PILOT STUDY

A Novel Use of Biomarkers in the Modeling of Cancer Activity Based on the Theory of Endobiogeny

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ABSTRACT

Introduction: Cancer is a complex disorder whose detection and monitoring remains challenging. A biological modeling system, the biology of functions (BoF), claims to be able to evaluate physiologic elements related to carcinogenic activity. A pilot study was undertaken to evaluate the accuracy of the BoF in detecting differences between cancer cases and matched controls.

Materials and Methods: A retrospective case control study was performed using the BoF analyses of 46 patients with all types of solid and hematgenous cancers, active and inactive (total cases), and 46 controls from a private practice. The standard BoF panel of 17 biomarkers was evaluated. Sixty-two of 150 BoF indices derived from these biomarkers were pre-selected for analysis based on their relationship to cancer physiology. The data was analyzed with the Wilcoxon Signed Ranks Test using SPSS software.

Results: Of the 62 indices, 7 were found to be statistically significant in comparing total cancer cases to controls: βMSH/αMSH, Estrogen Fraction #5, Comparative Genital Androgeny, Thyroid, Genito-thyroid, Catabolism/Anabolism and Pro-inflammatory.

Conclusions: In a small retrospective case control study, statistically significant differences were found between cancer cases and controls in 7 BoF indices. These indices are indicators of physiological conditions consistent with cancer growth. These results warrant further study of this biological modeling system in cancer patients.

INTRODUCTION

Over the past 20 years, the number of newly diagnosed cases of cancer and the overall mortality rate for most common cancers has declined.[1] While mortality rates for advanced breast and prostate cancer remain unchanged in older patients,[2] they have increased in patients under the age of 40 years.[3] This raises questions about how cancer is conceptualized and the methods used to detect the most aggressive cancers based on the conceptual model.

Cancer is a complex multi-factorial disease process but contemporary radiological and serum biomarker surveillance and screening methods remain largely uni-factorial in nature. Thus, they often lack sufficient sensitivity, specificity or both to distinguish benign from malignant tumors or to determine which tumors are more likely to metastasize. This raises the risk of two clinical failures. The first is a failure to diagnose cancer in those who have an active tumor. These patients are at risk of presenting at a later time with aggressive, metastatic disease. The second is a false positive diagnosis of cancer in patients with benign lesions that are subsequently removed resulting in scarring and possible psychological injury to the patient. The ability to identify and evaluate cancer activity and its response to treatment using simple, readily available blood tests would be a valuable addition to the clinical detection and surveillance of cancer.

Radiological procedures used for cancer screening include ultrasound, computed tomography, magnetic resonance imaging and positron emission tomography.[4] They typically require invasive procedures such as biopsies to confirm the diagnosis. Noninvasive and minimally invasive approaches to the diagnosis and management of cancer have some advantages over standard-of-care radiation-based imaging and biopsies. They are less expensive, less invasive, avoid exposure to radiation, and are readily reproducible in an outpatient setting. There are a number of blood-based approaches currently being used or evaluated that have certain advantages and disadvantages.

Circulating tumor cells (CTC) are of growing interest in cancer diagnosis and prognostication.[5] They offer two advantages over other methods. First, they are able to detect metastasis often before cancer cells are large enough to be detected by imaging or palpation. Second, they allow for the development of targeted therapy thanks to characterization of genetic and immunophenotypic changes through staining techniques.[6]

Protein and carbohydrate antigens such as CA 19-9, CA 125 or CA 15-3 have been used for decades. While they are used to detect cancer, they are more useful in the monitoring of response to treatment and detection of cancer recurrence. In general, they have limited sensitivity and specificity[7,8]as each biomarker may be elevated in a number of benign and non-benign tumors in various organs. For example, CA 19-9 may be elevated 500 fold in pancreatic cancer, but also in benign splenic cysts.[9]

Recently, cancer biomarkers evaluating sub-cellu-

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lar biologic phenomenon have been developed, such as telomerase activity[10] and survivin protein.[11] Telomerase activity has been reported in many malignant tumors. Survivin is one of a family of proteins that regulate cell death through the inhibition of apoptosis. It is abundantly expressed in cancer cells. The degree of expression is correlated with aggressiveness of disease.

We see three major shortcomings to the unifactorial methods noted above. First, they lack a global vision of physiology in which to contextualize the growth of cancer within the physiologic terrain of the individual patient. Second, they remain primarily a reactive modality of detection of an existing cancer. They lack a predictive assessment of both the tendency to develop a cancer and its rate of evolution. Third, they do not determine causative factors of cancer growth at the neuro-endocrine level—which we believe to be the true cause of cancer evolution because of its role in regulating cellular metabolism. Instead, they focus on the downstream sub-cellular events that are in fact merely consequences of upstream neuro-endocrine imbalances and not the cause of cancer development.

A number of multi-factorial sub-cellular biomarkers have also been proposed. These include deoxyribonucleic acid (DNA) methylation patterns[12] and serum DNA.[8] The determination of the methylation patterns of multiple genes may provide sensitive and specific tests for cancer diagnosis.[8] Circulating DNA has been shown to exhibit cancer-related alterations such as specific oncogene mutations, mitochondrial DNA mutations, and tumor-related viral DNA.[8]

A new class of RNA regulatory genes, known as micro RNAs (miRNA), are another evolving area of research for noninvasive cancer diagnosis.[7] Altered expressions of tissue miRNA has been found in multiple cancers and unique miRNA expression profiles have been found to have both diagnostic and prognostic significance for many diseases, including cancer.

Metabolomics is a promising field in the area of noninvasive, multifactorial assessment of cancer activity.[13] Metabolomics is the global quantitative assessment of the endogenous metabolites of cells, tissues, or biofluids. Since cancer cells have unique metabolic phenotypes, it is possible to identify specific metabolic fingerprints, profiles or signatures for cancer detection, prognosis or assessment of treatment effects. The clinical application of metabolomics in cancer has been limited, however due to technical limitations, database challenges, and costs.[13]

The multi-factorial methods summarized above hold promise and reinforce the concept that the complex and multi-factorial nature of cancer will likely require a method of biomarker evaluation. These methods provide a more nuanced, sensitive and specific manner by which to evaluate both the risk of cancer development as well as the nature of the specific cancer in the individual patient. The shortcomings of the aforementioned tests lie in a reductionist analysis, which considers cancer to be solely a cellular phenomenon, as opposed to a systemic disease expressed in a particular collection of cells, ie, a tissue or organ. A global systems approach may have a number of advantages over these multifactorial yet reductionist evaluations.[14]

Endobiogeny is a systems approach to biology that maintains a global vision of physiology. It is a theory of terrain that seeks to explain how human life develops, maintains and adapts itself.[14-16] The terrain refers to the sum of all factors that ensure the structure and function of the body, from its genetic heritage to its adaptive capacities against endogenous and exogenous aggressors. According to the endobiogenic theory, the endocrine system is the manager of the terrain because it is the only system in the body that is ubiquitous, self-regulating, and able to regulate other systems and subunits of activity.[14-17] Thus, endobiogeny evaluates how the endocrine system manages the terrain.

The biology of functions (BoF)[14-16] is a biological modeling system based on the principles of endobiogeny and its theory of terrain. Systems theory posits that the whole is more than the sum of its parts, sub-units of activity are integrated and inter-related, and that the qualitative relationships of these activities reflect the dynamic functional capacity of the system. Based on these concepts, when biomarkers are related through a series of ratios, they are able to capture the dynamic functioning of the organism *in toto*. The BoF evaluates seventeen serum biomarkers in such a fashion in order to derive an assessment of the basal and adaptive capacities of the organism as managed by neuro-endocrine activity, and characterize various complex physiologic, cellular, tissue and systemic metabolic activities, including carcinogenesis.

From these 17 biomarkers, a series of over 150 indices are derived.[16] In contrast to the aforementioned cancer biomarker evaluations, the BoF indices are used within a broader context of "real world" bedside clinical assessment of the patient, in an endeavor to create a truly personalized care plan. This makes endobiogeny and the use of the BoF indices unique amongst presently available biomarker assessments for cancer and other diseases processes.

The standard approach in oncology is to characterize tumors by the tissue of origin and to determine treatment based on staging protocols. Endobiogenic theory posits that cancer is the result of systemic dysregulation of neuro-endocrine activity that affects cellular growth and regulation. Therefore, the neuro-endocrine factors of dysregulation characterize the true "typing" of the cancer. Recent advances in nosology support the grouping of diseases, including cancer, by physiologic abnormalities rather than by symptom or anatomical origin.[17]

More recently, genetic anomalies and endocrine receptors are also used to characterize tumors and chose more targeted biologic therapies. However, recent studies in genomics confirm that within tumors of the same origin, staging and hormone receptor status, there exists a high degree of metabolic variability.[18]

This suggests that an individualized approach to cancer detection based on physiologic variables, such as that proposed by endobiogeny, may hold certain advantages to current methods of cancer detection and therapy selection.

PRIMARY STUDY OBJECTIVES

The goal of this study was to evaluate the validity of the endobiogenic theory of cancer by evaluating the accuracy of the biology of functions as a multifactorial assessment of terrain in distinguishing cancer patients from controls. Because we were evaluating the cancer terrain of patients, we did not distinguish between hematogenous and non-hematogenous cancers for this study. We sought to determine if statistically significant differences would be found between indices in cancer patients and controls consistent with the known physiological changes of cancer cells *in vitro*.

METHODS/DESIGN

All available data from the BoF analyses of 92 patients were analyzed for this study. Consent was obtained from all patients for the analysis of data from their clinical records. These cases included all patients with a history of cancer (n=46) and healthy controls (n=46) that were individually matched for both age and gender (Table 1). All cases and controls were white and were selected from the clinical records of a single physician specialized in the field of endobiogeny in San Diego, California. In general, cancer cases were free of major comorbidities so matching for this criterion was not necessary. This study received ethical approval from the San Diego State University Institutional Review Board.

All cancer cases were further subdivided into either inactive (n=13) or active (n=33) groups (Table 2). Inactive cancer cases were defined as cancer survivors who were in clinical remission for at least six months at the time of the BoF analysis. Active cancer cases included all patients with localized solid tumors, metastatic solid malignancies, or hematogenous malignancies. The active cases included some subjects receiving chemotherapy at the time of the BoF analysis (n=4) and a few subjects who were terminal (n=6) at the time of the first BoF evaluation. An additional analysis of the subgroups of breast (n=13), colon (n=5), and prostate (n=6) cancer was also performed for the 7 indices that were found to have a statistically significant difference in the total cases

Descriptive information, disease information such as tumor type and disease stage, and the BoF calculations were collected for all subjects. During the course of endobiogenic care of a patient, serial biology of functions are typically performed. For most cases and controls, the initial BoF results, prior to receiving any endobiogenic treatment, was selected, in order to eliminate possible beneficial anti-cancer effects from the endobiogenic treatment plan. In seven cases, the second set of BoF data were used because of insufficient data in the initial testing or in order to better assess the patient at the end stage of their disease.

The two groups of cancer cases and matched controls were compared using the Paired Wilcoxon Rank Sum Test. The Independent Wilcoxon Rank Sum Test was used to compare inactive and active cancer cases. These analyses were performed with SPSS version 16 software (IBM Corp, Armonk, New Jersey). All analyses were two-tailed, with a=0.05, without any correction for Type I error.

The standard BoF panel of 17 biomarkers[15] was drawn for all patients at Laboratory Corporation of America (Burlington, North Carolina), with normal ranges for the adult childbearing female provided by Laboratory Corporation of American as the standard reference. The biomarkers are measured using venous blood while fasting and the labs are typically drawn first thing in the morning. The complete blood count with differential and the sedimentation rate are taken from whole blood while the remaining biomarkers are taken from serum. A few of the BoF indices were not available for all cases due to missing laboratory data of the 17 biomarkers used to calculate the indices. Most of the 17 biomarkers are obtained from standard blood tests. Two of the biomarkers (osteocalcin and alkaline phosphatase bone isoenzyme) are considered to be specialty labs and were not available in all cases unless pre-ordered by the endobiogenic physician.

The data was entered into the BoF modeling software by a physician specialized in the field of endobiogeny and prepared for review. The BoF software relates the 17 biomarkers through a series of direct and indirect relationships described elsewhere[15,16] to derive more than 150 indices. A total of 62 indices related to cancer were selected prior to analysis by the authors for the purposes of this study. The selected indexes were chosen based on the endobiogenic theory of terrain, contemporary understandings of cancer biology, and empirical observations derived from the treatment of thousands of cancer patients using the BoF. The data was analyzed in consultation but independently from the physician who had collected the data.

Derivation of normative values of indices is described elsewhere.[15] The definition and normative value of indices found to be statistically significant are presented below. Because the indices are calculated ratios, there are no units associated with them.

Adaptation:

βMSH/αMSH Index (6-8): It expresses the relative level of participation of the beta- and alpha-melanocyte stimulating hormones (MSH) in directly stimulating cortisol activity vs. the general adaptation syndrome at the level of the pituitary.[16]

Anabolic Hormones:

Estrogen fraction #5 (7-20): It expresses the relative part of estrogens consecrated to the growth of tissues and organs.

Table 1 Baseline Characteristics of Cancer Cases and Matched Controls

	No.	Male	Female	Average Age, y	SD	Mimimum Age	Maximum Age	*P* value
Cancer Cases	46	19	27	54.15	13.48	9	78	.705
Control	46	19	27	54.75	13.38	10	84	

Table 2 Frequency Distribution of Cancer Diagnoses

Cancer Diagnosis	Male	Female	Active	Inactive
Abdominal sarcoma	1		1	
Acute lymphocytic leukemia		1		1
B-cell lymphoma	1		1	
Bladder and ureter carcinoma		1	1	
Breast carcinoma		13	8	5
Cervical carcinoma		1	1	
Chronic non-Hodgkin's lymphoma		1	1	
Chronic lymphocytic leukemia	1	1	2	
Colon carcinoma	5		4	1
Hepatocellular carcinoma	2		2	
Liposarcoma		2	2	
Lung carcinoma		1	1	
Melanoma	1		1	
Myelodysplastic syndrome		1	1	
Ovarian carcinoma		1	1	
Parathyroid carcinoma		1	1	
Prostate carcinoma	6		2	4
Renal cell carcinoma	1		1	
Stomach carcinoma		1	1	
Testicular carcinoma	1			1
Thalamic glioblastoma		1	1	
Uterine carcinoma		1		1
Total = 46	19	27	33	13

Comparative Genital Androgeny Index (0.1-0.3): It indicates the metabolic activity of androgen receptors at the tissue level and the anabolism of tissue.

Catabolic hormones:

Thyroid Index (3.5-5.5): It indicates the degree of efficiency of thyroid hormones in managing the metabolic energetic activity of the cell.[9]

Anabolic-catabolic endocrine harmony:

Genito-thyroid Index (1.5-2.5): It expresses the relative activity of the gonads in relationship to that of the thyroid.[16]

Metabolism:

Catabolism/Anabolism Index (1.8-3): It expresses the relative catabolic activity in relation to that of anabolic activity within the scheme of global metabolism of the organism.[16]

Immunity:

Proinflammatory Index (0.1-0.4): The pro-inflammatory index looks at the endogenous potential for inflammation due to thyrotropic over-activity and the degree to which cortisol is able to compensate for this.[16]

RESULTS

Cancer cases were well matched for age and sex with no significant difference for either variable (Table 1). Cancer type was heterogeneous with respect to type of malignancy (solid vs hematogenous) and tissue of origin (Table 2).

Statistically significant differences were found for 7 of the 62 selected indices (Table 3) between all cancer cases and controls. Of the seven, six showed statistically significant differences between all cancer cases and controls. In five indices, the mean value in the cancer cases was significantly higher than controls: Estrogen fraction #5 (P=.004), Genito-thyroid (P=.005), Thyroid (P=.039), βMSH/αMSH (P=.042), and Catabolism/Anabolism (P=.05). The Comparative Genital Androgeny index (P=.007) was significantly lower in cancer cases vs controls. The Proinflammatory index (P=.056) was not statistically significant between all cancer cases and controls.

Comparing active cancer cases with their controls, 3 of the indices were found to be statistically significantly: Thyroid (P=.009), Estrogen fraction #5 (P =.007), and βMSH/αMSH (P =.012).

Comparing inactive cancer cases with controls,

Table 3 Summary of Descriptive Statistics and *P* Values for the Significant Biology of Functions Indices

		Total Cases	Total Controls			Active Case	Active Controls			Inactive Cases	Inactive Controls		Active vs Inactive
INDEX	No.	Mean±SD	Mean ±SD	*P* Value	N	Mean ±STD	Mean ±STD	*P* Value	No.	Mean ±STD	Mean ±STD	*P* Value	*P* Value
Estrogen Fraction #5	45	18.64±16.87	10.58±5.30	.004[a]	32	21.47±19.15	10.91±5.78	.007[a]	13	11.68±4.73	9.77±3.96	.310	.437
Genito-Thyroid Index	45	3.46±2.68	2.25±0.85	.005[a]	32	3.70±3.05	2.32±0.80	.067	13	2.86±1.32	2.07±0.97	.006[a]	.622
Comparative Genital Androgeny	36	2.27±3.81	7.12±11.6	.007[a]	26	2.75±4.37	8.03±13.3	.06	10	1.03±1.05	4.74±4.21	.028[a]	.568
Thyroid Index	39	5.17±3.64	3.72±1.73	.039[a]	27	5.90±4.06	3.64±1.98	.009[a]	12	3.51±1.58	3.89±0.99	.433	.006
Beta MSH/Alpha MSH Index	39	5.64±3.86	4.11±1.98	.042[a]	27	6.45±4.30	4.00±2.25	.012[a]	12	3.83±1.59	4.38±1.20	.433	.003
Catabolism/ Anabolism Index	45	6.11±9.95	2.997±1.57	.050[a]	29	6.82±12.11	3.09±1.70	.198	14	3.47±1.77	2.85±1.74	.363	.910
Proinflammatory Index	42	1.64±2.80	0.73±0.70	.056	29	1.91±3.26	0.72±0.54	.249	13	1.04±1.25	0.74±1.01	.019[a]	.990

[a] Statistically significant at *P*=.05.

three of the indices were also statistically significant. Genito-thyroid (*P* =.006) and Pro-inflammatory (*P* =.019) indices were higher in subjects with inactive cancer, while the Comparative genital androgeny index (*P* =.028) was lower in subjects with inactive cancer as compared with controls.

Comparing active and inactive cancer cases, two indices were found to be statistically significant and higher in active cancer vs inactive cases: βMSH/αMSH (*P* =.003) and Thyroid (*P* =.006).

The results for the seven indices studied for the cancer subtypes of breast (n=13), colon (n=5), and prostate (n=6) are shown in Table 4. Only Estrogen Fraction #5 was found to be significantly higher in breast cancer cases vs controls (*P* =.03). The mean value was also greater in the breast cancer patients (23.29) vs all cancer patients (18.64).

DISCUSSION

This study of a heterogeneous population of cancer patients identified seven indices in the BoF that were significantly different between the varying groups. Cancer patients as a whole (active and inactive) had greater expression of indices that reflect a physiologic state of hyper-adaptation: βMSH/αMSH,[16] Elevated Anabolic Activity: Estrogen Fraction #5, Elevated Catabolic Activity: Thyroid,[16] as well as the coupling of estrogen activity for growth and thyroid response to this demand in order to increase the general metabolic rate: Genito-thyroid.[16] In addition, our study found an overall hyper-catabolic state (catabolism/anabolism) in all cancer patients—even cases deemed "inactive" or in remission. According to numerous studies, these physiologic conditions favor the growth of cancer cells.[16,19-21] These observations were maintained for the first four indices noted when comparing active cancer patients to controls.

It is interesting to note that inactive cancer patients have a terrain that continues to be less deranged than active cancer patients but more deranged than controls. The three indices found to be statistically significant in inactive cancer subjects as compared to controls, all relate to deranged adaptive activity: Comparative Genital Androgeny, Genito-thyroid, and Pro-inflammatory indices. This suggests that inactive cancer patients should not be classified as "survivors" with no further surveillance for cancer recurrence. Inflammatory tendency has been associated with increased risk of cancer.[22,23]

Finally, the BoF also distinguished active from inactive cancer cases with respect to adaptive activity. Both the βMSH/αMSH and Thyroid indices showed significantly elevated values in active cancer cases compared to inactive cases, witnessing the important role of dysregulated cortisol and thyroid activity in creating a terrain favorable to rapid tumor growth.

In endobiogenic clinical practice, no one index is used to diagnose or prognosticate any single type of cancer. There are particular patterns of global endocrine imbalances associated with specific types of tumors based on general tissue origin or specific activity of a tissue. These considerations are used to guide the specific approach to detection and treatment.

For example, we have observed within our indices that melanomas have different factors of initiation of growth compared to other cancers of epithelial origin such as colon or breast cancer. Hematogenous malignancies have different factors of initiation than solid tumors in general, with further differentiation between Hodgkin's and non-Hodgkin's lymphomas.

In addition to the specific association of indexes, there are general clusters of physiologic activity that are generally associated with tumors, which are what were characterized in this study of a heterogeneous cancer cohort. The fact that the indexes that were found to be statistically significant were general markers of

Table 4 Summary of Descriptive Statistics and *P* Values for the Significant Biology of Functions Indices Subdivided Into Breast, Colon, and Prostate Cancer

	Breast Cancer				Colon Cancer				Prostate Cancer			
	Total Cases		Total Controls		Total Cases		Total Controls		Total Cases		Total Controls	
Index	No.	Mean±SD	Mean ±SD	*P* value	No.	Mean ±SD	Mean ±SD	*P* value	No.	Mean ±SD	Mean ±SD	*P* value
Estrogen Fraction #5	13	23.29±22.89	11.38±7.24	.03[a]	5	20.60±21.18	7.20±1.48	.23	6	11.00±5.29	11.17±4.58	.83
Genito-Thyroid Index	13	3.56±1.98	2.35±0.81	.25	5	3.51±1.45	2.03±0.64	.14	6	2.87±1.83	1.98±0.46	.12
Comparative Genital Androgeny	13	2.14±2.95	6.38±12.61	.24	4	2.61±4.28	14.50±21.79	.07	6	1.50±1.13	4.30±1.56	.71
Thyroid Index	13	5.45±5.66	4.50±2.05	.64	5	6.08±5.23	2.42±1.21	.23	6	3.82±1.45	3.42±0.93	.46
Beta MSH/Alpha MSH Index	13	5.99±5.97	5.02±2.35	.70	5	6.51±5.18	2.66±1.42	.23	6	3.95±1.36	3.77±0.98	.75
Catabolism/Anabolism Index	13	4.94±4.80	3.24±1.96	.38	5	6.69±4.83	2.40±1.07	.23	6	4.33±4.64	3.21±1.61	.92
Proinflammatory Index	13	1.25±1.73	0.71±0.48	.94	5	1.23±0.92	0.65±0.40	.23	6	1.18±1.56	0.52±0.15	.14

[a] Statistically significant at *P*=.05.

dysadapted metabolism supports our theory that a global systems approach to human physiology can distinguish the causes of development of a cancerous vs. non-cancerous terrain without relying on an evaluation of the sub-cellular mechanisms of cancer growth.

On a sub-analysis of the most commonly occurring solid tumors (breast, colon, and prostate), breast cancers were noted to have the greatest mean estrogen activity (as noted by the Estrogen Fraction #5 Index), with prostate cancer having the lowest (but still elevated). This is consistent with known characterizations of the relatively greater role of estrogens in breast cancers in relationship to prostate cancer. It also reinforces the importance of understanding not only the global physiologic terrain that supports the development of a cancer, the tissue of origin and subtyping, but also the particular characteristics of the individual in the face of their tumor.

In summary, the biology of functions, a novel biological modeling system based on the theory of endobiogeny, was found to distinguish certain physiologic derangements between cancer patients and controls. Further studies are warranted to evaluate these differences, especially within different cancer subtypes and cancer stages. Comparisons between the BoF indices of cancer patients and other chronic diseases would be important additional studies in the future. Larger studies might also reveal additional indices of potential significance in the process of carcinogenesis.

LIMITATIONS

This study is limited by the fact that it is a small novel case control study of a heterogeneous population of cancer patients. However, the presence of significant findings in such a heterogeneous group supports the endobiogenic notion and current genomic approaches that suggest that cancer metabolism is a better indicator of the nature of a tumor than tissue of origin per se.[18,24]

Further categorization of the patients into more meaningful subgroups and analysis of other test variables such as age and sex was prohibited by the small population size. There was also no correction for Type I error in the analysis.

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