DEPRESSION AND INFLAMMATION IN MALE OSTOMATES, A STUDY OF COLORECTAL CANCER AND RISK FACTORS

By
JESSICA LYN RHEUDASIL

A Thesis Submitted to The Honors College

In Partial Fulfillment of the Bachelor's degree
With Honors in

Physiology

THE UNIVERSITY OF ARIZONA

May 2009

Approved by:

Zoe Cohen

Dr. Zöe Cohen, PhD
Physiology Department

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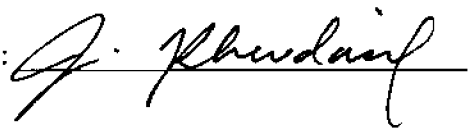
SIGNED: 

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Depression and Inflammation in Male Ostomates, a study of colorectal cancer and risk factors

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ABSTRACT

Objective

Inflammation resulting from an elevated basal metabolic index (BMI), coupled with the inflammation associated with clinical depression may augment the inflammation present due to colorectal cancer. Our hypothesis is that those subjects with both an elevated BMI and depression are at a greater risk for colorectal cancer development. It is our objective that results of this study support controlling BMI and depression as preventative measures for colorectal cancer.

Research Design and methods

Data was collected for analysis from *The VA Ostomy Health-Related Quality of Life Study*. Data was entered into tables for each research subject. Depression was determined by assessing patient responses on two Veteran surveys: the Abdominal Surgery Patient Survey and the Short Form 36 for Veterans (SF-36V). Elevated BMI was calculated using post-surgery weight indicated on the Medical Record Data for Ostomates sheets, and the BMI formula suggested by the National Institute of Health.[9]

Results

Data from 37 male ostomates was analyzed. Depression-associated responses to the surveys demonstrated that 35.1% of the sampled male ostomates were depressed. BMI calculations revealed that 59.5% of the sample had an elevated BMI. Of the 37 total subjects, 66.7% had both diagnosed depression and an elevated BMI; 53.8% had an elevated BMI and depression calculated via this study.

Conclusions

Our analysis demonstrates a positive correlation between depression and elevated BMI. For those with cancer, added inflammation due to these co-morbidities is assumed. For those without cancer, but with depression and/or an elevated BMI, the combined increase in inflammation should be noted as a risk factor for cancer development.

Introduction

Increasing knowledge of the pathology of cancer and advancements in cancer research in the last decade have shifted researchers' attentions to risk factors, with the hope of improving prevention strategies and prognoses. With increasing numbers of cancer survivors, more studies are assessing quality of life. Consequently, the amount of quality of life data available for use in the examination of unique disease-causing factors has increased.

Quality of life is defined by two components: physical and psychological. The physical aspect includes factors such as health, diet, and protection against disease, while the

psychological aspect includes stress and pleasure as negative and positive emotional states. This study examines the role of the psychological component of overall quality of life, using depression as an indicator of poor psychological health. Clinical depression, which is frequently associated with a cancer diagnosis, is hypothesized to play a role in cancer development and progression in adult males.

In addition, with the rate of adult obesity climbing in America, scientific research has been fast to uncover the negative effects of an elevated body mass index (BMI). While recently correlated with diabetes, the effects of obesity on cancer development are now being investigated. This study proposes that the combined effects of an elevated BMI and pre-cancer clinical depression may play a role in colorectal cancer development and progression in males.

Mixed Methods Research

Mixed methods research employs qualitative methods to interpret earlier quantitative results. While non-traditional, such comprehensive approaches have become increasingly important in psychology, evaluation research, and medicine.[1] Qualitative methods frequently utilize analytic procedures such as individual interviews or surveys. In this study, responses to surveys used to assess the patient's adaptation to cancer were used.

The importance of co-morbidities

Colorectal cancer arises from inflammatory growths, called polyps, that form in the colon or rectum. The colon, which is also called the large intestine, serves as a storage site for waste matter before it passes into the rectum for removal.[2] Common risk factors for colorectal cancer noted by the American Cancer Society include a personal history of inflammatory bowel disease and obesity.[3] Numerous studies confirm the systemic inflammation associated with obesity and colorectal cancer, independently. With attention to male ostomates post-surgery, this study will determine the percentage of colorectal cancer survivors, in a male Veteran population, that have an elevated BMI. Secondly, while it is often assumed that depression can result from a cancer diagnosis, depression has also been frequently noted to precede cancer development, especially in Veterans.[5] This study will evaluate depression in patients and propose that, when coupled with an elevated BMI, depression can augment the inflammatory damage of colorectal cancer. Whether or not this combined inflammation is enough to cause cancer is unknown; it is merely suggested that with the damaging inflammation from colorectal cancer, these two factors may increase disease likelihood and/or worsen prognosis.

Study Design and Analysis

Participants

All study subjects were VA patients seen at the Southern Arizona Veterans Affairs Health Care System in Tucson, Arizona. Patients were male colorectal cancer survivors that had previously undergone surgery for an ostomy. Data was collected from patients an average of 8.5 years post-surgery.[1] Ostomates were identified using the ICD-9 procedure codes available in the VA Patient Treatment File. Patient codes remain in the system for ten years.[1]

Setting

The Southern Arizona Veterans Affairs Health Care System of Tucson, Arizona is a highly affiliated tertiary-care referral system serving veterans in Arizona and surrounding states. Physical data was collected from the Medical Record Data for Ostomates forms (see appendix). Psychological evaluation was made by interpreting responses in the Abdominal Surgery Patient Survey and the SF-36V forms (see appendix). The University of Arizona served as the location for further topic research and data interpretation.

Study Implementation

The unique fashion of this study required completion in phases. Phase I involved collection of physical data and patient history, including age, height, post-surgery weight, and

the presence of depression as a diagnosed co-morbidity. Phase II involved interpretation of psychological data via patient surveys.

Phase I – patient data

Physical data from Medical Record Data for Ostomates sheets was reproduced into tables for easier interpretation.

Phase II – patient surveys

Survey responses were interpreted in order to determine the existence of depression. Question 8, with sub-questions a-i, was selected from the SF-36V survey. This question assessed symptoms and/or feelings that patients with depression typically experience. The response choices were as follows: all of the time, most of the time, a good bit of the time, some of the time, a little of the time, none of the time. Responses filled in as "a good bit of the time," "most of the time," or "all of the time" for those questions regarding depression symptoms were counted as a "yes" for depression; responses filled in as "some of the time," "a little of the time," or "none of the time" for those questions regarding happiness symptoms were counted as a "yes" for depression. For example, question 8d asks: "How much of the time, during the past 4 weeks, have you felt calm and peaceful?" A response of "none of the time," "a little of the time," or "some of the time" would count as an answer indicative of depression. On the flip side, questions like question 8f, which asks, "How much of the time, during the past 4 weeks, have you felt downhearted and blue?", assess feelings of depression. Therefore, a question aimed at determining the presence of a depressed mood would receive

a “yes” if the selected response were: “all of the time,” most of the time,” or “a good bit of the time.” For the data sheets, numbers were assigned to each of the possible responses, varying for whether or not the question assessed happiness or depression. For example, numbers 1, 2, and 3 corresponded to “all of the time,” “most of the time,” and a good bit of the time,” respectively, for the “depression” questions. For the “happiness” questions, numbers were kept the same, so 4, 5, and 6 corresponded to “some of the time,” “a little of the time,” and “none of the time,” respectively. When numbers corresponding to a “yes” for depression appeared, they were highlighted in the data sheets. Highlighted numbers were then totaled. Of the nine total questions, if six or more questions were highlighted, a depression percentile was figured.

From the Abdominal Surgery Patient Survey, question 53 was selected. Question 53 asked subjects to rate their overall quality of life on a scale of 0 to 10, with 10 corresponding to an excellent quality of life. Bubbled answers from 0 to 5 were highlighted as indicative of poor quality of life. A percentage of those patients whose responses demonstrated poor quality of life was then determined.

Subjects that did not answer all questions, or those subjects for which height or weight were not available, were excluded from the study.

Results

Table 1

Patients with Depression Indicated by Question 8a-i (%)	Patients with Diagnosed Depression (%)	Patients with Poor QOL Indicated by Question 53 (%)	Depressed Patients (adjusted for overlap; %)
27.0	16.2	35.1	35.1

Percentages were figured by counting the total number of patients that answered accordingly, out of 37 patients. Those patients with *diagnosed* depression were only those that selected "Major Depression" as a co-morbidity on the Medical Record Data for Ostomates form. The final percentage of depressed patients was figured by totaling the number of patients that were determined depressed by either one or more of the following: question 8 of the SF-36V, question 53 of the Abdominal Surgery Patient Survey, or the co-morbidity section of the Medical Record Data for Ostomates form. The total was calculated ensuring that those patients fitting into more than one category were not counted more than once.

Table 2

Patients with an Elevated BMI (%)	Patients with Diagnosed Depression + Elevated BMI (%)	Patients with Calculated Depression + Elevated BMI (%)
59.5	66.7	53.8

Of the 37 sampled ostomates, 59.5% had an elevated BMI. Of those patients with diagnosed depression, as reported via the Medical Record Data for Ostomates form, 66.7% also had an elevated BMI. Of those patients that were determined depressed via analysis of patient survey responses, 53.8% also had an elevated BMI (see Table 2).

Discussion

CANCER, DEPRESSION, AND IL-6

Clinical depression is of great interest in the treatment of cancer patients. As a clear indicator of decreased quality of life, depression has been correlated with negative treatment outcome in cancer patients.[4] A cancer diagnosis alone is a frequent and understandable manifestation of the disease, yet studies of depression in individuals with and without cancer reveal an incidence of depression that is comparable to that observed in patients with other inflammatory conditions, suggestive of a physiological explanation for depression.[4] As numerous studies indicate, a persistent state of inflammation is thought to produce the chronic damage leading to certain types of cancer.[6] Precursor legions of colorectal cancer, such as polyps, have inflammatory features evident by histological observation.[5] Specifically, pro-inflammatory genes have been recognized as important indicators of colorectal cancer progression and maintenance, with particular attention to the pro-inflammatory cytokine interleukin-6 (IL-6).[6]

With documented pro-inflammatory activity in the intestine, a study of colorectal cancer patients in Barcelona, Spain found the C-174 allele of IL-6 to be visibly associated

with an increased risk of colorectal cancer.[6] While it is noted that IL-6 could be related to colorectal cancer by causing a low-grade inflammatory state in the intestine, the presumptive affect of IL-6 on colorectal cancer via pro-inflammatory action was not limited to the C-174 allele. Interestingly, an elevated level of IL-6 is also consistent with studies of depressed individuals with, and without, cancer. The proposed link of IL-6 to depression, independent of cancer, is important to note in colorectal cancer patients. When considering the colorectal cancer patient without depression, the elevated level of IL-6 would most likely be the result of the inflammatory cancer. Then, when considering the colorectal cancer patient with depression, it is expected that an even greater elevation in IL-6 would be evident. This study proposed that an amplified level of IL-6, due to an elevated BMI and depression, negatively affects cancer progression, and perhaps even development, in adult males.

The mechanism of IL-6 further supports the link between inflammation and depression. Linking the sympathetic and adrenomedullary systems is the hypothalamic-pituitary-adrenal (HPA) axis, an endocrine unit that functions in maintaining basal and stress-related homeostasis. The hypothalamus and pituitary gland in the brain form the central part of the HPA axis, and are active even at rest, responding to blood-borne and sensory signals. These signals often come from cytokines, such as IL-6, which expresses the ability to downregulate glucocorticoid-receptor (GR) translocation and function. Present in all body cells, the GR controls genes that participate in development, metabolism, and immune response. Therefore, it makes sense that when in an increased inflammatory state, an induced

state of GR resistance would develop to control the hyperactive immune response. Downregulation of this receptor, however, also causes malfunction of the glucocorticoid-mediated feedback loop in the regulation of the HPA axis, chronically activating the axis. Interestingly, chronically depressed patients, both those with and without cancer, manifest with a significant disturbance of function in their HPA axes, suggesting an immune component of depression.[3] Whether due to depression or cancer, the increased activity of the HPA axis may lead to a failure to suppress an inflammatory response, initiating a vicious cycle of damaging inflammation.

BASAL METABOLIC RATE AND IL-6

Basal metabolic index (BMI) is a common measure of overweight individuals. Linking BMI to inflammation begins with measuring the concentration of aP2, a fatty-acid binding protein present in adiopocytes and macrophages. Concentration of this protein markedly increases in overweight to obese individuals, regardless of age.[7] Higher aP2 concentrations were correlated with markers of subclinical inflammation, including the pro-inflammatory marker IL-6, suggesting that an increase in aP2 plays a role in the systemic inflammation seen in the obese. This is supported by the understanding that human adipose tissue expresses and releases pro-inflammatory cytokines such as IL-6.[8] Moreover, recent reviews suggest that inflammation and BMI are related to mental stress. Acute mental stress, according to a psychoendocrinology study, induces the circulation of inflammatory factors.[8] This relationship between the inflammatory factors released from adipose tissue and the

mental stress-induced circulation of inflammatory factors further confirms the combined effect of such co-morbidities on inflammation.

Conclusion

Physical and psychological data sets from male Veteran ostomates were analyzed for elevated BMI and the existence of depression. While the Medical Record Data for Ostomates form had a space to clearly mark the existence of depression, other measures to assess depression were necessary, assuming that a significant amount of patients with depression are undiagnosed. This assumption is supported by the patient data collected for analysis. While only 6 of the 37 subjects selected depression as an existing co-morbidity, 10 subjects responded to questions on the SF-36V in a manner suggestive of depression. Furthermore, according to the Abdominal Surgery Patient Survey, 13 subjects indicated that their quality of life was poor, which is a common sign of depression.

Based on the existence of IL-6 in both obesity and depression, there should be significant overlap in overweight patients that are depressed. In other words, if obesity and depression are physiologically associated, then the individuals that are depressed are also likely to have an elevated BMI. Of the sampled ostomates, 59.5% had an elevated BMI. However, of those with diagnosed depression, as reported via the major depression co-morbidity, 66.7% had an elevated BMI, and of those with depression calculated in this study, 53.8% had an elevated BMI.

Data collected suggests that there is a positive correlation between depression and elevated BMI. For those who already have cancer, this may suggest an even higher level of IL-6. For those with depression and an elevated BMI, but without cancer, the combined increase in IL-6 should be noted as a risk factor for colorectal cancer development. Since colorectal cancer begins as polyps, and polyps have a histologically-verified presence of IL-6, an existing polyp may simply be a sign of an elevation in IL-6 that could lead to cancer. Furthermore, the circulating IL-6 that may have played a role in the polyp's development could have been a result of a co-morbidity such as depression, obesity, or both. While data does not suggest that all overweight and depressed individuals will get cancer, the data does serve as a positive notation that depression, obesity, and colorectal cancer are linked. Furthermore, the American Cancer Society affirms that while obesity does raise the risk of developing colon cancer in both men and women, the link seems to be stronger in men.[3] Therefore, it is important to note the co-morbidities of depression and elevated BMI in cancer development.

While the analyzed data supports the hypothesis of the study, limitations did exist. Foremost, it should be recognized that a sample size of only 37 was available for this study. Since previous data collected was from both ostomates and controls, as well as multiple sites, the prior study had a significantly larger sample set. This study eliminated the following: controls from the prior study, data from patients who had an ostomy for reasons other than colorectal cancer, data from patients whose ostomy was not linked to the colon or rectum,

and data from patients not associated with the SAVAHCS. Then, from this subject pool, subjects without all the required data were discarded. In future studies, a larger subject pool would be desired.

In addition, future studies could obtain levels of IL-6 from blood samples to support BMI and depression assumptions.

Acknowledgements

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[9] An NIH-sponsored calculator for BMI can be found at: http://www.nhlbisupport.com/bmi/bmicalc.htm

Medical Record Data for Ostomates

Subject ID	Age (yrs)	Height (inches)	Weight (Post Surgery; lbs)	Calculated BMI
1001	61	70	220	28.7
1002	86	70	158	22.7
1004	57	72	170	23.1
1015	76	74	190	24.4
1017	67	73	227	29.9
1020	76	69	170	25.1
1024	67	76	335	40.8
~~1036~~	~~60~~	~~71~~	~~213~~	
1037	82	72	185	25.1
1050	79	68	190	28.9
1053	79	66	507	81.8
1055	68	72	180	24.4
1060	77	68	160	24.3
1067	77	76	205	25
1070	72	69	215	31.7
1074	69	70	212	30.4
1075	69	66	200	32.3
1088	77	69	190	28.1
1092	68	70	180	25.8
~~1099~~	~~89~~	~~N/A~~	~~N/A~~	
1113	68	69	145	21.4
1117	74	71	180	25.1
1118	60	68	160	24.3
1127	69	70	112	16.1
~~1131~~	~~90~~	~~N/A~~	~~N/A~~	
1134	83	72	176	23.9
1143	69	70	200	28.7
1146	58	70	160	23
1151	82	70	145	20.8
1159	81	68	140	21.3
1161	81	71	150	20.9
1162	61	72	190	25.8
1163	75	70	200	28.7
1164	54	70	155	22.2
~~1166~~	~~58~~	~~67~~	~~248~~	
1168	81	68	200	30.4

1169	83	77	170	20.2
1171	74	71	194	27.1
1172	90	62	137	25.1
1174	74	75	235	29.4
1176	78	71	215	30

Medical Record Data for Ostomates – cont'd.

Subject ID	BMI Elevated? (Y/N)	Major Depression Comorbidity
1001	Y	0
1002	N	0
1004	N	0
1015	*N*	*1*
1017	Y	0
1020	Y	0
1024	*Y*	*1*
~~1036~~		
1037	Y	0
1050	Y	0
1053	Y	0
1055	N	0
1060	N	0
1067	*Y*	*1*
1070	Y	0
1074	Y	0
1075	Y	0
1088	Y	0
1092	Y	0
~~1099~~		
1113	N	0
1117	*Y*	*1*
1118	N	0
1127	*N*	*1*
~~1131~~		
1134	N	0
1143	*Y*	*1*
1146	N	0
1151	N	0
1159	N	0
1161	N	0
1162	Y	0
1163	Y	0
1164	N	0
~~1166~~		
1168	Y	0

1169	N	0
1171	Y	0
1172	Y	0
1174	Y	0
1176	Y	0
Totals	**22**	**6**

SF-36V Data

Subject ID	Question 8								
	a	b	c	d	e	f	g	h	i
1001	5	6	5	2	5	5	4	4	3
1002	2	6	6	1	2	6	6	1	5
1004	6	4	5	6	6	4	1	4	1
1015	3	5	6	2	4	6	4	2	4
1017	4	5	6	3	4	6	4	2	4
1020	5	4	4	4	4	4	2	5	2
1024	5	2	3	5	5	2	2	6	2
~~1036~~	~~2~~	~~4~~							
1037	5	6	5	2	5	5	3	4	2
1050	5	6	4	2	5	6	2	2	2
1053	4	4	6	3	4	5	3	3	3
1055	6	5	6	5	5	5	5	3	3
1060	2	6	6	1	2	6	6	1	6
1067	6	3	4	5	6	3	1	5	1
1070	2	6	5	3	4	3	5	2	5
1074	4	6	6	2	2	6	5	1	5
1075	3	5	5	2	5	6	3	2	4
1088	2	5	6	2	3	6	4	1	4
1092	3	4	4	4	3	4	4	3	4
~~1099~~	~~2~~	~~5~~	~~6~~	~~2~~	~~4~~	~~6~~	~~4~~	~~3~~	~~3~~
1113	5	6	6	2	6	6	4	2	2
1117	4	4	4	4	4	3	4	4	3
1118	6	4	5	5	6	3	3	5	3
1127	5	4	5	2	5	4	4	2	3
~~1131~~	~~4~~	~~4~~	~~5~~	~~2~~	~~5~~	~~5~~	~~4~~	~~3~~	~~3~~
1134	3	6	6	2	4	6	4	1	3
1143	2	6	6	2	2	5	5	2	5
1146	6	2	2	6	6	1	1	6	1
1151	4	5	5	4	4	5	5	3	4
1159	4	3	3	4	4	3	3	4	3
1161	6	4	2	5	6	2	1	5	1
1162	4	6	6	2	5	6	3	1	2
1163	2	6	6	2	2	6	6	1	5
1164	5	4	5	5	5	4	3	4	3
~~1166~~	~~5~~	~~5~~	~~4~~	~~4~~	~~5~~		~~4~~	~~4~~	~~2~~
1168	5	4	4	3	5	5	4	3	4

1169	4	6	6	4	5	6	6	3	5
1171	5	5	5	2	5	5	3	4	3
1172	4	5	5	3	4	4	4	4	4
1174	2	1	6	2	4	6	2	2	1
1176	4	5	4	4	4	4	4	2	4

SF-36V Data with Abdominal Surgery Patient Survey Question 53

Subject ID	Total	Overall Depression Percentile	ASPS Question 53
1001	4	0.44%	9
1002	0	0.00%	10
1004	6	0.67%	5
1015	1	0.11%	10
1017	2	0.22%	10
1020	6	0.67%	5
1024	9	1.00%	3
~~1036~~			
1037	5	0.56%	6
1050	4	0.44%	7
1053	4	0.44%	7
1055	4	0.44%	9
1060	0	0.00%	6
1067	8	0.89%	1
1070	2	0.22%	9
1074	1	0.11%	10
1075	2	0.22%	8
1088	0	0.00%	10
1092	1	0.11%	5
~~1099~~			
1113	3	0.33%	10
1117	6	0.67%	4
1118	7	0.78%	5
1127	3	0.33%	8
~~1131~~			
1134	2	0.22%	10
1143	0	0.00%	10
1146	9	1.00%	0
1151	1	0.11%	3
1159	9	1.00%	4
1161	8	0.89%	6
1162	4	0.44%	10
1163	0	0.00%	10
1164	6	0.67%	3
~~1166~~			

1168	2	0.22%	4
1169	3	0.33%	10
1171	5	0.56%	7
1172	3	0.33%	7
1174	4	0.44%	10
1176	3	0.33%	8

Depression and BMI Data

Depressed Subjects	BMI Elevated w/ Major Depression Comorbidity	BMI Elevated w/o Major Depression Comorbidity
1004		x
1020		x
1024	x	
1067	x	
1092		x
1117	x	
1118		
1146		
1151		
1159		
1161		
1164		
1168		x

APPENDIX: SAVAHCS Psychological Research Surveys

Examples of the following surveys are attached (in paper copy only):

(1) Medical Record Data for Ostomates

(2) SF-36V

(3) Abdominal Surgery Patient Survey