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C-REACTIVE PROTEIN AS AN INDICATOR OF CANCER

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Abstract

PURPOSE: Many conflicting reports exist concerning the use of C-reactive protein (CRP) as a biomarker to detect cancer. Several studies have found conflicting evidence of the relationship between CRP and the occurrence of cancer in some populations. Some studies show a positive relation between cancers such as lung and ovarian cancer, and elevated plasma CRP levels. Other studies show no relation between cancer onset and CRP. This study looks at the relation of CRP and cancer and investigates the utility of CRP as a screening method for cancer in a US population based sample.

METHODS: I used extant data from the National Health and Nutrition Examination Survey (NHANES), years 2005-2006. Logistic regression was used to determine the impact of CRP protein levels on cancer controlling for smoking status, gender, age, cardiovascular disease and BMI. CRP was assessed dichotomously as either high (>0.5 mg/dL) or low (<=0.5 mg/dL) according to results from a sensitivity analysis.

RESULTS: Approximately a fifth (19.8%) of participants showed elevated levels of CRP (above 0.5mg/dL). People with elevated CRP had reduced odds of not having cancer (0.684 odds ratio, 95% confidence interval, 0.525 - 0.890) with a sensitivity of 30 and a specificity of 76. Odds ratios for individual cancers differed from cancer taken as a whole.

CONCLUSION: C-reactive protein is not a specific predictor of cancer. While elevated plasma levels of CRP may be present in cancer patients, it is a very non-specific marker of inflammation and can be caused by many other conditions.

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I. Introduction

Current research has found that certain inflammatory chemicals cause damage to the DNA of cells that surround the site of actual inflammation and may subsequently lead to occurrence of diseases such as cancer. Understanding the mechanisms that cause DNA damage is important to inform the development of drugs against the processes, but finding the biomarkers to predict this type of inflammation is just as important (“DNA Damage” 2006). Biomarkers are molecules in the body that indicate a specific physiological status and offer important benefits to medicine, specifically, the potential for early disease diagnosis.

C-reactive protein (CRP) is a biomarker for inflammation that is produced in the hepatocytes in the liver and is stimulated by pro-inflammatory cytokines (Kruse 2010). Many diseases and medical conditions involve some degree of inflammation, which implies that CRP would be present in the blood. Extrapolating this to medical diagnostics, CRP could be used as a biomarker to predict or detect some medical conditions. Diseases such as cancer, which involves some level of inflammation, could benefit from an investigation into the associations between CRP and cancer. This thesis will examine the relationships between CRP and cancer to determine biomarker eligibility in order to aid in future medical diagnoses.

Cancer Threat

Cancer is the uncontrollable growth of cells that occurs in clusters known as tumors. If unchecked, these cells can break off from their clusters and can spread throughout the body, affecting other organs and increasing the likelihood of death. Common organs that are affected by cancer are a person’s breasts, prostate, colon, skin, liver, and lungs. Currently, cancer is the second highest cause of death, killing over 560,000 people per year. As of 2005, 11.1 million people who live in America have a history of cancer. Additionally, 1.5 million new cases were estimated to be diagnosed in 2009 (American Cancer Society 2009).

Treatment for cancer is difficult because of the uncontrollable nature of the disease and because of the patient side effects. Furthermore, it is not always successful no matter how hard the physician tries. For instance, chemotherapy treats cancer with drugs and medicines that target quickly dividing cancer cells, but also kills many healthy cells in the process. This causes patients to be more susceptible to anemia, hair loss, and fatigue. There is also radiation therapy which uses high doses of radiation (ie. X-rays) to target and kill cancer cells. Side effects of radiation include skin changes, loss of appetite, and fatigue. Immunotherapy, often used in collaboration with other treatments, harnesses the power of the immune system by providing artificial immune system proteins. For cancer that is especially hard to remove, organ transplant may be an option to replace the affected organ. This also has many side effects including infection, rejection, long term damage to the kidneys and liver, etc. (American Cancer Society 2009). These treatments all, unfortunately, risk the chance of relapse (regrowth of the cancer) or treatment failure which could result in death.

Potential Biomarker Solution

One reason cancer is such a problem in the US is due to the difficulty of early detection. Biomarkers, along with other physiological symptoms, present a possible solution to this issue because their presence in the blood can be measured and early treatment can be prescribed. Prostate-specific antigen (PSA) is a biomarker that when present in high elevations, can be an indicator of prostate cancer. The presence of the sexually transmitted virus Human Papillomavirus (HPV) on the cervix can warn physicians of potential cervical cancer since HPV is the primary cause of it. Yet another screening test that is specific to breast cancer is the mammogram which takes an x-ray of the breast to locate unusual masses of cells (National Cancer Institute 2006). Finally, there are a few cancers including breast, colorectal, ovarian, and prostate cancer that can be predicted using genetic screening. This can be both beneficial and detrimental – while the patient can take preventative measures and screen more carefully, he or she will be burdened by the fact that cancer is a probable diagnosis at some point during life. Unfortunately, though, the majority of cancer types remain undetectable until they have already begun to cause harm to the body.

Additionally, biomarkers can also predict how a person will react to different types of treatments. For instance, mutations in the gene coding for epidermal growth-factor receptor (EGFR) can indicate whether a lung cancer patient will respond to EGFR inhibitors or whether a colon cancer patient will respond to EGFR-specific antibodies (Sawyers 2008). C-reactive protein has the potential to be a biomarker, but because CRP is an indicator of the relative level of inflammation present in an individual, it is not specific and an indicator of many other conditions. The basal circulating concentration of CRP is genetically determined and has been analyzed (Heikkila 2010), but the levels of CRP can be altered by external factors. To take these into consideration, one must control for possible confounding factors such as Body Mass Index (BMI), cardiovascular disease (CVD) (Chang 2010), gender, age, smoking status, and other demographic characteristics. Nonetheless, many studies have hypothesized that high levels of inflammation increase the risk of some types of cancer. Investigating the correlation between levels of c-reactive protein in the blood and the incidence of cancer would allow for earlier detection of cancer in individuals who may not have known their status and get them treatment at an earlier and more manageable stage.

Current Evidence

Current scientific literature provides contradictory evidence regarding CRP's relationship with cancer. Some investigators present no correlation between high CRP levels and the incidence of cancer (Kruse 2010) (Allin 2010), and some show a relationship between high CRP levels and certain types of cancer (Aleksandrov 2010) (Chang 2010) (Heikkila 2010). The specific types of cancer that were proven to be associated with high CRP levels were colon (Aleksandrov 2010), gastric (Chang 2010), and lung (Heikkila 2010) cancers, and rectal (Aleksandrov 2010) and oral squamous cell carcinoma (Kruse 2010) were proven specifically to have no relation to CRP. In much of the literature, associations were evaluated purely by statistical analysis of CRP level. The levels are often not measured the same way, leaving discrepancies between the conclusions from studies because of the occasional mis-classification of high CRP levels. For instance, some studies use the cutoff point of 5mg/L to decide between low and high levels, while other studies use the groupings "low (<1 mg/L), average (1.0 - 3.0 mg/L), and high (>3.0 mg/L)" (American Heart Association 2010). However, as long as clear cutoff points are described, the discussion of each respective study is valid but must be carefully considered.

CRP Function and Possible Mechanism

When c-reactive protein is released into the blood stream, it primarily binds with phosphocholine residues in response to a damaged cell or inflammation. This binding signals a phagocytic immune response so that the cell can be destroyed. A secondary function of CRP is one that mimics the function of antibodies – binding to antigens – in the immune response. Therefore, CRP acts as a defense against infection in two ways. (Pepys 2003)

The direction of the possible relationship between CRP and cancer is undetermined and could occur either way – the cancer could cause the high CRP levels or the high CRP levels could contribute to the incidence of cancer. Circulating cancer cells that have broken off from the primary tumor and extravasated into the blood stream may appear as foreign to the body because of their non-uniform characteristics. If so, the immune system would respond and CRP levels would rise to perform either of the two functions listed above. Alternatively, the existence of high CRP levels could cause cancer to begin to form. CRP is triggered by inflammation, which can be caused by a whole host of problems. Therefore, the body is focusing all of its healing efforts on the problem at hand. This could create a more favorable environment for cancer to begin to form because the immune system is focused on problems other than eliminating uncontrollable cell growth. Therefore, because of the physiological problems that caused high CRP levels, cancer could potentially form more easily. While only hypothetical for the time being, these possible mechanisms could explain a relationship between CRP and cancer, if one is found.

The diagram shown in Figure 1 shows the known and hypothesized associations between different variables and elevated CRP levels. The demographic variables – gender, BMI, smoking status, and age – are related to both elevated CRP levels and clinical variables. Likewise, clinical diagnoses – cancer, cardiovascular disease, depression, and lack of sleep – affect and are affected by high CRP levels and demographic variables. This connection between all demographics, clinical diagnoses, and elevated DRP levels makes causality difficult to determine without other information, but does allow for helpful associations to be demonstrated.

Purpose

This thesis will use extant data from the 2005-2006 NHANES to examine the relationship between c-reactive protein and cancer, and whether or not CRP can be considered an early biomarker for cancer. Specifically, this thesis aims to:

1. Examine the predictors of CRP including demographic characteristics and psychological stressors.
    a. I predict that CRP will increase with age and BMI and will be relatively consistent between genders.
2. Examine the distribution of CRP levels across people with and without cancer. Analyze sensitivity and specificity of CRP with respect to cancer.
    a. I predict that people with cancer will have higher CRP than people without cancer.
3. Examine the association between elevated levels of CRP and having cancer accounting for demographic characteristics and psychological stressors.
    a. Taking into account the potentially confounding variables (demographic characteristics and psychological stressors), I predict that cancer will often coexist with elevated CRP levels.

High levels of CRP are expected to be related to the incidence of cancer because of existing empirical evidence in published articles' of an association with certain types of cancer. For example, associations between high CRP and colon cancer (Aleksandrova 2010) (Heikkila 2010) and high CRP and gastric cancer (Chang 2010) have been identified. Overall, the main goal of this thesis is to evaluate elevated CRP levels as an early indicator of cancer while controlling for potential confounding factors.

II. Materials and Methods

Data and Study Population

Data from the 2005-2006 National Health and Nutrition Examination Survey (NHANES) was used to complete this investigation. The NHANES is a survey that combines interviews with physical exams and laboratory tests to assess the physical, nutritional, and mental health of the United States population. The overriding goal of NHANES is to create a database of information to be used for epidemiologic studies nationwide. The study also allows the Center for Disease Control and Prevention (CDC), the sponsor of NHANES, to monitor the prevalence of major diseases and risk factors.

To gather the data, mobile health centers traveled across the country to perform physical exams on a sample of subjects that is representative of the US population. The same subjects were then interviewed in their homes. In the mobile center, electronic equipment like digital scales and stadiometers was used for transmission of the measurements to a database. Interviewers used laptop computers with touch screens to record responses that are entered by the subjects themselves.

The sample of people used includes 5,000 people from fifteen different counties across the U.S. All households in each county receive information mailed to them about the survey, and the media may advertise the survey as well. Furthermore, to ensure that people of all socioeconomic backgrounds are included, transportation is provided if necessary. All ages and races of the country's population are included in the survey, and to produce reliable data, African Americans, Hispanics, and people over the age of 60 years are over-sampled. Participants receive compensation and are provided with a medical report of all measurements taken.

Chart 1 shows that the population-based sample was split pretty evenly between male and female, with a mean age of 43 years and a BMI of 25.1 which is slightly overweight according to the national BMI standards.

Measurement

Outcome of Interest

C-reactive protein amounts (variable name LBXCRP) were evaluated by latex-enhanced nephelometry using samples of 500 microliters of blood drawn by a phlebotomist. Levels of c-reactive protein were stratified into 2 categories after a sensitivity analysis: low was considered below 0.5 mg/dL and high was greater than or equal to 0.5 mg/dL. The decision to separate low from high was based on the results in the sensitivity analysis in Chart 2.

Main Covariate of Interest

Cancer was identified by patients' self report of ever being diagnosed with cancer.

Cancer Status (MCQ.220): Have you ever been told by a doctor or other health professional that you had cancer or a malignancy of any kind?

Answers: Yes, No, Refuse, Don't Know

Other Covariates

Demographics

Specifically, age in years (code dmdhrage), gender (code riagendr), and BMI (code bmxbmi) were used for this study.

Other Covariates

The occurrence of proinflammatory diseases was controlled for because it provides external explanations for high CRP levels. Diabetes is associated with the risk of developing type II diabetes (Hu 2004) and CRP is confirmed as an independent risk factor of hypertension (Sung 2003). Other variables are cardiovascular disease (CVD) and smoking status. Theoretically, these variables all either have the capability of causing inflammation (and therefore, higher than normal CRP levels) or making one more susceptible to high CRP.

Cardiovascular Disease Status (MCQ.160c): Have you ever been told by a doctor or other health professional that you had coronary heart disease?

Answers: Yes, No, Refuse, Don't Know

Smoking Status (SMQ.040): Do you now smoke cigarettes…

Answers: Yes (Every day + Some days), Not At All, Refuse, Don't Know

Psychological stressors that will be considered are depression and lack of sleep.

Lack of Sleep Status (SLQ.060): Have you ever been told by a doctor or other health professional that you have a sleeping disorder?

Answers: Yes, No, Refuse, Don't Know

Depression Status (DPQ.020): Over the last 2 weeks, how often have you been bothered by the following problems: feeling down, depressed, or hopeless?

<u>Answers</u>: Not At All, Several Days, More Than Half the Days, Nearly Every Day, Refused, Don't Know

Analytic Method

Descriptive statistics including means and standard deviations for continuous variables and frequencies for categorical variables were assessed in order to describe the sample.

Methods for specific aim 1

Chi-square analysis was conducted to examine the bivariate relationship that demographic variables (age, BMI, gender) and psychological stressors (depression, lack of sleep) have with elevated CRP levels. Pearson's correlation coefficients were calculated among age, BMI, gender, depression, and lack of sleep. Additionally, correlation coefficients were determined for smoking habits and cardiovascular disease to evaluate and confirm their positive relationship with elevated CRP levels.

Methods for specific aim 2

Chi Square tests were employed and Pearson's correlation coefficients to study the bivariate relationship between elevated CRP levels and people with and without cancer. Additionally, sensitivity and specificity was calculated to assess the proportion of actual cancer cases which are correctly identified by CRP level and the proportion of negatives which are correctly identified.

Methods for specific aim 3

Logistic regression models were used to determine the relationship between cancer (outcome) and c-reactive protein levels controlling for gender, age, smoking status, and history of cardio vascular disease. Similarly, logistic regression was used to determine the relationship between high (>0.5mg/dl) versus low (<=0.5mg/dl) c-reactive protein levels and cancer controlling for gender, age, smoking status, and history of cardiovascular disease.

A multivariate linear regression model was used to determine the relationship between c-reactive protein levels and the occurrence of cancer controlling for gender, age, smoking status, and history of cardio vascular disease. The probability of low CRP (<=0.5mg/dl) was modeled in all regression models.

III. Results

Summary of Results

A sample population that was fairly representative of the true population yielded analyses that illustrated several important relationships between variables. Both bivariate analyses and logistic regressions were employed to evaluate these relationships. C-reactive protein was analyzed both as a dichotomous variable (split at 5 mg/dL) and as a continuous variable to check for errors that may have been introduced by using a cutoff (determined in Chart 2) rather than a continuous variable. Nevertheless, the associations between cancer and high CRP levels proved to be different from what was expected, but still proved to be enlightening.

Sample Descriptives

The average age of the sample is 43.6 and half is female. Approximately 8 percent of the sample had a personal history of cancer. Almost 20 percent had high CRP. Four percent had CVD, six percent diabetes, almost half of the sample had been past or are current smokers, six percent had a sleep disorder, and over 20 percent had a personal history of depression. The exact frequencies and strata sample sizes can be seen in Chart 1.

Results by Study

Results for aim 1

Chi-square tests were utilized to study the bivariate relationship between cancers and the other study variables to people with high and low CRP values. The bivariate relationships shown in Chart 3 indicate that some variables were associated with high c-reactive protein levels, while others were not. Several conditions and variables are statistically significant, having p-values below .05, and therefore have a relationship to high CRP levels. These include cancer, sleeping disorder, depression, diabetes, gender, and BMI. Cancer is associated with high CRP levels ($p=.0063$). Among people with high CRP, over 10% had cancer as opposed to 7.7% that have low CRP. Among people with high CRP, slightly less than 10% had sleep problems as opposed to 5.1% that have low CRP ($p<.0001$). Over a quarter of people with high CRP have depression compared to 20.1% of those with low CRP ($p=.0011$). The association between high CRP and diabetes is very strong ($p<.0001$). Approximately 16% of participants with high CRP had diabetes as opposed to 5% of those with low CRP.

Gender is strongly associated with high CRP ($p<.0001$), with women having higher CRP levels than men. Finally, BMI has a strong relationship with high CRP levels ($p<.0001$); people with high CRP levels have a higher average BMI than those with low CRP levels. Meanwhile cardiovascular disease ($p=.256$), smoking ($p=.369$), and age ($p=.373$) are statistically insignificant as indicated by their high p-values. Details of the chi-square analysis of the variables with elevated CRP levels can be found in Chart 3.

Results for aim 2

Chi-square tests were utilized to study the bivariate relationship between CRP levels and the other study variables to people with and without cancer, as shown in Chart 4. Several variables were found to have significant associations with the occurrence of cancer – high CRP levels, cardiovascular disease, sleeping disorders, diabetes, age, and BMI.

As noted previously, CRP is significantly related to a history of cancer. Among these with cancer, 30.2% had elevated CRP, compared to 24.1% of those without a history of cancer.

Cardiovascular disease has a strong relationship ($p<.0001$) with the occurrence of cancer. Over ten percent of individuals with cancer had CVD as opposed to 3.4% of those with no personal history of cancer ($p<0.0001$). Similarly, almost 13 percent of individuals with cancer had sleeping problems as opposed to 6.5% of those with no personal history of cancer ($p<.0001$). Diabetes has a similar strong relationship with cancer occurrence ($p<.0001$) and people with cancer are more likely to have a diabetes (11.5%) compared to individuals with no personal cancer history (10.9%). Age has a strong association with cancer ($p<.0001$); the average age for people with cancer (65) is significantly higher than the mean age for subjects who never had cancer (48). Finally, BMI has a significant relationship with cancer occurrence ($p=.0066$). This is because the mean BMI for cancer-stricken subjects (27.9) is less than the mean BMI for patients who never suffered from cancer (28.8). Smoking ($p=.4271$), depression ($p=.6381$), and gender ($p=.0813$) were not found to have significant relationships with the occurrence of cancer. The detailed values from the chi-square analysis can be located in Chart 4.

Chart 5 displays the results of the sensitivity and specificity analysis. While the level specificity is acceptable (0.76), meaning that CRP is a reasonable marker for identifying individuals who do not have cancer, it is not a sensitive marker (0.30), meaning that CRP is a poor identifier of those who do have cancer.

Results for aim 3

The logistic regression models in Charts 6, 7, and 8 provide important results in the analysis of the relationship between CRP and cancer. Prior to investigating the multivariable relationship between cancer and CRP controlling for clinical and socio-demographic variables, bivariate regression analysis shows that compared to individuals with low CRP, individuals with high CRP level, have lower odds (OR=0.735, CI; 0.589, 0.917, p=.0064) of being cancer-free.

Potentially confounding variables were included when the probability of not having cancer was modeled and CRP was split dichotomously at 5mg/dL in Chart 6. Results showed that people with high CRP have decreased odds (OR=0.68) of being cancer-free compared to those with low CRP (p=.0048). The same analysis proved significant relationships for cardiovascular disease, past smoking, sleeping disorders, gender, age, and BMI. The occurrence of cardiovascular disease (OR=0.63, p=.0302) and having a history of smoking (OR=0.63, p=.0010) were associated with decreased odds of cancer absence. Sleeping disorders proved a strong association (p<.0001) so that the odds of not having cancer was 2.3 fold greater for those who do not suffer from sleep disorders compared to participants with abnormal sleep patterns. Males versus females (OR=1.45) and individual with slightly increased BMI (OR=1.03) have increased odds of not having cancer. For each additional year of age, the odds of remaining cancer free are reduced by about 5% (OR=0.948).

Chart 7 details the probability of not having a history of cancer, but this time CRP was analyzed as a continuous variable. The major relationship between not having cancer and CRP was concluded insignificant because the p-value was above the conventional 0.05 level (p=.2172). The rest of the logistic regression yielded similar results as those in Chart 6. Some p-values were slightly different but all of the significant odds ratios stayed essentially the same, and the insignificant ones did as well.

Logistic regression modeling the probability of high CRP levels was modeled next to check the inverse of the cancer-CRP relationship. The analysis where CRP is dichotomous is shown in Chart 8. This analysis yielded few significant results, but those with low enough p-values were cancer, smoking, gender, and BMI. Individuals who have/have had cancer have odds of having high CRP that are 1.5 times greater than the odds for those with no personal history of cancer (p=.0021). Individuals who never smoked have decreased odds of high CRP levels compared to those who currently or formerly smoked (p=.0067).

IV. Discussion

CRP and Cancer

While this study found high CRP levels and cancer to be associated with each other, several studies found no connection between the two. Kruse (2010) and Allin (2010) both concluded that there was no correlation between the two, while looking at cancer as a single variable. Other studies looked at specific types of cancer. Pancreatic (Douglas 2010), rectal (Aleksandrov 2010) and oral squamous cell carcinoma (Kruse 2010) were found to have no relation to CRP levels, while colon (Aleksandrov 2010), gastric (Chang 2010), esophageal squamous cell carcinoma (Nozoe 2003) and lung (Heikkila 2010) cancers had unexplained, but significant relationships. These studies into specific types of cancers suggest that inflammation may be involved more in some cancers than in others and may explain why this study differed from the findings of Kruse (2010) and Allin (2010). The different patient populations and probably varying distributions of cancer types between this study and those of Kruse (2010) and Allin (2010) may elucidate the disagreement in conclusions.

Demographic Variables & Psychological Stressors

Although this study suggests an association between CRP and cancer, CRP is not specific to cancer. More broadly, it is related to inflammation throughout the body which can be associated with a variety of diseases and conditions.

Cardiovascular Disease

According to Brull, high CRP levels are indicators of both the prediction and pathogenesis of cardiovascular disease (Brull 2003). However, the results of this study found no significant relationship between high levels of CRP and cardiovascular disease. This is contradictory to all of the studies that have found such a connection (Ridker 2000) (Tracy 1997). Subjects for whom this relationship is significant may have been omitted from the analysis because of unmeasured variables, such as disability, which prevented them from participating in this study.

On the other hand, a relationship between cardiovascular disease and cancer was found by both bivariate analysis and logistic regression. This conclusion resonates in a study by Huddart that observed long-term testicular cancer survivors having twice the risk of developing cardiovascular disease compared to someone without cancer due to increased cholesterol and hypertension in these cancer survivors (Huddart 2003).

Smoking

A significant correlation between cancer and smoking was confirmed in multivariate logistic regression analysis, although not by bivariate analysis. Smoking is notorious for being a contributing cause of lung cancer. Smoking causes 90% of lung cancer in men and 80% of lung cancer in women (Center for Disease Control).

Smoking was concluded to be associated with high CRP levels by logistic regression (not bivariate analysis). Similar to findings from other epidemiologists, those who have never smoked have lower levels of CRP than those who currently or formerly smoked (Hastie 2008).

Sleeping Disorder

Sleeping disorders were strongly associated with high CRP in the bivariate analysis. A study from Stanford University performed a study on CRP levels and sleep-disordered breathing and (Guilleminault 2004) This could be attributed to sleeping disorders weakening the body's immune system so that the immune system is less able to deal with inflammation and residual inflammation (and thereby, high CRP) remains in the body longer.

Bivariate analysis results showed that a higher proportion of subjects with cancer had sleeping disorders when compared to the proportion of cancer-free subjects with sleeping disorders. Likewise, logistic regression showed that people without sleeping disorders were more likely to not have cancer than those with sleeping disorders. The regression results complement the results from the bivariate analysis.

Depression

Bivariate analysis concluded that more people with high CRP levels are concurrently depressed compared to subjects with low CRP levelss. This aligns with research done by Dr. Yunsheng Ma, who concluded that individuals with higher depression scores also have higher levels of CRP. However, this conclusion was limited to women due to insufficient support for a male depression-CRP relationship. One reason Ma proposed for this connection was because of "the impact that depression has on neuroendocrine pathways that influence the pathogenesis and progression of coronary atherosclerosis and subsequent heart disease [including inflammatory markers, particularly CRP]" (page 1, Ma 2010).

No association was found between cancer and depression. This contradicts with studies that concluded a relationship between cancer and depression. One of these studies by Dr. Sandra

Sephton confirmed this relationship in a study about breast cancer and proposed that cancer progression is facilitated by cortisol changes that alter immune defense mechanisms. Abnormal patterns of cortisol release are also linked with depression (Sephton 2009).

Diabetes

Diabetes showed a strong relationship with CRP by bivariate analysis. There are three times as many people with diabetes and high CRP when compared with people with diabetes and low CRP. The reason for this seems to be because CRP, along with interleukin-6, is a risk factor for diabetes (Pradhan 2001) (Hu 2004). This high CRP will continue throughout the diabetes diagnosis and cause the relationship. “Inflammatory cytokines secreted by adipose tissue exert an endocrine effect conferring insulin resistance in liver” (Hu 2004). These inflammatory cytokines released by fat cells trigger the production of CRP, which also promotes insulin resistance.

Cancer was also associated with diabetes in the bivariate analysis performed in this study. The percentage of people with cancer who had diabetes was higher than amoung people without a cancer history who had diabetes (11.5% vs. 10.9% respectively). This association is endorsed by assertions made by a research group in Catania, Italy. This group has found that “risk of several types of cancer (including pancreas, liver, breast, colorectal, urinary tract, and female reproductive organs) is increased in diabetic patients” (Vigneri 2009). Furthermore, Vigneri asserts that insulin is a growth factor, causing cell division, and acts in malignant cells both at the receptor and the post-receptor level (Vigneri 2009). Since hyperinsulinemia – a high concentration of insulin in the blood – is often associated with diabetes (Collazo-Clavell 2009), diabetes can be considered a potential promoter of cancerous growth.

Gender

Gender's relationship with high CRP levels showed that women are more likely to have higher CRP than men. Researchers from the University of Texas also found women to have higher CRP levels than men (Khera 2005). This conclusion was further validated by Lakoski's research group who found that CRP levels are 40% higher in women than men. This group also suggests that hormones, primarily estrogen, are responsible for this. Lakoski, et al. suggests that since female CRP levels are higher than men while women simultaneously have a lower risk of cardiovascular disease, medical professionals should consider creating different diagnostic cutoffs for men and women (Lakoski 2006).

Gender was not found to have an association with cancer by bivariate analysis, but logistic regression did find a notable relationship. Men were more likely not to have cancer than women. This is probably due to physiological differences between genders and their hormones. For instance, although a study by Naugler et al. illustrates men being more prone to liver cancer than women, it illustrates the effect of physiological differences (Naugler 2007). Considering the plethora of cancer types, these physiological differences create a net effect of women being more prone to cancer than men.

Age

As expected, age has a strong relationship with cancer. As the body ages, the amount of cell division cycles has become so great that mutations have accumulated and the odds of cancer increases. The Center for Disease Control confirms this age trend by reporting that between 2000 and 2003, the median age for cancer diagnosis was 67 years.

Age was not found to be associated at all with CRP in either logistic regression or bivariate analysis. This is different from the results of a study that found CRP levels increasing with age (Ferrucci 2005). Ferrucci suggested later in his study that this increase may be in part from higher prevalence of cardiovascular disease later in life, although when cardiovascular disease was analyzed as a confounding variable, it was only found to make a significant impact in male CRP levels. This suggests that female cardiovascular disease is related to something other than CRP.

BMI

Body Mass Index ranking was shown by bivariate analysis and logistic regression to be associated with high CRP levels. Several studies (Vissner 1999) (Frolich 2003) (Hak 1999) agree with this positive correlation between BMI and high CRP.

Subjects' BMI rankings had a surprising association with cancer. The mean BMI for cancer patients was lower than the mean BMI for cancer-free subjects, and people with higher BMI's were more likely to not have a cancer history than people with lower BMI's. While these conclusions from bivariate analysis and logistic regression agree with each other, they disagree with other studies that have been done. For instance, a study by Dr. Renehan in the United Kingdom found that increased BMI is associated with an increased risk of cancer (Renehan 2008). This disagreement may be attributed to the way questions were asked (NHANES asked if subjects had a history of cancer rather than only current cancer).

Study Limitations

It cannot be ignored that there are several limitations introduced both in the analysis of the NHANES data and the collection of the data itself. The type of analysis used to obtain these results was a cross sectional study. By nature, a cross sectional study cannot determine causation. While associations can be made, it cannot be said that one variable causes the desired outcome, in this case, cancer. Another limitation that is present because of the study's design has to do with the stratification of c-reactive protein levels. Despite the sensitivity analysis found in Chart 2, the cutoff levels might not have been suitable to detect associations if there were some.

The manner of looking at cancer also posed a limitation to the study. All types of cancers were looked at as one outcome for this analysis. While c-reactive protein levels did not show an association with all cancers, if individual cancer were looked at, an association could have been present. To determine definitively that there is no association between c-reactive protein and cancer, all cancers should be looked at individually. Finally, this study was limited because of the nature of the self-reported data. All of the questions regarding cancer and cardiovascular disease asked if the subject had ever been diagnosed with either condition. The problem with this type of question is that it was label people who have not been diagnosed but still have the disease as not having it. Furthermore, there is no data on the severity of the cancer or cardiovascular disease which could greatly affect the presence of c-reactive protein.

Summary

Each analysis that was performed in this study proved that there is some association between CRP and cancer occurrence. Unfortunately, no causality can be designated, so it is unknown whether CRP causes cancer or vice versa within the scope of this study. CRP does have associations with some of the covariates however, and these relationships were observed in the analyses and duly noted. Furthermore, although the bivariate analyses and regression studies proved significant relationships, the sensitivity and specificity analysis concluded that CRP is not sensitive enough to be used as a biomarker of cancer. However, since the concept of an early-cancer biomarker remains a valuable commodity, more research should be done to analyze other important molecules in the body. Investigation and discovery of new cancer biomarkers could lead to increased health and fewer deaths in developed countries where cancer remains to be an untamed threat.

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Appendices

Appendix A. Figures and Tables

Figure 1. Proposed mechanisms leading to high CRP levels

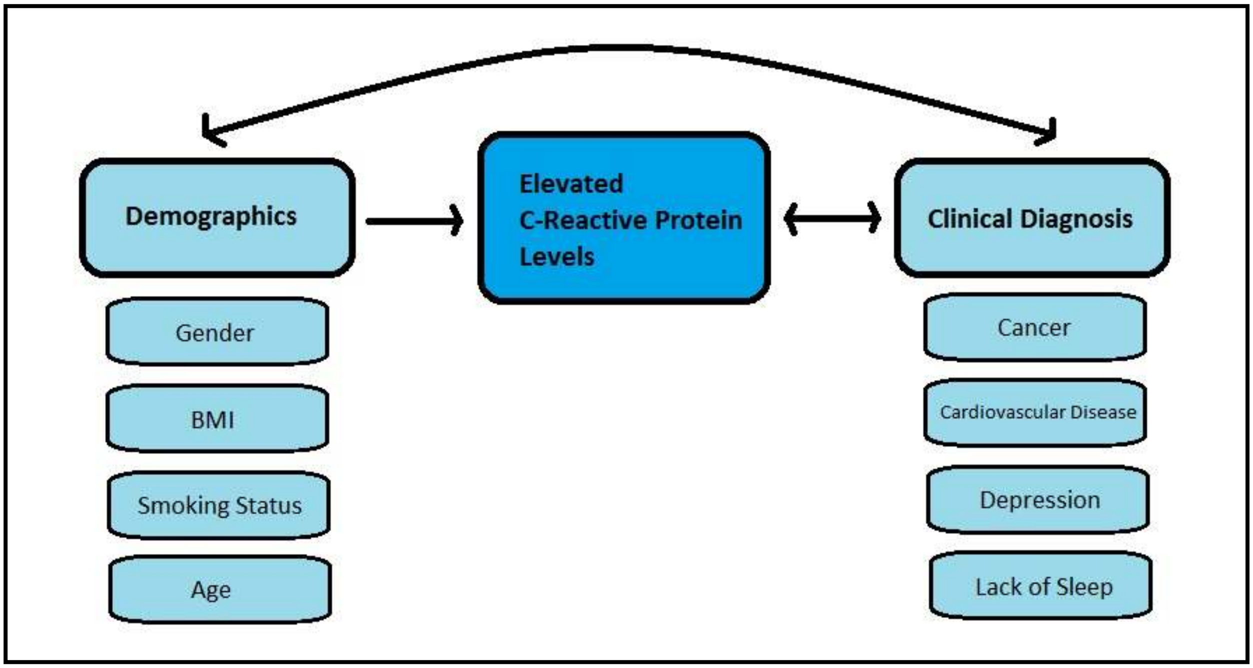

Chart 1. Frequency Distributions for Variables of Interest

	Frequency %	Sample size for strata (n)
Cancer		
Yes	8.3	411
No	91.7	4538
C-Reactive Protein		
<.5mg/dL	80.16	4921
>.5mg/dL	19.84	1218
Continuous	Xbar=0.488, (SD)=0.857	N=4465
Cardiovascular disease		
Yes	4.04	200
No	95.96	4749
Smoking		
Current	21.95	1085
Past	25.21	1246
Never	52.84	2612
Sleeping Disorder		
Yes	6.03	370
No	93.97	5763
Depression		
Yes	21.98	1064
No	78.02	3769
Diabetes		
Yes	6.36	624
No	93.64	9189
Gender		
Male	49.09	5080
Female	50.91	5268
Age	Xbar=43.6, (SD)=16.02	N=10348
BMI	Xbar= 25.09, (SD)= 7.55	N=8949

Chart 2. CRP Sensitivity Analysis

CRP Sensitivity Analysis		
		Point Estimate (Odds Ratio Estimates)
CRP Variable Cutoffs (mg/L)	1	.848 (.585, 1.230)
	2	.884 (.637, 1.227)
	3	.824 (.595, 1.141)
	4	.741 (.530, 1.035)
	5	.722 (.510, 1.021)
	6	.713 (.496, 1.024)
	7	.805 (.546, 1.187)
	8	.709 (.475, 1.058)
	9	.718 (.469, 1.098)
	10	.714 (.454, 1.122)
	Continuous	.897 (.745, 1.081)

**95% Walds Confidence Intervals*

Chart 3. Bivariate Analysis of CRP

N=9813	CRP<0.5mg/dL (n, %)	CRP>=0.5mg/dL (n, %)
Cancer *p=.0063		
%Yes	287, 7.7%	124, 10.2%
Cardiovascular disease p=.2560		
%Yes	144, 3.8%	56, 4.6%
Smoking Past p=.3690		
Current	827, 24.8%	258, 26.4%
Past	925, 22.2%	321, 21.0%
Never	1974, 53.0%	638, 52.4%
Sleeping Disorder **p<.0001		
Yes	250, 5.1%	120, 9.9%
Depression *p=.0011		
Yes	775, 20.1%	287, 25.5%
Diabetes **p<.0001		
Yes	429, 4.99%	195, 16.04%
Gender **p<.0001		
Male	1940, 52.0%	431, 35.9%
Female	1791, 48.0%	787, 64.1%
Age p=.373	Xbar(SD)= 49.161 (18.146)	Xbar(SD)= 49.695 (18.081)
BMI ~~p<.0001	Xbar(SD) = 27.468 (5.518)	Xbar(SD) = 32.543 (8.389)
*	X^2, sig at $p<.05$	
**	X^2, sig at $p<.0001$	
~	T-test, sig at $p<.05$	
~~	T-test, sig at $p<.0001$	

Chart 4. Bivariate Analysis of Cancer

	Cancer	No Cancer
CRP *p=.0063		
>0.5mg/dL	124, 30.2%	1094, 24.1%
<0.5mg/dL	287, 69.8%	3444, 75.9%
Continuous p=.2050	Xbar(SD) = .5418 (.7003)	Xbar(SD) = .4827 (.8692)
Cardiovascular disease **p<.0001		
Yes	44, 10.7%	156, 3.4%
Smoking Present p=.4271		
Current	67, 39.76%	1018, 23.89%
Past	180, 16.34%	2432, 22.46%
Never	180, 43.90%	2432, 53.65%
Sleeping Disorder **p<.0001		
Yes	53, 12.9%	288, 6.5%
Depression p=.6381		
Yes	79, 22.7%	853,21.6%
Diabetes **p<.0001		
Yes	78, 11.5%	507, 10.9%
Gender p=.0813		
Male	180, 43.8%	2192, 48.3%
Female	231, 56.2%	2347, 51.7%
Age ~~p<.0001	Xbar(SD) = 65.23(15.967)	Xbar(SD) = 47.85(17.616)
BMI ~p=.0066	Xbar(SD) = 27.86(5.8506)	Xbar(SD) = 28.843(6.815)
*	X^2, sig at p<.05	
**	X^2, sig at p<.0001	
~	T-test, sig at p<.05	
~~	T-test, sig at p<.0001	

Chart 5. Sensitivity and Specificity Chart

	Cancer	No Cancer	CRP Strata Totals
High CRP (>=0.5mg/dL)	124	1094	1218
Low CRP (<0.5mg/dL)	287	3444	3731
Cancer Totals	411	4538	4949

Sensitivity = 124 / (124+287) = 0.302

Specificity = 3444 / (3444+ 1094) = 0.759

Chart 6. Logistic regression. Probability of not having cancer was modeled. CRP is dichotomous

Variable	OR (CI)	P value
C-Reactive Protein (high vs. low)	.684 (.525, .890)	.0048
Cardiovascular Disease (yes vs. no)	.629 (.413, .956)	.0302
Smoking (present vs. never)	.963 (.679, 1.365)	.2542
Smoking (past vs. never)	.634 (.486, .826)	.0010
Sleeping Disorder (no vs. yes)	2.349 (1.613, 3.422)	<.0001
Depression (no vs. yes)	1.163 (.873, 1.550)	.3017
Diabetes (no vs. yes)	.997 (.722, 1.377)	.9871
Gender (male vs. female)	1.457 (1.138, 1.865)	.0028
Age	.948 (.941, .955)	<.0001
BMI	1.038 (1.016, 1.060)	.0005

Chart 7. Logistic regression. Probability of not having cancer was modeled. CRP is continuous

Variable	OR (CI)	P value
C-Reactive Protein (high vs. low)	.920 (.807, 1.050)	.2172
Cardiovascular Disease (yes vs. no)	.637 (.415, .976)	.0385
Smoking (present vs. never)	.940 (.661, 1.337)	.3126
Smoking (past vs. never)	.629 (.481, .823)	.0014
Sleeping Disorder (no vs. yes)	2.392 (1.636, 3.497)	<.0001
Depression (no vs. yes)	1.198 (.897, 1.599)	.2220
Diabetes (no vs. yes)	.964 (.692, 1.344)	.8302
Gender (male vs. female)	1.559 (1.213, 2.003)	.0005
Age	.949 (.941, .956)	<.0001
BMI	1.031 (1.009, 1.052)	.0044

Chart 8. Logistic regression. Model the probability of high CRP. CRP is dichotomous.

Variable	OR (CI)	P value
Cancer (no vs. yes)	1.519 (1.164, 1.982)	.0021
Cardiovascular Disease (yes vs. no)	1.112 (.760, 1.627)	.5855
Smoking (treated as continuous)*	.883 (.807, .966)	.0067
Sleeping Disorder (no vs. yes)	.922 (.693, 1.227)	.5763
Depression (no vs. yes)	.922 (.770, 1.103)	.3741
Diabetes (no vs. yes)	.885 (.704, 1.112)	.2926
Gender (male vs. female)	.488 (.417, .570)	<.0001
Age	.999 (.995, 1.004)	.7382
BMI	1.124 (1.110, 1.137)	<.0001

***Do to an artifact of the data (confidence interval and p-value were discordant), this variable was treated at continuous for this particular regression model. Numerically, smoking is listed from 2=smoker to 0=never smoker. So a one unit increase in smoking score corresponds to going from current to past and past to never.**

Appendix B. SAS Program

```
libname kelley '\\udrive.win.psu.edu\users\k\j\kjb5133\Desktop\HPA 440';
data kelley.thesis; set kelley.new;
if MCQ220 ne 9;
if MCQ160C ne 9;
**crp cutoffs for sensitivity analysis**;
if lbxcrp lt .1 then creact1=0; if lbxcrp ge .1 then creact1=1;
if lbxcrp lt .2 then creact2=0; if lbxcrp ge .2 then creact2=1;
if lbxcrp lt .3 then creact3=0; if lbxcrp ge .3 then creact3=1;
if lbxcrp lt .4 then creact4=0; if lbxcrp ge .4 then creact4=1;
if lbxcrp lt .5 then creact5=0; if lbxcrp ge .5 then creact5=1;
if lbxcrp lt .6 then creact6=0; if lbxcrp ge .6 then creact6=1;
if lbxcrp lt .7 then creact7=0; if lbxcrp ge .7 then creact7=1;
if lbxcrp lt .8 then creact8=0; if lbxcrp ge .8 then creact8=1;
if lbxcrp lt .9 then creact9=0; if lbxcrp ge .9 then creact9=1;
if lbxcrp lt 1.0 then creact10=0; if lbxcrp ge 1.0 then creact10=1;
**depression variable**;
if dpq020 = 1 then depress=1; if dpq020 = 2 then depress=1; if dpq020 = 3 then depress=1; if dpq020 = 0 then
depress=0;
if dpq020 ne 7 or 9;
**sleep variable**;
if slq060 = 1 then sleep=1; if slq060 = 2 then sleep = 0;
if slq060 ne 7 or 9;
**smoking variables**;
**overall**;
if smq020 eq 2 then smoke1=2;
if smq040 eq 1 or smq040 eq 2 then smoke1=1; **current**;
if smq040 eq 3 then smoke1=0; **past**;
**now versus never**;
if smq020 eq 2 then smokenow=0;
if smq040 eq 1 or smq040 eq 2 then smokenow=1; **current**;
**then versus never**;
if smq020 eq 2 then smokethen=0;
if smq040 eq 3 then smokethen=1; **past**;
**diabetes variable**;
if diq010 eq 1 or diq010 eq 3 then diabetes=1;
if diq010 eq 2 then diabetes=0;
if diq010 ne 7 or 9;
proc contents; run;
proc freq; tables MCQ220 MCQ160C creact6 riagendr sleep depress smokenow smokethen; run;
proc univariate;
var lbxcrp dmdhrage bmxbmi; run;
***bivariate crp outcome***;
 proc freq;
 tables creact5*(mcq220 mcq160c riagendr smokenow smokethen sleep depress diabetes)/ chisq; run;
***bivariate cancer outcome***;
 proc freq;
 tables mcq220*(creact5 mcq160c riagendr smokenow smokethen sleep depress diabetes)/ chisq; run;
```

```
***ttest for continuous data, crp outcome***;
 proc ttest;
 class creact5;
 var dmdhrage bmxbmi; run;
 ***ttest for continuous data, cancer outcome***;
 proc ttest;
 class mcq220;
 var dmdhrage bmxbmi lbxcrp; run;
***bivariate crp, cancer outcome, no other variables***;
proc logistic descending;
class creact5 (ref='0');
model mcq220 = creact5; run;
***bivariate crp, cancer outcome***;
proc logistic descending;
class creact5 (ref='0') riagendr sleep depress mcq160c diabetes smoke1;
model mcq220 = creact5 riagendr dmdhrage smoke1 sleep depress mcq160c bmxbmi diabetes; run;
***crp continuous, cancer outcome***;
proc logistic descending;
class riagendr sleep depress mcq160c diabetes smoke1;
model mcq220 = lbxcrp riagendr dmdhrage smoke1 sleep depress mcq160c bmxbmi diabetes; run;
***bivariate crp, crp outcome***;
proc logistic descending;
class mcq220 riagendr sleep depress mcq160c diabetes smoke1;
model creact5 = mcq220 riagendr dmdhrage smoke1 sleep depress mcq160c bmxbmi diabetes; run;
```

Appendix C. Exclusion Criteria

Excluded from Blood Collection and CRP Measurements

- Hemophiliacs
- Participants who received chemotherapy within last 4 weeks
- The presence of the following on both arms: rashes, gauze dressings, casts, edema, paralysis, tubes, open sores or wounds, withered arms or limbs missing, damaged, sclerosed or occluded veins, allergies to cleansing reagents, burned or scarred tissue, shunt or IV.

Appendix D: Curriculum Vitae

School Address:
255 S. Atherton St., Apt 301
State College, PA 16801
Cell: 570-765-1033

Kelley Bohm

kjb5133@psu.edu

Home Address:
829 Weller Hill Road
Middleburg, PA 17842
Home: 570-837-1235

EDUCATION

Schreyer Honors College of The Pennsylvania State University University Park, PA

- ***The College of Engineering***
  Bachelor of Science: Bioengineering, Chemical Option
  Honors in Health Policy and Administration

RESEARCH EXPERIENCE

Undergraduate Epidemiology Research Under Dr. Rhonda BeLue *PSU: April 2010 to Present*

- Analyze elevated c-reactive protein levels as an indicator of cancer, diabetes, and hypertension using statistical approaches. Presented poster discussing CRP and cancer at the American College of Epidemiology Annual Meeting in Sept. 2010. Culminates in honors thesis.
- Personal Project: C-Reactive Protein as an Indicator of Cancer

Undergraduate Biomechanics Research Under Dr. Cheng Dong *PSU: August 2008 to August 2010*

- Study signaling mechanisms leading to cancer metastasis. Blocked antigens to investigate the effects of soluble molecules on endothelial cell junctions during cancer metastasis.
- Personal Projects: Tumor-Mediated Changes in Endothelial Cell Junctions.

Pratt Engineering REU Fellowship *Duke University: Summer 2009*

- Used microfluidics techniques to culture tumors that will be used to study drug and bacteria interactions with cells. Engineered chamber parameters to promote effective aggregation.
- Personal Project: Protocol for Microfluidics Tumor Formation.

SKILLS

Matlab Solidworks Cell Culture Fluorescent Imaging Mass Spectrometry NMR and IR

UNIVERSITY ACTIVITIES AND LEADERSHIP

Physicians for Human Rights: Student Chapter – *President* (09-10) *PSU: Spring 2009 to Present*

- Founded local club (combining ideas from past groups) dedicated to learning about the inequities of global medicine through a bimonthly speaker series and an international service trip to Tanzania in May 2010.

Oriana Singers Choir – *Social Chairperson* (09) *PSU: Fall 2007 to Present*

- Organize group activities for the choir to cultivate familiarity and teamwork.

Alpha Epsilon Delta Pre-Med National Honors Society – *Honors Member* (08-10) *PSU: Fall 2008 to Present*

- Complete 24 hours of community service per semester, including sponsoring a childhood cancer victim (to raise money for treatment) during the annual Penn State Dance Marathon, participating in the Penn State-Michigan State Blood Cup, and holding a campus fair to raise public health awareness.
- Attend bi-weekly seminars which include presentations by medical professionals.

School of Engineering Design, Tech., and Prof. Programs – Teaching Assistant *PSU: Spring 2008 to Present*

- Assist in the classroom with SolidWorks (solid modeling software) and Microsoft Expression problem resolution in Engineering Design classes.
- Supervise computer lab on weeknights and assist students with SolidWorks projects.

Schreyer Honors College – *Orientation Mentor* *PSU: August 2008*

- Lead workshops to aid incoming freshmen in their transition to college life.

Community Service

- Traveled to rural Santiago Atitlan, Guatemala to educate students in elementary schools and special education schools about hygiene as well as assist teachers with instruction. *March 6-15 2009*
- Assist at Red Cross Blood Drives (30 hours). *Fall 2008 to Spring 2009*
- Organized nutrition fairs for local elementary school students as part of Leadership Jumpstart Course. *Fall 2007*

OTHER WORK EXPERIENCE

Zola New World Bistro, State College, PA-Waitress *April 2010 – Present*
Gabriel's Restaurant, New Berlin, PA-Waitress *Summer 2008 and May 2009*