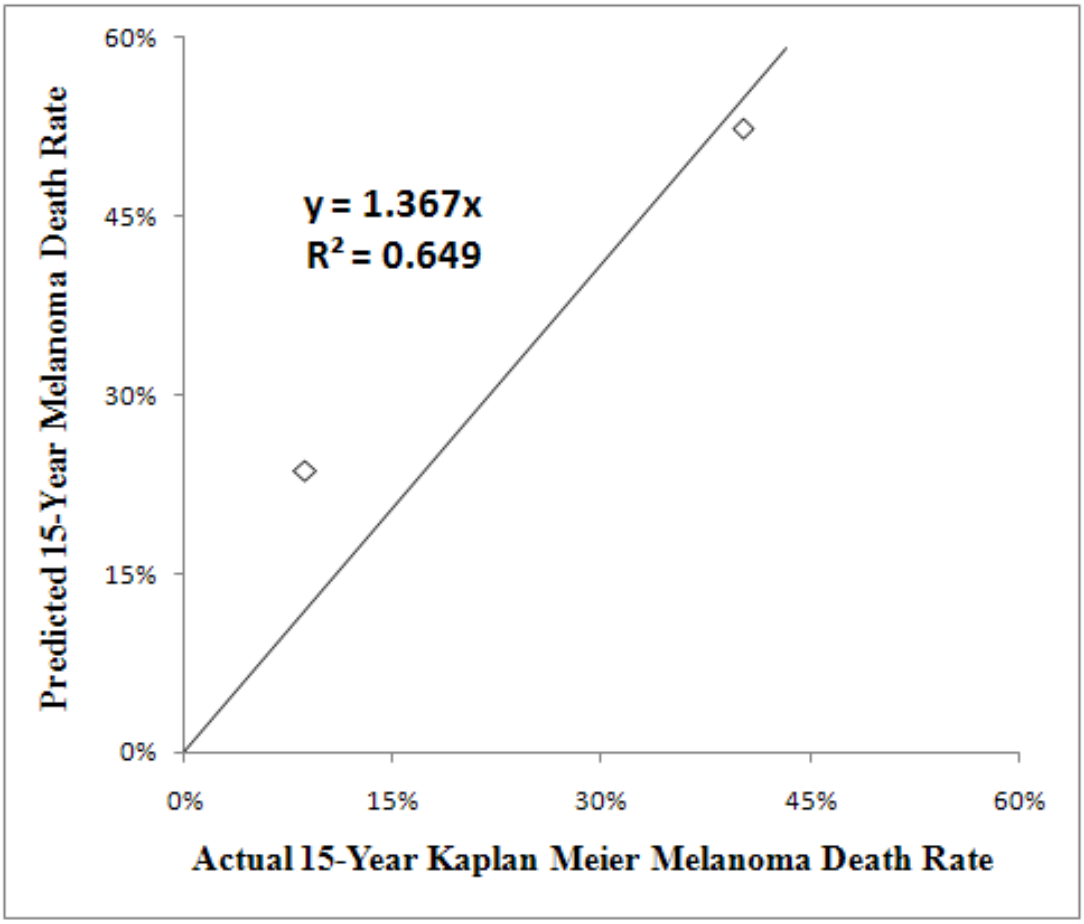


TABLE AND FIGURE A13

Risk of death estimated by the *SNAP* method among MGH melanoma patients grouped by Clark Level.

Grouped by Clark Level	SNAP Risk of Melanoma Death	Actual 15 Year Melanoma Death	Number of Patients
II	4.32%	5.88%	18
III	20.22%	14.19%	117
IV	30.87%	28.60%	452
V	61.21%	64.66%	50

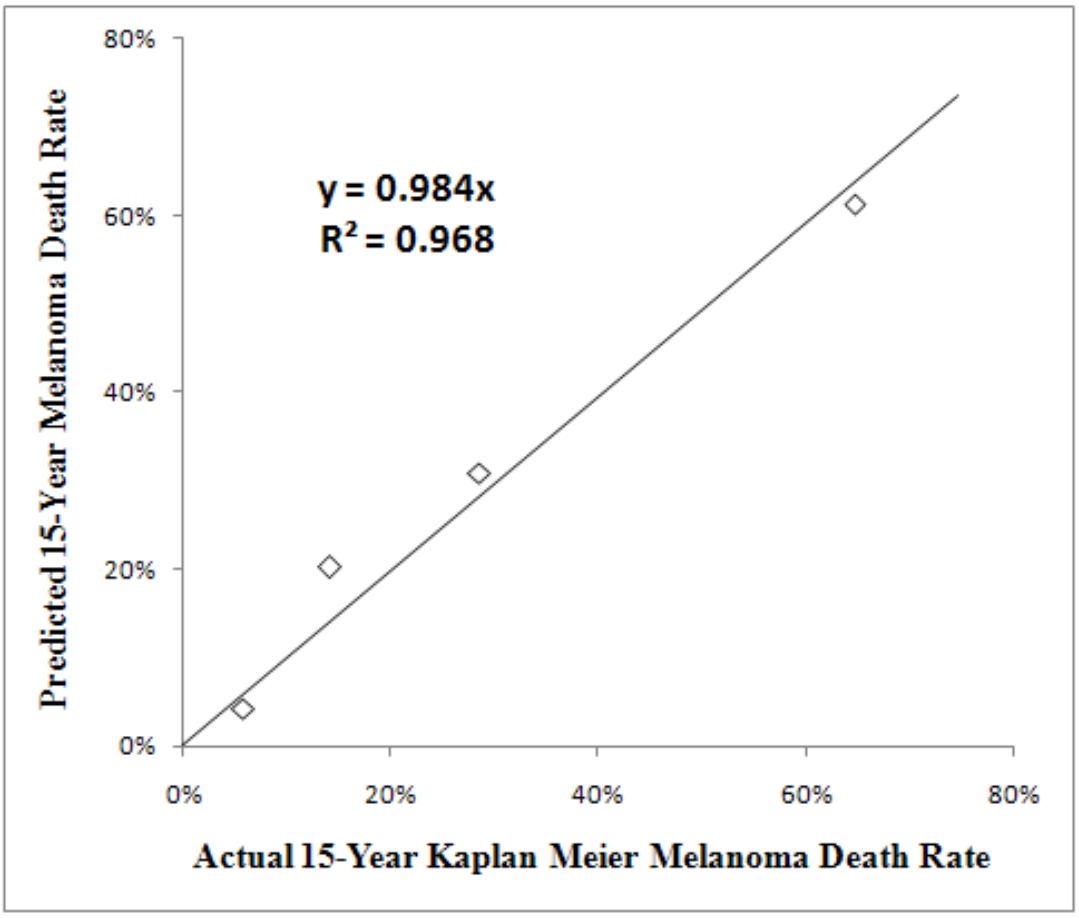


TABLE AND FIGURE A14

Risk of death estimated by the *SNAP* method among MGH melanoma patients grouped by nodal status.

Grouped by Nodal Status	SNAP Risk of Melanoma Death	Actual 15 Year Melanoma Death	Number of Patients
Node Negative	22.20%	20.39%	507
Node Positive	55.52%	53.21%	177

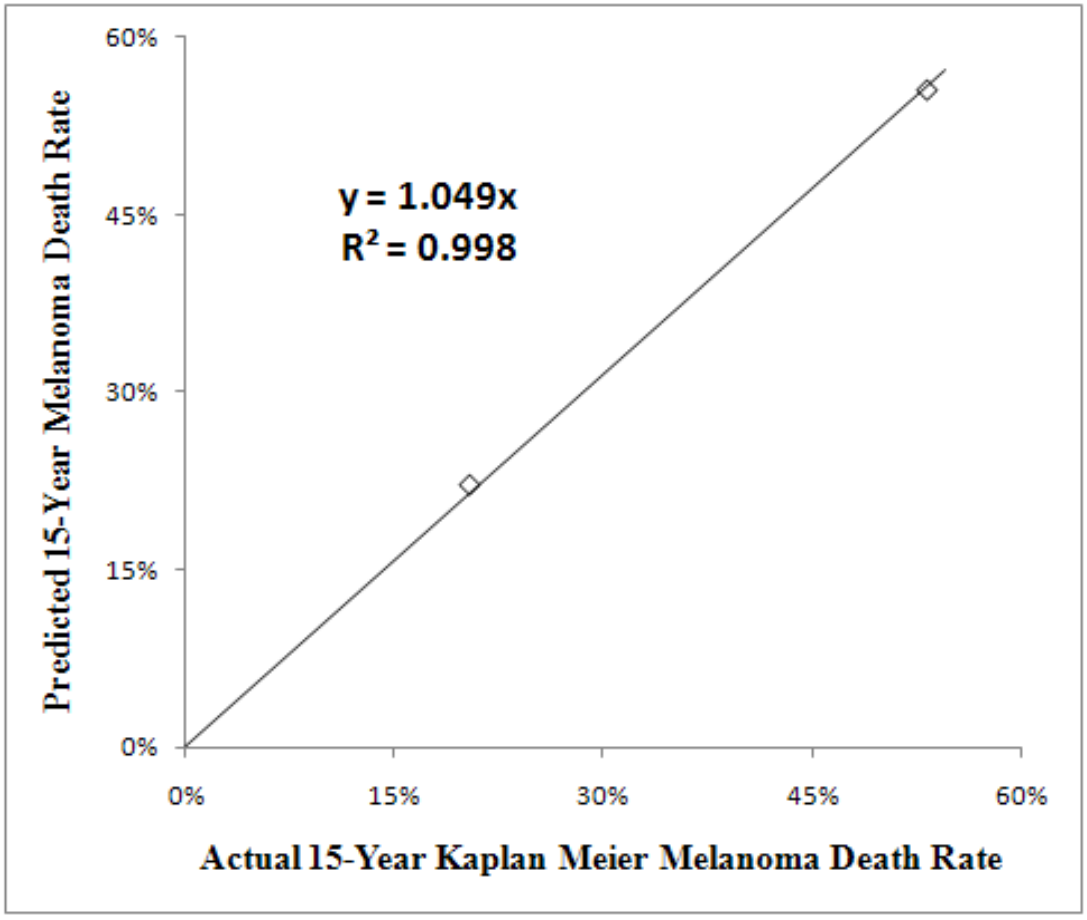
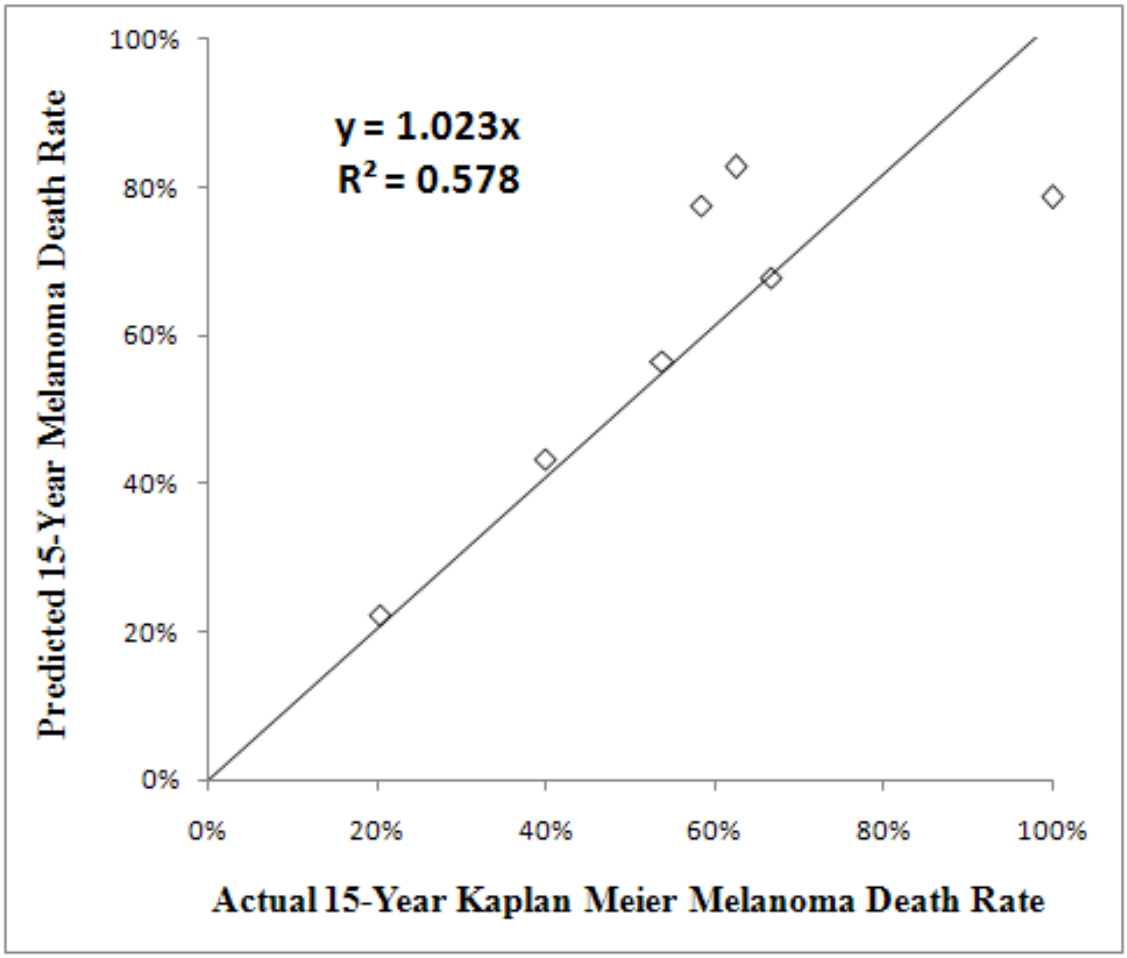


TABLE AND FIGURE A15

Risk of death estimated by the *SNAP* method among MGH melanoma patients grouped by number of positive nodes.

Grouped by Number of Positive Nodes	SNAP Risk of Melanoma Death	Actual 15 Year Melanoma Death	Number of Patients
0	22.20%	20.39%	507
1	43.22%	39.87%	92
2	56.60%	53.88%	35
3	67.85%	66.72%	21
4	77.45%	58.33%	6
5	78.60%	100.00%	6
6	82.67%	62.50%	8



Grouped by Number of Positive Nodes	SNAP Risk of Melanoma Death	Actual 15 Year Melanoma Death	Number of Patients
0	22.20	20.39	507
1	43.22	39.87	92
2	56.60	53.88	35
3	67.85	66.72	21
4 - 6	79.88	74.29	20

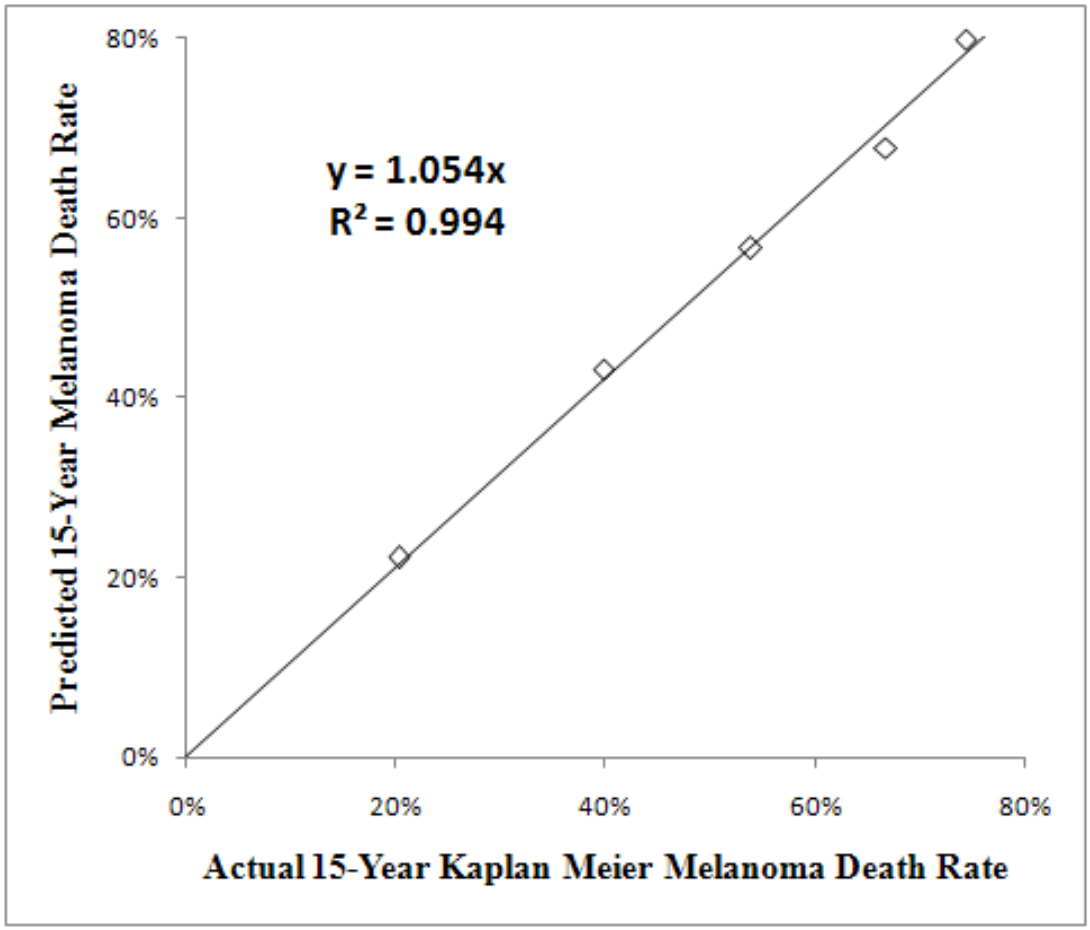


TABLE AND FIGURE A16

Risk of death estimated by the *SNAP* method among MGH melanoma patients grouped by primary site on skin.

Grouped by Primary Site on Skin	SNAP Risk of Melanoma Death	Actual 15 Year Melanoma Death	Number of Patients
Scalp/Neck	52.16%	32.75%	51
Trunk	32.45%	33.88%	224
Upper Limb and Shoulder	25.11%	23.64%	184
Lower Limb and Hip	28.42%	27.05%	176

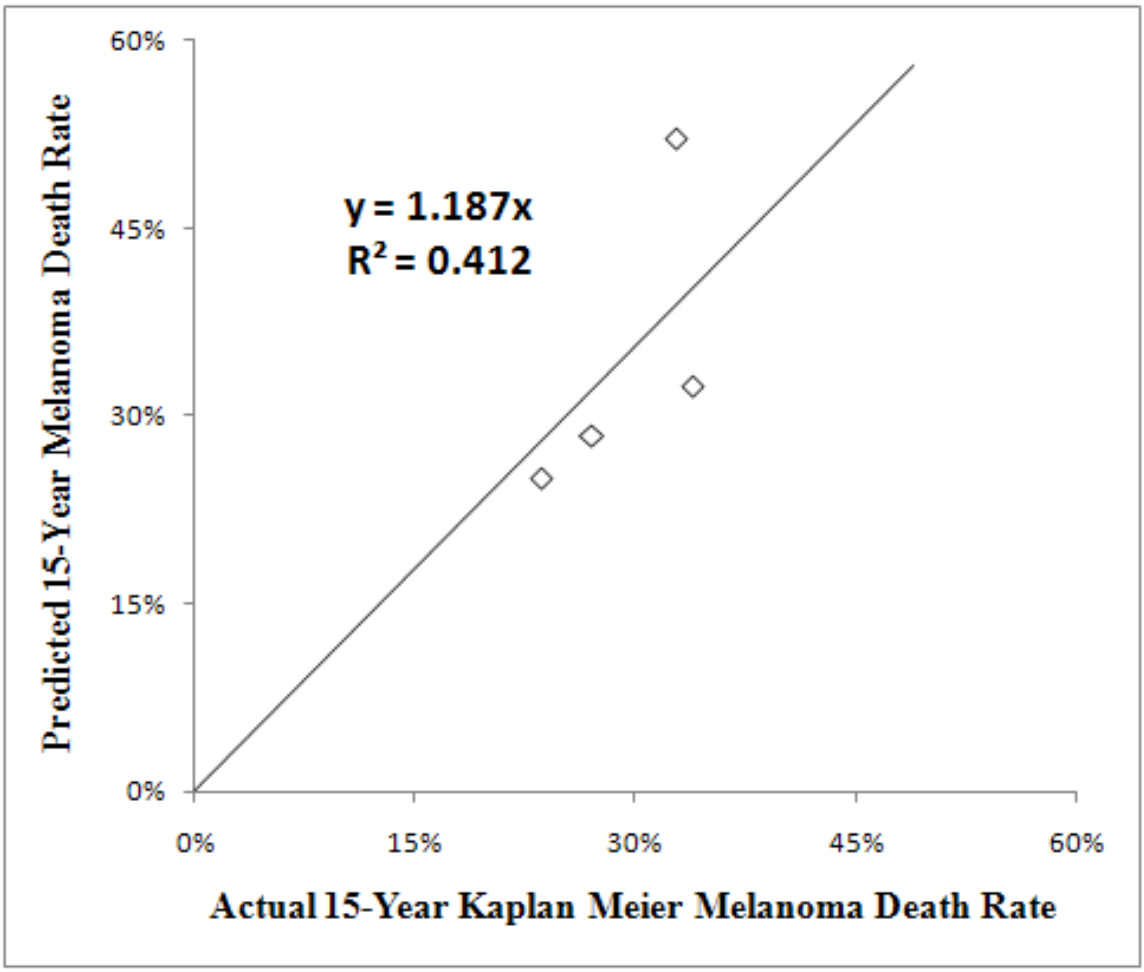


TABLE AND FIGURE A17

Risk of death estimated by the *SNAP* method among MGH melanoma patients grouped by histological type.

Grouped by Histological Type	SNAP Risk of Melanoma Death	Actual 15 Year Melanoma Death	Number of Patients
Nodular	44.05%	29.07%	181
Superficial Spreading	22.60%	25.67%	295
Acral Letiginous	59.32%	43.43%	24
Desmoplastic	28.52%	26.87%	15

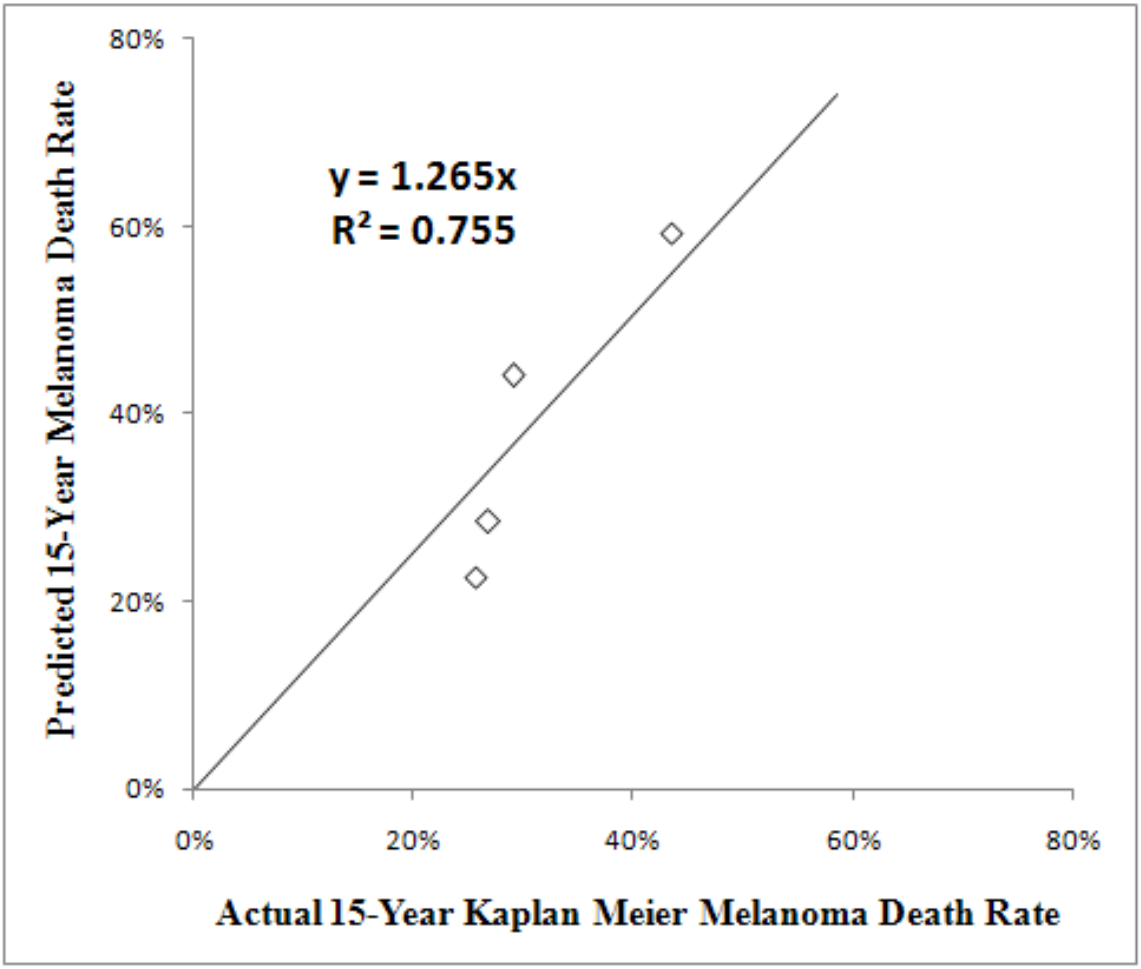
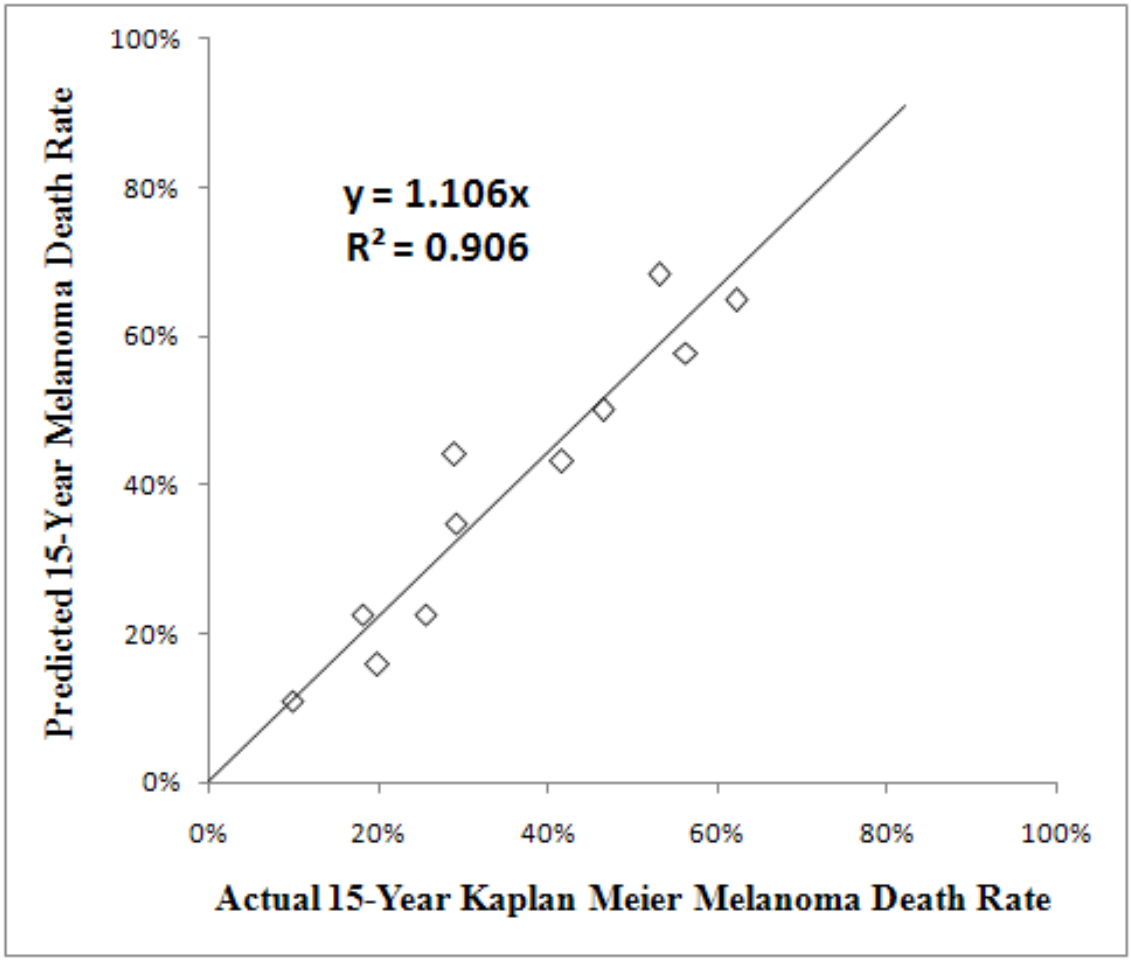


TABLE AND FIGURE A18

Risk of death estimated by the *SNAP* method among MGH melanoma patients grouped by tumor thickness.

Grouped by Tumor Thickness (mm)	SNAP Risk of Melanoma Death	Actual 15 Year Melanoma Death	Number of Patients
0.00 - 1.00 mm	11.08%	9.92%	89
1.01 - 1.50 mm	15.80%	19.96%	125
1.51 - 2.00 mm	22.60%	18.24%	129
2.00 - 3.00 mm	34.81%	29.13%	151
3.00 - 4.00 mm	43.20%	41.71%	87
4.00 - 5.00 mm	50.12%	46.60%	45
5.00 - 6.00 mm	57.70%	56.35%	17
6.00 - 7.00 mm	68.23%	53.10%	16
7.00 - 10.00 mm	64.85%	62.24%	15



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