

**LOWER SELENIUM STATUS AMONG ADULT WHITE AMERICAN MALES:
PREVALENCE, RISK FACTORS, AND IDENTIFICATION OF
AUGMENTATION STRATEGIES. A POTENTIAL
APPROACH TO REDUCE PROSTATE CANCER INCIDENCE.**

By

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MASTER OF SCIENCE

in the Department of Geography

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Abstract

Objectives: To establish the prevalence of lower serum selenium status (<106 ng/ml) among the adult white American male population, to determine whether certain social, economic, geographic, physical, and dietary characteristics are risk factors for lower selenium status, and to identify a selenium augmentation strategy for white adult men deficient in this trace element.

Design: An exploratory cross-sectional study using nationally representative data from the National Health and Nutrition Examination Survey III, 1988-1994 (NHANES III).

Methods: 2989 white men, aged 20 or greater in the NHANES III dataset had recorded serum selenium values. These men were divided in two groups based on selenium status, those with values of less than 106 ng/ml (n=288) and those with a status greater than or equal to 106 ng/ml (n=2701). Various demographic, physical, and dietary variables were then compared between the two selenium status groups in a bivariate analysis. Multiple logistic regression was then performed to assess possible risk factors for lower selenium status.

Results: This study estimated that 7.7% of white American adult men aged 20 years and older, a total of 4,751,618 individuals, had a selenium status less than 106 ng/ml. Several, of the more than forty, social, economic, geographic, physical and dietary characteristics examined were shown to be significantly associated with a lower selenium status. Risk factors for lower selenium status (<106 ng/ml) were, smoking, living in the Southern census region, being in either the 20-39 or the 60 years or older age groups, exercising less than their peers, having a lower income, and not consuming dark bread.

Conclusion: It would appear that certain physical, geographic, dietary and demographic characteristics are significantly associated with lower selenium status. While, this work was unable to identify a suitable selenium fortification vehicle to reduce the prevalence of lower selenium status, it did identify risk factors that may contribute to this condition.

Keywords: NHANES III, Prostate Cancer, Selenium Status, Nutritional Prevention of Cancer Trial, Cross-Sectional Study.

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Chapter I: Introduction

Medical Geography

In simple terms the study of medical geography is the use of “concepts and techniques of geography to investigate health related topics” (Meade and Earickson, 2000). This sub-discipline of geography applies an ecological perspective to the study of disease and health. Medical geography has been a recognized branch of the discipline for nearly 200 years, however, it can trace its roots back much further to the Hippocratic treatise *On Airs, Waters, and Place* written in 400 B.C. Hippocrates believed that in order to investigate medicine properly one must take a holistic approach which examined the time of year, the weather, location, water, exercise and diet (Hippocrates, c. 400 B.C.).

Whoever would study medicine aright must learn of the following subjects. First he must consider the effect of each of the seasons of the year and the differences between them. Secondly he must study the warm and the cold winds, both those which are common to every country and those peculiar to a particular locality. Lastly, the effect of water on health must not be forgotten. Just as it varies in taste and when weighed, so does its effect on the body vary as well. When, therefore, a physician comes to a district previously unknown to him, he should consider both its situation and its aspects to the winds. The effect of any town upon the health of its population varies according as it faces north or south, east or west. This is of the greatest importance. Similarly, the nature of the water supply must be considered; is it marshy and soft, hard as it is when it flows from high and rocky ground, or salty with a hardness which is permanent? Then think of the soil, whether it be bare and waterless or thickly covered with vegetation and well-watered; whether in a hollow and stifling, or exposed and cold. Lastly consider the life of the inhabitants themselves; are they heavy drinkers and eaters and consequently unable to stand fatigue or, being fond of work and exercise, eat wisely but drink sparingly?
(Hippocrates, c. 400 B.C.).

In more modern times Leonard Fink's *Versuch einer allgemeinen medicinisch-praktischen Geographie* of 1792-1795 is thought to be the first published works of medical geography (Valencius, 2000). Perhaps the most well known early study of medical geography was

the work of John Snow who, in 1848, mapped the location of cholera deaths in London (Stamp, 1964). In doing so, Snow discovered the disease was a result of a contaminated public water pump as opposed to foul air which was originally thought to be the cause.

Medical geography research in the late 19th and 20th centuries mostly dealt with the relationships between disease and the social and physical environments. Notable examples of this focus include Hirsch's (1883-1886) *Handbook of geographical and historical pathology*, May's (1958, 1950) *The Ecology of Human Diseases and Medical Geography: Its Methods and Objectives*, along with Stamp's (1964) *The Geography of Life and Death*.

In the 1960's, advances in computer technology spawned the quantitative revolution in many sub-disciplines of geography, including medical geography. With greater computing power, new techniques in biostatistics and methodologies for spatial analysis known as Geographic Information Systems (GIS) emerged and allowed researchers to study and understand more complex associations (Meade and Earickson, 2000). Some of the earliest research done using sophisticated quantitative techniques was conducted by Gerald Pyle (1971) who examined the spatial patterns of cancers, stroke, and heart disease in Chicago.

For much of the twentieth century, medical geography was divided into two main subfields. One branch concerned itself with the study of health care facility location and utilization, while the second was related to epidemiology and the ecology of disease (Pacione, 1986). The first area of research dealt with the availability and accessibility of health care. This type of research continues to be practiced and often examines the location of health care facilities, the inequalities in access to health care, and the use of health care services by patients (Mayer, 1982).

The main theme of research within the second subfield dealt with the ecology of disease. Work in this subfield continues to be done and seeks to identify the relationships between the environment and disease in order to establish cause and effect (Mayer, 1982). Examples of this type of work would include the mapping of disease incidences, the study of disease diffusion, and the relationship of disease mortality and morbidity to diet (Meade and Earickson, 2000) as just two of many other examples.

In the 1990's, the discipline of medical geography experienced significant transformations as many researchers heeded the appeal of Kearns' (1993) for a reformed medical geography that encouraged the engagement of public health concerns, and aspects of social theory, with a re-emphasis of place in research (Smyth, 2005). This change has led to an emergence of works that have examined the notion of 'healthy places' (Frumkin, 2003) and the creation of healthy communities (Srinivasan *et al.*, 2003)

As the discipline continues to evolve, medical geographical research is exploring new study areas. According to Mayer (2004), two more subfields have recently emerged and contemporary medical geography can now be divided into four major foci (Mayer, 2004). Disease ecology and the analysis of health care facility location and utilization are now joined by health and social geography and the political ecology of disease. Health and social geography refers to the "identification of spatial patterns of disease, and the explanation of those patterns based on the social, environmental, and cultural processes that generate those patterns" (Mayer, 2004, pg. 9521). The political ecology of disease deals with the consideration of health and disease in the broader context of society, political economy, and social structure (Mayer, 2004).

The Research in the Context of Medical Geography

The current thesis topic attempts to determine whether certain social, economic, geographic, physical, and dietary characteristics contribute to the status of a micronutrient in the body. This type of research is compatible with the disease ecology sub-discipline of medical geography that often examines the relationship between the physical and social environments in order to gain an understanding of disease etiology. Disease ecology is a holistic approach which takes into account the multifaceted nature of many diseases and is closely aligned with Lalonde's (1974) "Health Field Concept" model. This health-disease model identifies four major determinants of human well-being: human biology (genetics, gender, ageing, and the complex internal workings of the body), environment (physical, built, and biological), lifestyle (decisions made with regard to diet, exercise, hygiene, sexual habits, smoking, alcohol consumption, and drug use) and the health care system (Lalonde, 1974). When published in 1974, the "Health Field

Concept” and its simple delineation of the four main categories of factors influencing health had a marked impact on Canadian, American, European and Australian health planning (PHAC, 1997). In the years that followed its popularization, more interest was turned to the neglected dimensions of lifestyle and environment (PHAC, 1997).

Using a holistic approach that accounts for the various causal factors of a disease, researchers and health officials have been able to design and implement strategies which have successfully reduced, and in some cases nearly eliminated, the incidence of various sicknesses such as pellagra, rickets, and goiter (Park *et al.* 2000; Javitt, 2000) . Many of these strategies are preventive measures that often cost very little yet yield major public health benefits. This is particularly fortuitous since it has been estimated that 70% of American health care costs are a result of preventable illness (Fries *et al.* 1993).

With regard to preventing illness on a population scale, some of the most successful strategies have involved food fortification. Augmenting common foods with specific nutrients has helped to eliminate micronutrient deficiencies as public health problems in many Western countries. For example, in the early part of the 20th century, parts of the northern United States had endemic goiter. In some heavily affected counties, nearly 30% of the population suffered from the disease (Olin, 1924). Beginning in 1924, iodine was added to table salt in order to overcome the nutrient deficiency that causes this condition. This strategy was very successful and continues to this day. As a result, endemic goiter has been virtually eliminated from the US population (Javitt, 2000).

Another fortification success has involved the disease pellagra. Pellagra is a type of tryptophan and niacin (vitamin B3) deficiency that results in dermatitis, dementia, and ultimately death (Hegyí *et al.*, 2004). In the United States from 1906 to 1940, roughly 3 million people suffered from pellagra and over 100,000 died from it (CDC, 1999). Widespread fortification of grain products with niacinamide beginning in the mid 1930s helped virtually eradicate the disease in the United States by the 1960s (Park *et al.* 2000).

The most recent large scale fortification initiative in the United States began in 1998 with the addition of folic acid to grain products. The rationale for this program was that women supplemented with folic acid during their pregnancy reduced their risk for giving

birth to a child with a neural tube birth defect (MRC, 1991). Two years after this program was initiated, the Center for Disease Control estimated that the number of infants affected by neural tube defects had been reduced by 25%, and that much of this decline was because of folic acid fortification (CDC, 2004).

This thesis continues the tradition of developing and evaluating potential strategies to reduce disease. Specifically, the current work seeks to examine the associations, if any, between a range of biological, environmental and lifestyle factors and depressed male selenium status. Its final is to evaluate a potential dietary intervention that might be used to increase selenium status and as a result reduce the incidence of prostate cancer. Similar recent research would include Lee and colleagues' (2005) identification of socio-demographic, lifestyle and nutritional determinants of the blood lead levels of US women of reproductive age, and their subsequent intervention recommendations.

Chapter II: Introduction to the Research

Recently, the Nutritional Prevention of Cancer (NPC) trial demonstrated that selenium supplementation significantly reduced the risk of prostate cancer (Duffield-Lillico *et al.*, 2003). This American based experiment began in 1983 and tested whether supplementing individuals with selenium could play a role in preventing the development of cancer. Enrolled individuals were given either 200 µg of selenium per day, in the form of selenized yeast, or a placebo. The primary endpoint of this study was non-melanoma skin cancer among a high-risk population of 1312, mainly white people, living in the eastern USA (Duffield-Lillico *et al.*, 2003; Duffield-Lillico, personal communication, 2006). The secondary endpoints of the study included mortality from cancer as well as examining the incidence of lung, colon, and prostate cancer among participants.

After 13 years, the NPC trial reported that, although selenium supplementation did not seem to have any statistically significant effect on a primary endpoint of non-melanoma skin cancer, it did provide protection against other forms of cancer. Selenium supplementation, for example, was found to significantly reduce total cancer mortality (41%) and total cancer incidence (25%) (Clark *et al.*, 1996). The strongest inverse association between selenium supplementation and cancer was for prostate cancer. Clark and workers (1996) found that supplemented group was 52% less likely to develop prostate cancer than the placebo group. Subsequent analysis of the NPC data by Duffield-Lillico and colleagues (2003) showed that this inverse association between selenium supplementation and prostate cancer incidence was confined mainly to those men with blood plasma selenium levels in the lowest tertile (≤ 106.4 ng/ml).

Prostate cancer has both large human and financial consequences in the United States. For example, in 2002, 34,446 men died as a result of the disease and it is estimated that health care costs to treat it exceed \$1.5 billion per year (USDHHS, 2005). While not all men who develop prostate cancer have low selenium status and conversely, not all men with low selenium intake develop prostate cancer, a positive relationship may exist. Given that it has been demonstrated that men with low selenium status, who are supplemented with selenium (Se), significantly reduce their risk of developing the disease (Duffield-Lillico *et*

al., 2003), it seems very likely that some of these prostate cancer deaths could be prevented by increasing dietary intake of this trace element.

The exploratory research described in this thesis, therefore, seeks to identify some of the social, economic, physical and geographic characteristics of men who, if they augmented the selenium content of their diet, might be able to reduce their risk of developing prostate cancer. It is hoped that should the United States federal government wish to reduce the rate of prostate cancer using selenium supplementation/fortification, this thesis could be used to identify both the population towards whom such a project should be directed and the effective delivery vehicles.

Research Questions

To achieve those objectives, this study seeks to answer three main research questions:

1. What is the prevalence of lower (<106 ng/ml) serum selenium status among the adult white American male population?
2. Are social, economic, geographic, physical, and dietary characteristics of adult white men with lower serum selenium status significantly different than those males with higher levels of selenium status? If so, what are the key risk factors for lower selenium status?
3. What is likely to be the most successful selenium augmentation strategy for white adult men deficient in this trace element (<106 ng/ml)?

The Third National Health and Nutrition Examination Survey (NHANES III) was the data source for the analysis.

Chapter III: Literature Review

The Epidemiology of Prostate Cancer

Prostate cancer is a form of cancer that develops in the prostate, a gland in the male reproductive system used to produce and store seminal fluid. The vast majority (>99%) of diagnosed prostate cancers are adenocarcinoma (ACS, 2007). This type of cancer occurs when normal glandular cells in the prostate mutate into cancer cells. Over time these cancer cells multiply and spread to the surrounding prostate tissue and form a tumor (Bonkhoff, 2001). The disease may then continue to progress with the tumor spreading to surrounding organs such as the seminal vesicles or the rectum. The tumor cells may develop the ability to travel through the bloodstream, or the lymphatic system, and spread (metastasize) to distant organs such as bones, the bladder, lymph nodes, and the rectum (Moon, 1992).

Among American men, prostate cancer is the most commonly diagnosed form of the cancer, and represents a third of all male diagnosed cancers (ACS, 2007). The American Cancer Society (2007) estimated that in the United States, over 218,000 men will be diagnosed with prostate cancer in 2007 and that about 27,000 will die from the disease. Annually, it is believed that medical treatment costs for the disease exceeds 5 billion dollars, with much of this burden being paid by Medicare since two thirds of men diagnosed are over the age of 65 (NPCC, 2007).

There are several known risk factors that contribute to the development of prostate cancer. These include advanced age, race, geography, family history, and diet (Gann, 2002; NCI, 2008). Each of these risk factors is now discussed.

The National Cancer Institute (2008) in the United States has reported that age is the strongest risk factor for the disease. Prostate cancer is rarely diagnosed in younger men. For example, less than 0.1% of all cases are found in men less than 50 years old and the mean age of diagnosis in Western men is between 72-74 years (Gronberg, 2003). After the age of 40, the prostate gland enlarges as prostatic cells multiply, this cell growth may

make prostate tissue susceptible to malignancies or abnormalities (Sampson *et al.*, 2007). The exact reason for this growth is not understood, however, it is believed to be a result of changes in testosterone and/or estrogen levels (Thomas and Keenan, 1994).

The risk of developing prostate cancer is also significantly affected by a person's race or ethnicity. African-American men are more than twice as likely to die from prostate cancer and to be diagnosed with advanced stages of the disease as white men (Hankey *et al.* 1999). Compared with non-Hispanic whites in the United States, Hispanic men have one third less the incidence and mortality rates of prostate cancer (Stanford *et al.* 1999).

A number of reasons have been cited for the racial differences in prostate cancer incidence and mortality in the United States. Racial differences in dietary, hormonal, or molecular factors may create differences in tumor biology and result in more aggressive tumors in African-Americans (Morton, 1994; Pienta and Esper, 1993). Also, difference in access to health care and prostate cancer screening may explain some of the differences in rates (Bennett *et al.* 1998). Nevertheless, Hoffman and colleagues (2001) found that socio-economic, clinical, and pathologic factors could only account for 15% of the difference in incidence rates between African-Americans and non-Hispanic whites.

Along with age and ethnicity, a family history of the prostate cancer is a strong risk factor for developing the disease (NCI, 2008). A number of epidemiological studies have found an increased risk of prostate cancer for brothers and sons of men with the disease (Bratt, 2002). The risk of developing prostate cancer is further increased if the relative is diagnosed with prostate cancer before the age of 60 (Hemminki and Czene, 2002). It is estimated that hereditary factors are responsible for up to one-third of the prostate cancer cases diagnosed before the age of 60 and more than 40% of those diagnosed before the age 55 (Carter *et al.* 1992; Bratt *et al.* 1999).

Diet has also been identified as an important factor with regard to the development of prostate cancer. The consumption of cruciferous vegetables, such as broccoli, kale, cabbage, cauliflower have been shown to reduce the risk of developing prostate cancer (Cohen *et al.* 2000). Also, diets high in tomatoes reduce the risk of prostate cancer (Giovanucci, 2005). In his study, Giovanucci (2005) showed that men who consumed

more than 10 servings of tomatoes per week reduced their risk of developing prostate cancer by one third. Lycopene is believed to be one of the important prostate cancer fighting nutrients in tomatoes (Frusciante *et al.* 2007). In a case control study of men in Arkansas, subjects in the highest quartile of plasma lycopene had a 55% lower risk of prostate cancer than those in the lowest quartile (Zhang *et al.* 2007).

Research has also indicated that two foods commonly consumed in Asia, soy and green tea, have an impact on prostate cancer risk. Soy contains elevated levels of isoflavones, a nutrient which has been shown to reduce prostate cancer growth and proliferation (Goetzl *et al.* 2007; Messina *et al.* 2006). Green tea contains catechins which, in a small clinical trial, reduced the risk of developing prostate cancer among a group of high risk men (Bettuzzi *et al.* 2006).

In terms of increasing the risk of developing prostate cancer, epidemiologic evidence suggests a diet high in fat is linked to higher rates of the disease (Fleshner *et al.* 2004). Researchers have theorized that a higher fat intake may increase the risk of developing prostate cancer in a number of ways. These include a greater exposure to carcinogenic fat-soluble pesticides (Schrader and Cooke, 2000), increased androgen levels (Littman *et al.* 2006), and/or augmented oxidative stress in the body (Rao *et al.* 1999).

Geography plays a role in the development of prostate cancer (NCI, 2008). This is highlighted by the geographic variation in rates of prostate cancer incidence and mortality between and within nations. For example, Western nations in general have the highest rates of incidence while Asian countries have very low rates of the disease (see Table 1, pg. 11). While the age-adjusted rate of prostate cancer among white American men is 100.8 per 100,000, in China it is only 2.3 per 100,000 (Hsing *et al.* 2000; Parkin *et al.* 1997).

Prostate cancer incidence rates in all countries, for which reliable data are available, increased between 1973-77 and 1988-92 (Hsing *et al.* 2000). Prostate cancer is currently the most commonly diagnosed cancer among Western men (Parkin *et al.* 1997), whereas in China it is only the 15th most common form of cancer (Yang *et al.*, 2005)

Table 1: Age-Adjusted Incidence Rates of Prostate Cancer in Select Countries 1988-92.

Country	Number	Incidence Rate Per 100,000
U.S. Blacks	7,129	137.0
U.S. Whites	66,227	100.8
Canada (BC)	10,473	84.9
Zimbabwe* (Whites, Harare)	N/A	56.7
Sweden	25,253	55.3
Australia (NSW)	10,870	53.5
France (Bas-Rhin)	1,502	48.1
U.S. Japanese	N/A	43.1
Denmark	7,392	31.0
England (S. Thames)	9,529	29.3
Zimbabwe* (Blacks, Harare)	N/A	29.2
Italy (Varese)	884	28.2
Spain (Navarra)	641	27.2
U.S. Chinese	N/A	26.0
Israel (all Jews)	3,147	23.9
Singapore (Chinese)	415	9.8
Japan (Miyagi)	737	9.0
Hong Kong	1,185	7.9
India (Bombay)	764	7.9
China (Shanghai)	539	2.3

*Incidence rates in Africa should be viewed with caution because of lack of screening, misclassification, and underreporting

Source: Hsing *et al.* 2000 and Parkin *et al.* 1997.

The complex etiology of prostate cancer contributes to its wide geographic variation. Two of the strongest risk factors for the disease, ethnicity and lifestyle factors are thought to be responsible for these large spatial differences in incidence rates (Bostwick *et al.* 2004).

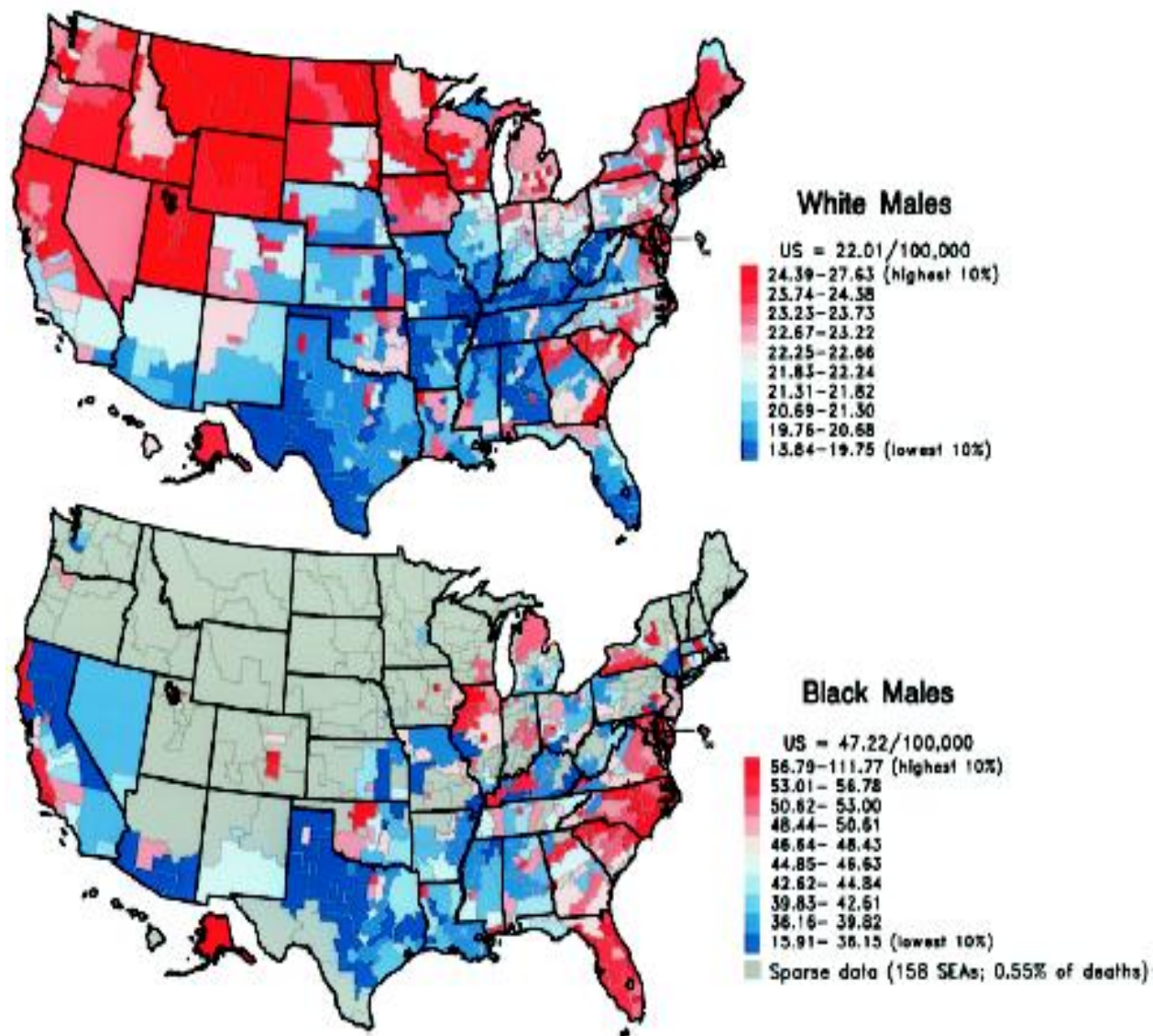
Ethnicity has been shown to be an important risk factor for the development of prostate cancer with obvious geographic implications (Hsing, *et al.* 2000). In general, prostate cancer risk is lowest, regardless of country of origin, among ethnic Asian men, whereas the highest risk is present among those of African ancestry (Hsing, *et al.* 2000). However, there are problems of multicollinearity since ethnicity and diet are often closely linked (Gann, 2002).

While, ethnicity plays a large role in the development of prostate cancer, dietary lifestyle factors are also very important. It would appear as though the adoption of a “westernized” way of life consisting of higher intake of meats, animal fats, and sugar along with a decrease in protective factors such as soy, green tea, antioxidants, and physical activity

significantly increases the risk of developing the disease (Hsing and Devesa, 2001). The hypothesis that a western lifestyle increases the risk of prostate cancer is bolstered by several observational studies that have shown incidence rates of the disease increase significantly among migrants from countries with low rates of prostate cancer, such as China and Japan, when they move to countries with higher rates of the disease (Maskarinec and Noh, 2004; Parkin *et al.* 1997; Shimizu *et al.* 1991; Haenzel and Kurihara, 1968). For example, the incidence rate for prostate cancer is 2.3 per 100,000 in Shanghai, China, whereas it's 26 per 100,000 for Americans of Chinese decent (Hsing, *et al.* 2000).

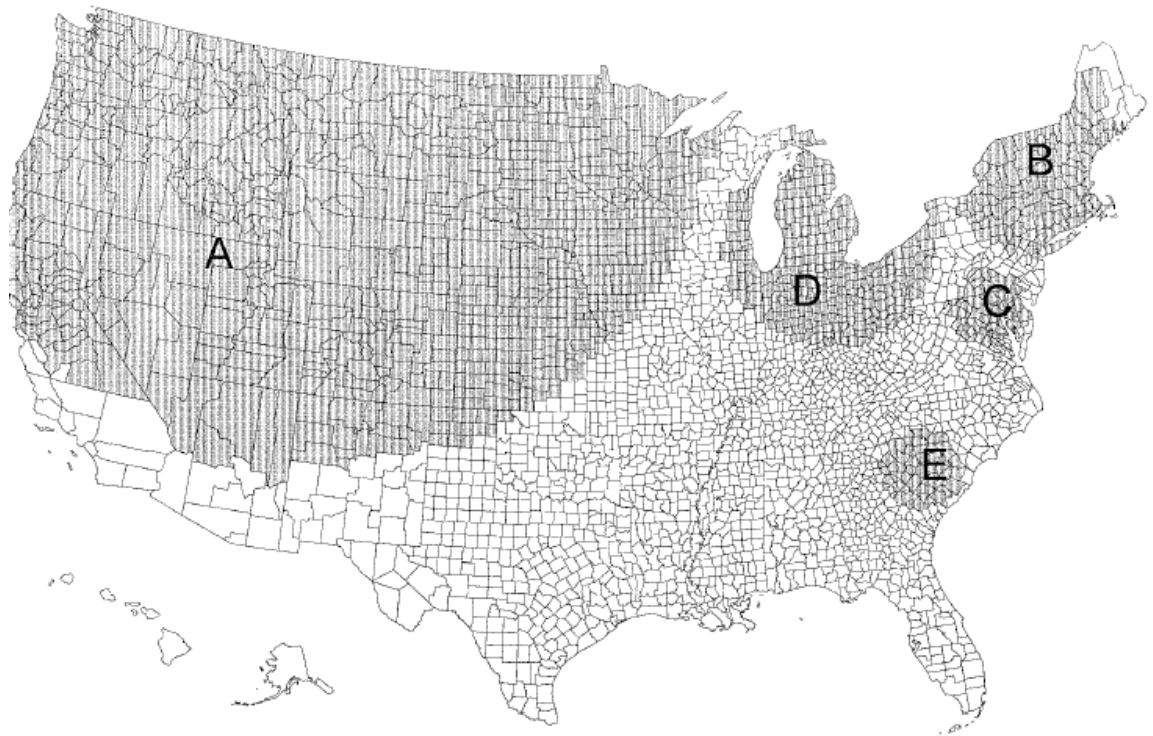
Within the United States there are marked geographical differences in prostate cancer mortality (see Figure 1, pg. 13). Jemal and colleagues (2002) have shown that certain regions had significantly higher rates of prostate cancer mortality than would be expected given the region's population characteristics. After controlling for demographic and socioeconomic factors they noted that among white men there were five clusters of elevated prostate cancer mortality risk. The primary cluster was located in the North West, followed by others in the eastern part of the north-central area, the Mid-Atlantic States, and the South Atlantic area (Figure 2, pg. 14).

Figure 1: Prostate Mortality Rates among Whites and Blacks by State Economic Area (1970-1994).



Source: Jemal *et al.* 2002.

Figure 2: The most likely clusters of prostate cancer mortality among White males (1970-1989)



The most likely cluster (A) and 4 secondary clusters (B–E) of prostate cancer mortality for 1970–89 among whites as identified by Jemal *et al.* 2002.

Source: Jemal *et al.* 2002

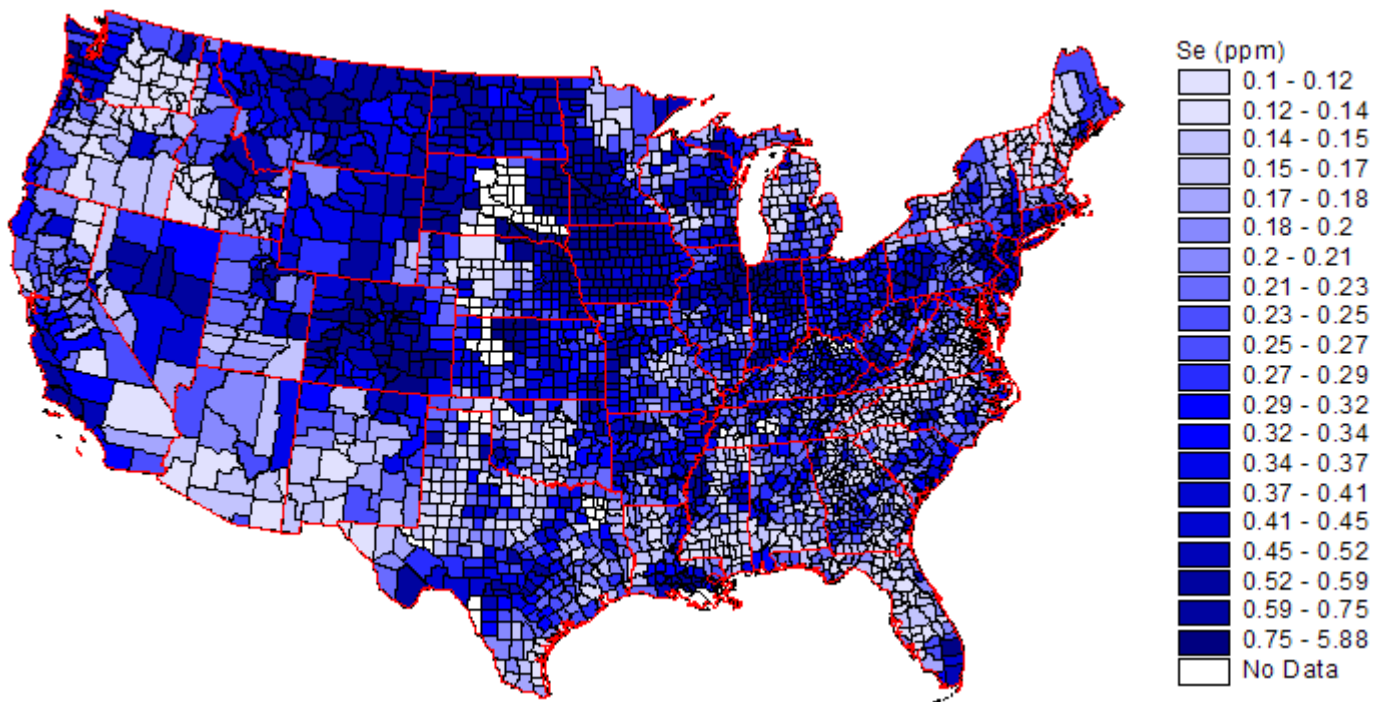
The Geography of Selenium

Selenium (Se), like other trace minerals, is unevenly distributed across the Earth’s surface. It enters the food chain through plants that obtain it from soils and by marine life which absorbs it directly from the water. Selenium initially is derived from volcanic sources and, as a consequence, tends to be more concentrated in soils of volcanic regions (Foster, 2002). On average, rocks contain approximately 0.09 ppm of Se (Lag, 1998). The concentration of selenium in soils, however, can range from less than 0.1 to greater than 100 mg/kg, with most soil concentrations ranging from 1.0 to 1.5 mg/kg (Berrrow and Ure, 1989).

Globally there is a high degree of variability in natural soil selenium levels. Areas of China, New Zealand, Finland, and Siberia have notably low soil Se while the Great Plains of Canada, Enshi County in China, portions of Ireland, Columbia, Venezuela, and Senegal have very high levels of the mineral present (Combs, 2001).

In the United States, soil selenium concentrations vary a great deal (Figure 3). The highest levels are found in the Midwest and Plains regions while the lowest concentrations occur in the Southwest, Northeast and portions of the Northwest (USGS, 2007).

Figure 3: Soil Selenium Levels in the United States



Source: United States Geological Survey, National Geochemical Survey.
<http://tin.er.usgs.gov/geochem/doc/averages/se/usa.html>. (Accessed Jan, 2007).

While the level of Se in the soil is the most important single factor for determining how much of this trace element enters the food chain, several other factors such as pH and the presence of other minerals, influence the rate and degree that plants uptake the mineral. The acidity or alkalinity of soils plays a significant role in the ability of plants to uptake selenium. Generally, plants growing in poorly aerated soils that have a lower pH (acidic) do not contain high levels of Se because, in such environments, the mineral occurs in forms (selenides and elemental Se) that are not readily taken up by plants (Lyons *et al.*, 2003). Conversely, soils that are naturally alkaline, or limed during agriculture practices, cause selenium to be oxidized, making the mineral more soluble and easily absorbed by

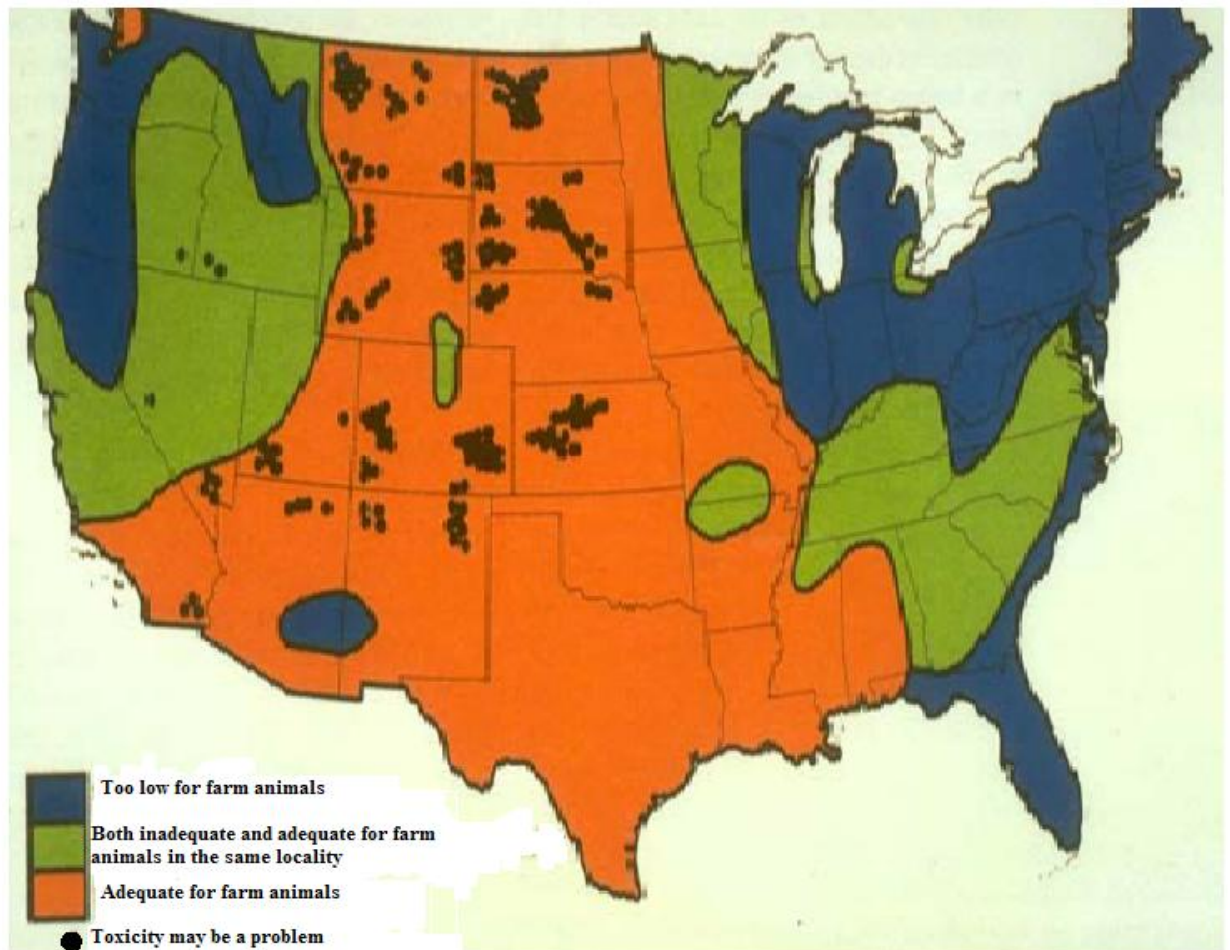
plants (Foster, 2002). In certain counties in China, the use of lime has caused selenium toxicity symptoms in the local populations (Yang *et al.* 1983).

Soil moisture also affects the ability of plants to uptake selenium. The element is most available to plants under conditions of low precipitation and low soil leaching (Combs, 2001). As a result, the availability of soil Se to crops can be affected by soil management procedures such as irrigation and aeration (Gissel-Nielsen, 1998).

The presence of other minerals in the soils can also influence the solubility of selenium making the mineral more or less available to plants. For instance, in lateritic soils with high amounts of iron, aluminum, and manganese, these minerals will bind to Se to form poorly soluble oxide or hydroxide complexes (Reilly, 1996; Lag, 1998). Mercury and selenium also form mercury selenide which is very insoluble and reduces selenium bioavailability (Shanker *et al.*, 1996)

Selenium is not considered an essential mineral for higher (vascular) plants (Terry *et al.* 2000), however, they passively absorb the mineral. Species of plants can differ markedly in their ability to absorb Se. To illustrate, certain varieties of *Astragalus*, such as two-grooved milkvetch (*Astragalus bisulcatus*), can accumulate very high levels of Se, up to 15,000 mg/kg dry weight, while wheat grown in the same soils typically contains 50 mg/kg (Beath *et al.*, 1937; Lyons *et al.*, 2003). Figure 4 (pg. 17) shows the geographical distribution of selenium in forage crops in the United States. In general, selenium levels in such crops are lowest in the Northwest and Eastern United States. In contrast, fodder crops grown in the central United States normally contain adequate selenium (Oldfield, 1999).

Figure 4: The Selenium Content in US Forage Crops



Source: Oldfield JE. 1999. *Selenium World Atlas*. Selenium-Tellurium Development Association. Belgium.

While natural rock, soil, plant, and climatic variations influence the amount of Se that enters our food, anthropogenic forces may also affect the uptake of the mineral. For example, it has been proposed that a general lowering in soil pH caused by acid rain, during the last century, has decreased the amount of selenium entering the food chain on a global scale (Frost, 1987). This is because increased soil acidity has reduced Se availability to plants (Mushak, 1985). In addition, soil agricultural practices such as fertilizer use, irrigation, aeration, liming and Se fertilization, may have an impact upon the selenium content of crops (Gissel-Nielsen, 1998). To illustrate, the addition of selenium to fertilizers has been mandatory in Finland for some 20 years, in an effort to overcome low

selenium status among its population and thus reduce heart disease mortality (Lyons *et al.*, 2003). The addition of selenium to fertilizers is also common in the South Island of New Zealand and in parts of China (Arthur, 2003; Lyons *et al.*, 2003).

Selenium and Health

Selenium was first recognized as an essential micronutrient for humans in 1957 (Schwarz and Foltz, 1957). Individuals who do not consume enough of this mineral are prone to deficiency diseases.

Keshan disease and Kashin-Beck disease are caused by a lack of selenium in the diet. Both are endemic to parts of China and Eastern Siberia where soil selenium levels are extremely low. Keshan disease is a type of cardiomyopathy that occurs mainly in children and women of childbearing age in these areas (Keshan Disease Research Group, 1979a,b). Symptoms of the disease include lower cardiac function, and cardiac enlargement arrhythmias (Reilly, 1996). The etiology of the disease is complex but it is believed to be caused by a lack of Se and vitamin E in the presence of the Coxsackie B virus (Yang *et al.*, 1994).

Kashin-Beck disease is a type of osteoarthritis that causes enlarged joints, shortened toes and fingers, and in dwarfism in severe cases (Levander, 1987). As in the case of Keshan disease, selenium deficiency is believed to be a pre-disposing factor for this condition (Peng *et al.* 1992). Other variables that may contribute to Kashin-Beck include fulvic acids in drinking water which increases free radicals in the body (Peng *et al.* 1999) and/or mycotoxins (Xiong *et al.*, 1998).

Low selenium status has also been linked to susceptibility to a range of viral infections (Taylor, 1997). It has also been shown that severe selenium deficiency when coupled with lower levels of vitamin E can increase the mutation rates of RNA-viruses (Beck, 1997), such as the Coxsackie B virus, measles, influenza, hepatitis and HIV (Combs, 2001). With regard to HIV, selenium deficiency is a significant predictor of mortality for HIV-related illnesses and viral load (Campa, *et al.*, 1999; Baum *et al.*, 1997). Foster (2004) has reported that supplementation with selenium and certain amino acids can reverse the

symptoms of AIDS and reverse the decline of HIV-positive patients with the disease (Namulemia *et al.*, 2007). In the case of people infected with Hepatitis B or C, selenium seems to protect against the development of cirrhosis and liver cancer (Yu *et al.*, 1997, 1999).

While selenium is an essential mineral for humans, consuming excessive amounts can be harmful. Too much selenium intake may lead to selenosis. The symptoms of chronic selenosis include, garlic odor of the breath, thickened and brittle fingernails, dry hair, red, swollen skin of hands and feet that may blister, excessive tooth decay, and nervous system abnormalities such as numbness, convulsions and paralysis (Koller and Exon, 1986). The intake required to produce symptoms of selenosis varies from person to person, however, the Food and Nutrition Board of the American Institute of Medicine (2000) has set the tolerable upper intake level for selenium at 400 ug/day for adults. This threshold was established based on the prevention of hair and nail brittleness and loss as early signs of chronic selenium toxicity (FNBIM, 2000).

The Function of Selenium in the Human Body

Selenium is converted into at least 11 known selenoproteins in the body, each of which perform essential metabolic roles. These selenoproteins and their functions are outlined below.

Selenophosphate synthetase

Before being transformed into a selenoprotein, selenium must first be incorporated in the body as the amino acid selenocysteine. The conversion of selenocysteine into a selenoprotein requires direction from the genetic code along with the presence of several compounds, including selenophosphate synthetase (Stadtman, 1996). Therefore, the selenoprotein selenophosphate synthetase is required to create all the other known selenoproteins.

Glutathione peroxidases

Of the eleven known selenoproteins, four belong to a group of enzymes called glutathione peroxidases (GPxs). These four, cellular or classical GPx, plasma or extracellular GPx, phospholipid hydroperoxide GPx, and gastrointestinal GPx are each distinct proteins yet

perform similar roles as antioxidant enzymes (Holben and Smith, 1999). Such antioxidants in cells prevent damage due to the action of reactive oxygen species. The latter include hydrogen peroxide, hypochlorous acid, and free radicals such as the hydroxyl radical and the superoxide anion (Halliwell, 2003). Such molecules are unstable and highly reactive, and can damage cells by chemical chain reactions such as lipid peroxidation, or the formation of DNA adducts that can lead to cellular mutations or cell death (Halliwell, 2003). Foster (2007) has argued that the glutathione peroxidases act as the first line of defense in the immune system, giving protection for example, against many viruses.

Thioredoxin reductase

Thioredoxin reductase works with the compound thioredoxin to regenerate several antioxidant systems, possibly those including vitamin C (Mustacich and Powis, 2000). In conjunction with thioredoxin, thioredoxin reductase is important for regulating cell growth and viability (Holben and Smith, 1999). It has been shown that low levels of selenium may lead to a decrease in thioredoxin reductase activity and decreases a cell's ability to undergo apoptosis (programmed cell death), consequently increasing cancer risk (Gallegos *et al.* 1997).

Iodothyronine deiodinases

There are three types of Iodothyronine deiodinases, also known as thyroid hormone deiodinases, types I, II, and III. All three are involved in activating and deactivating thyroid hormone which is essential in normal growth and development and contain selenium (Holben and Smith, 1999).

Selenoprotein P

Plasma glutathione peroxidase and selenoprotein P are the only as yet identified plasma selenoproteins (Burk and Hill, 1994). The precise function of selenoprotein P is not known, but it is believed to be a transport protein as well as an antioxidant that protects endothelial cells, which line blood vessels, from damage caused by a reactive nitrogen species called peroxynitrite (Holben and Smith, 1999).

Selenoprotein W

Selenoprotein W is named for a possible relationship with white muscle disease, a degenerative disease of the cardiac and skeletal muscles of larger animals, particularly sheep and goats (Whanger, 2000). This is known to be associated with very low dietary

selenium. While the precise function(s) of this selenoprotein is not yet known, it is believed to be an antioxidant and be involved in muscle metabolism (Holben and Smith, 1999).

Selenium and Cancer

Some animal, epidemiological, geographical, case-control and intervention studies have provided evidence that selenium probably plays a preventative role in many cancers. The evidence is now briefly summarized.

One of the first published animal experiments to show the anti-carcinogenic effects of selenium supplementation were performed by Clayton and Baumann in 1949. These researchers showed that dietary selenite (5 ppm) significantly lowered the incidence of tumors in rats exposed to p-dimethylaminoazobenzene-3 carcinogenic dye (Clayton and Baumann, 1949). Further animal studies have shown an anti-tumorigenic effect of selenium supplementation on various types of cancer including that of the skin (Hanada *et al.*, 1986), colon (Temple and Basu, 1987), breast (Schrauzer *et al.*, 1976), lung (Liu *et al.*, 1987; el-Bayoumy *et al.*, 1993), liver (Yu *et al.*, 1988; Popova, 2002), esophagus (Guttenplan *et al.*, 2002), and kidneys (Poirier and Milner, 1983).

Selenium supplementation has been shown to be protective against prostate cancer in animals. Waters and colleagues (2003) supplemented male beagles, a species of dog that commonly develops spontaneous prostate cancer, with Se as selenomethionine or high-Se yeast, at 3 or 6 $\mu\text{g}/\text{kg}$ body weight per day for 7 months. In total forty-nine elderly (i.e., 8.5- to 10.5-year-old) sexually intact male, retired breeder dogs weighing 9–18 kg were included in the study. After 4 weeks of acclimation, ten of the dogs were randomly assigned to a control group and were fed a maintenance diet that contained 0.3 ppm selenium; the other thirty-nine were placed into to one of the four daily treatment groups. The diets of the other treatment groups were either the maintenance diet plus 3 $\mu\text{g}/\text{kg}/\text{day}$ selenomethionine (n = 10 dogs), 6 $\mu\text{g}/\text{kg}/\text{day}$ selenomethionine (n = 10 dogs), 3 $\mu\text{g}/\text{kg}/\text{day}$ high-selenium yeast (n = 10 dogs), or 6 $\mu\text{g}/\text{kg}/\text{day}$ high-selenium yeast (n = 9 dogs). The daily selenium intake for the dogs in the control group was approximately 6 $\mu\text{g}/\text{kg}$ body weight and all the dogs were determined to have had nutritionally adequate selenium status prior to the start of the experiment with a mean pretreatment plasma selenium

concentration of 275 ng/ml (range = 228–339 ng/ml). After 7 months of treatment, the percentage of prostate epithelial cells and peripheral blood lymphocytes with extensive DNA damage was statistically significantly lower in the selenium-supplemented dogs than in dogs fed the control diet. The mean percentage of prostate cells with extensive DNA damage was 79.1% in the control group and 57.2% in the selenium-treated groups (difference = 21.9%, 95% confidence interval CI = 13.6% to 30.1%, $P < .001$). The mean percentage of peripheral blood lymphocytes with extensive DNA damage was 20.7% for the control group and 15.9% for the selenium-treated groups (difference = 4.8%, 95% CI = 1.7% to 7.9%, $P = .003$). There were no statistically significant differences in mean percentage of peripheral blood lymphocytes with extensive DNA damage or in mean percentage of prostate cells with extensive DNA damage between the four treatment groups.

Some epidemiological and geographic studies have shown an association between elevated crop selenium levels and depressed cancer incidence in regions. For example, Foster (1990) noted that in the United States, from 1950 to 1967, at the state level, higher levels of soil selenium were associated with lower cancer mortalities rates. Clark and colleagues (1991) investigated the association between U.S. county forage selenium status and site- and sex-specific county cancer mortality rates from 1950-1969 and found significant (p less than .01) inverse associations for cancers of the lung, breast, rectum, bladder, esophagus, and uterus. Schrauzer and colleagues (1977), found an inverse relationship between the estimated dietary selenium intakes among adults in 27 countries (including United States, Canada, the United Kingdom, and West Germany) between the years 1964 and 1966 and age-corrected mortalities cancers of the large intestine, rectum, prostate, breast, ovary, lung and with leukemia from 1964 to 1965.

Several case-controlled studies have examined whether there is a relationship between selenium status (i.e. the amount of the mineral present in the body) and cancer. Some case-controlled studies have identified lower selenium status in cancer patients than in controls (Yoshizawa et al., 1998; Yu et al., 1999; Brooks et al., 2001), while others have not (Lipsky, et al., 2004; Goodman et al., 2001).

Two large intervention studies have investigated selenium as a single chemopreventative agent against cancer. Yu and colleagues (1997) conducted the Quidong intervention trial in China among a general population of 130,471 people living in a five township region, known for its high rates of viral hepatitis and liver cancer. This trial provided table salt enriched with sodium selenite to the population of one township (20,847 people) while using the other four townships as controls for a period of five years beginning in 1984. During an 8-year follow-up period, the average incidence of liver cancer was reduced by 35% in the selenium-enriched population, while no reduction was found in the control population.

As part of the Quidong experiment, a clinical trial was also conducted to investigate the effect of selenium supplementation on people with chronic hepatitis B infections. For four years, 226 individuals with evidence of chronic hepatitis B infections were given either 200 ug of selenium in the form of a selenium-enriched yeast tablet or a placebo daily. At the end of the treatment, 7 of the 113 individuals taking the placebo developed primary liver cancer, while none of the 113 subjects supplemented with selenium did so (Yu *et al.*, 1997).

The second large clinical trial was the American based Nutritional Prevention of Cancer (NPC) trial. This experiment began in 1983 and tested whether supplementing individuals with selenium affected the incidence of cancer. The primary endpoint of this study was non-melanoma skin cancer among a high-risk population of 1312 people living in the eastern USA. Both men and women with a history of basal cell or squamous cell carcinomas of the skin were included in the study. The mean age of the participants was 63 years and their ages ranged from 18 to 80 years. Participants were randomized from 1983 through 1991 and were treated for a mean (SD) of 4.5 (2.8) years and had a total follow-up of 6.4 (2.0) years. Patients enrolled into the NPC trial were primarily Caucasian (Duffield-Lillico, personal communication, 2006). The secondary endpoints of the study included mortality from cancer as well as the incidence of lung, colon, and prostate cancers. Individuals were given either 200 ug of selenium per day in the form of selenized yeast, or a placebo.

After 13 years, the NPC trial found that although selenium supplementation did not seem to provide any protection against the primary endpoint of non-melanoma skin cancer, it did give protection against several other forms of cancer. It was found to have significantly reduced total cancer mortality (41%) and total cancer incidence (25%) (Clark *et al.*, 1996). The strongest association between selenium supplementation and reduction of a specific type of cancer was for prostate cancer. The supplemented group was found to be 52% less likely to develop prostate cancer than the placebo group (Clark *et al.*, 1996).

Currently there is a large intervention study underway to test the effectiveness of selenium supplementation in preventing the development of prostate cancer. The SELECT study (Selenium and Vitamin E Cancer Prevention Trial) is a clinical trial funded by the National Cancer Institute and tests whether 200 ug of selenium and/or 400 IU of vitamin E per day may reduce the risk of developing prostate cancer. Enrollment for this study began in 2001 and ended in 2004.

This project will continue for 7 years after the last enrollment so that each man will have the opportunity to participate for 7 years or longer depending on when they joined the study. Over 32,400 men, 55 years and older, from 400 sites in the United States, Canada, and Puerto Rico are currently taking part (Lippman *et al.* 2005). Preliminary project results were expected to be available sometime in 2007, however at time of writing (Jan. 2008) none have been published.

Selenium Status and Prostate Cancer

Numerous case-control and case-cohort studies have examined the relationship between selenium status and the development of prostate cancer. Results have been mixed. While some have found no significant association between physical selenium levels and prostate cancer (Knekt *et al.* 1990; Allen *et al.* 2004; Lipsky *et al.* 2004; Goodman *et al.* 2001; Ghadirian *et al.* 2000; Virtamo *et al.* 1987) others have suggested a significant relationship (Li *et al.* 2004; Nomura *et al.* 2000; Yoshizawa *et al.* 1998; Van den Brandt *et al.* 2003; Brooks *et al.* 2001). A number of factors may have contributed to this diversity of results.

These include a difference in selenium levels between studied populations in conjunction with a possible threshold effect for the protectiveness of selenium. For example, studies conducted among European populations generally have mean selenium levels below those of their North American (see Table 2, pg. 29). Some researchers have indicated that serum selenium levels above a range from 115 to 147 ng/ml are protective against prostate cancer (Normura *et al.*, 2000; Willette *et al.*, 1983; Brooks *et al.*, 2001). Therefore, many studies contain controls with selenium levels below the threshold needed to prevent carcinogenesis (Brinkman *et al.* 2006).

As discussed earlier, the Nutritional Prevention of Cancer (NPC) trial found that while selenium supplementation did not reduce the risk of the primary endpoint of non-melanoma skin cancer risk it did for several secondary endpoints, including prostate cancer (Clark *et al.*, 1996). Upon further analysis of the NPC data, Duffield-Lillico and colleagues (2003) found that the inverse association between selenium supplementation and prostate cancer incidence was confined mainly to the 317 men with blood plasma selenium levels in the lowest tertile (≤ 106.4 ng/ml). Among males in the lowest selenium status tertile, supplementation reduced the risk of developing prostate cancer by 86% (95% C.I.= 59-97, P =0.009) (Duffield-Lillico *et al.*, 2003).

Selenium Status

Selenium status refers to the amount of the mineral present in the body. There are several tests that can be employed to establish selenium status. The most common tissues tested for the mineral are blood, finger and toenails, as well as hair (Thomson, 2004). Blood selenium status has been shown to most strongly correlate with recent dietary selenium intake (Longnecker *et al.*, 1996). Urinary excretion of the mineral can also be used as an indicator of status (Neve, 1991). Serum, plasma, and urine selenium values are generally considered to be measures of short term selenium status that can vary daily with dietary changes (Al-Saleh and Billedo, 2007). Erythrocyte, hair, and toenail levels are thought to provide long term indications of body selenium levels because they are from tissues which are not as sensitive to daily intake fluctuations (Neve, 1991).

The literature on mean selenium status shows that it varies among healthy adults from country to country (see Table 2, pg. 26). The statistics presented in this table should be

viewed with caution since apart for the United States data, mean selenium levels are not from nationally representative samples. For example, the Lemoyne and colleagues (1988) study that provides the Canadian figure is derived from a sample of 10 adults (5 men and 5 women) from Southern Ontario who were the healthy controls in a case-control experiment.

Table 2: Selected reports of blood (serum or plasma) selenium concentrations (ng/ml) of healthy adults

Country	Mean	Standard Deviation	Reference
Austria	67	24	Tiran <i>et al.</i> 1992
Australia	92	15	Dhindsa <i>et al.</i> 1998
Canada	132	8	Lemoyne <i>et al.</i> 1988
Denmark	84	20	Grandjean <i>et al.</i> 1992
France	81	9	Pucheu <i>et al.</i> 1995
Germany	86	13	Meissner, 1997
Italy	92	13	Menditto <i>et al.</i> 1995
The Netherlands	106	24	Bukkens <i>et al.</i> 1990
Norway	110	13	Bibow <i>et al.</i> 1993
Spain	81	10	Torra <i>et al.</i> 1997
Sweden	88	19	Hardell <i>et al.</i> 1995
USA	125	0.2 ¹	Niskar <i>et al.</i> , 2003.

¹ Standard Error

While the optimal level of the Se in body has not been determined, it has been suggested that nutritional adequacy of the mineral occurs when Se serum levels are between 70 and 100 ng/ml (Neve, 1995; Rayman, 1997; Thompson *et al.* 1993). This is because it is within this range that the activity of two of the most well known selenoproteins, glutathione peroxidase and selenoprotein P, are maximized (Duffield *et al.* 1995). Various health implications of different levels of serum Se status are outlined in Table 3 (pg. 27). From this table it can be seen that the serum selenium levels required to maximize the activity of the main selenoproteins (>78-95 ng/ml) are well below those thought to be protective against certain cancers (>118 ng/ml).

Table 3: Health Implication of Serum Selenium Concentrations

	Se concentration (ng/ml)
Prevention of Keshan disease	> 20
Optimal activity of IDI's	> 65
Maximizations of plasma GPx, selenoprotein P	>78-94
Protection against some cancers	> 118

IDI (Iodothyronine deiodinases); GPx (Glutathione Peroxidase)

Sources: Yang *et al.*, 1984; Duffield *et al.* 1999; Marchaluk *et al.*, 1995; Clark *et al.* 1996

Selenium Status Determinants

With the variability of selenium status between individuals and populations, research has sought to identify some of significant influences to selenium status. The following section discusses some of the factors that have been demonstrated to play a role in the amount of this trace mineral in the body. These include diet, geography, age, smoking status, alcohol consumption, body composition, education, income, and gender.

Diet

Selenium naturally enters the food chain through plants which uptake the mineral from the soils, or from marine life (fish, shellfish, kelp, etc.). The origin of selenium in the aquatic food systems chain is believed to begin with marine plants that uptake it from the seabed floor, and plankton (zoo and phyto) that absorb the mineral directly from surrounding waters (Sandholm *et al.* 1973). Selenomethionine is the organic form of selenium that occurs naturally in foods and it is readily absorbed (90%) by the human body (IOM, 2000). Certain types of foods contain more of the mineral than others.

Not surprisingly, selenium status is directly related to dietary intake of the mineral (Arnaud, *et al.* 2006). The amount of selenium in different foods varies widely (see Table 4, pg. 28). The highest sources of dietary selenium are from Brazilian nuts, meat, fish and cereals. People with diets that are high in these types of foods can expect to have higher selenium status (Bergmann *et al.* 1998, Hagmar *et al.* 1998, Hansen *et al.* 2004, Arnaud, *et al.* 2006).

Table 4: Select Foods and Selenium Content

Food	Micrograms (ug)	% Daily Value
Brazil nuts, dried, unblanched, 1 ounce	63	95
Tuna, light, canned in oil, drained, 3 ounces	35	50
Beef, cooked, 3½ ounces	34	50
Spaghetti w/ meat sauce, frozen entrée, 1 serving	32	45
Cod, cooked, 3 ounces	32	45
Turkey, light meat, roasted, 3½ ounces	23	35
Beef chuck roast, lean only, roasted, 3 ounces	20	30
Chicken Breast, meat only, roasted, 3½ ounces	17	25
Noodles, enriched, boiled, 1/2 cup	15	20
Macaroni, elbow, enriched, boiled, 1/2 cup	14	20
Egg, whole, 1 medium	12	15
Cottage cheese, low fat 2%, 1/2 cup	12	15
Oatmeal, instant, fortified, cooked, 1 cup	12	15
Rice, white, enriched, long grain, cooked, 1/2 cup	10	15
Rice, brown, long-grained, cooked, 1/2 cup	10	15
Bread, enriched, whole wheat, commercially prepared, 1 slice	5	8
Walnuts, black, dried, 1 ounce	4	6
Bread, enriched, white, commercially prepared, 1 slice	4	6
Cheddar cheese, 1 ounce		

*Daily Value (DV). DVs are reference numbers developed by the United States Food and Drug Administration. The DV for selenium is 70 micrograms (ug).

Source: U.S. Department of Agriculture, Agricultural Research Service. 2003.

Selenium can also be obtained from supplements. Sodium selenate and sodium selenite, for example, are two inorganic forms of selenium that are widely available as supplements, but differ in the manner in which they absorbed in the body. Sodium selenate is almost entirely absorbed, however, much of its selenium is excreted in the urine before it is incorporated into selenoproteins (IOM, 2000). Selenium selenite on the other hand is absorbed roughly half as well as selenium selenate but is better retained once absorbed (IOM, 2000).

The most common selenium supplement available in Canada and United States is selenized yeast which contains 65% of its selenium in the form of selenomethionine (Bird

et al. 1997). As previously stated, selenomethionine is the type of selenium naturally found in foods and is well absorbed (IOM, 2000). This was the type of selenium supplementation used in the NPC trial (Clark *et al.*, 1996) and is currently being used in the SELECT trial (Lippman *et al.* 2005).

Geography

Geography plays an important role in the amount of selenium in various foods. The selenium content of crops varies according to the amount of the element available in soils. As a consequence, dietary selenium intakes are affected not only by the types of foods that a person consumes but also where it is grown, or in the case of meats, the origin of the animal's feed. Between and within nations there are large differences in selenium intake and status (Combs, 2001). To illustrate, in China, there are regions of both extreme selenium excess and deficiency (Levander, 1987).

With regard to the United States, selenium status has been shown to differ amongst the four broad geographic regions (Northeast, Midwest, South, and West) by research that analyzed the NHANES III dataset (Niskar *et al.* 2003, Kafai and Ganji, 2003). Both of these studies found that, amongst adult males, mean selenium status was lowest in the South and highest in the Midwest.

Serum selenium levels have not found to differ between urban and rural dwellers (Niskar *et al.* 2003), however, they do differ regionally. After controlling for age, serum cotinine concentration (a surrogate measure of smoking status) and alcohol consumption, there are statistically significant differences in the United States amongst the four regions with regard to selenium status (Kafai and Ganji, 2003). In both males and females, those living in the Midwest and West of the United States generally had significantly higher serum selenium values than those living in the South and Northeast geographical regions (Kafai and Ganji, 2003). Selenium levels were lowest among those living in the South ($p=0.0002$).

Age

Along with diet and geography some published studies have indicated that age plays a significant role with regard to selenium status. Dickson and Tomlinson (1967), for example reported a marked decline in plasma selenium status with aging. In the Baltimore

Longitudinal Study of Aging, plasma selenium status decreased with age in 52 men with prostate cancer and in 92 matched controls (Brooks *et al.* 2001). Lloyd and colleagues (1983) also found that individuals older than 55 years had reduced whole blood selenium concentrations. These researchers suggested this decline was because of less efficient absorption or greater excretion of selenium, rather than a lower dietary intake of the trace element in this age group (Lloyd, 1983).

However, other studies have not shown that age has a significant influence over selenium status. For example, after controlling for dietary intake, Swanson and colleagues (1990) determined that although age was inversely associated with selenium status, it was not significantly predictive of either toenail or whole blood selenium levels. Also, Arnaud and colleagues (2006) found that among 13,017 French adults aged 35-65 years, selenium status was not significantly affected by age. Similarly, two studies that used NHANES III survey dataset did not show selenium status to be influenced by age among a nationally representative sample of 18,597 individuals in the United States (Kafai and Ganji, 2003; Niskar *et al.* 2003).

Smoking Status

The evidence from the few available studies appears to suggest that smokers have lower selenium status than non-smokers. Two research projects that used serum cotinine levels as a surrogate measure of smoking status, and that analyzed the NHANES III data set, found that serum selenium was lower in smokers than non-smokers among the adult American population. Cotinine is the main metabolite of nicotine, and its serum or plasma level have been shown to provide a more accurate measure of smoking status than self-reporting (Patrick *et al.* 1994, Bramer and Kallungal, 2003). This is because smokers often underestimate the number of cigarettes they smoke and do not accurately describe smoking intensity (i.e., frequency of puffs and depth of inhalation) (Ogden, 1997, Bramer and Kallungal, 2003).

Wei and colleagues (2001) found that male smokers had serum selenium levels that were 4% lower than those of male non-smokers; however, there was not a clear negative association between serum levels of selenium and smoking. These researchers did not find any significant difference in selenium status between female smokers and non-

smokers. Using the NHANES III data, however, Kafai and Ganji (2003) discovered that serum cotinine levels were a significant predictor of selenium status among both males and females. The conflicting results, with regard to gender and selenium status, between the Wei (2001) and the Kafai and Ganji (2003) studies may be explained by differing ages of the subjects included in each study. Kafai and Ganji (2003) examined individuals aged 14 to >90 years, while Wei and colleagues (2001) studied a sample population that ranged in age from 17 to 50 years.

Four smaller research projects that used self-reported smoking status produced conflicting results with regard to selenium status. Three of these studies found that male smokers had significantly lower selenium status than non-smokers (Ghadirian *et al.* 2000; Elis *et al.* 1984; Lloyd *et al.* 1983). In contrast, a study among New Zealanders suggested that smoking was unrelated to selenium status (Robinson *et al.*, 1983).

While some research has shown that smokers have significantly lower selenium status than non-smokers, why this may be the case has not been widely examined. In a study of 44 adults residing in the seleniferous (very high soil selenium) area of South Dakota and Wyoming, Swanson and colleagues found that smokers had whole blood and serum selenium levels significantly below those of non-smokers (Swanson *et al.* 1990). After multivariate analysis, the authors concluded that the lower selenium concentrations of smokers were a result of low dietary intake of selenium and not a smoking effect (Swanson *et al.* 1990). They found that on average smoker's diets contained approximately 20% less selenium, probably because the smokers in general, consumed less food (Swanson *et al.* 1990). Fehily and colleagues (1984) also confirmed that smokers consume a diet that is less dense in nutrients, including selenium, compared with non-smokers.

Alcohol Consumption

A limited number of studies have found that alcohol consumption has a significant impact on selenium status. To illustrate, a moderate level of alcohol consumption, 1 to 2 drinks per day, has been shown to increase selenium levels when compared with both non- and heavy drinkers (Snook 1991, Kafai and Ganji, 2003; Arnaud *et al.* 2006). Kafai and Ganji (2003), for example, have shown that among Americans, male moderate drinkers on

average had 1.1% higher selenium status values than non-drinkers, while moderate females drinkers had 2.2% higher selenium status values than non-drinkers.

While, moderate alcohol consumption appears to increase selenium status, alcohol abuse seems to have an inverse relationship with selenium status (Robberecht and Deelstra, 1994). Such reduced levels of selenium status in heavy drinkers have been attributed to a decrease in dietary selenium intake (Dutta *et al.* 1983), or reduced hepatic storage of selenium because of liver damage caused by drinking (Korpela *et al.* 1983).

Body Composition

Obesity has been shown to increase oxidative stress in the body that may result in lower selenium status since it increases the demand for glutathione peroxidase, a selenoprotein (Fenster *et al.* 2002). Upon investigation however, it would appear that effect of body composition may be gender dependent. For example, Arnaud and colleagues (2006) found that in France, selenium serum concentrations were lower among obese women than non-obese women, but in the same study, obesity did not appear to influence the selenium status of men (Arnaud *et al.* 2006). Two other studies also found that body composition had no impact on selenium status in men (Pizent *et al.* 2001; Koyama *et al.* 1995). How and why gender and obesity may influence selenium status is not clearly understood (Arnaud *et al.* 2006). However, dietary differences may exist between obese men and women which could account for the differences (Swanson *et al.* 1990).

Education

The limited number of studies that have examined selenium status and education have produced conflicting results. Some researchers have reported a positive relationship between selenium status and education. A French study, for example, identified a positive relationship between education and selenium status. This relationship was found by Berr and colleagues (1998) when examining the 1389 French men and women, aged between 60 and 70 years, participating in the EVA (Etude du Vieillissement Artériel) study.

Similarly, Kilander and colleagues (2001) found that among 2301, 50 year old Swedish men, there was a significant, positive relationship between education level and selenium status. These researchers found the mean serum selenium levels for the low (less than

secondary school graduation), medium (secondary school completed) and high levels (some or complete post-secondary) of education groups to be 73.3 ug/l, 77.7 ug/l and 83.0 ug/l respectively.

In contrast, Arnaud and colleagues (2006) found that among the 13,017 adults aged 35 to 60 participating in the French SU.VI.M.AX (Supplémentation en Vitamine et Minéraux Antioxydants) study, selenium status was not affected by education level.

Income

Research is both limited and conflicting with respect to selenium status and income. It is believed that higher income expands food choices, and is also related to factors that tend to improve the quality of diet, including higher education, better access to well-stocked grocery stores, and greater diet and health knowledge (McCabe-Sellers *et al.* 2007). A study of American diets using a nationally representative sample of the United States (NHANES III), for example, found that low-income groups tended to have poorer quality diets that contained higher contents of saturated fats and simple sugars, and a lower content of complex carbohydrates and micronutrients than high-income groups (Lin, 2005). With regard to selenium status, another study that used the NHANES III data, found a significant positive relationship between income level and selenium status (Niskar *et al.* 2003).

However, in a study of residents of Utah County, Utah by Christensen (1988) income did not significantly affect selenium status or intake. It is important to note that much of the population of Utah consists of Mormons, who, because of their religious beliefs, may have an atypical lifestyle with regard to smoking habits, alcohol consumption, and diet (Enstrom, 1978).

Gender

Research that has examined gender and selenium status appears to indicate that females have a lower level selenium status than men (Arnaud *et al.* 2006; Kafai and Ganji, 2003; Niskar *et al.* 2003; Pavao *et al.* 2003; Swanson *et al.* 1990). Such gender variations have been attributed to a number of different factors, including differences in body weight (Alfthan and Neve, 1996) body composition (Swanson *et al.* 1990), and diet (Alfthan and Neve, 1996).

Selenium Status in the United States

Niskar (2003) and colleagues analyzed the NHANES III survey and determined the mean serum selenium concentration of Americans to be 125 ng/ml, with a median concentration of 123.5 ng/ml (n= 18,597). The minimum serum selenium value recorded was 39.5ng/ml while the maximum was 625.4 ng/ml. Among American adults, selenium status has been shown to differ significantly by gender, race, income, and geography (Niskar *et al.*, 2003; Kafai and Ganji, 2003).

Gender affects selenium status with men having significantly higher values ($p<0.0001$) than women (Niskar *et al.*, 2003; Kafai and Ganji, 2003). With regard to race-ethnicity, non-Hispanic blacks had lower mean selenium levels ($p<0.0001$) than both non-Hispanic whites and Mexican-Americans (Niskar *et al.*, 2003). Mean selenium levels also increases with income ($p=0.0007$) (Niskar *et al.*, 2003). In general, in both men and women subjects, those living the Midwest and West had significantly higher serum selenium values than those living in the South and Northeast geographical regions (Kafai and Ganji, 2003). Selenium levels were lowest among those living in the South ($p=0.0002$) (Kafai and Ganji, 2003). Serum selenium levels did not differ significantly between persons living in urban and rural areas (Niskar *et al.*, 2003).

Fortification as a strategy to reduce disease

The *Codex Alimentarius*, the World Health Organization's collection of international food standards, defines fortification as the addition of one or more essential nutrients to a food, whether or not it is normally contained in that food, for the purpose of preventing or correcting a demonstrated deficiency of one or more nutrients in the population or specific populations groups (Food and Agriculture Organization, 1996). Using fortification as strategy to reduce disease has the advantage that it does not require any change in behaviors or food habits to bring about the desired result, unlike other interventions such as dietary supplements.

Beginning in the early part of the 20th century fortification was used to target specific diseases. These included goiter with iodized salt, rickets with vitamin D-fortified milk, beriberi, pellagra and anemia with B vitamins and iron enriched cereals, and most recently *spina bifida* with folic acid fortified cereals (Darnton-Hill and Nalubola, 2002).

Fortifying food with Se in order to overcome low dietary Se intakes though not widely practiced, has occurred. Se-enriched foods that have been developed include the Se-fortified table salt used in the Linxian Trials in China (Yu *et al.*, 1997). In 2005, the British food company Waitrose, launched a selenium-fortified bread in Great Britain that contained approximately 40 ug of selenium per 100g (Nutrilaw, 2005). The company marketed their selenium enriched bread and flour as a means to overcome reported lower intakes of mineral in Great Britain (Nutrilaw, 2005). Unfortunately for Waitrose, sales of the product were slow and the bread was later pulled from the shelves. The company blamed a lack of public awareness of the benefits of selenium for the sluggish sales (Daniells, 2006).

For over thirty years selenium enhanced fertilizers have been used to increase Se levels in various foods (Lyons *et al.* 2003). In experiments, high-Se Brussels sprouts (Stoewand *et al.*, 1989), high-Se broccoli (Finley, 1999), high-Se garlic (Ip *et al.*, 1992), high Se-celery (Lee and Park, 1999), high-Se mint, and chamomile (Sekulovic *et al.*, 1996) have been developed.

Widespread use of selenium enriched fertilizers has occurred in New Zealand, China, and Canada to overcome low selenium status in humans and/or livestock (Lyons *et al.* 2003; Oldfield, 1999). Analysis of crops from these countries has shown that selenium fertilizers can effectively increase levels of selenium with minimal cost (Lyons *et al.* 2003, Gupta and Watkinson, 1985).

In the 1970's, Finnish dietary selenium intake was found to be very low (20-30 ug per day) as a result of the low selenium content of domestic food products (Varo and Koivistoinen, 1981). In 1983, the Finnish Ministry of Agriculture and Forestry mandated that fertilizers be fortified with selenium (16 mg kg⁻¹ to fertilizers for grain production and 6 mg kg⁻¹ to those for fodder production) (Aro *et al.* 1995). This policy decision was

made in part because of a prospective epidemiological study by Salonen and workers (1982) of Finnish cohorts, studied in the 1970's, that suggested that low serum selenium status (less than 45 ng/ml) might be a risk factor for cardiovascular diseases (Koivisto and Huttunen, 1986).

After mandating the use of selenium fortified fertilizers, changes were noted with regard to selenium measurements taken from before the program was in place. As a result of this program, increases were noted in the selenium content of foods grown in Finland, the per capita consumption of the mineral and the selenium status of the Finnish people (Aro *et al.* 1995). While the per capita consumption and status of selenium has been augmented among Finnish people, no quantifiable health impact that can be attributed to the fortification program, has been clearly identified (Varo *et al.* 1994). Negative environmental impacts of Se fertilizing in Finland seem to be minimal as accumulation of Se to toxic levels in soils does not appear to have occurred (Vuori *et al.* 1994).

Chapter IV: Methods

Dataset Description

This thesis is based on data from the third National Health and Nutrition Examination Survey, 1988-1994 (NHANES III). A complex stratified multistage probability design was utilized in this study to examine a nationally representative sample of the United States civilian non-institutionalized population. NHANES III collected data on body measurements, demographics, physical function, dietary intake, health condition, lifestyle behaviors, and biochemical measurements of blood and urine from 39,695 individuals who were considered representative of the US population as a whole (NCHS, 1996). There are a number of benefits to using this NHANES dataset.

First, because it is nationally representative, any findings can be used to make inferences of the entire US population. Second, this dataset is easily accessed via the World Wide Web at no charge to the user. Data at this scale and quality would be impossible for any single individual to collect.

Because of the size and complexity of the NHANES dataset, sophisticated statistical software was required to conduct the analysis. Secondary analyses of these data for the current study were performed using a Statistical Analysis System software (SAS) callable version of SUDAAN. This program is able to account for the complex survey design and sampling weights of NHANES III (SAS, 2006; Shah *et al.* 2006).

Methodology Introduction

In the current study, three steps were taken in order to evaluate interventions aimed at augmenting the dietary selenium intake among American men with lower selenium status. The first step involved identifying the white men in the NHANES III study who had serum selenium values less than 106 ng/ml. The decision to use the value of <106 ng/ml as a delimiter was based on the work of Duffield-Lillico and colleagues (2003). Their study showed that in a sample of mainly white men, those with blood plasma selenium levels below 106.4 ng/ml, when supplemented with 200 ug of selenium, significantly reduced their risk of developing prostate cancer (Duffield-Lillico *et al.* 2003).

In total, 2989 white men, aged 20 or greater in the NHANES III dataset had recorded serum selenium values. Of these, 288 had a selenium status of less than 106 ng/ml, while 2701 individuals had selenium status values greater than or equal to 106 ng/ml. Dichotomizing these men into two groups created this study's dependent variable, selenium status.

The second step in the methodology was a bivariate analysis that involved comparing the independent variables (to be described in detail later) between members of the two selenium status groups. Chi-square tests and confidence intervals were created for all categorical independent variables. T-tests were used to evaluate the differences between the low and high selenium status groups for continuous normally distributed independent variables. This analysis enabled the author to identify variables that differed significantly between the two selenium status groups and that could then be examined further in a multivariate analysis.

The third step in the methodology was to perform a multiple logistic regression. This analysis was used to evaluate the relationship between the dependent variable (i.e., selenium status < 106 ng/ml) and the significant independent variables from the bivariate analysis. As mentioned earlier, a SAS (Statistical Analysis System software) callable version of SUDAAN was used for all statistical analyses.

It should be noted that this research is exploratory in nature and that a large number of independent variables were selected for study. Some of these variables have not been linked to selenium status in published literature. Furthermore, many of the characteristics that were examined, while known to be significantly related to selenium status, have not been shown to have a causal relationship with it. For example, the levels of other antioxidants such as beta-carotene and vitamin C are strongly correlated with selenium status, although this link is likely to be the result of diet, rather than any causal relationship (Bates *et al.* 2002). This is because the foods that make up a high quality, healthy diet are high in levels of vitamin C, beta-carotene, and selenium along with a host of other essential trace minerals and vitamins (Bates *et al.* 2002).

Variables

Dependent Variable

The dependent variable of this study is the selenium status of white males dichotomized into lower and higher groups. In NHANES III, serum selenium concentrations were measured in two Perkin Elmer graphite furnace atomic absorption spectrophotometers (Model 3030 and Model 5100) using Zeeman atomic absorption spectrometry methods (NCHS, 1996). Data from the Model 3030 were mathematically adjusted to make them comparable to those measured by the more precise Model 5100 (NCHS, 1996).

To create a dichotomized variable, all white men, aged twenty and older with serum selenium values in NHANES III were divided into two groups; those with lower selenium status (LSS) (values less than 106 ng/ml) and those with higher selenium status (HSS), (values equal to or greater than 106 ng/ml). In total, 2989 white men aged 20 or greater were included in this study. Of these, 288 had a selenium status less than 106 ng/ml, while 2701 had selenium status values greater than or equal to 106 ng/ml.

Independent Variables

The next step was to discover whether there were significant differences in 40 different characteristics between men with higher and lower selenium status. No causal relation was implied. Indeed, the current research includes many variables that have not been shown to be statistically associated, causally or otherwise with selenium status, or have not previously been studied with regard to selenium levels. The independent variables studied were chosen based on their documented influence on selenium status and/or prostate cancer, and in consultation with the researcher's supervisors. These studied independent characteristics are listed below where they are divided into 4 categories: demographic, health status, dietary, and physical measures.

Demographic Variables

Age

In NHANES III, the age of a surveyed participant was calculated using the birth date obtained from the Screening Questionnaire. The variable for age is coded HSAGEIR. Ages of 90 years or greater were recoded into a single category of 90+ years to help protect the confidentiality of survey participants. Since the sample size of those with low

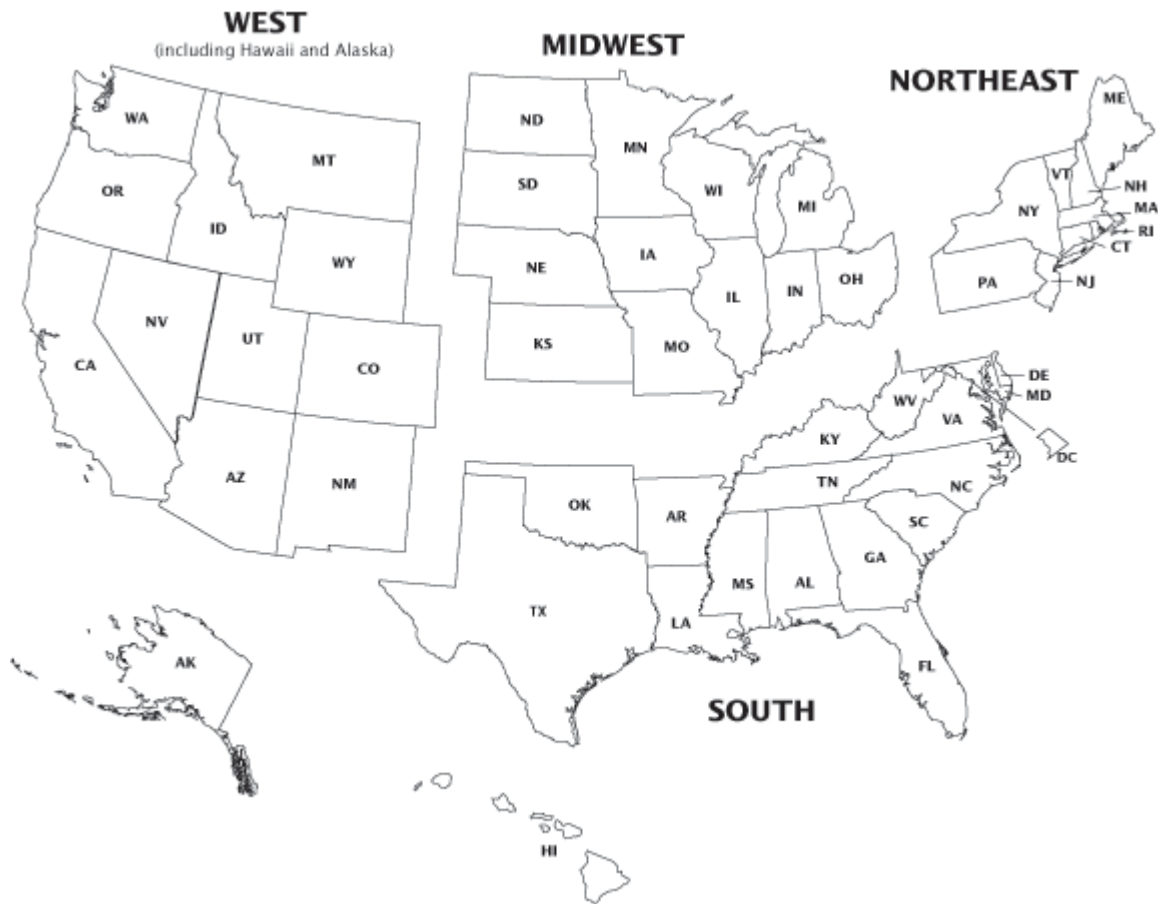
selenium status was small, with only 288 individuals, this study followed the NHANES III analytical guidelines for trend analysis with a smaller sample, and divided the subjects into the 3 age groups recommended by the guidelines; 20-39, 40-59, and 60+ years (NHANES, 1996).

Geographic Location

In NHANES III, the United States was divided into four broad geographic regions as defined by the Bureau of Census; Midwest, Northeast, South and West (see Figure 5, pg. 44) (NHANES III, 1996). This variable is coded DMPCREGN in the dataset.

State or County level data are not available for each individual surveyed because of privacy issues. Such a geographical scale data would have been desirable as it would have allowed for a more precise description of lower selenium status distribution. However, this study still found that the overall and within region prevalence of men with lower selenium status differed significantly between the four regions.

Figure 5: The Census Regions of the United States



Source: U.S. Census Bureau. Census Regions Cartographic Boundary Files Descriptions and Metadata. Geography Division, Cartographic Operations Branch. http://www.census.gov/geo/www/cob/rg_metadata.html. (Accessed November, 2005).

Level of Education

In NHANES III, surveyed individuals were asked what the highest grade or year of school they attended and if they completed that grade or year. The resulting variable was titled, “What is the highest grade or year of regular school --has completed?” coded HFA8R in the dataset (NHANES III, 1996).

In the United States, excluding kindergarten, there are twelve years of publicly funded schooling. This study divided the surveyed individuals into two groups; those that completed 12 years of schooling or more (graduated from high school) and those that finished less than 12 years of schooling (did not graduate from high school).

Income (Poverty Index Ratio)

To compare the economic status of men with lower and higher levels selenium status this study used the poverty index variable in the NHANES III dataset. This variable is coded DMPPIR. The poverty index is a calculated variable based on family income and family size using tables published each year by the Bureau of the Census in a series, “Current Population reports”, on poverty in the United States. This is considered the best measure of income when comparing data over time because it is relatively standardized for inflation and other factors such as regional differences in the cost of living (NHANES III, 1996).

The primary reporting categories for the poverty index are;

- <1 (Below poverty)
- ≥ 1 (At or above poverty)

For more specific analysis, NHANES Analytical Guide recommends applying the specific poverty index thresholds used by USDA food assistance programs (Special Supplemental Nutrition Program for Women, Infants, and Children (WIC), Food Stamp Program, School Lunch and Breakfast Programs). The income categories to use in these options are:

- 0.000-1.300 (Low)
- 1.301-3.500 (Middle)
- 3.500 and above (High)

Or

- 0.000-1.850 (Low)
- 1.851-3.500 (Middle)
- 3.500 and above (High)

Middle income eligibility cut points of 1.300 or 1.850 are acceptable (NHANES III, 1996). In this thesis, the 1.851 cut off was used to define the middle income threshold, because at this point prevalence in the low income category was increased and this in turn increased the statistical reliability of the Chi-Square test.

Health Status

Health Conditions

In the selected conditions section of NHANES, participants were asked if they had ever been told by a doctor that they had a specific health condition. The following are the health conditions included in this study followed by their respective NHANES III variable codes.

- Doctor ever told you had: stroke (HAC1D)
- Doctor ever told you had: arthritis (HAC1A)
- Doctor ever told you had: congestive heart failure (HAC1C)
- Doctor ever told you had: asthma (HAC1E)
- Doctor ever told you had: emphysema (HAC1G)
- Doctor ever told you had: cataracts (HAC1I)
- Doctor ever told you had: gout (HAC1M)
- Doctor ever told you had: skin cancer (HAC1N)
- Doctor ever told you had: cancer (HAC1O)
- Doctor ever told you had: diabetes or sugar diabetes (HAD1)

Self reported health status

Participants in NHANES III were asked, “Would you say your health in general is excellent, very good, good, fair or poor?” This variable is coded HAB1 in the dataset. A dichotomous variable was created similar to that used by Cloutier-Fisher (2005) in a previous epidemiological study. Two groups were identified; those that said their health was excellent, very good, or good and those that evaluated it as fair or poor.

Self reported physical activity level

In the exercise portion of the NHANES II survey participants were asked, “Compared with men/women your age would you say you are more active, less active, or about the same?” This variable is coded HAT28 in the dataset. This study created a dichotomous variable by combining in one group those that answered they were more active than their peers with those that said their activity was about the same. The other group consisted of those who replied that they were less active than men their age.

Physical Measures

Body Mass Index

Body Mass Index (BMI) is a number calculated by the formula, $\text{weight (kg)} / [\text{height (m)}]^2$. It is widely used as a screening tool to determine if a person has a healthy weight (CDC, 2007). While often used in epidemiological research, this measure cannot be used as diagnostic measure to determine if a person is obese, or overweight, because it can be unreliable in certain circumstances (CDC, 2007).

The unreliability of this measure is most apparent in athletes and the elderly. To illustrate, a muscular athletic male may have a high BMI which would suggest that they were obese. However, this is not the case because this extra weight is caused by lean muscle mass and not fat. Body mass index may also be unreliable among the elderly because of weight loss as a result of osteoporosis and muscle loss (NHLBI, 1998).

The standard weight status categories associated with BMI ranges for adults, as reported by the Centers for Disease Control are shown below in Table 5.

Table 5: Weight Status and BMI

BMI	Weight Status
< 18.5	Underweight
18.5-24.9	Normal
25.0-29.9	Overweight
> 30	Obese

Source: CDC, 2007

Using the NHANES variables, Reported height without shoes (HAM5S) and Reported weight without clothes (HAM6S), a BMI was calculated for each man included in the study. The men were then divided into two groups, one group being those at a weight that could be considered healthier, a BMI of less than 25 (underweight or normal weight) and the other group being those at a weight that may be less healthy, a BMI greater than or equal to 25 (overweight or obese). The rationale for the dichotomous grouping is based on information from the National Institute for Health's, National Heart Lung and Blood Institute (NHLBI). The NHLBI reported that men who's BMI indicates they are overweight or obese are at a greater risk for developing a number of conditions including

hypertension, type 2 diabetes, coronary heart disease (CHD), stroke, gallbladder disease, osteoarthritis, sleep apnea and respiratory problems as well as some types of cancer (prostate and colon) (NHLBI, 1998).

Serum Beta carotene

Beta carotene is a phytochemical that is a member of the carotenoid group of chemicals (Hinds *et al.* 1997). Carotenoids are the yellow, orange, and red pigments synthesized by plants (Hinds *et al.* 1997). The orange pigment in carrots and the red pigment in red peppers are examples of such pigments (Higdon, 2004). In the body, Beta-carotene, in the presence of iodine, can be converted to form retinol (vitamin A), which is essential for normal growth and development, immune system function, and vision (Higdon, 2004).

Serum lycopene

Like beta carotene, lycopene is a type of carotenoid, and is the red pigment seen in tomatoes, pink grapefruit and watermelon (Higdon, 2004). Lycopene is the most common carotenoid in the body and is a potent antioxidant (Di Mascio *et al.* 1989).

In NHANES III, serum concentrations of lycopene were measured as ug/dl and were coded as LYP in the laboratory section of the dataset (NHANES, 1996).

Serum Calcium

Calcium, which is used to form bones and teeth, is the most common mineral in the human body (Shils, 1999). The majority of this element is found in the bones and teeth, however, a small amount (~1%) is present in the blood and soft tissues (Higdon, 2004).

In NHANES III, serum total calcium was measured as mmol/l and was coded as CAPSI in the laboratory section of the dataset (NHANES, 1996).

Serum Cotinine (smoking status)

This study used serum cotinine levels in order to determine smoking status. Cotinine is a major metabolite of nicotine and can be measured in blood, saliva, or urine (Wall *et al.* 1988). Nicotine is a highly specific indicator of tobacco smoking (Jarvis *et al.* 1987). Epidemiological studies often use serum cotinine data as a surrogate measure of smoking

status as it considered more reliable than self-reported smoking status (CDC, 2006). Self-reported data have been shown to misclassify or underestimate smoking status by 1% to 4.2% (Clark *et al.* 1996., Ogden *et al.* 1997., Perez-Stable *et al.* 1992., Wafenknecht *et al.* 1992)

Previous studies using the NHANES dataset utilized threshold levels of serum cotinine of 10 ng/ml (Niskar *et al.* 2003) and 14 ng/ml (Kafai and Ganji, 2003, Wei *et al.* 2001) to indicate a non-smoker vs. smoker. This study uses a serum cotinine concentration ≥ 14 ng/ml and < 14 ng/ml to designate individuals as smokers and non-smokers respectively.

In NHANES III, cotinine was measured in the blood serum using high-performance liquid chromatography and atmospheric-pressure chemical ionization tandem mass spectrometry and is coded as the variable COP in the dataset (NHANES III, 1996).

Serum cholesterol

Total serum cholesterol (mg/dl) was measured in the laboratory section of the NHANES III, and is coded as TCP in the dataset. High total serum cholesterol is a risk factor of heart attack and stroke (AHA, 2007). The ranges of serum cholesterol and their corresponding risk for developing a heart attack or stroke as reported by the American Heart Association (2007) are listed below in Table 6.

Table 6: Serum Cholesterol and Health

Total Serum Cholesterol (mg/dl)	Classification
<200	Desirable
200-239	Borderline High Risk
>239	High Risk

Source: American Heart Association, 2007.

In order to create a dichotomous serum cholesterol variable, this study divided its sample into two groups, one being those men with a desirable total serum cholesterol level of less than 200 mg/dl with the second group being those with values greater than, or equal to, 200 mg/dl.

Serum triglycerides

Serum triglycerides (mg/dl) were measured in the laboratory section of the NHANES III, and is coded TGP in the dataset. Having high serum triglycerides is a risk factor for heart attack and stroke (AHA, 2007). The ranges of serum triglycerides and the corresponding risk for developing heart attack or stroke as reported by the American Heart Association (2007) are listed below in Table 7.

Table 7: Serum Triglycerides and the Risk of Heart Disease

Serum triglycerides (mg/dl)	Risk
<150	Normal
150-199	Borderline High
200-499	High
>500	Very High

Source: AHA, 2007.

To create a dichotomous variable, this study divided the men into two groups, one group being those with a normal serum triglyceride of less than 150 mg/dl, with the second group being those men with values greater than or equal to 150 mg/dl.

Serum vitamin C

Vitamin C, or ascorbic acid, is an essential water-soluble vitamin which is obtained by humans through dietary intake. It is required for the synthesis of collagen, an important component of blood vessels, tendons, ligaments, and bone (Higdson, 2004). Vitamin C is also required in the synthesis of several neurotransmitters such as dopamine, noradrenaline and adrenaline (Higdson, 2004). In addition, this vitamin is required to create carnitine which is involved in the transport of fats to mitochondria in cells to create energy (Carr and Frei, 1999). Lastly, vitamin C is also an important antioxidant that scavenges reactive oxygen and nitrogen species such as superoxide and hydroperoxyl radicals, aqueous peroxy radicals, singlet oxygen, and ozone (Halliwell, 2003).

Several epidemiologic and a limited number of clinical trials have shown that increased vitamin C status or intake is associated with a reduction in the morbidity and mortality from various chronic diseases. These conditions include cardiovascular diseases (Enstrom *et al.* 1992; Osganian *et al.* 2003), cancers of the mouth, throat, vocal chords, esophagus, stomach, colon-rectum, and lung (Kromhout, 1987), as well as cataracts (Simon and Hudes, 1999),

In NHANES III, serum concentrations of vitamin C (mg/dl) were measured using a total vitamin C, fully reduced method using high-performance liquid chromatography with electrochemical detection analysis (NHANES, 1996). This variable was coded as VCP in the laboratory section of the dataset.

Serum vitamin E

Vitamin E, is a fat soluble vitamin, which exists in eight different forms or isomers, four tocopherols, alpha-, beta-, gamma- and delta-, and four tocotrienols (also alpha-, beta-, gamma- and delta-) (Higdson, 2004). Of these, Alpha-tocopherol is thought to be the most active form of vitamin E in humans, and is a powerful biological antioxidant (Mustacich *et al.*, 2007). Unlike some other antioxidants, when Alpha-tocopherol neutralizes a free radical its antioxidant capacity is lost (Traber, 1999). However, Alpha-tocopherol has a synergistic relationship with other antioxidants such as vitamin C which regenerate the antioxidant capacity of the vitamin (Packer *et al.* 1979).

Increased Vitamin E intake has been shown to reduce the risk of death from a myocardial infarction (Knekt *et al.* 1994; Kushi *et al.* 1996). Also, among a group of male smokers, vitamin E supplementation of 50 mg/day has been shown to significantly reduce morbidity and mortality from prostate cancer (Heinonen *et al.*, 1998).

Serum Vitamin E (ug/dl) was measured in the laboratory section of the NHANES III, and is coded VEP in the dataset.

Blood Lead Levels

Environmental and occupational exposure to lead is associated with long term adverse health effects. In particular, elevated concentrations of lead have been shown to affect cognition (Payton *et al.* 1998). Elevated levels can also cause renal dysfunction and peripheral arterial disease (Muntner *et al.* 2003).

In NHANES III, blood lead concentrations were measured by graphite furnace atomic absorption spectrophotometry and expressed in micrograms per deciliter (ug/dl). This variable is coded PBP in the laboratory section of the dataset.

Dietary Variables

In the NHANES III survey respondents were asked how often over the past month they had eaten specific food items (NHANES, 1996). It is important to note that portion sizes were not defined. Thus, responses represent "number or times" as determined by the respondent and not the quantity of the food item (NHANES, 1996). Foods were reported as number of times consumed per day, per week, per month, or never. Variables were standardized as "times per month" using the conversion factors 4.3 weeks/month and 30.4 days/month rounded to the nearest whole number (NHANES, 1996). If the frequency of consumption was reported as "never," the value was recorded as zero (NHANES, 1996).

In addition to the analysis of individual foods, foods were grouped so that consumption by food groups could also be studied. For example milk products (milk, yogurt, cheese, ice cream) were combined into a single variable and analyzed. Thresholds were individually set for each food and food group based on consumption levels and taking into account the goal of evaluating foods that could serve as fortification vehicles. The foods and food groups examined in this study are listed in Table 8.

Table 8: Foods and Food Group Variables

Individual Foods	Food Groups		
	Meats	Cereals	Fruit and Vegetables
vitamins	Bacon/sausage/processed meats	cereals: All-Bran, etc	orange juice
coffee	liver/organ meats	cereals: Total, etc.	other fruit juices
Hi-C, Tange, Koolaid	beef	all other cold cereals	citrus fruits
diet sodas	pork and ham	cooked, hot cereals	melon
regular sodas	shrimps, clams, etc		peaches, nectarines
dark bread	fish	Starchy Vegetables	any other fruits
white bread	chicken and turkey	white potatoes	carrots
cornbread	eggs	sweet potatoes, yams, etc.	broccoli
			Brussels sprouts/cauliflower
	Dairy	Sugar Rich Foods	tomatoes
	chocolate milk	cakes, cookies, brownies	spinach
	milk to drink or on cereal	chocolates, candy and fudge	tossed salad
	yogurt/frozen yogurt		cabbage/Cole slaw
	ice cream, ice milk, milkshakes		hot red chili peppers
	cheese		other peppers

Chapter V: Results

Bivariate Analysis

Several, of the more than 40 different characteristic examined in the study differed significantly between men with higher and lower selenium status. The following presents the bivariate analysis results.

Overall Prevalence

The overall prevalence of selenium status below 106 ng/ml among white American adults 20 years of age and older is 7.7% (95% C.I. = 6.5-8.8) with a weighted estimate of 4,751,618 individuals. Compared with other western countries, the prevalence of men with lower selenium status is quite small since several nations have *mean* selenium status values below 106 ng/ml. It has been estimated, for example, that more than 50% of the adult population of Austria, Germany, Spain, and Poland have serum selenium levels below 70 ng/ml (Combs, 2001).

Demographic Variables

As shown by results of the demographic bivariate analysis, summarized in Table 9 (pg. 51), four of the five demographic variables examined; geographic location, age, level of education and income differed significantly between the two selenium status groups.

Table 9: Demographic Bivariate Results

Selenium Status (ng/mL) (White U.S. Males age >=20years)				
Characteristic	Lower (<106 ng/mL)		Higher (≥106 ng/mL)	
	Number	%(95% C.I.)	Number	%(95% C.I.)
Overall Prevalence and Proportion	4,751,618	7.7 (7.1-9.3)	57,024,796	92.3 (91.2-93.41)
Mean Age	4,751,618	45.43 (43.7-47.1)	57,024,796	43.60 (43.1-44.2)
Age**				
20-39	1,974,553	41.55 (33.7-49.4)	25,381,585	44.5 (41.9-46.6)
40-59	1,269,727	26.72 (20.1-33.4)	19,449,637	34.1 (31.3-35.7)
60+	1,507,733	31.72 (25.8-37.6)	12,193,573	21.3 (20.7-23.6)
Income**				
Low (poverty index ratio <= 1.85)	1,265,099	28.06 (21.6-34.6)	10,542,907	19.4 (17.6-21.2)
Medium (poverty index ratio 1.851-3.5)	1,931,989	42.9 (35.1-50.56)	19,039,406	35.0 (32.7-37.7)
High (poverty index ratio => 3.501)	1,310,131	29.06 (21.6-36.6)	24,763,722	45.6 (43.1-48.0)
Education (years attended) **				
≥ 12	1,512,733	69.9 (63.3-75.9)	45,484,599	79.9 (78.1-81.6)
< 12	3,475,348	30.3 (24.0-36.6)	11,445,280	20.1 (18.3-21.8)
Geography (% living in)**				
North East	875,556	18.4 (12.5-24.3)	12,944,136	22.6 (21.5-23.9)
Mid West	952,311	20.0 (14.4-25.6)	15,914,787	27.9 (26.6-29.2)
South	2,579,221	54.3 (47.0-61.5)	17,752,173	31.3 (29.8-32.3)
West	344,530	7.3 (2.7-11.8)†	10,413,700	18.7 (16.9-19.6)
Geography (within region prevalence ¹) **				
North East	875,556	6.3 (4.0-8.6)		
Mid West	952,311	6.6 (3.9-7.3)		
South	2,579,221	12.6 (10.3-15.0)		
West	344,530	3.2 (1.0-5.3)†		

Source: The National Health and Nutrition Examination Survey NHANES III (1988-1994)

Notes: All reported values represent weighted estimates using Final Exam Weight: WTPFEX6. As per NHANES III analytical guidelines all coefficients of variation above 30% are flagged with †.

**statistically significant chi-square test results

* statistically significant chi-square test results (95%)

¹ Chi-square analysis of prevalence of lower selenium status by region

Geographic Distribution

Using Chi-Square analysis, this study found statistically significant ($p \leq 0.01$) differences amongst the four geographic regions in terms of regional and national prevalence rates of men with selenium status less than 106 ng/ml. When comparing regions, the highest prevalence of white men with a selenium status below 106 ng/ml occurs in the South, with 12.6% (95% C.I. = 10.3-15.0) of the total white adult male population exhibiting this characteristic. This rate is nearly twice that of the Northeast and Midwest at 6.3% (95% C.I. = 4.0-8.6) and 6.6% (95% C.I. = 3.9-7.3) respectively, and almost 4 times greater than the prevalence in the West region at 3.2% (95% C.I. = 1.0-5.3). In the United States as a whole, the majority of men with a selenium status below 106 ng/ml, live in the Southern census region (54.3%, 95% C.I. = 47.1-61.5), 20.0% (95% C.I. = 14.4-25.6) are in the Midwest, 18.4% (95% C.I. = 12.5-24.3) live in the Northeast, while 7.3% (95% C.I. = 2.7-11.8) are in West. The results of this study show that like documented geographic differences in mean selenium status (Niskar *et al.* 2003, Kafai and Ganji, 2003), the prevalence of men with lower status also varies by region within the United States.

Age

Based on the bivariate analysis, it would appear as though low selenium status is more prevalent among older men. In the low selenium status group 31.7% (95% C.I. = 25.8-37.6) are above the age of 60, whereas in the higher selenium group, 21.31% (95% C.I. = 20.7-23.6) are in the oldest age category. This finding seems to be in agreement with studies (Dickson and Tomlinson, 1967; Lloyd *et al.* 1983; Brooks *et al.* 2001) that have reported a decrease in selenium status with age. Though not statistically significant at the 95% confidence level, mean age is higher in the low selenium status group (45.43 years, 95% C.I. = 43.73-47.13) compared with the higher selenium status group (43.60 years, 95% C.I. = 43.05-44.15).

Income

There were significant differences between the two selenium status groups with regard to the three income levels. The prevalence of poverty was greater in the low selenium status group than in the higher one (28.6%, 95% C.I. = 21.6-34.6 vs. 19.4%, 95% C.I. = 17.6-21.2). Also, men with lower selenium status were less likely to have a high income compared with those in the higher selenium status group (29.06%, 95% C.I. = 21.6-36.6

vs. 45.6%, 95% C.I. = 43.1-48.0). In the middle income category, prevalence rates were not significantly different between the two selenium status groups.

Based on this analysis, it would appear that those with lower selenium status tend to be more financially disadvantaged compared with their higher selenium status cohorts. Fewer of them belong to the high income group and more of them are in the lowest income category. As reported in the literature, higher income is positively correlated with education level. It may be that people with higher incomes are more aware of healthy eating habits and may include more foods rich in selenium in their diet. As they have more money, they may also be more able to afford such a diet should it be more expensive than a diet that does not contain such foods.

Education

There were significant differences in education between the two selenium status groups. The lower selenium status group contained a significantly higher prevalence of individuals that did not graduate from high school compared to those in the higher selenium status group (30.3%, 95% C.I. = 24.0-36.6 vs. 20.1%, 95% C.I. = 18.3-21.8).

Such results support the conclusions of other studies that found a positive correlation between education and health status. People with more education are generally more informed about healthy dietary practice and tend to consume foods richer in nutrients including selenium (Kilander *et al.* 2001).

Health Status Variables

Of the 12 health status variables examined only four, smoking status, self-reported health status, self-reported physical activity level, and a cataract diagnosis differed significantly between the two selenium status groups. Table 10 (pg. 54) presents the results from the bivariate analysis performed with the health status variables. It is interesting to note that while statistically not significant, the prevalence rates of many chronic diseases, including congestive heart failure, arthritis, cancer, skin cancer, and diabetes were more common within the lower selenium status group.

Table 10: Health Variables Bivariate Results

Selenium Status (ng/mL) (White U.S. Males age >=20years)

Characteristic	Lower (<106 ng/mL)		Higher (≥106 ng/mL)	
	Number	%(95% C.I.)	Number	%(95% C.I.)
Self Report Health Status**				
Fair or poor	865,542	17.2 (13.1-21.4)	6,500,634	11.4 (10.0-12.7)
Excellent, very good or good	4,144,031	82.7 (78.5-86.8)	50,504,170	88.6 (87.25-89.9)
Exercise Activity Level*				
less than peers	1,150,331	24.6 (20.1-29.0)	9,947,108	17.7 (15.8-19.6)
more or same as peers	3,520,129	75.4 (71.0-79.8)	46,141,661	82.3 (80.3-84.10)
Smoker (Serum Corinne >= 14 ng/mL = smoker)**				
yes	1,673,114	59.91 (51.2-68.5)	10,407,624	38.5 (35.5-41.6)
no	1,119,379	40.08 (31.4-48.7)	16,572,751	61.5 (58.3-64.4)
Doctor ever told: cataracts**				
Yes	532,128	11.1 (7.8-14.5)	3,222,438	5.6 (4.8-6.4)
No	4,477,445	89.3 (86.3-92.3)	53,802,357	94.4 (93.5-95.1)
Doctor ever told: congestive heart failure				
Yes	170,927	3.6 (1.2-5.9)	1,071,007	1.9 (1.4-2.4)
No	4,580,690	96.4 (94.1-98.7)	55,953,789	98.1 (97.6-98.6)
Doctor ever told: stroke				
Yes	170,927	3.6 (1.2-5.9)	1,071,007	1.9 (1.4-2.4)
No	4,580,690	96.4 (94.1-98.8)	55,953,789	98.1 (97.6-98.6)
Doctor ever told: arthritis				
Yes	925,984	19.5 (14.8-24.2)	8,813,552	15.5 (13.8-17.1)
No	3,825,634	80.5 (75.8-85.2)	48,204,415	84.5 (82.9-86.2)
Doctor ever told: asthma				
Yes	309,333	6.5 (3.2-9.7)	4,524,339	7.9 (6.6-9.3)
No	4,442,285	93.5 (90.3-96.8)	52,500,457	92.1 (90.7-93.4)
Doctor ever told: emphysema				
Yes	234,714	4.9 (2.5-7.4)	1,579,760	2.8 (2.2-3.4)
No	4,516,904	95.1 (92.6-97.5)	55,423,214	97.2 (96.4-97.8)
Doctor ever told: gout				
Yes	264,187	5.6 (3.0-8.0)	2,412,023	4.2 (3.3-5.1)
No	4,487,431	94.4 (91.9-96.9)	54,612,773	95.8 (94.9-96.7)
Doctor ever told: skin cancer				
Yes	285,855	6.0 (3.6-8.4)	3,189,124	5.6 (4.8-6.4)
No	4,465,763	94.0 (91.6-96.4)	53,835,671	94.4 (93.6-95.2)
Doctor ever told: other type of cancer				
Yes	162,970	3.4 (1.6-5.3)	1,656,493	2.9 (2.3-3.6)
No	4,588,647	96.6 (94.7-98.4)	55,368,303	97.1 (96.4-97.7)
Doctor ever told: sugar diabetes				
Yes	278,784	5.9 (3.4-8.3)	2,754,481	4.3 (3.9-5.8)
No	4,472,834	94.1 (91.7-96.6)	54,248,907	95.7 (94.2-96.1)

Notes: All reported values represent weighted estimates using Final Exam Weight: WTPFEX6. As per NHANES III analytical guidelines all coefficients of variation above 30% are flagged with †.

** statistically significant chi-square test results (99%)

* statistically significant chi-square test results (95%)

Self-Reported Health Status

The prevalence of men who stated that their health was fair or poor was significantly higher, 17.2% (95% C.I. = 13.1-21.4) vs. 11.4% (95% C.I. = 10.0-12.7) in the lower selenium status group than in the higher selenium status group. This would be expected since the prevalence of many chronic conditions was higher in the lower selenium status group.

Smoking Status

Of the variables studied, smoking status presented the most striking difference between the two selenium status groups. Using serum cotinine levels as a surrogate measure for smoking status, it was found that the majority (59.9%, 95% C.I. = 51.2-68.5) of those in the lower selenium group were smokers, while less than 40% (38.5%, 95% C.I. = 35.5-41.6) were smokers in the higher selenium status group. This relationship is in agreement with other studies which found that smokers have lower selenium status than non-smokers (Kafai and Ganji 2003; Wei *et al.* 2001; Swanson *et al.* 1990; Ellis *et al.* 1984; Lloyd *et al.* 1983)

Activity Level

This study found that more men in the lower selenium status group say they are generally less active than those with higher selenium (24.6%, 95% C.I. = 20.1-29.0 in lower group vs. 17.7%, 95% C.I. = 15.8-19.6 in the higher group). This is not a finding that has been documented in previous studies. It could be that exercise is a covariate of other factors which have a demonstrated effect on selenium status such as smoking, income, and education.

Cataracts

Of the range of health conditions examined, the prevalence of only one, cataracts, differed statistically significantly between the two selenium status groups (5.6%, 95% C.I. = 4.8-6.4 in the higher group vs. 11.1%, 95% C.I. = 7.8-14.5 in lower group). It is interesting to note that intervention studies in China showed that among elderly adults in the Linxian region, a vitamin supplement that included selenium significantly reduced cataract development by 33 to 46 percent (Sperduto, *et al.* 1993). However, because selenium was

mixed with other nutrients in the supplement its individual role, if any, in the prevention of cataracts could not be determined (Sperduto, *et al.* 1993).

This result may also be related to the difference in age distribution of the selenium status groups. Cataracts are highly correlated with age and since the prevalence of men aged 60 or older is significantly higher amongst the lower selenium group perhaps this is a covariate.

Dietary Variables

Of the 13 individual foods and food groups examined, only two differed significantly among the selenium status groups. Fewer men in the lower selenium status group take a vitamin supplement (29.5 %, 95% C.I. = 22.6-36.4 in the lower group vs. 38.2, 95% C.I. = 35.9-40.5 in the higher group). Also, more men in the lower status group report not eating dark bread (40.5%, 95% C.I. = 32.8-48.2 in the lower group vs. 30.3, 95% C.I. = 28.2-32.4). The results of the bivariate dietary analysis are presented in Table 11 (pg. 57) and Table 12 (pg. 58).

Table 11: Dietary Variable Summary

Selenium Status (ng/ml) (White US Males age >=20years)				
	Lower (<106 ng/ml)		Higher (≥106 ng/ml)	
Characteristic	Number	%(95% C.I.)	Number	%(95% C.I.)
Have you taken vitamins/minerals in past month*				
Yes	1,276,112	29.5 (22.6-35.4)	23,136,412	38.2 (35.9-40.5)
No	3,048,381	70.5 (64.6-77.4)	37,440,535	61.8 (59.5-64.1)
Dairy Servings Per Month				
<30	1,124,706	26.0 (18.8-33.2)	12,423,909	20.5 (18.7-22.4)
30-59	1,688,109	39.0 (31.3-46.8)	24,788,272	40.9 (38.6-43.3)
>60	1,511,679	35.0 (27.5-42.4)	23,334,133	38.5 (36.3-40.8)
Meat Servings Per Month				
<30	840,923	19.4 (13.4-25.5)	13,826,558	22.8 (20.9-24.8)
30-59	2,330,544	53.9 (46.1-61.7)	30,937,235	51.1 (48.8-53.4)
≥60	1,153,026	26.7 (20.1-33.2)	15,777,575	26.1 (24.0-28.1)
Fruit and Vegetable Servings Per Month				
<60	1,386,639	32.1 (24.3-39.8)	16,891,090	27.9 (25.8-30.0)
60-119	1,819,827	42.1 (34.2-50.0)	25,389,361	41.9 (39.6-44.3)
≥120	1,118,026	25.8 (19.6-32.1)	18,265,864	30.2 (28.1-32.2)
Cereals Servings Per Month				
<10	2,316,019	53.6 (45.7-61.44)	32,499,575	53.6 (51.3-56.0)
10-29	1,211,444	28.0 (21.0-35.0)	17,180,364	28.4 (26.2-30.5)
≥30	797,030	18.4 (13.2-23.7)	10,907,633	18.0 (16.3-19.7)
Serving of Dark Bread Per Month*				
0	1,751,833	40.5 (32.8-48.2)	18,343,404	30.3 (28.2-32.4)
1-9	1,291,724	29.9(22.4-37.4)	18,984,227	31.4 (29.1-33.6)
≥10	1,280,936	29.6 (22.6-36.7)	23,196,566	38.3 (36.1-40.6)
Servings of White Bread Per Month				
<10	1,200,664	27.8 (30.4-35.2)	19,498,801	32.2 (30.0-34.4)
10-29	963,941	22.3 (15.5-29.1)	14,164,832	23.4 (21.3-25.6)
≥30	2,159,888	49.94 (42.0-57.9)	26,882,682	44.4 (42.1-46.7)
Regula colas and sodas Per Month				
0	1,510,097	34.9 (27.6-42.3)	20,330,226	33.6 (31.4-35.8)
1-14	1,055,982	24.4 (17.2-31.7)	16,829,068	27.8 (25.7-29.9)
≥15	1,758,415	40.7 (32.9-48.5)	23,368,256	38.6 936.3-40.9)
Diet colas and sodas Per Month				
0	2,908,042	64.2 (59.6-74.9)	37,035,249	61.2 (58.9-63.5)
1-14	623,677	14.4 (9.1-19.8)	9,686,552	16 (14.3-17.7)
≥15	792,774	18.3 (11.6-25.0)	13,781,425	22.8 (20.7-24.8)

Notes: All reported values represent weighted estimates using Final Exam Weight: WTPFEX6. As per NHANES III analytical guidelines all coefficients of variation above 30% are flagged with †.

* statistically significant chi-square test results (95%)

Table 12: Dietary Variable Summary (continued)

Selenium Status (ng/ml) (White US Males age >=20years)				
Characteristic	Lower (<106 ng/ml)		Higher (≥106 ng/ml)	
	Number	%(95% C.I.)	Number	%(95% C.I.)
Hi-C, Tang, Koolaid, etc. Per Month				
0	2,745,322	63.5 (55.6-71.4)	39,856,926	66.9 (63.7-68.1)
1-14	1,117,064	25.8 (18.4-33.3)	14,710,240	24.3 (22.7-26.4)
≥15	462,107	10.7 6.0-15.4)	5,915,365	9.8 (8.4-11.1)
Regular coffee per Month				
0	9,767,703	22.6 (16.6-28.60)	17,618,947	29.2 (27.0-31.3)
1-29	734,203	17 (10.1-23.8)	9,154,127	15.1 (13.4-16.9)
30-59	1,347,902	31.2 (24.2-38.1)	15,217,603	25.2 (23.2-27.1)
≥60	1,265,685	29.3 (21.7-36.9)	18,438,221	30.5 (28.3-32.7)
Sugar Rich Foods per month				
0-14	2,624,476	60.7 (53.2-68.2)	34,724,470	57.4 (55.1-59.7)
19-29	585,549	13.5 (8.5-19.0)	10,715,873	17.7 (15.8-19.6)
≥30	1,114,668	25.8 (19.2-32.3)	15,086,176	24.9 (23.0-26.9)
Potatoes, sweet potatoes, yams. Per Month				
0-9	1,487,755	34.4 (26.7-42.1)	21,590,947	35.6 (33.4-37.9)
10-19	1,511,382	34.9 (27.1-42.4)	23,267,759	38.4 (36.1-40.8)
≥20	1,325,356	30.6 (23.3-38.0)	15,728,865	26.0 (24.0-28.0)

Notes: All reported values represent weighted estimates using Final Exam Weight: WTPFEX6. As per NHANES III analytical guidelines all coefficients of variation above 30% are flagged with †.

* statistically significant chi-square test results (95%)

Servings of Dark Bread

The only significant difference between the two serum selenium groups with regard to specific food or food group, involved the consumption of dark bread. In the lower selenium group, 40.5% of respondents said they no servings of dark bread per month vs. 30.3% in the higher selenium status group.

According to United States Department of Agriculture (2003), whole wheat bread, often referred to as dark bread, contains 36.6 ug of selenium per 100g, while white bread contains only 17.3 ug per 100g. While it is possible that the higher prevalence rate of dark bread consumption amongst the higher selenium status group may, in part be responsible for that group's higher selenium status, a more likely scenario may be that dark bread consumption is a surrogate measure for overall healthier eating.

One problem with the NHANES survey is that it simply asks for the number of servings of a certain food or food group that a person consumes per month. This type of survey is problematic for a number of reasons. First, NHANES does not define a standard serving size for each food or food group so one person may consider a serving of dark bread to be one slice, whereas another would consider it to be two slices. Second, NHANES does not account for different nutrient levels in the same type of food. For example, various types of dark bread may contain different concentrations of nutrients, including selenium.

Other problems include memory lapses which create what is known as recall or reporting bias in the survey (Coughlin, 1990). Also, interviewees may wish to appear more concerned about their health than they really are, a phenomenon known as social desirability bias may affect the survey. Social desirability is the tendency of an individual to convey an image in keeping with social norms (Fisher, 1993). In a dietary survey this may result in the respondent claiming to eat less unhealthy foods and more healthy alternatives than is the case (Herbert et al. 1995).

Vitamins/minerals consumption

The two selenium status groups also differed in their stated use of vitamin supplements. Not surprisingly, the prevalence rate for those that took a supplement was greater in the higher selenium status group than the lower selenium status group (38.2% vs. 29.5%). Unfortunately, the NHANES survey does not specify what types of vitamins or minerals an individual takes, and therefore there is no way of knowing whether an individual's supplement contained selenium, and if it did, how much. Of course, whether a person takes a vitamin or mineral supplement could be a surrogate measure of diet quality and/or health conscientiousness. This in turn, may play more of a role in selenium status than just supplemental effect of the selenium contained in the vitamin or mineral supplement.

Physical Measures

The bivariate analysis showed that men with lower selenium status differed significantly from men with higher levels of the mineral on a number of physical measures. The results from the physical variable bivariate analysis are discussed in the following section and are presented in Table 13 (pg. 64) and Table 14 (pg. 65). .

Body Mass Index and Cholesterol

When looking at measures of cholesterol and at body mass index, the prevalence rates of men who are considered obese or overweight, or who have high cholesterol, did not differ significantly between the two selenium status groups (Table 13). These relationships are in agreement with Bates and colleagues (2002) who found that among a nationally representative sample of people aged 65 years and over, living in Britain, plasma selenium was not associated with either serum triglycerides (cholesterol) or body mass index. However, Bates and colleagues (2002) did report a strong ($p \leq 0.01$) positive relationship between plasma selenium and total cholesterol.

Table 13: Prevalence of selected health characteristics of American Men age 20 and over with higher and lower selenium status.

Selenium Status (ng/ml) (White US Males age \geq20years)				
Characteristic	Lower (<106.4 ng/ml)		Higher (>106.4 ng/ml)	
	Number	%(95% C.I.)	Number	%(95% C.I.)
LDL Cholesterol				
Normal	1,582,032	83.9 (74.3-93.4)	19,114,719	80.0 (77.2-82.8)
High or Very High	304,453	16.1(6.6-25.7)	4,769,294	20.0 (17.2-22.7)
Serum Triglycerides				
Normal	2,693,802	77.5 (70.2-84.8)	35,012,979	78.6 (76.4-80.9)
High or Very High	782,187	22.5 (15.2-29.8)	9,509,224	21.4 (19.1-23.6)
Total Cholesterol				
Normal	4,049,366	85.2 (79.4-91.0)	46,695,648	81.9 (80.1-83.7)
High or Very High	702,252	14.8 (9.0-20.6)	10,324,385	18.1 (16.3-19.9)
Body Mass Index				
Normal Weight	1,514,447	32.7 (25.9-39.5)	21,860,526	38.7 (36.3-41.1)
Obese or Overweight	3,112,878	67.3 (60.7-74.1)	34,600,849	61.3 (58.9-63.6)

Source: The National Health and Nutrition Examination Survey NHANES III (1988-1994)

Notes: All reported values represent weighted estimates using Final

* statistically significant chi-square test results (95%)

Micronutrients and Toxins

Of the five micronutrients examined, the mean levels of three, lycopene, calcium, and beta-carotene were significantly lower in the low selenium group (see Table 14). The levels of the other two micronutrients, vitamins C and E, were also lower in this group, though not significantly. These findings agree with a previous study which found strong positive ($p \leq 0.01$) relationships between serum selenium and vitamin C, vitamin E, lycopene, beta-carotene, and calcium (Bates *et al.* 2002).

Mean lead (Pb) levels were significantly higher in the lower selenium group (4.81 ug/dl vs. 4.18 ug/dl, $p \leq 0.05$). Limited research has looked at the relationship, if any, between selenium status and levels of lead in the body. Osman and coworkers (1998) found that among Polish children, blood lead levels were negatively associated with several surrogate measures of selenium status (whole blood, serum, selenoprotein P, and serum glutathione peroxidase). These researchers found this relationship mainly in children with low concentrations of lead and theorized that selenium reduced blood lead levels by altering how it is absorbed and distributed among tissues in the body (Osman *et al.*, 1998).

Table 14: Selected Mean blood Micronutrient and Toxin levels of American Men Age 20 and over with higher and lower selenium status.

Selenium Status (ng/ml) (White US Males age ≥ 20 years)				
	Lower (<106.4 ng/ml)		Higher (>106.4 ng/ml)	
Characteristic	Number	Mean (95% C.I.)	Number	Mean (95% C.I.)
Serum Vitamine E (ug/dL)	4,728,599	1076.3 (995.8-1156.8)	56,783,214	1171.0 (1147.2-1196.5)
Serum Beta Carotene (ud/dL)*	4,728,599	14.55 (13.14-16.0)	56,783,214	17.5 (16.6-18.4)
Serum Vitamin C (ug/dL)	4,717,095	0.61 (0.54-0.68)	56,353,064	0.69 (0.67-0.71)
Serum Lycopene (ud/dL)*	4,728,599	22.4 (20.2-24.6)	56,783,214	25.5 (25.0-26.1)
Serum Calcium (mmol/L)*	4,678,005	2.26 (2.25-2.28)	56,248,603	2.31 (2.30-2.32)
Serum Lead (ug/dL)*	4,751,617	4.81 (4.37-5.24)	56,992,361	4.18 (4.05-4.32)

* statistically significant t-test results (95%)

Multivariate Analysis

An exploratory multiple logistic regression was performed to evaluate the relationship between the dependent variable (i.e., selenium status < 106 ng/ml) and the significant independent variables from the bivariate analysis. In the multiple logistic regression, geographic regions were dichotomized into South and Non-Southern. This was done in order to test whether living in the South was a significant risk factor for low selenium status. Recall from the bivariate analysis that the majority of men (54%) with lower selenium status in the United States live in the South. Similarly, the income variable was also dichotomized, with the middle and upper income levels combined and low income category remaining the same, in order to test whether low income was a significant risk factor for lower selenium status. With regard to age, men in the middle age group were used as the reference category because in the bivariate analysis, this group had the lowest prevalence rate of lower selenium status. Micronutrients and toxins were not added to the model as they have not been shown in the literature to have a causal relationship to selenium status. The results of the multivariate analysis are presented below in Table 15.

Table 15: Multiple Logistic Regression Results for Selenium Status <106 ng/ml

Dependent Variable	P value	Odds Ratio	95 % C.I.	
			Lower	Upper
Selenium Status <106 ng/ml				
Age Group (reference= 40-59)				
Age (20-39)	0.0012	1.28	1.10	1.49
Age (>=60)	<.0001	1.58	1.37	1.84
Region (1= South)	<.0001	2.59	2.32	2.89
Income (1=lower income)	0.0003	1.22	1.10	1.36
Smoking Status (1= smoker)	<.0001	2.24	1.87	2.68
Dark Bread Consumption (reference= high consumption)				
Dark Bread Consumption (medium consumption)	0.1445	1.23	0.93	1.64
Dark Bread Consumption (no consumption)	<.0001	1.57	1.30	1.90
Exercise (1= less active)	0.0014	1.26	1.09	1.46
Education (1= not graduated)	0.7239	0.98	0.89	1.09

Multiple logistic regression analysis indicated that all but one of the explanatory variables in the model were significantly associated with a selenium status less than 106 mg/ml. The results of this analysis showed that those in the 60 and over age category and those in the 20-39 age category had significantly increased odds of having lower selenium status compared with the 40-59 age groups (i.e., age 20-39 vs. age = 40-59, OR= 1.28, 95% C.I.=1.10-1.49, age => 60 vs. age = 40-59, OR= 1.58, 95% C.I.= 1.37-1.84). In addition, living in the South appears to be significant risk factor for lower selenium status when compared with the other regions (i.e. South vs. Non-Southern; OR= 2.59, 95% C.I. = 2.32-2.89). As well, lower income increases the likelihood of having lower selenium status (OR=1.22, 95% C.I. = 1.10-1.36) as does being a smoker (OR=2.24, 95% C.I. = 1.87-2.68). With regard to the lone dietary variable, those that consume no servings of dark bread per month are more likely to have lower selenium status than those who consume many servings (≥ 10) of this food per month (OR= 1.57, 95% C.I. = 1.30-1.90). However, there is no significant increased risk for lower selenium status when comparing no dark bread consumption versus medium (1-9 servings per month) consumption (OR= 1.23, 95% C.I. = 0.93-1.64). Also, men that say they exercise less than their peers are significantly more likely to have a selenium status below 106 ng/ml (OR= 1.26, 95% C.I. = 1.09-1.46). Finally, after controlling for the other explanatory variables, not graduating from high school was not significantly associated with a lower selenium status (OR 0.98, 95% C.I. = 0.89-1.09).

Chapter VI: Discussion and Conclusions

In 2003, Duffield-Lillico and colleagues demonstrated that white men with a selenium status below 106 ng/ml significantly reduce their risk of developing prostate cancer when given 200 ug of selenium per day (Duffield-Lillico *et al.* 2003). Building on this finding, the current study set out to determine the prevalence of lower blood serum selenium status (<106 ng/ml) among the adult white American male population. It also sought to determine whether certain social, economic, geographic, physical, and dietary characteristics were risk factors for lower selenium status. The last goal of this project, secondary to the analysis was to identify and evaluate a selenium augmentation strategy for white adult men deficient in this trace element. To date, this is the first exploratory and secondary analysis that has identified various factors which contribute to, or are associated with, a serum selenium status below 106 ng/ml in a nationally representative sample of white American men.

Within the context of the objectives set forward in this study, a number of conclusions can be drawn:

1. Using the NHANES III survey this study estimated that between the years 1988-1994, 7.7% of white American adult men aged 20 years and older, a total of 4,751,618 individuals, had a selenium status of below 106 ng/ml.
2. Several, of the more than forty, social, economic, geographic, physical and dietary characteristics examined by this study were shown to be significant risk factors for lower selenium status. The following describes and discusses each of the risk factors in detail.

Smoking

Using serum cotinine as a surrogate measure for smoking status, this study found that current smokers were at a greater risk for lower selenium status than non-smokers. This finding is in line with other research that has indicated that smokers have lower selenium status than those who do not smoke (Kafai and Ganji 2003; Wei *et al.* 2001; Swanson *et*

al. 1990; Ellis *et al.* 1984; Lloyd *et al.* 1983). This may be because smokers' diets have been shown to contain less selenium and not that smoking itself depletes the body of selenium (Swanson *et al.* 1990; Fehily *et al.* 1984).

Geography

This study found that men living in the Southern census region of the United States were at a greater risk for lower selenium status when compared with those living in the other 3 regions. Other studies have indicated that average selenium status differs significantly by region in U.S. and that the Southern census region has the lowest levels (Niskar *et al.* 2003, Kafai and Ganji, 2003). Why living in this region presents such a risk for lower selenium status is unclear. This presents an opportunity for further research and such work should look for significant regional dietary and lifestyle differences.

Age

After grouping the men of this study into three age categories (20-39, 40-50, and 60+) the analysis revealed that those in the youngest (20-39) and the oldest (60+) groups had a significantly higher risk for lower selenium status than those in the middle age group. This finding appears to be in agreement with other research. A number of studies have suggested there are age specific differences with regard to selenium status (Campbell *et al.* 1989; Brooks *et al.* 2001; Lloyd, 1983). Also, using the NHANES III data set, Kafai and Ganji (2003) found among a nationally representative sample of American adults that serum selenium status was highest among men in the 31-50 year age group. The mechanism of how age affects selenium status is unclear; however Lloyd (1983) believed it was because of general decrease in food consumption and a resulting lower selenium intake with age, but this does not explain the why being in the lowest age group was a significant risk factor for lower selenium status in the current work. Given this finding, more research is needed to investigate the how age affects selenium status.

Level of Physical Activity

Exercising less than ones peers was found to be a significant risk factor for lower selenium status in this study. The relationship between activity level and selenium status has not been widely studied by other researchers. This work may be the only study to associate this variable with selenium status. Given the lack of published data, investigations as to why and how exercise levels affect lower selenium status are warranted.

Income

Being in the lowest income level was determined to be a significant risk factor for lower selenium status when compared with those in middle and upper income groups. Research in the area of income and selenium status is both limited and conflicting. One study using the NHANES III dataset found a significant positive relationship between income level and selenium status (Niskar *et al.* 2003). It is believed that higher income expands food choices and may lead to better quality diets (McCabe-Sellers *et al.* 2007). Therefore, a lower income could present a risk factor for depressed selenium status because those that earn less may not be able to afford a diverse diet and thus potentially may be limiting their intake of the mineral.

Dark Bread Consumption

This study found that those men who did not consume dark bread were at a significantly higher risk for lower selenium status when compared with those who consumed many servings (≥ 10) per month. This finding could be explained by the amount of selenium contained in dark bread. The United States Department of Agriculture (2003) determined that whole wheat bread, often referred to as dark bread, contains 36.6 ug of selenium per 100g. Conversely, white bread contains only 17.3 ug per 100g. The higher selenium content of dark bread may be protective against lower selenium status, however dark bread consumption could also be a surrogate measure for overall healthier eating.

3. The final goal of this study was to identify an intervention strategy to increase the selenium status among men with lower levels of the mineral. Based on the findings of this work it is difficult to identify any such measure for a number of reasons. In the past, certain micronutrient deficiencies and their associated illnesses were successfully overcome with large scale food fortification, as was the case with iodized salt to prevent goiter, vitamin D fortified milk to prevent rickets, and folic acid supplemented grains to reduce the incidence of spinal defects in babies. These programs were successful because they were inexpensive, required no change in eating habits of the target population, and posed little or no health risk to those not in the target population.

Based on the findings of this study a case cannot be made with regard to supplementing a specific food in order to augment the selenium intake of those men with lower selenium status. The ideal food candidate for supplementation would be one that was consumed

significantly more by men in the lower selenium status than in the higher group. With such a food, one would have the best chance of augmenting the selenium of status those with lower serum levels of this mineral and minimize the odds (however small) of providing those with already higher levels of the with too much of this trace element. However, of the 13 individual foods and food groups examined in this study, none were consumed significantly more by the lower selenium status group than by the higher status group.

The only dietary variable shown to be significantly associated with lower selenium status was dark bread consumption. Eating this food might have a protective effect against lower selenium status since not consuming it presented a significant risk. The obvious reason for this protective effect could be because dark bread has been shown to contain more than twice the amount of selenium per 100g than white bread (36.6 ug vs. 17.3 ug) (USDA, 2003). However, this may not be the only explanation, as the consumption of brown bread may be a surrogate measure for an overall healthy diet in general.

Given that dark bread consumption appears to have some positive influence on selenium status, widely promoting the consumption of dark bread might reduce the prevalence of lower selenium status. While, this would require a change in eating habits, the health benefits could extend beyond increased selenium status. Dark, whole-grain bread is considered healthier than white bread as it contains more fiber, vitamins B6 and E, magnesium, zinc, folic acid and chromium (CNPP, 2002).

A case could also be made for augmenting the selenium content of all white breads to the same level of dark bread. This could have a positive effect with regard to reducing the prevalence of lower selenium status without having to change consumption habits. Based on the bivariate analysis almost 50% (95% C.I. = 42-57) of men in the lower selenium status group eat 30 or more servings of dark bread per month. Thus, if white bread were supplemented with selenium it could have a positive impact with regard to selenium status among a large portion of those that are low in the mineral. Furthermore, because many men in the lower selenium status group consumed this type of food often (i.e. >30 servings per month), a small augmentation, that would limit the possibility of selenium toxicity, could have a large benefit.

A clear fortification vehicle aimed at white American men with low selenium status was not identified by the study. However, increasing the selenium content of common food stuffs, in order to augment selenium status on a population level, is a strategy that should be considered and merits further investigation. As mentioned earlier, selenium supplementation has been shown to decrease the incidence rates of various types of illness from cancer to viral infections. Large scale fortification of foods with selenium, by means of widespread fertilization, has been safely conducted in Finland since 1984. Further research in this area could include estimating the impact of various levels of selenium in fertilizers and subsequent impacts on national and global (because of food exports) selenium status.

Of all the variables examined, smoking was one of the most striking risk factors for lower selenium status. Could a case be made then for fortifying tobacco with selenium? Based upon limited research, it is unclear whether this would be a good strategy to increase selenium status among men with depressed levels of the mineral. Laboratory experiments that have added selenium to tobacco show this practice reduces the mutagenicity and toxicity of cigarette smoke (Yates et al. 1986; Chortyk et al. 1988). Yates (1986) suggests that the mechanism by which selenium generates relief in cigarette smoke induced toxicity is to react with the constituents in the smoke itself and not by stimulating a protective mechanism in the cell. Thus, the action of adding selenium to tobacco appears to reduce the toxicity of the smoke as opposed to having a supplemental effect. In any case, the effect of fortified tobacco with regard to selenium status in humans has not been studied. While this may be a good strategy to reduce the harmful effects of tobacco smoke with regard to lung disease, further research is needed to determine whether adding selenium to tobacco would have a positive effect upon selenium status.

Finally, the need to identify and perhaps implement one specific intervention aimed at augmenting selenium status is perhaps redundant. The modifiable factors for lower selenium status identified by this study were smoking, exercising less, and poverty. All of these are risk factors for many other diseases and are currently being addressed by several public health agencies and non-governmental organizations in the United States. For example, the American Heart Association, American Cancer Society and the Centers

for Disease Control support and promote programs aimed at smoking cessation, healthy eating, and physical activity.

Limitations of the Study

While the findings presented in this study provide an interesting insight into some of the risk factors that may contribute to lower selenium status among white American adult men, there are some important limitations that should be considered when interpreting the results of this work.

NHANES III Survey Population

The NHANES III survey examined the non-institutionalized civilian population of the United States, thus it does not include persons in institutions such as hospitals, nursing homes, or prisons. Therefore, the results of this study cannot be interpreted as representing the entire white, adult male population in the United States.

Recall and Social Desirability Bias

Because many of the variables used in this survey such as food frequency and physical activity level were self-reported, they are subject to recall and social desirability bias. Recall bias may be a particular problem with the food frequency portion of the NHANES survey. People were asked to remember the number of times they ate a certain food during the past month. Under such circumstances, it may be difficult for some people to accurately estimate the number of times certain foods had been consumed.

Longitudinal Considerations

The conclusions of this study are based upon a survey that was conducted from 1988-1994, thus, applying the results to today's (2008) population should be done with caution. Some notable changes in the American population have occurred since the survey was conducted and have implications with respect to the findings of this study. For example, the prevalence of smoking has dropped between the NHANES III study years and today. The Centers for Disease Control (2007) reported that in 1990, 28.4% of adult males were current smokers, in 2006, after 16 years of slow decline, 23.9% of adult men said they smoked.

Also, since the NHANES III survey period some changes in dietary habits have occurred, notably the emergence of low-carbohydrate, high-protein diets. In a population-based cross-sectional survey, conducted in 2002, Blanck and colleagues (2006) found that 12% of the American population reported ever trying a low-carbohydrate, high-protein diet, while 3% said they were currently using this type of diet. The effect upon selenium status that such diets have has not been documented.

Food Frequency Survey Limitations

The dietary variables analyzed by this study were calculated using the monthly food frequency portion of the NHANES III survey. As discussed earlier, food frequency surveys can be problematic as they are subject to recall bias. To this end, future research could use a different dietary survey to perhaps gain a more accurate perspective of the eating habits of men with lower selenium status. A type of dietary survey that may yield more accurate results could be a multiple 24 hour recall food survey, instead of the monthly food frequency one used in this study. In a multiple 24 hour survey, the participants are asked about their dietary habits during the past 24 hours on subsequent days. The advantage to this type of survey method is that it may reduce the recall bias of the participants as they are only required to remember their dietary consumption from the previous day as opposed to an entire month (Freudenheim, 1993).

Potential Risk Factors Not Considered

This study considered many of the determinants of selenium status that were indicated in the literature, along with a range of other characteristics. While numerous variables were examined, this work in no way analyzed an exhaustive list of risk factors for lower selenium status. A number of other potential determinants of lower selenium status could exist and merit further investigation.

Implications of the Research

The findings of this study may have further significance should ongoing clinical trials involving selenium demonstrate that supplementing with this mineral has a protective effect against prostate cancer among men with lower selenium status. The SELECT study (Selenium and Vitamin E Cancer Prevention Trial) involving over 32,000 men 55 years and older, from 400 sites in the United States, Canada, and Puerto Rico should be

releasing their results soon. If it is found that selenium is protective against prostate cancer among men with lower status by the SELECT trial, then the current study could be used to identify a target population that would benefit most from selenium supplementation. Furthermore, this work could also be used as an initial screening tool by physicians to assess who may benefit from a selenium supplement. Patients presenting with risk factors for lower selenium status might have their blood tested to determine if this was the case, and if so, prescribed a daily selenium supplement.

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