Original Article

Why Cancer at the Primary Site and in the Lymph Nodes Contributes to the Risk of Cancer Death

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BACKGROUND: Cancer at both the primary site and in the lymph nodes is associated with lethality, although the mechanism by which lethality arises from each site has been poorly understood. For breast carcinoma, each positive lymph node contributes an approximately 6% risk of death, and each millimeter of primary tumor greatest dimension contributes approximately 1%; whereas, for melanoma, each positive lymph node contributes an approximately 23% risk, and each millimeter of tumor thickness contributes approximately 8%: This is described by a pair of linked equations, the *Size+Nodes* method. **METHODS:** A simple expression, the *ProbabilityEstimation* equation, which was derived from the authors' binary-biologic model of cancer metastasis, was used to calculate the probabilities of spread of cancer cells from data on tumor size, lymph node status, and death rate. **RESULTS:** In this report, the authors demonstrated, that when similar masses of cancer are compared, the chance of lethal spread of a cancer cell to the periphery is approximately the same whether the spread emerges from a lymph node or from the primary site. The greater the number of cells at the primary site (tumor size) or the greater the number of cells in the lymph nodes (number of positive lymph nodes), the greater is the aggregate chance that 1 or more cells has undergone a lethal event of spread, a process captured by the *Size+Nodes* equations. **CONCLUSIONS:** The lethal contributions of cancer at the primary site and lymph nodes can be explained by a simple mechanical process of the spread of cancer cells occurring with definable probabilities per cell. The presence of cancer in the lymph nodes does not indicate an intrinsic change in a malignancy but, rather, an increased mass of cancer from which spread can emerge. **Cancer 2009;000:000–000. © 2009 American Cancer Society.**

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It long has been appreciated that, for many cancers, primary tumor size, lymph node status, and survival are related qualities, although the mechanism by which these interactions occur has been poorly

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understood. We have observed that, when information is available only on tumor size, a simple expression, the *SizeOnly* equation, accurately captures the relation between primary tumor size and lethality, as observed from our data on patients with breast carcinoma, renal cell carcinoma, and melanoma[1-4] (for the *SizeOnly* equation, see Equation 1 from the accompanying article[4]). We also have observed that the relation between tumor size and the risk of cancer in the lymph nodes is captured well by a variant of the *SizeOnly* equation, the *NodalSizeOnly* equation (see Equation 1n in the accompanying article[4]), as indicated by data from patients with breast carcinoma and patients with melanoma. In addition, we have observed that the relation between tumor size and the risk of death for patients with lymph node-negative melanoma and or breast carcinoma is captured by another variant of the *SizeOnly* equation, the *PrimarySizeOnly* equation. We also have observed that, for breast carcinoma, each positive lymph node is associated with an approximately 6% risk of death, and each millimeter of primary tumor greatest dimension is associated with an approximately 1% risk of death; whereas, for melanoma, each positive lymph node is associated with an approximately 23% risk of death and, each millimeter of primary tumor greatest dimension is associated with an approximately 8% risk of death.[4] For both cancers, the overall risk of death is the sum of the risks of death from the lymph nodes and the primary site, which takes the form of a pair of linked equations, the *Size+Nodes* method.[5] In the current report, we examine the underlying basis for these observations.

Underlying the macroscopic features of cancer growth, spread, and lethality (the size of a cancer at the primary site and in the lymph nodes, the number of positive lymph nodes, and the risk of death) lie the microscopic events that affect the fate of cells, such as the spread of cancer cells from 1 location to another. Such events of cellular spread are intrinsically discrete, either/or events, because cells intrinsically are discrete entities.[6] Either a cancer cell in a primary tumor will travel to the periphery and give rise to metastatic disease and death, or it will not. Either a cancer cell in a primary tumor will travel to a local lymph node and give rise to a cancer mass seen by the pathologist, or it will not. Either a cancer cell in a lymph node will travel to the periphery and lead to death, or it will not. This either/or quality makes it possible to characterize the spread of cancer cells in terms of probabilities. By taking such an approach, which we call the binary-biologic model of cancer metastasis, it is possible to conclude the values of the probabilities of these microscopic events of the spread from data on the macroscopic features of cancer. For example, we will be able to ask how the probability of the lethal spread of a cancer cell from a primary site compares with the probability of the lethal spread of a cancer cell from a lymph node. The mathematical framework for the binary-biologic model of cancer metastasis is outlined in the accompanying article in this issue of *Cancer*.[4] In this report, we demonstrate that applying this framework to actual data will allow us to determine how cancer at the primary site and in the lymph nodes contributes to lethality.

MATERIALS AND METHODS

Patients and Mathematical Methods

This research is described in detail in the accompanying article.[4]

Measurement of Lymph Node Deposits

The sizes of cancer deposits in the lymph nodes were measured with a Zeiss microscope (Zeiss, Thornwood, NY) and an Insight digital camera with SPOT-cam software for measuring cross-sectional areas and the greatest dimension (Diagnostic Instruments, Inc., Sterling Heights, Mich). The relation between melanoma thickness and cross-sectional area was estimated with data by Temple et al ($thickness = 0.6073^{*}area^{0.5086}$; $R^2 = 0.65$).[7]

RESULTS

Pathways of the Spread of Cancer Cells and Their Probabilities

The spread of cancer cells can occur along a variety of pathways, each with its characteristic probability: from the primary site to the lymph nodes ($p_{primary\text{-}to\text{-}nodes}$); from AQ4 lymph node to lymph node ($p_{node\text{-}to\text{-}node}$); from a lymph node to the periphery, leading to death ($p_{node\text{-}to\text{-}periphery}$); from the primary site to the periphery. leading to death in lymph node-negative patients ($p_{primary\text{-}to\text{-}periphery}$); or from the primary site to the periphery, leading to death in patients as a whole ($p_{overall}$ or p, which is the aggregate of

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AQ6 **Table 1.** Pathways of the Spread of Cancer Cells and their Probabilities

Pathway of Spread	Observed In	Fraction of Patients With a Manifestation of Spread	Probability of Spread, per Cell
Lethal spread from the primary site to the periphery (directly only)	Fraction of patients dying (=15-year Kaplan-Meier cancer death rate) among lymph node-negative patients	$L_{primary}$	$p_{primary\text{-}to\text{-}periphery}$
Nonlethal spread from the primary site to the local lymph nodes	The fraction of patients with positive lymph nodes	$L_{to\text{-}nodes}$	$p_{primary\text{-}to\text{-}nodes}$
Lethal spread from the lymph nodes to the periphery	Lethal contribution per positive lymph node	—	$p_{node\text{-}to\text{-}periphery}$
AQ8 Nonlethal spread from lymph node to lymph node	The no. of positive lymph nodes (M)	—	$p_{node\text{-}to\text{-}node}$
Lethal spread from the primary site to the periphery (the aggregate consequence of the pathways of spread characterized by $p_{primary\text{-}to\text{-}periphery}$, $p_{primary\text{-}to\text{-}nodes}$, $p_{node\text{-}to\text{-}periphery}$, and $p_{node\text{-}to\text{-}node}$)	Fraction of patients dying (=15-year Kaplan-Meier cancer death rate) among all patients	L	p

AQ9 *Based on equations from the accompanying article (Michaelson 2009[4]).

T1 F1 all of these probabilities) (Table 1) (Fig. 1). For this report, we used clinical data to calculate the probabilities of these events of spread.

To understand the general idea for such calculations, consider a group of patients who have primary cancers of approximately 100 million cells ($N \approx 10^8$ cells). If the cancer death rate in these patients was ~10% ($L \approx 0.1$), then it would follow that the probability of the lethal spread of cancer cells from the primary site to the periphery, p, will be approximately 1 event of spread for every billion cells in the primary mass ($p \approx [L/N] \approx [0.1 \text{ of } 10^8] \approx 10^{-9}$ cells). More precisely (see derivation in the accompanying article in this series[4]), the probability of the spread of a cancer cell, p_x, can be calculated with the expression we call the *ProbabilityEstimation* equation:

$$p_x = -\ln(1 - L_x)/N \qquad (7)$$

Recall that, by definition, p_x does not consider events of spread that do not lead to a macroscopic manifestation, nor does it assume that p_x is a be constant, nor does it require that every cell in the mass of cancer have the potential for spread, although this may be the case (see the mathematical derivation of the *ProbabilityEstimation* equation [Equation 7 in the accompanying article in this series]). Thus, in the example given above ($L \approx 0.1$, $N \approx 10^8$), whether every cell in the cancer mass has the potential for spread, or whether only 1 in 1 million cells in the cancer mass has the potential for spread, the probability, p, of an event of spread *per cell* in the cancer mass still will be 1 in 1 billion ($p \approx 10^{-9}$).

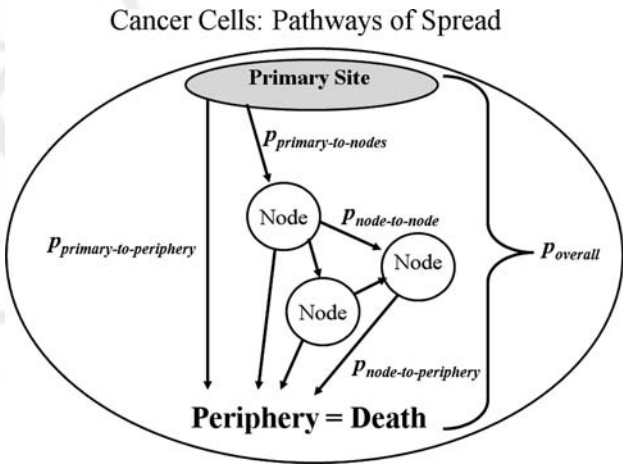

FIGURE 1. This chart illustrates cancer cells and the pathways of spread.

The Per-Cell Probability of the Spread of Cancer Declines as Tumors Get Larger

Cancer cells conceivably may spread from a primary mass to the local lymph nodes (resulting in cancer observed in the lymph node on pathologic analysis) or from a primary mass to the periphery (resulting in death). Lethal spread also conceivably may occur directly from the primary site to the periphery or indirectly from the primary site to a

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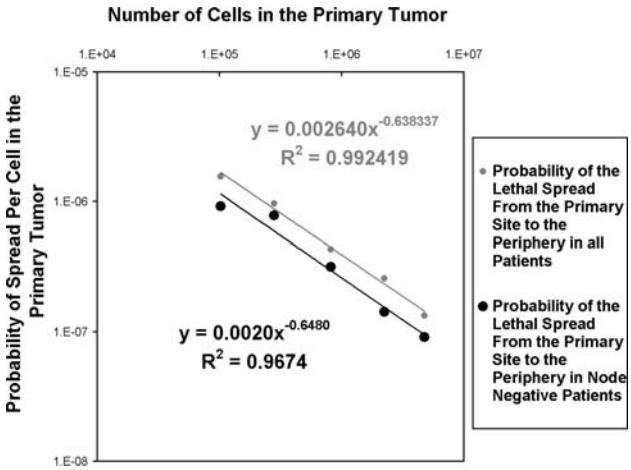

FIGURE 2. This chart illustrates calculations with the *ProbabilityEstimation* equation (Equation 7 in the accompanying article[4]) of the probabilities of lethal spread of breast carcinoma from the primary site to the periphery using tumor size/survival data for all patients and of the lethal spread of breast carcinoma from the primary site to the periphery with tumor size/survival data for lymph node-negative patients using Equation 13 from the accompanying article.[4] Note that, in both cases, the correlation between the probability of spread and tumor size is well fit by a power function. Tumor sizes groups examined included 1 mm to 10 mm, 11 mm to 20 mm, 21 mm to 25 mm, 26 mm to 30 mm, and 31 mm to 35 mm. Cell numbers were estimated by using Equation 8 from the accompanying article.[4]

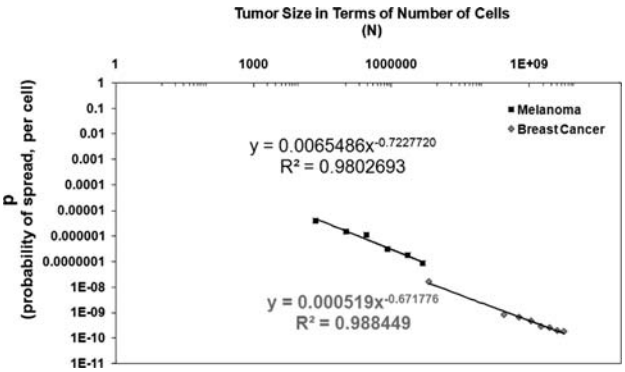

FIGURE 3. This chart illustrates calculations with the *ProbabilityEstimation* equation (Equation 7 from the accompanying article[4]) of the probabilities of nonlethal spread of breast carcinoma from the primary site to the lymph nodes using data on the fraction of patients who are lymph node positive and the of probabilities of nonlethal spread of melanoma from the primary site to the lymph nodes using data on the fraction of patients who are lymph node positive. Note that, in both cases, the relation between the probability of spread and tumor size is well fit by a power function. The tumor size groups examined included the following: for melanoma, 0 mm to 1 mm, 1 mm to 1.5 mm, 1.5 mm to 2 mm, 2 mm to 3 mm, and 4 mm to 5 mm; and for breast carcinoma, 1 mm to 10 mm, 11 mm to 20 mm, 21 mm to 25 mm, 26 mm to 30 mm, 31 mm to 35 mm, 36 mm to 40 mm, 41 mm to 45 mm, and 45 mm to 50 mm. Cell numbers were estimated by using Equation 8 from the accompanying article.[4]

lymph node and then to the periphery (Table 1) (Fig. 1). The *ProbabilityEstimation* equation (see Equation 7 in the accompanying article) allowed us to calculate the probability of such events (the spread of cancer cells). These calculations (Figs. 2 and 3) reveal the remarkable finding that, as tumors increase in size, the per-cell probability of the spread of cancer leaving a mass does not remain constant but declines in value.[1,3] Furthermore, this decline occurs in a very characteristic fashion, such that the relation between the probability of the spread of cancer cells and the size of the mass from which the cells emerge, N, is well fit by a power function:

$$p_x = aN^b. \quad (9)$$

in which b is $\approx -2/3$, and a is characteristic of each malignancy. This holds true in each of 5 different contexts for which we have had the data to perform these calculations: the spread of cancer cells from the primary site to the lymph nodes ($p_{primary\text{-}to\text{-}nodes}$; observed in the fraction of patients who have cancer identified in the lymph nodes [$L_{to\text{-}nodes}$]), as reported in data from patients with breast cancer and melanoma; the spread of cancer cells from the primary site to the periphery, leading to death in lymph node-negative patients ($p_{primary\text{-}to\text{-}periphery}$; observed in the fraction of lymph node-negative patients who die of cancer [$L_{primary}$]), as reported in data from patients with breast cancer; and the spread of cancer cells from the primary site to the periphery, leading to death in all patients (p; observed in the fraction all patients who die of cancer [L]), as reported in data from patients with breast cancer and melanoma (Figs. 2 and 3).

Why would this decline in the value of p_x occur as tumors get larger? One possible explanation is that a is the intrinsic probability that a cancer cell will spread, but that only a fraction of cells in the mass are capable of spreading, and the size of that fraction is N^b. Another possible explanation is simple geometry: Every cell in a primary mass may be capable of spreading; however, as tumors get larger, there are simply more and more cells that must be "pushed aside" before any individual cell can escape from

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that mass. Indeed, we have demonstrated mathematically[3] that just such a process should be expected to result in a reduction in the per-cell probability of spread, such that the relation between p and N is well fit to Equation 9 in the accompanying article, $p = aN^b$, in which b is $\approx -2/3$.

Note that the value of a in Equation 9 is at least 5-fold greater for melanoma than breast carcinoma and at least 15-fold greater for renal cell carcinoma. Indeed, a describes the probability of spread of cancer cells at the extrapolated point in time when the tumor was only a single cell in size and, thus, when there were no other cells to be "pushed aside" ($p = a$ in Equation 9 when $N = 1$). Thus, the component a in Equation 9 appears to be a measure of tumor biology before the impact of the size of the primary mass can be sensed.

Spread of Cancer Cells From Lymph Node to Lymph Node

Cancer in a lymph node well may be the result of the spread of a cell from a primary mass; however, is the primary mass the only source for such cells? In fact, there are powerful indications that, once cancer gets to a lymph node, it may form a mass from which progeny may spread to other lymph nodes. Note that we observed from Equation 9 that the probability of nonlethal spread of cancer cells to the local lymph nodes, $p_{primary\text{-}to\text{-}nodes}$, for breast carcinomas that measured from 20 mm to 29 mm was $\sim 1/3 \times 10^9$ cells. Because tumors of this size contain approximately 7×10^8 cells, it follows that, if all of the deposits in the lymph nodes came from cells at the primary site, then we should expect that approximately $(1/3 \times 10^9 \times 7 \times 10^8 \text{ cells})^M$ patients would have M positive lymph nodes (ie, approximately 25% of patients should have 1 positive lymph node, approximately 6% of patients should have 2 positive lymph nodes, approximately 1% of patients should have 3 positive lymph nodes, approximately 0.4% of patients should have 4 positive lymph nodes, and approximately 0.1% of patients should have 5 positive lymph nodes). However, the number of patients with 3, 4, 5, and more positive lymph nodes is much greater than expected for spread directly from the primary site (Fig. 4). The most direct inference is that, once cancer has spread to a lymph node, there is opportunity for further spread to another lymph node (Table 1) (Fig. 1).

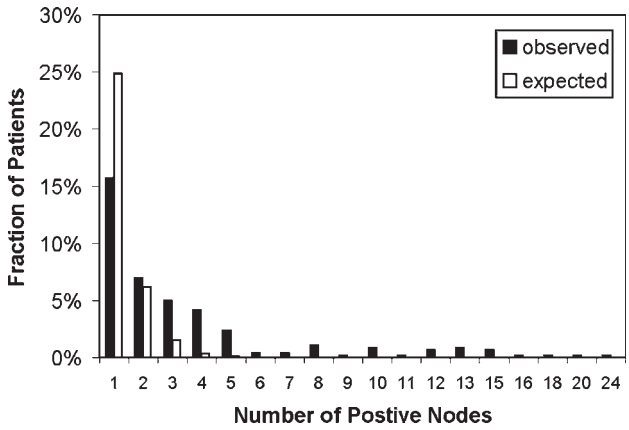

FIGURE 4. This histogram illustrates the number of patients with lymph node-positive breast carcinoma who had tumors that measured from 20 mm to29 mm sorted by the number positive lymph nodes observed together with the number of lymph nodes expected if cancer in the lymph nodes originated only from the primary site, occurring with a per-cell probability of spread of $p = 1$ of 3×10^9 cells. Solid bars indicate the observed fraction of patients with various numbers of positive lymph nodes; open bars, the fraction of patients with various numbers of positive lymph nodes expected if cancer in the lymph nodes originated only from the primary site.

Spread of Cancer Cells From a Lymph Node to the Periphery, Causing Death

In the accompanying article,[4] we demonstrated that, for melanoma, the presence of cancer in a lymph node is associated with an approximately 23% greater chance of death than that in lymph node-negative patients who have primary masses of the same size; whereas, for breast carcinoma, each positive lymph node is associated with an approximately 6% extra chance of death.[4,5] These values may be used in the *ProbabilityEstimation* equation (Equation 7) to estimate the value of the probability of the lethal spread of a cancer cell from a lymph node to the periphery, $p_{node\text{-}to\text{-}periphery}$, if we also have information on the size of the cancer in the lymph nodes, N. To provide such information, we measured of the sizes of the cancer deposits in 50 positive lymph nodes from patients with melanoma and in 49 positive lymph nodes from patients with breast carcinoma (Tables 2 and 3). These measurements revealed an average size of the lymph node deposits of 28 mm^2 for melanoma and 51 mm^2 for breast carcinoma. Translating these values into estimates of the number of cells, N (Equation 8), allows us to use the *ProbabilityEstimation*

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Table 2. Sizes of Melanoma Lymph Node Deposits

Lymph Node No.	Measured Area of the Cancerous Deposits in This Lymph Node, mm	Contains Approximately the Same No. of Cells as a Primary Mass of Thickness, mm	Lethal Contribution Expected From a Primary Mass of This Size, Using the *SizeOnly* Equation, %*
1	0.034	0.13	2
2	0.116	0.25	3
3	0.133	0.27	3
4	0.157	0.29	4
5	0.187	0.32	4
6	0.201	0.33	4
7	0.271	0.38	5
8	0.348	0.44	5
9	0.424	0.48	6
10	0.673	0.61	7
11	0.775	0.66	8
12	0.853	0.69	8
13	0.907	0.71	8
14	1.047	0.76	9
15	1.285	0.85	9
16	1.496	0.92	10
17	1.73	0.99	11
18	1.768	1.00	11
19	1.936	1.04	11
20	2.793	1.26	13
21	2.798	1.26	13
22	3.236	1.36	14
23	3.409	1.39	14
24	4.095	1.53	15
25	4.6	1.62	16
26	5.567	1.79	17
27	7.868	2.13	20
28	10.261	2.44	22
29	12.322	2.68	24
30	13.33	2.79	25
31	14.706	2.93	26
32	16.575	3.11	27
33	21.894	3.59	30
34	29.045	4.14	33
35	29.457	4.17	33
36	30.372	4.24	34
37	31.314	4.30	34
38	33.183	4.43	35
39	46.069	5.24	39
40	46.621	5.27	39
41	57.695	5.87	42
42	59.6	5.97	43
43	63.617	6.17	44
44	86.59	7.22	48
45	86.59	7.22	48
46	103.869	7.92	51
47	117.859	8.44	53
48	132.732	8.97	55
49	153.93	9.67	58
50	153.938	9.67	58
Average	28.005	3.00	23

* Based on an equation from the accompanying article (Michaelson 2009[4]).

Table 3. Sizes of Breast Carcinoma Lymph Node Deposits*

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Lymph Node No	Greatest Dimension, mm	Estimated Area of the Cancerous Deposits in This Lymph Node, mm	Fraction of the Metastatic Area Containing Cancer	Contains Approximately the Same No. of Cells as a Primary Mass With a Greatest Dimension Measuring, mm	Lethal Contribution Expected From a Primary Mass of This Size (*SizeOnly* Equation), %
1	0.3	0.09	1	0.3	0.12
2	1	1.05	1	1	0.62
3	1	1.05	1	1	0.62
4	1.1	1.27	1	1.1	0.70
5	1.4	2.05	1	1.4	0.97
6	1.9	3.78	0.65	1.5	1.06
7	2	4.19	1	2	1.56
8	2	4.19	0.95	2	1.56
9	2.1	4.62	1	2.1	1.66
10	2.5	6.54	0.93	2.4	1.98
11	2.7	7.63	0.95	2.6	2.21
12	3	9.42	0.95	2.9	2.55
13	3	9.42	0.1	3	2.67
14	3	9.42	0.95	3	2.67
15	3.2	10.72	0.1	3.2	2.90
16	3.4	12.11	0.95	3.3	3.02
17	3.4	12.11	0.93	3.3	3.02
18	3.9	15.93	0.86	3.6	3.39
19	3.7	14.34	0.95	3.7	3.52
20	3.9	15.93	0.1	3.9	3.77
21	4.3	19.36	0.95	4.2	4.15
22	4.5	21.21	0.95	4.4	4.41
23	5.5	31.68	0.76	4.8	4.95
24	5.5	31.68	0.78	4.9	5.08
25	5.4	30.54	0.86	5	5.22
26	5.4	30.54	0.95	5.2	5.49
27	8	67.02	0.43	5.2	5.49
28	5.4	30.54	0.1	5.4	5.77
29	6	37.70	0.08	5.4	5.77
30	7.1	52.79	0.06	5.5	5.91
31	6	37.70	0.09	5.7	6.19
32	6.4	42.89	0.1	6.4	7.19
33	11	126.71	0.35	6.5	7.33
34	10	104.72	0.49	7	8.07
35	7.1	52.79	0.1	7.1	8.21
36	7.1	52.79	0.1	7.1	8.21
37	7.7	62.09	0.95	7.5	8.81
38	9	84.82	0.72	7.6	8.96
39	10.7	119.89	0.55	7.9	9.42
40	9	84.82	0.08	8	9.57
41	10	104.72	0.65	8.1	9.72
42	12.5	163.62	0.45	8.4	10.18
43	9	84.82	0.09	8.5	10.34
44	9.8	100.57	0.84	9	11.11
45	10	104.72	0.86	9.3	11.58
46	10	104.72	0.95	9.7	12.21
47	11	126.71	0.95	10.7	13.80
48	14.5	220.17	0.85	13.4	18.19
49	15	235.62	0.1	15	20.83
Average	5.95	51.30	0.644	5.31	5.97

AQ14 *Based on equations from the accompanying article (Michaelson 2009[4]).

Table 4. The Per-Cell Probability of the Lethal Spread of Cancer Cells From the Primary Site and the Lymph Nodes

Cancer Type	Average Lymph Node Size, (D_{nodes}), mm	Estimated No. of Cells (N_{nodes}) at 10^8 cells/cc*	Lethal Contribution per Lymph Node ($L_{per\text{-}node}$)	Probability of Lethal Spread per Cell From the Lymph Nodes to the Periphery: $p_{node\text{-}to\text{-}periphery} = -\ln(1-L_{per\text{-}node})/N_{nodes}$ (Eq. 7n)	Probability of Lethal Spread per Cell From the Primary Site to the Periphery (for the Case in Which the Cancer at the Primary Site is the Same Size as the Average Cancer Deposits Observed in a Positive Lymph Node): $p=aN_{nodes}^{b}$ (Eq. 9n)
Breast carcinoma	5.31	7.8×10^6	0.0608	8.0×10^{-09}	
	7.4×10^{-09}				
Melanoma	3.00	1.4×10^6	0.22527	1.8×10^{-07}	2.5×10^{-07}

*Estimates of the average number of cells per lymph node deposit (N_{nodes}) were made by assuming spherical geometry and 10^8 cells per cc based on equations from the accompanying article (Michaelson 2009[4]).

equation (Equation 7) to determine the value of $p_{node\text{-}to\text{-}periphery}$ (Table 4). These calculations revealed that, for breast carcinoma, $p_{node\text{-}to\text{-}periphery} = 8.0\text{-}10^{-9}$ cells; whereas for melanoma, $p_{node\text{-}to\text{-}periphery} = 1.8 \times 10^{-7}$ cells.

Chance of Lethal Spread is Approximately the Same Whether From a Lymph Node or From the Primary Site

The values for the probability of the lethal spread of cancer cells from a lymph node to the periphery described above ($p_{node\text{-}to\text{-}periphery} = 8.0 \times 10^{-9}$ cells for breast carcinoma; $p_{node\text{-}to\text{-}periphery} = 1.8 \times 10^{-7}$ cells for melanoma) are remarkably similar to the values of the probability of the spread of cancer cells from the primary site to the periphery, $p_{primary\text{-}to\text{-}periphery}$, when the primary masses are the same size as the masses that are seen in the lymph nodes ($p_{primary\text{-}to\text{-}periphery} = 7.4 \times 10^{-9}$ cells for breast carcinoma, $p_{primary\text{-}to\text{-}periphery} = 2.5 \times 10^{-7}$ cells for melanoma) (Table 4). These calculations reveal that the probability of the lethal spread of cancer cells to the periphery is remarkably similar whether the cells originate from a mass of cancer that is present in a lymph node or from an equally sized mass of cancer at the primary site.

The Risk of Death Associated With Cancer at the Primary Site and Lymph Nodes Reflects the Amount of Cancer Present

Another way to examine the question of the lethal contributions from cancer at the primary site and in the lymph nodes is to ask how the lethal contribution from each site is related to the amount of cancer present there. The *SizeOnly* equation (Equation 1) allows us to estimate what the risk of cancer death would be if the amount of cancer present in a positive lymph node magically could be moved to the cancer's primary site. Such calculations reveal that, if the amounts of breast carcinoma observed in the 49 breast carcinoma-containing lymph nodes had been present instead at the primary sites in the breasts of 49 patients, then we would have expected a breast carcinoma death rate of 5.97% (Table 3). This value is nearly the same as the approximately 6% extra chance of death that was correlated with the presence of each positive lymph node in patients with breast carcinoma as observed

from actual survival data.[4,5] Similarly, if the amounts of cancer present in the 50 melanoma-containing lymph nodes had been present instead at the primary sites in the skin of 50 patients, then we would have expected a melanoma death rate of 23% (Table 2). Again, this value is nearly the same as the approximately 23% extra chance of death that was correlated with the presence of each positive lymph node in patients with melanoma as observed from actual survival data.[4]

DISCUSSION

The data presented in this and the accompanying article[4] provide an integrated explanation for why cancer at the primary site and in the lymph nodes contributes to lethality; either site can provide a source of cancer cells, 1 or more of which can spread to the periphery, giving rise to lethal distant metastatic disease. The data presented here also indicate that there is a characteristic probability, per cell, that an event of spread will occur, and the greater the number of cancer cells at the primary site (as observed in the size of the primary tumor) or the greater the number of cancer cells in the lymph nodes (as observed in the number of positive lymph nodes), the greater is the overall chance that 1 or more of these cells will undergo such a lethal event of spread. Conversely, similar masses of cancer appear to make similar lethal contributions, whether they are present at the primary site or in the lymph nodes. For example, for breast carcinoma, the average size of the cancer in a positive lymph node was approximately 6 mm, and the lethal contribution associated with each positive lymph node was approximately 6%, whereas the cancer death rate for patients who had breast carcinoma with primary masses of approximately 6 mm was approximately 6%. A similar parallel was observed for melanoma. Apparently, the probability of an event of lethal spread, per cell, is the same regardless of the site from which the cancer cells originate.

It often has been wondered whether mutation at the time of spread is a requirement for metastasis[8-17]; however, following the reasoning outlined previously,[3] the values for the probabilities of metastatic spread of breast carcinoma, renal cell carcinoma, and melanoma cells presented here are difficult to reconcile with such genetic change: *First*, the value of the probability of lethal spread for the smallest melanomas (0.1 mm), at approximately 1 event of spread for every 500 cells, is many orders of magnitude greater than that expected for a genetic change. *Second*, the probability of metastatic spread per cell from the primary site declines as the tumor increases in size. Although this decline is consistent with several explanations that are mechanical—using this term in the sense in which it is used in physics as "pertaining to the relations of force and matter"—such as the effect of tumor geometry on the escape of cells from the primary mass, it is not what would be expected for genetic events. Indeed, the probability of genetic events over time should be expected either to remain constant (if only a single genetic event is required) or to increase with time (if the accumulation of multiple genetic events is required). *Third*, the occurrence of 1 event of spread—the spread of a breast cancer cell from the breast to the local lymph nodes—does not appear to increase the probability of a second event of spread—the spread of a breast cancer cell from the local lymph nodes to the periphery. In other words, the occurrence of the initial event of spread does not lead to a cell-heritable change in the tendency of the progeny of that cell to spread. This finding indicates that the presence of cancer in the lymph nodes is not a marker of a genetic change in the tumor but, rather, simply a sign that there is more cancer from which cancer cells can emerge.

The current data suggest a mechanical model of the spread of cancer cells that is the simplest mechanism that can be envisaged. The image that comes to mind is of the spread of bricks from the back of a brick truck. Just as each cancer cell in a mass of cancer has certain probability of leaving the primary mass and spreading to the periphery, leading to death, each brick on our truck has certain probability of flying off and killing a pedestrian. The bigger the pile of bricks in the truck, the greater will be the overall chance that 1 or more of these bricks will fly off the truck, causing death. Curiously, the bigger the pile of bricks, the lower will be the chance that any individual brick will fly; a brick on the bottom of the pile would have to "push aside" a lot of other bricks before it could escape. Indeed, the same decline in the per-brick probability of lethal spread correlated with the increase in the size of the brick pile might be expected for the decline in the per-cell probability of lethal spread correlated with the increase in the size of the primary cancer mass. Indeed, we have demonstrated elsewhere that the form of Equation 9, with $b = -2/3$ (which describes how the decline in the per-cell

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probability of lethal spread is correlated with the size of the primary tumor mass) is precisely what would be expected for such geometric considerations.[3] Of course, the analogy would be closer if the bricks increased in number by mitosis, if the bricks had a chance for nonlethal spread to a local site (a fender?) from which a second event of lethal spread could occur, and if the pile was approximately spherical mass.

Several biologic models of the development of breast cancer lethality have been proposed that have had widespread impact on thinking about cancer lethality generally, including the model of contiguous extension proposed by Halsted,[18] the systemic model by Fisher,[19] and the spectrum model described by Hellman.[20] The binary-biologic model of cancer metastasis, which we have outlined in the accompanying article in this series and have used in this report, is based on the idea that the macroscopic manifestations of cancer can be understood by modeling the underlying microscopic events of the spread of cancer cells. This model has allowed us to calculate the values for the probabilities of the spread of cancer cells with which we can assess the theories of Halsted, Fisher, and Hellman. We have borrowed the inspiration for the binary-biologic model from statistical mechanics in physics, in which the large-scale physical properties of matter are understood as the macroscopic consequences of the underlying microscopic events of molecules. The findings made with this approach—that the relation between tumor size and the risk of death can be captured with the *SizeOnly* equation, that the relation between tumor size and the chance of cancer in the lymph nodes can be captured with the *NodalSizeOnly* equation, that each positive lymph node contributes a relatively constant amount of extra lethality, as captured by the *Size+Nodes* method, and that the events of spread of cancer cells most likely do not require mutation at the time of spread—are not assumptions of the binary-biologic model but are conclusions that could be extracted from the data with the model. Nonetheless, these findings fit the biologic intuitions of the Hellman spectrum model[20] more closely than they fit the idea by Halsted that breast cancer is a disease that progresses by contiguous extension[18] or the suggestion by Fisher in his systemic model that cancer in the lymph nodes is a sign that the disease has progressed and is not an instigator of distant disease.[19]

In summary, the data outlined here and the inferences made from these data suggest that the lethal contributions of cancer at the primary site and in the lymph nodes can be explained best by a simple mechanical process for the spread of cancer cells that occurs with definable probabilities per cell. Similarly, the nonlethal spread of cancer from the primary site to the lymph nodes also can be explained by such a mechanical process of the spread of cancer cells. The presence of cancer in the local lymph nodes does not indicate an intrinsic change in these malignancies but, rather, an increased mass of cancer from which distant spread can emerge.

Conflict of Interest Disclosures

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Why Cancer at the Primary Site and in the Lymph Nodes Contributes to the Risk of Cancer Death

James S. Michaelson, L. Leon Chen, Melvin J. Silverstein, Justin A. Cheongsiatmoy, Martin C. Mihm Jr, Arthur J. Sober, Kenneth K. Tanabe, Barbara L. Smith, Jerry Younger, Griffin Weber, and Daan Livesto

The lethal contributions of cancer at the primary site and lymph nodes can be explained by a simple, mechanical process of the spread of cancer cells that occurs with definable probabilities per cell. The results from this study indicated that the presence of cancer in the local lymph nodes does not indicate an intrinsic change in these malignancies but, rather, an increased mass of cancer from which distant spread can emerge.

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