Obesity Induced Colorectal Cancer

THESIS

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ABSTRACT

More than 1.4 billion people in the world are overweight or obese [32]. Colorectal cancer takes the lives of 608,000 people each year[32]. It is important to study the negative impact of obesity on the body and population and the etiology of colorectal cancer. My goal was to create a mathematical model that relates obesity and insulin and captures the impact of increasing levels of insulin on the insulin growth factor -1 (IGF-1) pathway. The model is able to predict a risk of colorectal cancer based on a given insulin level.
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CHAPTER 1
THE RELATIONSHIP BETWEEN OBESITY, INSULIN AND COLORECTAL CANCER

1.1 Obesity

In 2008, more than 1.4 billion adults aged 20 or older, were overweight. Of these, more than 200 million men and nearly 300 million women were obese [32]. Obesity affects not only a staggering amount of adults but children as well. More than 40 million children under the age of five worldwide were overweight in 2010 [32]. Obesity is a global problem that is associated with an increased risk of premature death due to the complications associated with increased adipose tissue [12]. A meta-analysis showed that a 5 kg/m$^2$ increase in body mass index (BMI) raises the risk of colon cancer by 24% in men [29]. Obesity has a direct and independent relationship with colorectal cancer [14]. It is the strongest determinant of insulin resistance and hyperinsulinemia [18]. Obesity is strongly associated with physiological function changes in adipose tissue causing problems such as insulin resistance, chronic inflammation and cancer [17][9].
1.2 Hyperinsulinemia and colorectal cancer

Childhood obesity is linked to adult health complications and hyperinsulinemia. The National Health and Nutrition Examination Study (NHANES) data from 1999-2000 estimated that 15.5% of 12-19 year olds and 15.3% of 6-11 year olds were overweight [9]. Being overweight in childhood and adolescence is significantly associated with insulin resistance in young adulthood [26]. The Bogalusa Heart Study reported that overweight schoolchildren, in comparison with their lean counterparts, were 12.6 times more likely to be hyperinsulinemic [26]. Hyperinsulinemia is a symptom of type 2 diabetes and associated with colorectal cancer [17]. A person with hyperinsulinemia has decreased IGF-binding protein (IGFBP) levels and increased free IGF-1 levels [10][18]. The risk of colorectal cancer is increased twofold for people with hyperinsulinemia [18] because it may indirectly advance colorectal carcinogenesis by inducing changes in circulating IGF-1 and IGF binding proteins [21]. Increases in IGF-1 due to hyperinsulinemia may inhibit apoptosis of transformed and abnormal cells [21].

1.3 Obesity and diabetes

Obesity is correlated with type 2 diabetes, which is characterized by problematic insulin levels. Type 2 diabetes is caused by a resistance to the insulin produced by the β-cells in the pancreas. The blood sugar does not get into the fat, liver, or muscle cells for storage; therefore, high sugar levels build up [15]. In contrast, type 1 diabetes is an autoimmune process that destroys the pancreatic β-cells that synthesize insulin [30]. Risk of type 2 diabetes is nine fold higher for obese than for lean men [12]. Adolescents with type 2 diabetes mellitus are almost always obese [26]. Children and adolescents are more likely to develop full blown type 2 diabetes on a shorter time
scale than adults [9]. β-cell function problems and insulin resistance can be reversed by drastic and sustained energy deficits [13].

1.4 Colorectal Cancer

Colorectal cancer is the third most common cause of cancer deaths [19]. Each year more than 1 million cases of colorectal cancer are diagnosed worldwide [27]. TNF-α appears to contribute to the development of the tissue architecture necessary for tumor growth and metastasis [17]. TNF-α is involved in carcinogenesis because of its ability to activate NF-κB [17]. People with type 2 diabetes have up to a threelfold increased risk of colorectal cancer compared to those without diabetes [10]. Hyperinsulinemia might contribute to cancer development through the growth-promoting effect of elevated levels of insulin [18]. Insulin has been shown to increase the growth of colon epithelial and carcinoma cells in vitro [21]. Diet is linked to as many as 70% of colorectal cancer deaths [1]. For a $2\frac{kg}{m^2}$ increase in BMI, the risk of colorectal cancer increased by 7% [14]. For a 2-cm increase in waist circumference, the risk increases by 4% [14]. The relative risk of colorectal cancer in obese was 1.46 (95% CI, 1.36-1.56) [14].

1.5 Insulin growth factor

When food is consumed the pancreas releases insulin. Insulin signals cells to store or use the glucose from the blood. Chronic excess energy intake causes obesity [18]. Increased adiposity leads to increased insulin resistance [26]. Insulin is less effective in obese than in non-obese in stimulating glucose uptake [20] because of dysregulation of circulating adipokines and cytokines [12]. Increased adiposity increases synthesis of proinflammatory cytokines, such as interleukin 6 (IL-6) [18] and TNF-α [9]. IL-6
regulates immune cell growth, cell differentiation and regulates chronic inflammation [17]. TNF-α inhibits insulin signaling and causes insulin resistance [10]. In response to insulin resistance, β-cells in the pancreas secrete more insulin, but the body is unable to process the insulin and the blood glucose levels rise [21]. As time passes, β-cell function declines linearly [13]. Insulin resistance modifies the insulin growth factor (IGF) system[10], by activating liver production of IGF-1, both of which promote cancer cell proliferation because they act as growth factors [17]. Insulin is positively related to IGF-1 bioavailability [21]. The IGF system consists of two ligands (IGF-1 and IGF-II), two receptors (IGF-1R and IGF-II), six high-affinity-binding proteins and several binding-protein proteases [18]. IGF-1 is produced by most body tissues [31], but predominantly in the liver [21]. It is important in cell growth and development and necessary for cell cycle progression [24]. Once insulin binds with its receptor, the mitogen-activated protein kinase (MAPK) and phosphatidylinositol 3-kinase (PI3K) pathways are activated [29]. The activation leads to increased proliferation and decreased apoptosis [10][21]. IGF-1 levels are elevated during obesity [29]. The concentration of IGF-1 is positively correlated with the risk of pre-menopausal breast, colorectal and prostate cancers [18]. The expression level of IGF-1R is associated with the tumor stage [24]. Increases in IGF-1 bioavailability over long periods of time may increase risk of colorectal cancer [21][17]. Blocking IGF-1R inhibits the growth and survival of human colorectal cancer cells [21].
CHAPTER 2
A MATHEMATICAL APPROACH

2.1 Model Background

The model is based on the relationship among obesity, insulin and the associated risk for colorectal cancer. The input values of insulin come from a meta-analysis conducted to analyze the relationship between BMI and relative risk of colorectal cancer [14]. Moghaddam et al. groups BMI into several ranges and then gives a 95% confidence interval for associated relative risk. I have run a regression analysis on the male cohort studies data and used the average of the BMI range as the BMI value. The regression analysis produced a regression line of relative risk = 0.168445 + .042675* average BMI. I used this data along with the relationship between BMI and insulin as found in Palaniappan et al. [16]. Below is the linear regression plot I created using SAS in Figure 2.1.

The model I derived from the IGF-1 pathway includes insulin as the input and colorectal cancer as the output, so I needed a way to relate BMI and insulin to insulin and colorectal cancer risk. This is why I used the paper by Palaniappan et al. This paper studies the relationship between BMI and fasting insulin among different races of people [16]. I used the male insulin data from the paper in my model. Below is the plot of the relationship where I found the insulin measurements in Figure 2.2.
2.2 Model Schematic

The mathematical representation is based on the IGF-1 pathway, activation of this pathway promotes cancer cell proliferation and inhibition of apoptosis [10][21][18]. Once the ligand binds with the receptor, PI3K is activated which then activates AKT [33][8]. Extracellular signal-regulated kinases (ERK) inhibit mammalian target of rapamycin (mTOR) and mTOR acts on AKT [8] and inhibits PI3K [33]. AKT also inhibits mTOR [8][25]. Rat sarcoma (RAS) activates proto-oncogene serine/threonine-protein kinase (RAF) which activates ERK and inhibits mTOR [7][25] but RAS also
activates mTOR[25]. IGF-1 activates RAS which activates RAF and MAPK leading to cell proliferation and cell survival [17][29]. IGF-1 also activates PI3K which activates AKT activating mTOR leading to cell proliferation and cell survival [17]. Since many of the rates of the proteins are unknown, I have grouped together RAS, RAF, MAPK and ERK as one variable called R. PI3K and AKT are grouped together and called P for simplicity of the model. Below is a schematic of the pathways involved in the development of colorectal cancer in Figure 2.3.
Figure 2.3: A model of the IGF1-R pathway leading to the development of colorectal cancer. Red bars represent inhibition and green arrows represent activation.

### 2.3 Mathematical Model

A mathematical model was derived based on the behavior of the IGF-1 pathway and the activation and inhibitions of the proteins as described in Section 2.2.

\[
\frac{dR}{dt} = k_{IR}I \frac{\bar{R} - R}{k_R + (\bar{R} - R)} - \mu_R R \tag{2.3.1}
\]

\[
\frac{dP}{dt} = k_{IP}I \frac{\bar{P} - P}{k_P + (\bar{P} - P)} \frac{M + c_M}{k_M + M} - \mu_P P \tag{2.3.2}
\]
\[
\frac{dM}{dt} = \frac{\lambda_1 P + \lambda_2 R}{k_{PR} + P} + \frac{\bar{M} - M}{k_M + (\bar{M} - M)} - \mu M \quad (2.3.3)
\]

\[
\frac{dC}{dt} = \epsilon R + \kappa M \quad (2.3.4)
\]

Modeling was done in MATLAB. Below are the various parameters found in the Table 2.1. Note that most parameters are estimated. Due to approximations, various values for the rate of insulin to RAS, RAF, MAPK, ERK \((k_{IR})\) were selected based on the resemblance of their behaviors in real life. The plots can be found in Figures 2.4, 2.5, 2.6 and 2.7. Figure 2.4 shows four plots where time has been changed in each plot and \(k_{IR}\) is 10\(\mu M\). Figure 2.5 shows two plots where time is .001 minutes and \(k_{IR}\) is 10\(^{-2}\)\(\mu M\) in (a) and 10\(^{-1}\)\(\mu M\) in (b). In Figure 2.6, \(k_{IR}\) is fixed at 10\(^{-2}\)\(\mu M\) and time is .01 minutes in (a) and .02 minutes in (b). In Figure 2.7, \(k_{IR}\) is 10\(^{-1}\)\(\mu M\) and time is .01 minutes in (a) and .02 minutes in (b). As final time is increased, the colorectal cancer number increases. As time increases, R, P and M approach 1 while colorectal cancer increases relatively linearly.

\subsection{2.4 Discussion}

Even with estimated parameters, the model is able to capture the behaviors of the actual data. It has been shown that increasing levels of BMI correlate with increasing risk for colorectal cancer [14]. It has also been shown that increases in BMI have been shown to correlate with increasing levels of insulin [16]. It is important to note that correlation does not suggest causation and the relationship between obesity, insulin and colorectal cancer should be further researched. I believe it is important to further research the impact of childhood obesity and how that impacts the IGF-1 pathway and the risk of colorectal cancer in the future.

An example of the model’s practicality is evaluating the changing risk of colorectal cancer for men with changing BMI. For example, an adult man with a height of 5 feet...
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<td>$c_M$</td>
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Table 2.1: Parameter values for the model.

9 inches weighing 230 pounds has a BMI of 34. If that man were to lose 65 pounds and weigh 165 pounds, his BMI would be 24.4, which is considered a normal BMI [32]. Palaniappan et al. shows that the man’s insulin levels would decrease with the drop in BMI [16]. Using the BMI and corresponding insulin levels, the model is able to predict that the man’s risk for colorectal cancer also decreases. The magnitude of the decrease depends on which parameters ($k_{IR}$ or the final time) have been selected.
2.5 Conclusions

The goal was to create a mathematical model that relates obesity and insulin while capturing the impact of increasing levels of insulin on the insulin growth factor -1 (IGF-1) pathway. The model is able to predict a level of colorectal cancer based on a given insulin level that is related to BMI. It is a simplified model because most of the parameters are estimated, so the model could be improved by further studying the rates of the parameters in the model.
The final time is .001 minutes. The final time is .002 minutes.

The final time is .003 minutes. The final time is .004 minutes.

Figure 2.4: The top plots represent the levels of all of the proteins in the model. The bottom plots represent the varying levels of insulin and the respective level of colorectal cancer. Measurements are in $\mu$M. $k_{IR} = 10$. As the final time increases, an increase in colorectal cancer is observed.
The final time is .001 minutes with $k_{IR} = 10^{-2}$.

The final time is .001 minutes with $k_{IR} = 10^{-1}$.

Figure 2.5: The top plots represent the levels of all of the proteins in the model. The bottom plots represent the varying levels of insulin and the respective level of colorectal cancer. As $k_{IR}$ decreases, the relationship between insulin and colorectal cancer changes. With small values of $k_{IR}$, colorectal cancer is not increasing as quickly since the insulin is not activating the RAS, RAF, MAPK, ERK pathway as quickly.
The final time is .01 minutes with $k_{IR} = 10^{-2}$.

The final time is .02 minutes with $k_{IR} = 10^{-2}$.

Figure 2.6: The top plots represent the levels of all of the proteins in the model. The bottom plots represent the varying levels of insulin and the respective level of colorectal cancer. Measurements are in $\mu$M. Time is varied in these two plots.
The final time is .01 minutes with $k_{IR} = 10^{-1}$.

The final time is .02 minutes with $k_{IR} = 10^{-1}$.

Figure 2.7: The top plots represent the levels of all of the proteins in the model. The bottom plots represent the varying levels of insulin and the respective level of colorectal cancer. Measurements are in $\mu\text{M}$. Time is varied in these two plots.


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