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COMPARING EXACT TESTS AND ASYMPTOTIC TESTS WITH COLORECTAL CANCER VARIABLES WITHIN THE NATIONAL HEALTH AND NUTRITION EXAMINIATION SURVEY III

by

JOSEPH L. MUSIAL III

DISSERTATION

Submitted to the Graduate School

of Wayne State University,

Detroit, Michigan

In partial fulfillment of the requirements

For the degree of

DOCTOR OF PHILOSOPHY

1999

MAJOR: EVALUATION AND RESEARCH

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DEDICATION

This paper is dedicated to my loving parents, Joane and Joseph for their support and unconditional love.

ACKNOWLEDGEMENTS

It is with honor that I take this time to acknowledge my major advisor, Dr. Shlomo Sawilowsky who has supervised me during the entire proposal and writing process. His mentoring will never be forgotten. Thanks to Dr. Donald Marcotte for his invaluable training in statistics. Thank you also to Dr. Lori Rothenberg who helped me to prepare for the qualifying exams. Additionally, I am grateful to Dr. Patrick Bridge for his editorial and technical assistance. These esteemed committee members have collectively, and individually, provided guidance, encouragement, and expert advise throughout my graduate training.

I would like to recognize several colleagues whom I also consider friends; Dr. Elaine Hockman; from the Research Support Laboratory at Wayne State University, for her technical assistance. Dr. Anil Aranha; from General Internal Medicine at Wayne State University, who provided much needed editorial feedback and technical assistance. Dr. R. Stewart Robertson; the former Division Head of General Internal Medicine at Wayne State University, for his encouragement and support. Also, Kenneth Martin; a close friend who provided manuscript assistance. Their efforts were essential to my success and will not be forgotten.

Finally, and most importantly, I want to publicly thank my dear wife, Nicol, for bringing balance into my life by marrying me on July 27, 1999. I love you.

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CHAPTER 1

INTRODUCTION

Cancer remains a major public health concern that affects people on many levels, from global to personal. Indeed, many people have witnessed a relative or close friend face the physical and psychological trauma associated with cancer. Many cancers can be treated very effectively with early detection through routine screening such as mammography, pap smears, and the prostate specific antigen test. Many Americans, however, do not take advantage of common screening procedures for an array of reasons, including lack of adequate health care insurance, out-of-pocket expenses, high co-payments, and lack of transportation. Women, children, minorities, illegal aliens, and the homeless are least likely to possess health care insurance. Thus, cancer prevention procedures will not reach a large portion of our society.

According to Landis, Murray, Bolden & Wingo (1998), cancer researchers estimate that there will be 1,228,600 new cases of invasive cancer diagnosed in calendar year 1998. Approximately 564,800 Americans will die from cancer (294,200 males and 270,600 females). This equates to roughly more than 1,500 deaths per day. These estimates do not include basal cell and squamous cell skin cancer, nor does it include carcinoma in situ except in the urinary bladder. Among men, the three leading forms of cancer deaths are: Lung and bronchus 93,100 (32%), prostate 39,200 (13%), and colon and rectum 27,900 (9%). Among women, the three leading forms of cancer deaths include: Lung and bronchus 67,000 (25%), breast 43,500 (16%), and colon and rectum 28,600 (11%). Worldwide, colorectal cancer is the fourth most common form of cancer and was estimated in 1996 to account for 875,000 newly diagnosed cases (WHO, 1997).

Epidemiologists who study cancer obtain their results from an array of populations. For instance, some cancer studies range in size from small convenience samples to populations exceeding ten thousand participants. Large data sets are frequently made available to the public in order for secondary analyses to be conducted, and usually contain data that are either continuous or categorical. Using a public database saves time and money because the data has already been collected.

Colorectal Cancer: Definitions & Concepts

The colon is part of the large intestine that is about 1.5 meters long. It extends from the cecum to the rectum. The colon is comprised of four major areas: ascending, transverse, descending, and sigmoid colon. The colon begins with the ascending colon, which is 12 to 20 cm long, and extending from the ileocecal valve to the right colic flexture. The ascending colon functions in absorption. The transverse colon ranges in size between 40 to 50 cm long and runs diagonally across the upper abdomen and extends from the right to the left colic flexures. The descending colon extends from the left colic flexure to the brim of the pelvis and functions in storage and elimination. The final stage is the sigmoid colon that ranges in length from 15 to 80 cm and appears as an S-shaped loop. The sigmoid colon is involved with storage of the feces prior to defecation in the rectum (Moore, 1985; Steele & Osteen, 1986). The large intestine's main role is with the absorption of water, electrolytes and some vitamins (Williams, 1997).

Winamer et al. (1997) purported that colon cancer "is classified in stages according to the extent to which it has extended from its origins in the mucosa through

the wall of the bowel, to regional lymph nodes, and to distant sites, especially the liver"(p.606). There is also general agreement "that most cancers of the colon and rectum develop from adenomatous polyps" (p.607). An adenomatous polyp is an abnormal growth on the wall of the large intestine that may progress to colorectal cancer. Cancer can be defined as the spread and uncontrolled growth of abnormal cells (Anderson JV & Van Nierop MR, 1989).

Hill, Morson, and Bussey (1974) were the first to introduce the pathogenic model that explained colorectal cancer. The adenoma-carcinoma hypothesis proposes that a colorectal lesion first appears in the form of a benign adenomatous polyp. The polyp then undergoes further cellular and tissue disorganization which then may lead to the development of cancer in the form of an adenomacarcinoma. Very few adenomatous polyps, however, progress to cancer. It is estimated that about 2.5 adenomatous polyps per 1,000 per year develop into an adenocarcinoma (Eide, 1985). Colorectal cancer can be conceptualized as a genetic disease that presents itself with an abnormal growth, which can be triggered by genetics or environmental factors. There are two forms of inherited colorectal cancer. Familial adenomatous polyposis (FAP) is the condition in which several hundred or several thousand polyps appear in the colon at an early age and requires surgical removal of the infected location. FAP accounts for about one percent of all colorectal cancer cases. The other form of inherited colorectal cancer is Hereditary Non-Polyposis Colorectal Cancer (HNPCC), which also arises at an early age and accounts for six percent of the total colorectal cancer cases. HNPCC is primarily located in the right side of the colon (Cawkwell & Quirke, 1996).

According to the American Cancer Society's Guidelines on cancer prevention (American Cancer Society, 1996), colorectal cancer is expressed in five different stages, including:

Stage 0: The cancer is in the earliest stage and has not grown beyond the inside layer (mucosa) of the colon or rectum.

Stage I: The cancer has grown through the mucosa and muscularis mucosae and into the submucosa. It may also grow into the muscularis propria, but does not spread to other tissues.

Stage II: The cancer has grown through the wall of the colon or rectum and into nearby tissues but has not spread to the lymph nodes.

Stage III: The cancer has spread to the lymph nodes but has not infected other parts of the body.

Stage IV: The cancer has spread to other distant organ sites such as the liver or ovary.

Statistical Assumptions

Cancer researchers often employ a wide array of population parameters. For instance, some studies base their findings on a small sampling from a single outpatient medicine clinic (Hatahet & Musial, 1998), while other studies base their findings from several thousand participants. Regardless of population size, there should be a concern about the appropriate use of the statistical analysis as well as the assumptions associated with the test statistic. For example, Bridge & Sawilowsky (1999) identified numerous studies in which the data had violated normal distribution theory. Prior to running

parametric analysis one should meet the following assumptions: 1) independent observations; 2) observations drawn from a normally distributed population; 3) populations having the same variance; and, 4) variables should be measured on at least an interval scale (Siegel & Castellan, 1998). More importantly, no statistic can recover from a violation of independence. In order to avoid the parametric assumptions, one may use nonparametric statistics. The assumptions of nonparametric statistics include: 1) the ability to treat categorical or rank data; 2) using observations from different populations; 3) using small sample sizes; and, 4) fewer underlying assumptions (Siegel & Castellan, 1998).

Exact Tests

Besides addressing the statistical assumptions, researchers are also concerned with using the most accurate p value. Exact tests provide researchers with the most accurate method for calculating significance levels in order, "to make reliable inferences when your data are small, sparse, heavily tied, or unbalanced and the validity of the corresponding large sample theory is in doubt" (SPSS Inc, 1995, p.iii). The Cytel Software Corporation developed software to calculate exact algorithms in the early 1990's, and later joined the SPSS Inc., with version 3.0. SPSS is a popular statistical software used in academia, business, and government. SPSS (1995) provided numerous statistical examples in which the exact p value calculation was shown to be more accurate than the asymptotic p value.

StatXact-3 for Windows (CYTEL Software Corp., 1995) computes exact p values for most nonparametric tests using categorical or continuous data. Once the

statistics have been calculated, the researcher can either reject, or fail to reject, the null hypothesis. The exact p values are based on computing all possible permutations. Consequently, exact p values are also referred to as permutational p values.

Asymptotic Tests

According to Bollen (1989), asymptotic theory, "describes the behavior of random variables (or constants) as the sample size increases toward infinity" (p.466). An asymptotic p value provides researchers with an approximation of the exact p value. Asymptotic p values are based on the large-sample assumption. In fact, within large data sets, there are very few differences between asymptotic p values and exact p values (CYTEL Software Corp., 1995). The appeal of asymptotic p values is that the p values can be calculated by hand. Calculating the exact p value, however, requires the use of a personal computer and expensive software. By default, StatXact-3 for Windows (CYTEL Software Corp., 1995) provides output with both exact p values and asymptotic p values.

Monte Carlo

Monte Carlo algorithms are employed when data sets are too large to calculate exact p values. For instance, some computers may not be able to perform all of the permutations within the large data set in a reasonable amount of time, which could result in the computer shutting down. The Monte Carlo method solves this problem. The Monte Carlo method is a repeated sampling plan that presents an accurate, unbiased estimation of the exact p values. Further, SPSS (1995) generates confidence intervals

with any Monte Carlo output, which allows one to make probabilistic statements about the p value.

More importantly, there is a need within the statistics literature, to provide researchers with the most powerful statistical analysis when using real, small samples data. There is also a need to evaluate significance levels when using both asymptotic and exact tests. Publicly available databases, which contain cancer variables, may be ideally suited to investigate these statistical issues.

Purpose of the Study

The purpose of this study is two-fold:

H1 To determine which statistical test is more powerful when analyzing small samples ($n \leq 30$) categorical data: exact tests or asymptotic tests;

$H2_a$ To determine if there is a relationship between a high meat diet and the incidence of colorectal cancer;

$H2_b$ To determine if a diet high in calcium reduces the incidence of colorectal cancer;

$H2_c$ To determine if aspirin and nonsteroidal anti-inflammatory medication reduces the incidence of colorectal cancer.

Accordingly, there are two research questions being proposed.

Research Questions

1. How do exact tests and asymptotic tests compare in terms of power when analyzing small samples categorical data from a data set using real people?
2. To what extent does a diet high in meat, calcium, daily aspirin, or nonsteroidal anti-inflammatory medication effect the development of colorectal cancer?

Significance of the Study

The following research study has several key components. First, researchers do not know whether asymptotic or exact tests provide more powerful results when analyzing small samples, categorical variables associated with colorectal cancer. StatXact-3 for Windows (CYTEL Software Corp, 1995) purported to provide more powerful results than traditional asymptotic tests:

> The exact and Monte Carlo methods provide a *powerful way* of obtaining accurate results when your data set is small, the tables are unbalanced, or sparse, the data are not normally distributed, or the data fail to meet any of the underlying assumptions for reliable answers using the asymptotic method (p.61), emphasis added.

Exact p values are certainly more accurate; however, does this guarantee a greater opportunity to find significant differences?

Further, in terms of substantive hypotheses, the etiology of colorectal cancer remains unknown. In fact, most patients who develop colorectal cancer do not present with any predisposing genetic factors (Fleischer, Goldberg et. al, 1989). A person diagnosed with colon cancer is estimated to lose, on average, between six to seven years of his/her life (US Preventive Services Task Force, 1989). Proportionally, Colorectal cancer will strike one in seventeen Americans over a lifetime (ACS, 1997).

Additionally, Donovan and Syngal (1998) found colon cancer to be, "highly curable when diagnosed at an early stage" (p.45). Cancers of the colon originate from various types of polyps, removing the polyp (polypectomy) during colonoscopy, will prevent the polyp from ever developing into cancer.

Moreover, in 1994 there were over 160,000 new cases of colon cancer diagnosed in the United States with 58,000 fatalities; it was considered the second leading form of fatal cancer. Approximately 50% of colon cancers display a strong inherited factor, however, dietary and lifestyle factors are thought to play a key role within the carcinogenic process for the other cases (Cohen, Winawer, Friedman & Gunderson, 1995). Next, treating patients with advanced colorectal cancer is highly unsuccessful. For the most part, Americans do not participate in colon cancer screening (Winawer et al., 1997). As a result, by the time most patients determine they have a problem with their colon, such as a bleeding tumor or change in bowel habits, the cancer may have spread so invasively throughout the lymph nodes that treating the cancer is not an option.

Finally, despite the alarming rates of colon cancer nationally and internationally, there is reason for optimism. Wingo, Ries, Rosenberg, Miller, and Edwards (1998) note that for all cancer sites combined, cancer rates decreased by an average of 0.7% per year from 1990 through 1995. This rate contrasts with previous increased trends. Wingo et al. advance the idea of continued cancer research by noting the, "need to maximize cancer control efforts in the future so that even greater in-roads in reducing the cancer burden in the population are achieved" (p.1197). Recent recommendations from the

World Cancer Research Fund/American Institute for Cancer Research (1997) reported that:

> The most effective approach to the examination of the relationship between food and nutrition and cancer is to conduct analyses at all levels of: individual dietary constituents; foods and drinks; food groups; methods of food processing; and diets as a whole. Overall, epidemiology backed by cogent experimental and biological findings can provide strong evidence of causal relationships between diet and cancer (p. 80).

Indeed, most nutritional studies that investigate the link between food intake and cancer outcomes often employ convenience sampling and causal-comparative sampling. For instance, there were 1,185,239 participants in the Cancer Prevention Study II. The participants were friends, neighbors or acquaintances of the American Cancer Society volunteers (Thun, Namboordi, and Heath, 1991). In contrast, Campbell and Stanley (1963) refer to the lack of experimenter control as being a quasi-experimental design. True experimental designs, however, are marked by random assignment. Sawilowsky (1997) emphasized the importance of randomization by noting, "there are no satisfactory substitutes for randomization" (p.1). Thus, the inference from most nutritional studies can only be referred back to the sample from which it was obtained.

The NHANES III database attempts to correct these types of problems by employing a host of factors that allow the database to be more statistically powerful than previously established databases. For instance, NHANES III employed a complex, stratified, multi-stage probability design. All findings derived from the database can be inferred back to the civilian, non-institutionalized population residing in the United States and the District of Columbia. NHANES III also over-sampled African Americans, Hispanics, young and older people in order to ensure adequate

representation. NHANES III is the first nutritional database that does not place an age cap on elderly participants. Due to the large sample size of NHANES III, the assumption for the test statistic to converge to a limiting normal or chi-square distribution has been met (SPSS Inc, 1995, p.12).

Limitations of the Study

There are several limitations to this study. First, because other researchers designed the questionnaire and had conducted the field interviews, one cannot attest to the accuracy or reliability of the data. However, comparable data purporting to measure the nutritional practices of United States non-institutionalized civilians is not available. The second limitation is that food is a universal exposure, in other words, people need to eat in order to survive. Deriving outcome measures from everyday caloric intake is much more difficult than measuring an outcome from ingesting a known carcinogen (Clinton & Giovannucci, 1997). Third, many of the chronic diseases, such as cancer or diabetes, are multi-factorial. This means that besides accounting for nutrition, one may also have to account for such factors as genetics, age, sex, socioecoeconomic status, and environmental factors (Clinton & Giovannucci, 1997). Fourth, most data generated from nutritional studies do not employ large, randomized prospective trials which are considered to be the most "definitive" approach to measuring associations between fat intake and cancer, however, the expense to do so often makes it cost prohibitive (Willett, 1997, p.560). The fifth limitation is the fact that the human diet contains thousand of chemicals and chemical reactions that we do not fully understand or have

even begun to measure (World Cancer Research Fund, American Institute for Cancer Research, 1997, p.78).

CHAPTER II

REVIEW OF LITERATURE

Red Meat

There have been numerous studies undertaken in order to explore the relationship between dietary factors and colon cancer. Willet, Stampfer, Colditz, Rosner, and Speizer (1990) conducted a prospective study using data from The Nurses' Health Study Cohort. A total of 88,751 women between the ages of 34 and 59, whom did not have cancer, polyps, or inflammatory bowel disease, were followed prospectively. Each nurse was administered a semiquantitative food-frequency questionnaire. At follow-up, a total of 150 participants had developed colon cancer. The research found that a high intake of animal fat increased the risk of colon cancer. Total energy and body-mass index (BMI), however, were not significantly associated with the incidence of colon cancer nor was it related to risk.

Kono, Imanishi, Sinchi, and Yanai (1993) studied the relationship between dietary factors and the risk of developing adenomas (type of polyp) among male Japanese military retirees between the ages of 49 and 55. During the retirement health examination, a colonoscopy procedure was performed. A total of 187 participants had identifiable adenomas and 1,557 had unremarkable colonoscopies. The research found that after controlling for smoking, alcohol use, military rank and BMI, low rice consumption and high meat intake ($\geq$ 4x/week) were independently associated with an increased risk of developing large adenomas ($\geq$ 5mm). The data suggested that a diet low in rice and high in meat intake might promote adenoma growth that would increase the risk of developing colon cancer. Probst-Hensch, Sinha, Longnecker, Witte, Ingles,

Frankl, Lee, and Haile (1997) proposed that the association between red meat intake and colon cancer could be partially attributed to heterocyclic amines. Heterocyclic amines are mutagenic, are present in cooked meat, and have been found to cause intestinal tumors in animals. Pursuing this line of reasoning, a sigmoidoscopy case-controlled study of 488 health maintenance organization (HMO) matched pairs of participants from two California Kaiser Permanente Medical Centers was employed. A more than twofold incidence of distal colorectal adenomas were noted among the participants who had: a) eaten red meat more than one time per week; b) fried their meat dish greater than ten percent of the time; and, c) prepared the meat dish until it had a darkly browned surface (Odds Ratio 2.2, 95% Confidence Interval 1.1 to 4.3). The increased frequency of frying red meat was associated with an increased adenoma prevalence.

Freudenheim, Saxon, Marshall, Haughey, and Wilkson (1990) conducted a case-control study of diet and rectal cancer among Caucasian women and men 40 years of age or older who resided in three western New York state counties: Buffalo, Niagara Falls and Rochester. A total of 277 case-control pairs of males and 145 case-control pairs of females participated in a food frequency interview between the years 1978 to 1986. The data indicated that rectal cancer risk was associated with an increased intake of kilocalories, fat, carbohydrates and iron. An inverse association of rectal cancer was noted with an increased intake of vitamin C, carotenoids and fiber from vegetables. Vitamin E, calcium, retinol and fiber from grains, however, did not lower the risk of rectal cancer.

Stemmermann, Abraham, and Heilbrun (1986) assessed the impact of fat and energy consumption and the incidence of colon cancer prospectively among 8,006 Hawaiian Japanese men. The data demonstrated a weak inverse association between the mean fat intake and colon cancer. A weak positive association between fat intake and rectal cancer was observed. There was also a statistically inverse association between the mean daily fat intake and all other cancer sites.

In contrast, participants from the U.S. male health professional database who were cancer-free in 1986, between the ages 40 and 75 years old at baseline, were prospectively tracked for colon cancer. A total of 205 new colon cancer cases were diagnosed between 1986 and 1992. Total fat intake, saturated fat, and animal fat were found to be unrelated to colon cancer. An elevated risk of colon cancer was found to be associated with red meat intake (relative risk, 1.71; 95% Confidence Interval, 1.15-2.55 between high and low quintiles; p=0.005 for trend). Further, there was no statistically significant inverse association between any single fruit category, fiber or vegetable intake and colon cancer risk (Giovannucci, Rimm, Stampher, Colditz, Ascherio, and Willet, 1994).

Gaard, Tretli, and Loken (1996) obtained dietary information from 50,535 Norwegian men and women between the ages of 20 and 54 in order to measure the association between certain food groups and colon cancer. A total of 143 colon cases were identified at follow-up (mean time 11.4 years). The frequency of consuming general meals comprised of various meat groups was not associated with colon cancer risk. The prospective study also found no association between the intake of fish, energy, fiber or calcium. Goldbohm, van den Brandt, van't Veer, Brants, Dorant,

Sturmans, and Hermus (1994) investigated, prospectively, the consumption of meat and fat intake with the risk of colon cancer among 120,852 men and women between the ages of 55 and 69 whom resided in the Netherlands. A total of 215 cases of colon cancer (110 women and 105 men) were detected at the 3.3 year follow-up period. The data did not find any association between the intake of fresh meat, pork, beef, minced meat, chicken or fish fat from meat, and the incidence of colon cancer among the participants. There was an increased risk of colon cancer in both men and women for processed meat intake (Relative Risk 1.17; 95% Confidence Interval, 1.03-1.33) for every increment of 15 grams/day.

Besides using human subjects, animal studies are often used to model nutritional intake in humans. Tang, Shivapurkar, Frost, and Alabaster (1996) conducted an animal study, using laboratory rats, in order to examine the relationship between fat and colon cancer. The rats were fed under a closely controlled environment. The data revealed that the incidence of colon cancer and mammary cancer increased when the rat's fat intake was increased from 15% to 30% of total calories.

Calcium

Meyer and White, (1993) also assessed the association between nutrients and colon cancer incidence among middle-aged men and women between the ages of 30 and 62 whom resided in western Washington State. The population-based case-controlled study was conducted from 1985 to 1989. A total of 424 colon cancer cases were identified (186 female and 238 male) with 414 controls (190 female and 224 male). Data from a food frequency questionnaire found that alcohol intake was strongly

associated with colon cancer risk in men and women. A high dietary fiber diet was associated with lower risks of colon cancer for both sexes. Calcium intake was associated with a decreased incidence of colon cancer among women only. There was no association between fat, protein or dietary vitamins and colon cancer. Kampman, Giovannucci, van't Veer, Rimm, Stampfer, Colditz, Kok and Willett (1994) also explored the hypothesis that calcium and vitamin D may lower the risk of developing colorectal cancer. A total of 350 women and 331 men diagnosed prospectively with adenomatous polyps of the left colon and or rectum were identified from two large national databases: The Nurses' Health Study and The Health Professionals follow-up Study. The participants were matched with adenoma-free controls (8,585 women and 9,159 men). The data indicated that total calcium intake from milk consumption and fermented dairy products was not associated with adenoma risk. Vitamin D from supplements was not statistically inversely associated with colorectal cancer risk.

Similarly, Bostick, Potter, Sellers, McKenzie, Kushi & Folsom (1993) pursued the same reasoning prospectively among 35,215 Iowa women between the ages of 55 and 69 years of age who were cancer-free in 1986. A total of 212 cases of colorectal cancer were identified in 1990. After adjusting for age, calcium and vitamin D intake were found to be significantly inversely associated with colorectal cancer risk.

In contrast, Kampman, Van't Verr, Jan Hiddink, Van Aken-Schneijder, Kok and Hermus (1994) researched the relationship between calcium and colorectal cancer by employing a case-control study in the Netherlands. A total of 232 colorectal cancer cases were matched with 259 controls. The results demonstrated that the increased consumption of fermented and unfermented dairy products, hard cheese, and other

dietary calcium was not associated with a decreased risk of colon cancer. In a review of the calcium and colorectal cancer hypothesis, Martinez and Willett (1998) recommend that future studies should "study the relationship in far greater detail" (p.163).

Aspirin and Nonsteroidal Anti-Inflammatory Drugs

Thun, Namboodiri, and Heath (1991) pursued the hypothesis that aspirin and nonsteroidal anti-inflammatory drugs (NSAIDs) provide protection against colon cancer. Aspirin and NSAIDs share analgesic, anti-inflammatory, and antipyretic properties (Clark, Brater and Johnson, 1992). Their prospective study followed a total of 662,424 men and women from the Cancer Prevention Study II. The sample was drawn from the total population of 1,185,239 participants. Aspirin and NSAIDs use were measured from 1982 through 1988. The data indicated that death rates from colon cancer decreased significantly for both women and men who used aspirin or NSAIDs more than sixteen times per month and for at least one year. The relative risk for women was 0.58 (95% Confidence Interval, 0.37 to 0.90) and the relative risk for men was 0.60 (95% Confidence Interval, 0.40 to 0.89), respectively. Wilmink (1997) advanced the need for additional aspirin and NSAIDs research by noting that, "Conclusive evidence of the effectiveness of primary prevention of colorectal cancer via dietary measures or nonsteroidal anti-inflammatory drugs is lacking" (p.483). Further, Roy (1998) noted that the therapeutic aspirin dosage and duration remains unknown.

Measurement Issues

Within the context of cancer studies, important measurement issues are often neglected. For instance, the power of exact tests versus asymptotic tests, when dealing with small sample size ($n \leq 30$) data sets. Cohen (1969) defines the power of a statistical test as "the probability that it will yield statistically significant results" (p.1). Power is equal to one minus beta ($1-\beta$) where beta is defined as the probability of committing a Type II error (Cohen, 1969). The power of a test depends upon the significance level, the sample size, and the effect size. For instance, the power of a test may be reduced if the nominal alpha is set too low, such as .001. Cohen (1969) conceptualizes the effect size as an index of departure from the null hypothesis, or any nonzero value. An effect size of 0.2 is considered to be small, 0.5 as medium, and 0.8 as being large.

Fisher (1925) questioned the merit of large-samples' theory when conducting small, laboratory research:

> Little experience is sufficient to show that the traditional machinery of statistical processes is wholly unsuited to the needs of practical research. Not only does it take a cannon to shoot a sparrow, but it misses the sparrow! The elaborate mechanism built on the theory of infinitely large samples is not accurate enough for simple laboratory data. Only by tackling small sample problems on their merit does it seem possible to apply accurate tests to practical data (p. viii).

Exact tests provide the most accurate p value and are considered to be the gold standard for small, sparse, unbalanced, and heavily tied data (SPSS Inc, 1995). Exact tests are comprised of two types of algorithms: complete enumeration and Monte Carlo enumeration. Complete enumerations are one hundred percent accurate. In contrast,

Monte Carlo enumerations provide an unbiased, accurate estimate, of the exact p value. Monte Carlo enumerations can provide up to ninety-nine percent accuracy because the researcher can set the confidence levels. Exact tests are not guaranteed to generate exact p values for very large data sets, or for very small data sets (SPSS Inc, 1995). The appeal of using an asymptotic test is the ability to calculate by hand.

Research Hypotheses

Hypothesis$_1$: Exact tests and asymptotic tests will demonstrate similar power when analyzing real-live, small samples categorical data sets ($n \leq 30$).

Exact tests provide the most accurate, reliable, and robust p values, when the large-sample assumption is not met. Asymptotic tests provide similar results to exact tests when the data set is large and well-balanced. The developers of StatXaxt-3 for Windows (CYTEL Software Corp, 1995) contend that exact procedures are more powerful than asymptotic tests. The developers, however, do not provide theory or applications to support this observation. This study will help to determine which statistic is the most powerful when using real, small samples ($n \leq 30$) categorical data through exact and asymptotic tests. The effect size will also be determined.

Hypothesis$_{2a}$: A diet marked by the high intake of dietary meat products ($\geq$ 4x/week) will be associated with an increased risk of colorectal cancer.

Slattery et al. (1991) examined cross-sectional longitudinal data from the Coronary Artery Risk Development study. The participants included 5,115 young men and women between the ages of 18 and 30. The data demonstrated that individuals who consumed red meat and poultry less than one time per week were found to be

significantly more physically active, less likely to drink alcohol, displayed lower cholesterol rates, and took in more fiber than comparable frequent meat consumers. The infrequent meat eaters also maintained significantly lower Body Mass Indexes (calculated by $Kg/(m)^2$). Frentzel-Beyme and Chang-Claude (1994) found that a vegetarian diet maintained for at least twenty years was associated with decreased cancer mortality. According to the World Cancer Research Fund/American Institute for Cancer Research (1997), "there is general agreement that the risk of colorectal cancer is reduced by diets high in vegetables and unrefined plant foods, and by exercise"(p.50). Antioxidant vitamins, such as vitamins A and C, defend the body against free radicals and reactive oxygen molecules, are abundant in plant foods (Pence and Dunn, 1998).

This hypothesis will allow researchers to gain a better understanding about the true relationship between meat intake and the risk of colorectal cancer. The statistical analysis will be based on secondary data from NHANES III, which to date, is the most powerful database available to researchers analyzing the relationship between nutrition and cancer.

$Hypothesis_{2b}$: Diets marked by high calcium intake ($\geq$ 800mg/day) will be found to be negatively associated with colorectal cancer.

There is general agreement that calcium provides some form of protective affect against colorectal cancer. However, data from the Nurses' Health Study found no significant inverse association between whole milk, cheese, or ice cream intake, and the risk of colorectal cancer (Willett, Stampfer, Colditz, Rosner and Speizer, 1990). Using participants from Hawaii, Heilbrun, Hankin, Nomura and Stemmermann (1986) also did not find an inverse association between calcium intake and colon cancer. Hawaii's

location relative to the equator was cited as a potential confounder because vitamin D can be processed by direct sun exposure. Arguably, individuals who consume milk during each meal may also be more likely to demonstrate healthier food selections throughout their entire diet. This hypothesis will help to clarify these contradictions within the literature. NHANES III data also provides the type of milk selection including skim, whole, and 2%.

Hypothesis$_{2c}$: Regular intake of aspirins and nonsteroidal anti-inflammatory drugs (1x/daily at least for 1 year) will be found to be negatively associated with colorectal cancer.

Regular aspirin use is thought to lower ones risk of colorectal cancer. This may be due to the inhibition of prostaglandin synthesis or other factors (Thun, Namboodiri and Heath, 1991). However, evidence supporting the benefits of regular aspirin and NSAIDs is not convincing. The detailed reporting within NHANES III, including food recall questionnaires and the mobile medical exam data will provide more accurate, and enriched data that will allow hypothesis$_3$ to better clarify this debate within the literature.

CHAPTER III

METHODOLOGY

Research Design

The following research study will compare the power properties of exact tests and asymptotic tests using secondary colorectal cancer data contained within the third National Health and Nutrition Examination Survey (NHANES III). The data analysis will be restricted to participants who were 17 years of age or older during their interviews. Periodically, the National Center for Health Statistics of the Center for Disease Control conducts national surveys in order to measure and assess the health of U.S. residents. NHANES III is one such survey and is seventh in an ongoing series since the 1960's designed to measure nutritional epidemiological data among U.S. residents.

Sampling Plan

The participants who comprised NHANES III included clustered samples of the civilian, non-institutionalized United States residents who reside in the fifty states plus the District of Columbia. Participants were two months of age or older. African Americans, Hispanics, young and older people were over-sampled to ensure adequate representation. The study was conducted from October 1988 through October 1994 using two three-year phases. The first phase was conducted from October 18, 1988 through October 24, 1991. The second phase was conducted from September 20, 1991 through October 15, 1994. NHANES III employed complex, stratified, multi-stage probability design. The results provide an unbiased estimate of the civilian, non-institutionalized population residing in the United States and the District of Columbia.

NHANES III was designed to be self-weighting within the Primary Sampling Units (PSU's) for the age, sex, and race-ethnic groups.

The first step of the sample design included selecting 81 PSU's that consisted primarily of individual counties. There were several instances in which smaller counties were combined to maintain an adequate PSU population size. Primary Sampling Unit's were then stratified and chosen with probability proportional to size and without replacement. The first phase used 44 stands (survey locations) and the second phase used 45 stands for a grand total of 89 stands. A total of 93,653 households were screened from which 19,528 were selected. During the six-year period, a total of 39,695 designated persons were selected of which 33,994 (86%) were interviewed within their homes. All participants were also invited to participate in the mobile examination center (MEC) of which 30,818 (78%) did so and 493 persons received a limited examination within their homes. The Wayne State University Human Investigation Committee approved this secondary analysis.

Sample

NHANES III is comprised of five data files: Household Adult Data File, Household Youth Data File, Examination Data File, Laboratory Data File and the Dietary Recall Data File. Trained field researchers interviewed eligible participants who were at least 17 years of age inside their households. Proxy interviews were used for the young. Participants were required to provide written consent as a condition of participation. The questionnaires administered in the household were as follows: Household Screener Questionnaire, Family Questionnaire, Household Adult

Questionnaire, and, the Household Youth Questionnaire. The Household Adult Data File (N=20,050) was used in this study.

Measures

Each participant also received a limited physical and dental examination inside the mobile examination center (MEC). The MEC examination used the following computer automated questionnaires: MEC Adult Questionnaire, MEC Youth Questionnaire, MEC Proxy Questionnaire, 24-Hour Dietary Recall, and the Dietary Food Frequency (12-16 years of age). Various contract laboratories obtained an array of biological samples and measurements from the participants. The samples and measurements included: blood and urine specimens, glucose/allergy tolerance tests, x-rays, bone density, electrocardiograph, spirometry, hearing and cognitive tests, physical measurements, and central nervous system functions. An abbreviated version of the home examination was administered to persons between 2-11 months of age and those 20 years of age and older who were unable to visit the MEC.

The reliability of a dietary instrument measures the consistency of scores over time. Willett, Sampson, Stampfer, Rosner, Bain, Witschi, Hennekens, and Speizer (1985) measured the reliability of a semi-quantitative food frequency questionnaire among 173 participants. Test-retest reliability estimates ranged from 0.41 for total vitamin A without supplements to 0.79 for vitamin B_6 with supplements. Van Leeuwen, De Vet, Hayes, Van Staveren, West and Hautvast (1983) conducted a four-year retrospective dietary assessment using a seven-day food record that was obtained in

1977 and assessed in 1981. The test-retest reliability estimates for 79 participants varied from 0.38 for animal meat, 0.68 for total fat, and 0.82 for alcohol intake.

The 24-hour dietary recall provides an estimate of the actual food and beverage intake from the previous 24-hours. The instrument is open-ended and provides adequate estimations of group means. The 24-hour dietary recall is the most commonly used dietary assessment in the United States (Willett, 1998). Trained interviewers used food and chart models in order to assist respondents. For instance, the participant could be shown a plastic model, referred to as a portion-size measurement aid, of a small, medium, or large size apple. This also means that respondents did not have to be literate to complete the recall assessment.

Dietary validity purports to measure what it is intended to measure. Dietary validity is usually evaluated by comparing the instrument to a different dietary instrument. For instance, Fanelli and Stevenhagen (1986) compared the 24-hour dietary recall with the food record method. The food record method entails listing all foods consumed over several days. Older adults between the ages of 65 and 74 years of age were surveyed between 1977 and 1978 as part of the USDA nationwide survey. Energy intake using the 24-hour recall was 1,430 ±542 kcal for women, and 1,929 ±735 kcal for men, respectively. Energy intake using the food record method was 1,439 ±555 kcal for women, and 1,924 ±739 kcal for men, respectively. The 24-hour recall to food record ratio was 0.99 for women, and 1.00 for men, respectively.

Ferraroni, Declari, Franceschi, La Vecchia, Enard, Negri, Parpinel, and Salvini (1996) compared alcohol consumption using both 7-day dietary records and food frequency questionnaires among 395 volunteers. Test-retest reliability estimates for

wine and total alcohol was greater than 0.75 in both men and women. The food frequency questionnaire was found to provide satisfactory levels of validity and reliability. It was suggested that the 7-day dietary records were affected by seasonal availability of wine. The validity of food frequency questionnaires has also been demonstrated through the measurement of calcium intake among young to middle aged women (Wilson and Horwath, 1996).

Beer-Borst and Amado (1995) investigated the validity of self-administered 24-hour dietary recalls among 3,653 males and females seven years of age and older. The estimated intake of carbohydrates, fat, protein and alcohol differed by only 2.4%. Spearman r correlation coefficients ranged from 0.35 to 0.60. The data indicated that the 24-hour dietary recall was a valid method for estimating the mean and median dietary intake among the participants.

Data Analysis

The complex sampling data comprising NHANES III will first be entered into a data file using a pentium microprocessor. The data will be analyzed using SPSS Exact Tests for Windows, Release 6.1 (SPSS Inc, 1995). The applied variables including, red meat, calcium, and aspirin/NSAID will be dichotomized into low and high use. The variables will then be entered into 2 x 2 tables comparing them with the presence or absence of a colon cancer diagnosis. Pearson's Chi-Square two-tailed asymptotic test, continuity correction, likelihood ratio, and Fisher's exact test will be calculated. Further, the Pearson's Chi-Square exact test and likelihood ratio will also be calculated.

Two theoretical variables will also be created from the database. Health status will be re-coded into a dichotomous variable: 1) Good to excellent, and 2) Poor to fair. Cancer location will also be re-coded into a dichotomous variable: 1) A positive colon cancer diagnosis, and 2) Other cancer diagnosis. Both sets of variables were restricted to participants greater than or equal to fifty-five years of age. This allowed for an adequate sample size in order to run Pearson's Chi-Square Asymptotic and Pearson's Chi-Square Exact Tests. A Chi-Square analysis using asymptotic and exact procedures was used to analyze randomly sampled small samples categorical variables. The sample sizes are as follows: n = (2,2,2,2), n = (5,5,5,5), n = (10,10,10,10), n = (15,15,15,15), n = (20,20,20,20), and n = (25,25,25,25).

The colon cancer variable will be re-coded into a dichotomous variable: 1) No colon cancer diagnosis, and 2) Colon cancer diagnosis. A total of 646 cases of "other types of cancers" will be excluded from the analysis in order to prevent confounding. A total of 18 missing cases will also be omitted from the analysis. The red meat variable will be re-coded into: 1) Low red meat intake, and 2) High red meat intake. The calcium variable will be re-coded into: 1) Low calcium intake (less than or equal to 26,009 mg in the previous thirty days), and 2) High calcium intake (at least 26,010 mg or more in the previous thirty days). Aspirin will be re-coded into: 1) Low aspirin intake (less than daily intake), and 2) High aspirin intake (at least daily or more). Similarly, ibuprofen was re-coded into 1) Low ibuprofen intake (less than daily intake), and 2) High ibuprofen intake (at least daily or more).

Pearson's Chi-Square Asymptotic Test and Pearson's Chi-Square exact tests will be used to analyze the data. Also, the significance will be calculated for each test.

According to Cochran (1954) the minimum cell count for all cells should be at least five. For tables exceeding 2 x 2, it is recommended that the minimum cell count of one be permitted only if no more than 20 percent of the cells have values below five. Each participant in NHANES III was identified by a unique number (SEQN).

CHAPTER IV

RESULTS

The following results are comprised of an applied section followed by a theoretical section. The applied section includes a Chi-Square analysis which measures the association between the absence or presence of a colorectal cancer diagnosis and the following dichotomous variables: 1) High or low red meat intake; 2) High or low calcium intake; 3) High or low aspirin intake; and, 4) High or low ibuprofen intake. The results and tables include both asymptotic and exact p values. The applied tables run from Table 4.1 through Table 4.4.

The second half includes the theoretical results and tables. The Chi-Square analysis uses a re-coded health status variable of 1) Good to excellent; and 2) Poor to fair. The other re-coded variable includes cancer diagnosis type: 1) Colon cancer; and, 2) Other type of cancer. The power analysis used sample sizes of: n = (2,2,2,2); n = (5,5,5,5); n = (10,10,10,10); n = (15,15,15,15); n = (20,20,20,20); and n = (25,25,25,25). The theoretical tables include both asymptotic and exact p values. The theoretical tables run from Table 4.5 through Table 4.10.

Table 4.1: Chi-Square Analysis of Red Meat Intake by Colon Cancer Diagnosis.

Diagnosis	Red Meat		Row Total	χ^2	df	signif.
	Low	High				
No Colon Cancer	14,206	3,978	18,184 99.47%	7.3525	1	0.0067*
Yes Colon Cancer	86	10	96 0.53%			
Row Total	14,292 (78.18%)	3,988 (21.82%)	18,280 (100%)			

*p < 0.05

Chi-Square Asymptotic Test	Value	DF	Significance
Pearson	7.3525	1	0.0067
Continuity Correction	6.6960	1	0.0096
Likelihood Ratio	8.6640	1	0.0033
Fisher's Exact Test			
One-Tail			0.0028
Two-Tail			0.0060

Chi-Square Exact Test	Significance
Pearson	
One-Tail	0.0028
Two-Tail	0.0089
Likelihood Ratio	
One-Tail	0.0028
Two-Tail	0.0044

Minimum Expected Frequency – 20.944

Using the dichotomous red meat variable and the dichotomous colon cancer variable, Pearson's Chi-Square asymptotic test found a significant association between the variables ($\chi^2 = 7.3525$, $p = 0.0067$). Participants who had reported ingesting red meat more than four times per week over the previous thirty days were designated as high red meat. In fact, a total of n = 18,280 (91.17%) participants had reported some red meat intake during the previous month. These results also suggest that red meat is an important dietary component among civilian, non-institutionalized, United States citizens. Further statistical analysis should explore the relationship between red meat intake and colorectal cancer.

Table 4.2: Chi-Square Analysis of Calcium Intake by Colon Cancer Diagnosis.

Diagnosis	Calcium		Row Total	χ^2	df	signif.
	Low	High				
No Colon Cancer	18,189	1,095	19,284 99.47%	0.1143	1	0.7354
Yes Colon Cancer	97	5	102 0.53%			
Row Total	18,286 (94.33%)	1,100 (5.67%)	19,386 (100%)			

*p < 0.05

Chi-Square Asymptotic Test	Value	DF	Significance
Pearson	0.1143	1	0.7354
Continuity Correction	0.0152	1	0.9018
Likelihood Ratio	0.1194	1	0.7296
Fisher's Exact Test			
One-Tail			0.4762
Two-Tail			1.0000

Chi-Square Exact Test	Significance
Pearson	
One-Tail	0.4762
Two-Tail	0.8347
Likelihood Ratio	
One-Tail	0.4762
Two-Tail	0.8347

Minimum Expected Frequency – 5.788

Using the dichotomous calcium variable and the dichotomous colon cancer variable, Pearson's Chi-Square asymptotic test did not find a significant association between the variables ($\chi^2 = 0.1143$, $p = 0.7354$). The designation of high calcium intake was assigned if the participant had exceeded the RDA recommended daily intake of 800 milligrams per day during the previous thirty days. The data did reveal, however, that over ninety-six percent (n= 19,386) of the participants had ingested some form of calcium during the previous thirty days.

Table 4.3: Chi-Square Analysis of Aspirin Intake by Colon Cancer Diagnosis.

Diagnosis	Aspirin		Row Total	χ^2	df	signif.
	Low	High				
No Colon Cancer	4,567	1,543	6,110 99.32%	19.1411	1	0.0000*
Yes Colon Cancer	19	23	42 0.68%			
Row Total	4,586 (74.54%)	1,566 (25.46%)	6,152 (100%)			

*p < 0.05

Chi-Square Asymptotic Test	Value	DF	Significance
Pearson	19.1411	1	0.0000
Continuity Correction	17.6176	1	0.0000
Likelihood Ratio	16.3909	1	0.0000
Fisher's Exact Test			
One-Tail			0.0000
Two-Tail			0.0000

Chi-Square Exact Test	Significance
Pearson	
One-Tail	0.0000
Two-Tail	0.0000
Likelihood Ratio	
One-Tail	0.0000
Two-Tail	0.0000

Minimum Expected Frequency – 10.691

Using the dichotomous aspirin variable and the dichotomous colon cancer variable, Pearson's Chi-Square asymptotic test found a significant association between the variables ($\chi^2 = 19.1411$, $p = 0.0000$). A total of n = 6,152 (30.68%) participants had reported some form of aspirin use in the past thirty days.

Table 4.4: Chi-Square Analysis of Ibuprofen Intake by Colon Cancer Diagnosis.

Diagnosis	Ibuprofen		Row Total	χ^2	df	signif.
	Low	High				
No Colon Cancer	3,143	399	3,542 99.63%	9.5112	1	0.0020*
Yes Colon Cancer	8	5	13 0.37%			
Row Total	3,151 (88.64%)	404 (11.40%)	3,555 (100%)			

*p < 0.05

Chi-Square Asymptotic Test	Value	DF	Significance
Pearson	9.5112	1	0.0020
Continuity Correction	7.0028	1	0.0081
Likelihood Ratio	6.3888	1	0.0115
Fisher's Exact Test			
One-Tail			0.0110
Two-Tail			0.0110

Chi-Square Exact Test	Significance
Pearson	
One-Tail	0.0110
Two-Tail	0.0110
Likelihood Ratio	
One-Tail	0.0110
Two-Tail	0.0110

Minimum Expected Frequency – 1.477

Using the dichotomous ibuprofen (nonsteroidal) variable and the dichotomous colon cancer variable, the Pearson's Chi-Square asymptotic test indicated a significant association between the variables ($\chi^2 = 9.5122$, $p = 0.0020$). A total of 3,555 (17.73%) participants reported ibuprofen use in the previous thirty days.

Table 4.5: Chi-Square Analysis of Health Status by Cancer Type n= (2,2,2,2).

Health Status	Cancer Location		Row Total	χ^2	df	signif.
	Colon	Other				
Good to Excellent	1	2	3 37.5%	0.0356	1	0.8504
Poor to Fair	2	3	5 62.5%			
Row Total	3 (37.5%)	5 (62.5%)	8 (100%)			

*p < 0.05

Chi-Square Asymptotic Test	Value	DF	Significance
Pearson	0.0356	1	0.8504
Continuity Correction	0.0000	1	1.0000
Likelihood Ratio	0.0358	1	0.8499
Fisher's Exact Test			
One-Tail			0.7143
Two-Tail			1.0000

Chi-Square Exact Test	Significance
Pearson	
One-Tail	0.7143
Two-Tail	1.0000
Likelihood Ratio	
One-Tail	0.7143
Two-Tail	1.0000

Minimum Expected Frequency – 1.125

The results from table 4.5 were based upon a theoretically small sample categorical data set of n = (2,2,2,2) using the variables health status and cancer type. Pearson's Chi-Square Asymptotic Test found no statistically significant association between the two variables ($\chi^2 = 0.0356$, $p = 0.8504$). There was also no statistically significant association between the variables using Pearson's Chi-Square Exact Test ($\chi^2 = 0.0356$, $p = 1.0000$). The Pearson's Chi-Square asymptotic p value was smaller than the Pearson's Chi-Square exact p value (0.8504 vs. 1.0000).

Table 4.6: Chi-Square Analysis of Health Status by Cancer Type n = (5,5,5,5).

Health Status	Cancer Location		Row Total	χ^2	df	signif.
	Colon	Other				
Good to Excellent	3	12	15 75.0%	0.0000	1	1.0000
Poor to Fair	1	4	5 25.0%			
Row Total	4 (20.0%)	16 (80.0%)	20 (100%)			

*p < 0.05

Chi-Square Asymptotic Test	Value	DF	Significance
Pearson	0.0000	1	1.0000
Continuity Correction	0.0000	1	1.0000
Likelihood Ratio	0.0000	1	1.0000
Fisher's Exact Test			
One-Tail			0.7183
Two-Tail			1.0000

Chi-Square Exact Test	Significance
Pearson	
One-Tail	0.7513
Two-Tail	1.0000
Likelihood Ratio	
One-Tail	0.7513
Two-Tail	1.0000

Minimum Expected Frequency – 1.000

The results in Table 4.6 were based on a theoretically small sample data set of n = (5,5,5,5). The dichotomous variables included health status and cancer type. The Pearson's Chi-Square asymptotic test indicated that there was no statistically significant association between the two variables ($\chi^2 = 0.0000$, $p = 1.0000$) In fact; both procedures lead to identical results.

Table 4.7: Chi-Square Analysis of Health Status by Cancer Type n = (10,10,10,10).

Health Status	Cancer Location		Row Total	χ^2	df	signif.
	Colon	Other				
Good to Excellent	6	15	21 52.5%	0.9346	1	0.3337
Poor to Fair	3	16	19 47.5%			
Row Total	9 (22.5%)	31 (77.5%)	40 (100%)			

*p < 0.05

Chi-Square Asymptotic Test	Value	DF	Significance
Pearson	0.9346	1	0.3337
Continuity Correction	0.3453	1	0.5568
Likelihood Ratio	0.9516	1	0.3293
Fisher's Exact Test			
One-Tail			0.2802
Two-Tail			0.4570

Chi-Square Exact Test	Significance
Pearson	
One-Tail	0.2802
Two-Tail	0.4570
Likelihood Ratio	
One-Tail	0.2802
Two-Tail	0.4570

Minimum Expected Frequency – 4.275

The results from Table 4.7 were based on the theoretical sample of n = (10,10,10,10). Using the dichotomous health status variable and dichotomous cancer type variable, Pearson's Chi-Square Asymptotic Test found no statistical significant association between the two variables ($\chi^2 = 0.9346$, $p = 0.337$). The Pearson's Chi-Square asymptotic p value was found to be smaller than the Pearson's Chi-Square exact p value (0.3337 vs. 0.4570).

Table 4.8: Chi-Square Analysis of Health Status by Cancer Type n = (15,15,15,15).

Health Status	Cancer Location		Row Total	χ^2	df	signif.
	Colon	Other				
Good to Excellent	7	25	32 53.3%	0.1507	1	0.6979
Poor to Fair	5	23	28 46.7%			
Row Total	12 (20.0%)	48 (80.0%)	60 (100%)			

*p < 0.05

Chi-Square Asymptotic Test	Value	DF	Significance
Pearson	0.1507	1	0.6979
Continuity Correction	0.0042	1	0.9484
Likelihood Ratio	0.1514	1	0.6972
Fisher's Exact Test			
One-Tail			0.4761
Two-Tail			0.7560

Chi-Square Exact Test	Significance
Pearson	
One-Tail	0.4761
Two-Tail	0.7560
Likelihood Ratio	
One-Tail	0.4761
Two-Tail	0.7560

Minimum Expected Frequency – 5.600

The results from Table 4.8 measured the theoretical relationship between the dichotomous health status variable and dichotomous cancer location variable using a sample set of n = (15,15,15,15). The results indicate that there was no association between the two variables using Pearson's Chi-Square Asymptotic Test ($\chi^2 = 0.1507$, $p = 0.6979$). The Pearson's Chi-Square asymptotic p value was found to be smaller than the Pearson's Chi-Square exact p value (0.6979 vs. 0.7560).

Table 4.9: Chi-Square Analysis of Health Status by Cancer Type n = (20,20,20,20).

Health Status	Cancer Location		Row Total	X^2	df	signif.
	Colon	Other				
Good to Excellent	10	35	45 56.3%	0.0045	1	0.9462
Poor to Fair	8	27	35 43.8%			
Row Total	18 (22.5%)	62 (77.5%)	80 (100%)			

*p < 0.05

Chi-Square Asymptotic Test	Value	DF	Significance
Pearson	0.0455	1	0.9462
Continuity Correction	0.0000	1	1.0000
Likelihood Ratio	0.0046	1	0.9462
Fisher's Exact Test			
One-Tail			0.5776
Two-Tail			1.0000

Chi-Square Exact Test	Significance
Pearson	
One-Tail	0.5776
Two-Tail	1.0000
Likelihood Ratio	
One-Tail	0.5776
Two-Tail	1.0000

Minimum Expected Frequency – 7.875

Results from Table 4.9 measured the theoretical relationship between the dichotomous health status variable and the dichotomous cancer location variable. Using a sample set of n = (20,20,20,20) the results indicate that there was no association between the two categorical variables when using Pearson's Chi-Square Asymptotic Test ($\chi^2 = 0.0455$, p = 0.9462). The Pearson's Chi-Square asymptotic p value was found to be smaller than the Pearson's Chi-Square exact p value (0.9462 vs. 1.0000).

Table 4.10: Chi-Square Analysis of Health Status by Cancer Type n= (25,25,25,25).

Health Status	Cancer Location		Row Total	χ^2	df	signif.
	Colon	Other				
Good to Excellent	10	42	52 52.00%	0.8691	1	0.35122
Poor to Fair	13	35	48 48.00%			
Row Total	23 (23.00%)	77 (77.00%)	100 (100%)			

*p < 0.05

Chi-Square Asymptotic Test	Value	DF	Significance
Pearson	0.8691	1	0.3512
Continuity Correction	0.4822	1	0.4874
Likelihood Ratio	0.8696	1	0.3511
Fisher's Exact Test			
One-Tail			0.2437
Two-Tail			0.4762

Chi-Square Exact Test	Significance
Pearson	
One-Tail	0.2437
Two-Tail	0.4762
Likelihood Ratio	
One-Tail	0.2437
Two-Tail	0.4762

Minimum Expected Frequency – 11.04

The results from Table 4.10 are based upon the theoretical dichotomous health status variable and the dichotomous cancer location variable. Using a sample set of n = (25,25,25,25) Pearson's Chi-Square Asymptotic Test found no association between the two variables ($\chi^2 = 0.8691$, $p = 0.3512$). The Pearson's Chi-Square asymptotic p value was found to be smaller than the Pearson's Chi-Square exact p value (0.3512 vs. 0.4762).

Table 4.11: Frequencies for the Applied and Theoretical Variables

Applied Variables	Ingested past 30 days (%)	No use past 30 days (%)	High use criteria	Blank but applicable	Don't Know	Total # in denominator
Red Meat	18,882 (94.36)	1,127 (5.63)	≥4x/week	28	13	20,009
Aspirin	6,388 (32.23)	13,432 (67.77)	Daily	211	19	19,820
Ibuprofen	3,652 (18.32)	16,283 (81.68)	Daily	107	8	19,935
Calcium*	20,050 (100.00)	0 (0.00)	≥800mg/day	N/A	N/A	20,050

(*proxy for calcium: Cheese + Milk)

Theoretical Variables	Total (%)
Health Status	
Good	15,004 (74.88)
Poor	5,033 (25.12)
Cancer Location	
Colon	102 (13.64)
Other	646 (86.36)

Table 4.12: Theoretical Analysis: Health Status by Cancer Location

				Chi-Square Asymptotic Test				Chi-Square Exact Test	
n	χ^2	df	signif.	Pearson's	Continuity Correction	Likelihood Ratio	Fisher's Exact 2-Tail	Pearson's 2-Tail	Likelihood Ratio 2-Tail
2,2,2,2	0.0356	1	0.8504	**0.8504**	1.0000	0.8499	1.0000	**1.0000**	1.0000
5,5,5,5,	0.0000	1	1.0000	1.0000	1.0000	1.0000	1.0000	1.0000	1.0000
10,10,10,10	0.9346	1	0.3337	**0.3337**	0.5568	0.3293	0.4570	**0.4570**	0.4570
15,15,15,15	0.1507	1	0.6979	**0.6979**	0.9484	0.6972	0.7560	**0.7560**	0.7560
20,20,20,20	0.0045	1	0.9462	**0.9462**	1.0000	0.9462	1.0000	**1.0000**	1.0000
25,25,25,25	0.8691	1	0.3512	**0.3512**	0.4874	0.3511	0.4762	**0.4762**	0.4762

*p<0.05

CHAPTER V

DISCUSSION

The purpose of this study was two-fold. First, the applied analysis included examining the relationship between the dichotomous colorectal cancer variable and the intake of red meat, calcium, aspirin, and nonsteroidal anti-inflammatory medication. Second, a theoretical power study, using small samples categorical data ($n < 30$), was simulated using the re-coded dichotomous cancer location variable and the re-coded dichotomous self-reported health status variable. The variables were then analyzed and compared using Pearson's Chi-Square Asymptotic Test and Pearson's Chi-Square Exact Test.

Within the context of the applied analysis, the Pearson's Chi-Square Asymptotic Test found an association between the dichotomous colon cancer variable and the dichotomous red meat intake variable ($\chi^2 = 7.3525$, $p = 0.0067$). This would suggest that future research should examine the variables in far greater detail and could include longitudinal studies. Furthermore, future analysis should include examining the individual cells and the residuals in order to determine which variable was significant. A participant was re-coded as high red meat intake if he/she had reported ingesting red meat at least four times per week over the past month. According to the NHANES III, red meat appears to be a major staple in the diets of the participants because approximately ninety-four percent of the participants had reported red meat intake during the previous month. This proportion illustrates the need for future research. Additionally, further bench research should continue to measure the impact of known carcinogens created during the preparation of red meat meals.

The second applied variable measured was calcium intake. The literature search indicated a general disagreement among researchers about the specific association between calcium intake and the incidence of colon cancer. In order to maximize variance, the calcium variable was re-coded into a proxy calcium variable by combining the milk and cheese variable. A participant received the designation of high calcium intake if they had exceeded the RDA recommended daily intake of 800 mg of calcium per day over the past month. The Pearson's Chi Square Asymptotic Test did not find an association between the dichotomous calcium variable and the dichotomous colon cancer variable ($\chi^2 = 0.1143$, $p = 0.7354$). Despite the lack of significance, researchers may consider creating a different proxy variable for calcium within the NHANES III database. For example, one could include combining broccoli, vitamin supplements, and fortified juices. The individual cells and residuals could also be examined in order to determine which cells are significant. More important, recent calcium use was reported by every participant in the NHANES III database. This suggests that calcium intake is a vital dietary component.

The third applied variable measured in the study was aspirin and nonsteroidal anti-inflammatory drug (NSAIDs) use. The designation of high aspirin and NSAIDs was assigned and re-coded if the participant had reported daily use over the past month. Aspirin is the most inexpensive NSAID available. The NSAID ibuprofen was used because it was the second most commonly reported NSAID in the NHANES III database. The Person's Chi-Square Asymptotic Test found an association between the dichotomous aspirin variable and the dichotomous colon cancer variable ($\chi^2 = 19.1411$, $p = 0.0000$). The Pearson's Chi-Square Asymptotic Test also found an association

between the dichotomous ibuprofen variable and the dichotomous colon cancer variable ($\chi^2 = 9.5122$, $p = 0.0020$). This suggests that future research should examine aspirin and NSAID's in far greater detail. Furthermore, one may also want to examine the individual cells and residuals in order to determine the significance of each cell.

A power analysis was also conducted using small samples categorical data from a "real" data set using health status and cancer location variables. Both asymptotic and exact results were compared in order to determine the significance and power with the small samples. The asymptotic p value was found to be smaller (more significant) than the exact p value in five out of six simulations, including sample sizes: n = (2,2,2,2); n = (10,10,10,10); n = (15,15,15,15); n = (20,20,20,20); and n = (25,25,25,25). The sample size n = (5,5,5,5) had identical p values. Note however, that the statistical decisions, failing to reject the null hypothesis, were the same in all six simulations. The theoretical component of this study questions the advantages of exact procedures when using "real", small samples data sets. Promotional materials generated by the software industry argue that exact tests are more powerful, however, the analysis found this to be untrue. It is common knowledge that the exact procedures are correct and the asymptotic procedures are only estimates. Therefore, software manufacturers should advertise that their procedures are more accurate, not more powerful. Indeed, because the statistical decision made between exact and asymptotic procedures were identical in all six cases, the use of exact tests should be questioned in terms of cost and computer time.

Recommendations

In order to validate this study, future research may include replicating the methodology in order to determine if one may derive similar results. Within the applied context of this study, one may consider analyzing the individual cells in order to determine the residuals as well as determining which individual cells may lead to significance. A Monte Carlo study could also be conducted in order to determine the possibility of a situation in which the asymptotic p value was statistically significant and the exact p value was not significant. Additionally, future research may re-analyze the same variables using the correction formula found in the SUDDAN software. SUDDAN provides better estimates of variance and standard errors when databases employ complex, stratified, multi-stage probability designs. Studies in this area may also facilitate an increased understanding of the relationship between certain nutritional variables and colorectal cancer. Finally, contrary to power claims made by the software industry, future theoretical studies may be better served by using asymptotic p values when using small samples categorical data.

APPENDIX

BEHAVIORAL Protocol Summary Form

Wayne State University
Human Investigation Committee

University Health Center, 8C
4201 St. Antoine Blvd.
Detroit, MI 48201
(313) 577-1628 Office
(313) 993-7122 Fax

PLEASE TYPE

HIC Use Only

HIC Protocol Number: Assigned IRB: B03

Section A: Principal Investigator (PI), Project Title, & Certification

1 PI Name: Joseph L. Musial III
Campus Address: 3375 Scott Hall
Department: Curricular Affairs
Phone: 577-1518 Pager:
Fax: 577-1382 E-mail jmusial@med.wayne.edu
College/School: School of Medicine

2. Project Title:

Modelling Cancer Outcomes in the Third National Health and Nutrition Examination Survey (NHANES III), 1988-94

Check one: This is a Research Proposal _X_ Thesis/Dissertation Other

3. Please check PI status: Undergraduate _X_ Graduate student _X_ Faculty/Staff member ___ Other

All students and those individuals who are not WSU faculty or employees of WSU or an affiliated health care institution, must provide:
Home Address: Home Phone:

4. Principal Investigator, Supervisor, & Departmental Certification

In signing this description of the research project, the PI agrees to accept primary responsibility for the scientific and ethical conduct of the investigation, as approved by the HIC. The project cannot begin until the investigator has received documentation of HIC review and final approval.

Joseph L. Musial III — Psychometric Service Officer I — 07/16/98
Signature of Principal Investigator — Title — Date

For individuals completing item 3 above, a WSU faculty supervisor's signature is required. In signing the description of the research project, the faculty supervisor certifies that he/she has reviewed the research plan and APPROVED the scientific and ethical aspects of this research. The faculty supervisor will supervise all compliance with the human subjects' guidelines.

[signature] — Professor & Program Coordinator — 7/16/98
Signature of Faculty Supervisor — Title — Date

351 College of Education — 577-1656
Faculty Supervisor's Campus Address — Department Phone #

In signing this description of the research project, the Department Chairperson or Institute/Center Director certifies that (1) appropriate [illegible] will be provided for the project and (2) appropriate scientific and ethical oversight has and will be provided.

[signature] — Assistant Dean, School of Education — 7/17/98
Signature of Department Chair, Dean, or Institute/Center Director — Title — Date

Approved by B03 December 11

4/15/98

Section B: Research Project Characteristics

5. Do you wish to have this project considered for Exempted Review? X Yes No

   If Yes, identify the Exemption category you believe covers your project. (See enclosure A-1) # 4

6. Do you wish to have this project considered for Expedited Review? X Yes No

   If yes, identify the Expedited Review section you believe covers your project. (See enclosure A-2) # 8

7. Inclusive dates of project: (PROJECT MAY NOT START PRIOR TO APPROVAL)

   From: 8/7/98 To: 3/1/99

8. How long is the active involvement of participants in the study? (e.g. 6 half hour sessions over 6 months)

9. Sponsor/Source(s) of funding, if any. (please include name, address and phone number)

   Public use data files are made available by the National Center for Health Statistics (NCHS) of the Centers for Disease Control. Data Dissemination Branch (301) 436-8500.

10. Is this a Multi-Center, International or National Collaborative Study? ___ Yes X No

11. Research location.
    a) Where will the research be performed? *

    The data was collected in the 50 states and the District of Columbia of the United States. The sample consists of 81 primary sampling units.

    *NOTE: If the research will be conducted in a school or other institution (i.e., hospital or residential facility) include letter, on letterhead stationery, of permission from that institution and/or approval from its IRB.

    b) Is letter of permission (or IRB approval) included X NA Yes No

Section C: Subject Recruitment

12. Indicate which, if any, of the following groups will be research subjects (check all that apply):

X Adult Volunteers	X Minorities	X Pregnant Women
___ Children	___ Terminally Ill	___ Cognitively Impaired
X Students	___ WSU/DMC Employees	X Physically Disabled
___ Prisoners	___ Non-consenting Subjects	___ Mentally Disabled
___ Institutional Residents		

13. Is selection of research subjects based on gender? Yes X No
    If yes, provide scientific justification.

14. Is subject selection based on racial/ethnic criteria? X Yes ___ No
If yes, provide scientific justification.
African American and Hispanic subjects were oversampled in order to obtain key health variables that would be cost prohibited in a random survey. I will be taking a course on SUDAAN in order to make the required statistical adjustments (7/27-7/31) at the University of Michigan School of Public Health Summer Epidemiology Session 1998.

15. What is the approximate number of subjects to be recruited?
There are n= 33,994 participants within the data base.

16. What is the age range of the participants?
I will restrict my analysis to adults 17+ and above. The data has subjects that are 11 months old.

17. What is the source of the subject list? (Provide letter authorizing you to use this list.)
The data base reports that the data is available to the public.

18. Who will contact the subjects?
NA

19. How will the subjects be contacted? Check all that apply.

___ Advertisements*
___ Telephone Lists
___ Student pool*
___ Random Telephone Dialing
___ Letters
___ Notices
___ Direct person-to-person solicitation
_X_ Other (please specify) Data already exists.

*NOTE: If any type of advertisement is to be used to recruit subjects, a copy must be submitted to the Behavioral IRB for approval. If subjects are recruited from WSU classes or the PSY 101 subject pool, indicate whether students are receiving course credit (regular or extra credit) and, if so, what alternatives are offered to those students who do not wish to participate in research. For letters, notices, advertisements, and other—submit verbatim copies.

20. Data collection methods (check all that apply):

___ Questionnaire or Survey
___ Interview
___ Observation
___ Video or Audio Taping
___ Archival Data
___ Intervention
___ Focus Groups
___ Testing/Evaluation
___ Instruction/Curriculum
_X_ Other (please describe) Data already exists.

21. If deception or experimental manipulation is used, explain why deception and/or manipulation are necessary (as opposed to convenience) for this study. Please include plans for how and when subjects will be debriefed.
NA

22. Does any part of this activity have the potential for coercion of the subject? Yes X No
If yes, explain and describe the proposed safeguards.

Approved by BO3 December 11, 1997

Section D: Consent of Research Subject

23. What type of consent will be used?
X
___ Written Consent ___ Information Sheet Assent
___ Oral Consent ___ Waiver

24. Will assent from children between the ages of 7 and 17 years be obtained? ____ Yes ____ No

25. If you are using a written consent, and/or assent, provide copies.
Consent was obtained by the field researchers. Names are not available to data users.

26. If you are using an oral consent
a) describe the rationale

b) describe how consent will be documented

c) provide a copy of the oral presentation.

27. If you are using an information sheet
a) describe the rationale for this as opposed to a written consent

b) provide a copy of the information sheet

28. If you are requesting that consent be waived, explain why consent should be waived. Cite relevant literature where possible.

Section E: Confidentiality

29. Where will consent forms be kept?
X N/A

30. How will research subjects be identified in the research data?
Subjects cannot be identified within the data base.

31 Will there be a link between data and research subjects
(i.e. names, social security numbers, medical record numbers) Yes X No

32. Describe the provision for security of research data and research subjects' consent/assent forms.
The National Center for Health Statistics did NOT disclose subject identification

33. Will research data be available to anyone other than IRB, sponsor, and/or study personnel? X Yes No

34. If yes, describe how the data will be safeguarded so that individual subjects cannot be identified.
The data base is available to the public.

35 Could any part of this activity result in the potential identification of child/adult/older adult abuse? Yes X No

36. Is the mandatory reporting of child/adult abuse outlined in your consent? Yes X No

37. Could any part of this activity result in the potential identification of communicable diseases or criminal activities? ___Yes X No

38. If there is a potential for communicable disease or criminal activities, have you requested a Certificate of Confidentiality? X N/A ___Yes ___No

Section F: Benefits and Risks to Research Subjects

39. Are the direct (specifically to the subject) and indirect benefits to the research subjects for involvement in this project described in the consent? X Yes No

40. Are the nature and degree of potential risks to research subjects, including psychological injury described in the consent? X Yes No

41 What precautions will be taken to minimize the risks described above?

The data has already been collected and will represent a secondary analysis.

Section G: Compensation for Research Subjects

42. Will research subjects be compensated or rewarded? ___Yes X No

If Yes, provide: (a) the type and amount of compensation_____

(b) the amount and milestone for each payment_____

Section H: Consultation and Collaboration (provide ALL investigators names. Use additional page if necessary)

43.	Co-Investigator Names	Division/ Department	Phone	Signature
a.				
b.				
c.				
d.				

Approved by BOI December 11, 1997

4/15/98

Section I: Narrative Description

11 Provide a **CONCISE**, narrative description of the research project. Explain the rationale for and the significance of the experimental procedures described in the research protocol. Use non-technical language and avoid abbreviations to the extent possible. Do not "paste" text from the protocol, and do not refer to the protocol page numbers or include literature citations. Information given here should provide the first-time reader with a clear understanding of the proposed research. Complete the narrative in no more than 2 or 3 pages.

There is an ongoing debate within the cancer literature that indicates disagreement among researchers who measure the variables associated with certain forms of cancer. For instance, many researchers believe that there is an association between a high fatty diet and the risk of colon cancer. In contrast, there is also a significant amount of research that indicates no association between a high fat diet and colon cancer. The prostate cancer literature also displays an even disagreement among researchers who believe that there is and is not an association between a high fat diet and the risk of developing clinically significant prostate cancer. More important, a large number of cancer studies that purport to measure nutritional practices and cancer outcomes often subscribe to questionable sampling practices. This would include studies which restrict to only males (Hawaiian Japanese males), restrict by religion (Seventh Day Adventists), restrict by occupation (health care professionals), omitting by race due to the geographical sampling location, as well as small sample sizes that are not large enough to detect certain forms of cancers.

The following dissertation proposes to provide additional information that will help to clarify the debate among researchers who investigate the nutrition/cancer link. Advanced statistical models will be developed using the Third National Health and Nutrition Examination Survey (NHANES III), 1988-94 database. NHANES III was conducted by the National Center for Health Statistics of the Centers for Disease Control. The survey measures the nutritional and health practices among 33,994 civilian, noninstitutionalized United States residents. The data is available to the public and does not disclose participant identification. The data was collected from eighty-one different primary sampling units in the United States and District of Columbia. African Americans, Hispanics, elderly and young children were over-sampled in order to assure representation within the database.

Statistical models developed within the database will provide a better understanding of the relationship between nutrition and cancer. Because of the large sample size, the data will provide for more statistical power than previous described databases and will be more generalizable than other studies cited in the cancer literature. One may also apply previous sample designs within the context of the NHANES III database in order to test previously described hypotheses.

Approved by BO3 December 11 1997

4/15/98

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ABSTRACT

COMPARING EXACT TESTS AND ASYMPTOTIC TESTS WITH COLORECTAL CANCER VARIABLES WITHIN THE NATIONAL HEALTH AND NUTRITION EXAMINATION SURVEY III

By

JOSEPH L. MUSIAL III

December 1999

Advisor: **Shlomo S. Sawilowsky, Ph.D.**

Major: **Evaluation & Research**

Degree: **Doctor of Philosophy**

***Background & Purpose*:** Colorectal cancer is a major health problem. There are many statistical procedures available to analyze cancer data. Software developers contend that exact procedures are the most powerful tests, without providing theory or applications. The following study is two-fold: 1) Evaluate the relationship between colon cancer and red meat, calcium, aspirin and ibuprofen use, and 2) Compare the power of exact and asymptotic tests using "real", small samples categorical data.

***Methods*:** A secondary analysis was performed on the adult data file (N = 20,050) from the National Health and Nutrition Examination Survey III (NHANES III). NHANES III employed complex, stratified, multi-stage probability design. The information was based on in-depth interviews. Statistical significance was established at the nominal alpha level of 0.05.

***Results*:** There was a significant association between red meat, aspirin, ibuprofen use, and the dichotomous colon cancer variable. The power study found no association

between health status and the type of cancer diagnosis. The asymptotic p value was found to be smaller than the exact p value in five out of six simulations. The statistical decisions were the same in all cases.

***Conclusions*:** Within the context of the evaluation, several variables were associated with the dichotomous colon cancer variable including red meat, aspirin, and ibuprofen. This suggests that future research should investigate the relationship in more detail. The theoretical power study used real, small samples categorical data. Because the asymptotic p values were smaller than the exact p values in five out of six simulations, one could counter the software industry's claim of providing more powerful tests. The exact procedures are correct; the asymptotic procedures are only estimates. The statistical decisions made between asymptotic and exact procedures were identical in all cases. Subsequent questions arise concerning cost and computer time.

AUTOBIOGRAPHICAL STATEMENT

Joseph L. Musial III

Joseph L. Musial III is employed full time as the Coordinator of Instructional Assessment at Henry Ford Community College in Dearborn, MI. He received his Associates of Arts degree from Henry Ford C.C., (1985); Bachelors of Arts in Psychology from the University of Michigan-Dearborn, (1987); Masters degree in Public Administration from Rackham Graduate School at the University of Michigan, Merit Scholarship, (1992); and will receive his Ph.D. in Educational Evaluation and Research from Wayne State University, (1999). He is a member of the American Statistical Association, American Educational Research Association, National Council on Measurement in Education, and Psi Chi: the National Honor Society of Psychology. Joseph also maintains a respected publication record. His most recent manuscript titled, "Use of an Open-Ended Question to Supplement a Patient Satisfaction Questionnaire in a Medical Residents' Clinic", will appear in the December 1999 edition of *The American Journal of Managed Care.* He and his wife Nicol live in Dearborn.