6-1-2013

A review of serum 25-hydroxyvitamin D levels in Alaska native and non-natives in southwest Alaska

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A Review of Serum 25-Hydroxyvitamin D Levels in Alaska Native and Non-Natives in Southwest Alaska

by

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Thesis

Submitted to the College of Health and Human Services

Eastern Michigan University

in partial fulfillment of the requirements

for the degree of

MASTER OF SCIENCE

in

Human Nutrition

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June 1, 2013

Ypsilanti, Michigan

ACKNOWLEDGEMENT

It is a pleasure to thank those who made this thesis possible. I had the great honor, early in my graduate studies, of working with Dr. George Liepa- from the selection of Eastern Michigan University for my graduate studies, to assisting me with developing a plan of study that allowed me to learn and yet met the needs of my life, and in selecting vitamin D as the focus of my research. Dr. Liepa had a vast knowledge of the field of vitamin D and was eager to explore the field further; his enthusiasm was contagious. His passing was a great loss to us all.

I would like to express my sincere gratitude to Dr. John Carbone, for his encouragement, patience, enthusiasm, guidance, and support throughout the project. I'd also like to thank Dr. Judith Brooks for all of her assistance in refining the product and her support in the process. I'm so thankful to have been able to participate in this excellent learning experience with this team of professionals.

I'd like to acknowledge the Bristol Bay Area Health Corporation and the people of the Bristol Bay region for allowing me to conduct this project and for welcoming my family into their lives.

I would also like to thank my wonderful husband and five children for allowing me to work this project into our already full lives. Without their support, I wouldn't have been able to take one class let alone complete this project. I love you all very much.

ABSTRACT

Background: Vitamin D insufficiency and deficiency have been documented throughout the world, correlating with disease processes including: cancers, bone disorders, autoimmune diseases, and cardiovascular disease. Factors affecting people of Southwest Alaska, such as northern latitude (above 34 ºN), low dietary intake of vitamin D, reduced sun exposure, high body mass index, and darker skin pigmentation increase risk for Serum 25-hydroxyvitamin D [25 (OH)D] deficiency and insufficiency.

Purposes of the Study: To evaluate the incidence of 25(OH)D insufficiency and deficiency in Southwest Alaska, differences in deficiency rates between Alaska Natives and non-Natives, and seasonal trends in 25(OH)D levels.

Subjects: Forty-nine adults with 25(OH)D levels obtained by a provider from the Bristol Bay Area Health Corporation (April 1, 2008- March 30, 2011).

Results: Mean 25(OH)D was 30.9 +/- 4.4 ng/ml. 49% (24/49) of measures were ≤ 30ng/mL (insufficiency) and 20% (10/49) were ≤ 20ng/mL (deficiency), indicating widespread 25(OH)D insufficiency/deficiency. No difference in 25(OH)D levels was observed between Alaska Natives and Non-Natives. Mean 25(OH)D levels were lower for measures obtained in winter/spring relative to summer/fall.

Conclusions: This study confirms a high prevalence of 25(OH)D deficiency in the peoples of southwest Alaska, both Alaska Natives and Whites, throughout the year with a seasonal drop in winter/spring.

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Chapter 1

Introduction

Vitamin D insufficiency and deficiency have been clearly documented throughout the world, correlating with a host of disease processes (1-7). The body of research evaluating vitamin D is extensive due to the countless variables involved in the absorption, activation, and transport of the vitamin in humans. While extensive vitamin D research has been conducted worldwide, few studies have evaluated the status of serum 25-hydroxyvitamin D [25(OH)D] levels in remote, Alaskan populations at northern latitudes and the seasonal changes that may occur in response to alterations in sun exposure. Furthermore, no research has been conducted comparing 25(OH)D levels of Alaska Natives with non-Native individuals in the region to determine whether or not a disparity exists.

Background

Interest in vitamin D has made a resurgence in the past decade and knowledge regarding the importance of vitamin D in human health has been expanding. Prevalence of vitamin D deficiency and insufficiency have been well documented and have been correlated with numerous disease processes (5,8,9).

Vitamin D is a fat-soluble vitamin, which enters the body in two ways: by exposure to sunlight in the form of vitamin D_3 (cholecalciferol) and from ingestion of dietary sources in the forms of vitamin D_2 (ergocalciferol) from plants and vitamin D_3 from vertebrate animals. Eighty to ninety percent of total vitamin D intake is obtained through exposure to sunlight and the remaining 10-20% is from dietary sources (8).

The cutaneous synthesis of vitamin D is a multi-step process (10). The vitamin D precursor 7-dehydrocholesterol is formed in the liver and initially activated upon the skin's exposure to Ultraviolet B (UVB) rays from the sun to 25(OH)D. The kidneys then convert 25(OH)D to the active form 1,25-dihydroxyvitamin D. Several factors including season, latitude, time of sun exposure, use of sunscreen, skin pigmentation, clothing, aging, clouds, pollution, and window glass all have an effect on the initial activation of vitamin D_3 in the skin (11). At northern latitudes (above 34°N), no vitamin D can be produced in the skin during winter months due to the angle of the sun's rays (12). At increased angles, the UVB rays are absorbed by the ozone. A meta-analysis conducted in 2007 further confirmed that 25(OH)D insufficiency was widespread even at lower latitudes, such as the equator in darker pigmented individuals, and that the inverse association between latitude and vitamin D levels was present in Caucasians only (11).

Dietary sources of vitamin D, in the forms of vitamin D_2 and vitamin D_3, also affect serum 25(OH)D levels but to a much lesser extent than endogenous production due to sun exposure (2,8). Furthermore, studies have shown inadequate intake of both fortified and naturally occurring dietary sources of vitamin D in many areas worldwide (8). Naturally occurring sources of vitamin D include fatty fish, liver, egg yolks, meat, and dairy fat. Fortified sources most frequently consumed include fortified milk and ready-to-eat cereals (13). In the United States as a whole, fortified sources of vitamin D contribute more daily vitamin D than naturally occurring sources. The current Recommended Daily Allowance (RDA) for Vitamin D is 400 IU/day for all infants under 1 year of age, 600 IU per day for people age 12 months to 70 years of age, and 800 IU per day for individuals over 70 years of age (14). Additional factors also influence levels of 25(OH)D, including body mass index (BMI), renal function, and age (15). Elevated Body Mass Index correlates with lower levels of 25(OH)D as fat sequesters 25(OH)D, thus reducing circulating levels. As renal function is impaired, less conversion of

25(OH)D to the active form 1,25-dihydroxyvitamin D occurs, ultimately reducing 25(OH)D levels. As age increases, changes within the skin's epidermal layers reduce the absorption of vitamin D_3, also leading to lower 25(OH)D levels.

Serum 25(OH)D is considered the best clinical indicator of overall vitamin D adequacy (5). It reflects vitamin D produced in the skin and dietary intake. Although an "optimal" 25(OH)D level has not yet been established, there is some consensus within the literature defining vitamin D deficiency as $\leq$50 nmol/L, insufficiency between 51-74 nmol/L, and adequate levels at 75 nmol/L or greater (5).

The setting for the current study is the Bristol Bay region of remote southwest Alaska. Several unique factors are present in the southwest region, factors which may both positively and negatively impact 25(OH)D levels in the people residing there, including living at a high northern latitude (55.91 ºN - 59.98 ºN), the ethnic diversity of the people with varying skin tones, subsistence lifestyles including traditional eating practices and increased outdoor exposure, lengthy and harsh winters, and reduced access to vitamin D fortified products including vitamin D fortified milk. Lactose intolerance may also contribute to a reduced consumption of fortified milk and milk products, affecting up to 80% of Native Alaskans (16).

The people of Bristol Bay have a rich and varied cultural history. Its Native tribes−Yup'ik, Aleuts, and Athabascans−have resided in the Bristol Bay region for centuries. The total population in the region is 7,597 people, of whom 72% are Alaska Native (17).

Alaska Natives and non-Natives commonly practice subsistence lifestyles in the Bristol Bay region, which may impact vitamin D status. Subsistence lifestyles are those in which a group obtains the necessities of life through self-provisioning, through means such as hunting and gathering. These lifestyles have been practiced for centuries by Alaska Natives and have been shared with non-Natives as well. Subsistence lifestyles in rural Alaska are practiced for a variety of reasons. Fish, game, berries, and other natural vegetation are plentiful and are a part of the Alaska Native culture. Practicing in this way also offsets the extremely high cost of purchased food, which must be flown or barged into rural villages.

Subsistence lifestyles may have an impact on vitamin D_2 and vitamin D_3 exposure within the population of southwest Alaska. Salmon is a staple food throughout the region, as the region is known to be the "Salmon Capital of the World." Salmon is one of the highest naturally occurring sources of vitamin D_3. Salmon is consumed daily by many: eaten smoked, dried, baked, and canned. Customary Native Alaskan practices include adding salmon to many dishes, including akutaq "Eskimo ice cream" (a combination of Crisco, sugar, and berries). Other marine foods may also contribute to vitamin D status, including whale blubber and whale skin.

Subsistence lifestyles also contribute to increased time spent outdoors while performing the food gathering/preparing tasks and thus potentially increasing exposure to vitamin D_3 from the sun. These variables create a unique setting for studying 25(OH)D levels in rural, predominantly Alaska Native populations in southwest Alaska.

Statement of the Problem

The extensive body of research available correlates low 25(OH)D levels with a multitude of disease states. Studies have correlated hypovitaminosis D with various types of cancers, bone disorders, autoimmune diseases (1), cardiovascular disease (18,19), diabetes/impaired blood glucose regulation (20), multiple sclerosis (6), and metabolic syndrome (21).

Factors such as northern latitude (above 34°N), low dietary intake of vitamin D, reduced sun exposure, high body mass index, and darker skin pigmentation increase risk of 25(OH)D deficiency and insufficiency. It is suspected that many of these factors are present in the people of southwest Alaska.

One study has identified the presence of low 25(OH)D levels in southeast Alaska Natives (22). Of the 83 Alaska Natives tested, only nine (11%) had levels that were sufficient. It remains unclear as to what extent hypovitaminosis D is present in Native and non-Native adults living in the southwest region of Alaska, if levels differ between Alaska Native versus non-Native individuals, and if seasonal patterns in 25(OH)D levels exist.

Purposes of the Study

Objective 1: To determine the incidence of 25(OH)D insufficiency and deficiency in Alaskan adults living in rural, southwest Alaska (latitude 55.91 ºN - 59.98 ºN).

Hypothesis 1: This study is designed to test the hypothesis that 25(OH)D insufficiency and deficiency are present in Alaskan adults living in rural, southwest Alaska.

Objective 2: To determine if there are differences in deficiency rates between Alaska Native and non-Native participants.

Hypothesis 2: This study further seeks to test the hypothesis that there is no difference between 25(OH)D levels of Alaska Native and non-Native participants, in spite of differing skin tones and suspected differences in dietary practices.

Objective 3: To identify seasonal trends in 25(OH)D levels in the region.

Hypothesis 3: This study will also test the hypothesis that 25(OH)D insufficiency and deficiency are prevalent year-round, but with lowest levels occurring in the winter and spring months (December through May).

Significance of the Study

Earlier studies conducted in other regions in Alaska and in other countries at northern latitudes have indicated a high prevalence of vitamin D deficiency. Current research has identified correlations between vitamin D status and many of the health issues facing both Alaska Natives and non-Natives alike. Cancer is the leading cause of death in Alaskans and disproportionately affects Alaska Natives. In recent years, a sharp rise in type 2 diabetes, obesity, and heart disease has been noted throughout the state, as well. Evaluating the prevalence of 25(OH)D deficiency in Alaska Natives and non-Natives provides additional insight into the current health status of Alaskans and is an essential step in laying the foundation for further vitamin D research.

Limitations of the Study

The study is a non-randomized study. All Bristol Bay Area Health Corporation patients that have had 25(OH)D levels obtained over the past 3 years were evaluated. These individuals may have been identified by their medical provider as being at high risk for vitamin D deficiency due to a history of hypovitaminosis D, obesity, having been on medications that can impact vitamin D status, or other clinical indicators. The sampling is not controlled. The subjects may be consuming varying levels of dietary vitamin D or vitamin D supplementation. The results of this study provide baseline incidence data only and are not correlating or indicating causation with any disease processes.

Chapter 2

Review of Related Literature

The collective body of vitamin D research published to date is extensive. Studies have identified correlations between vitamin D status and numerous conditions and have also identified factors affecting 25(OH)D status. The focus of this study is to reveal rates of deficiency in rural Alaskans. Additionally, this study seeks to identify seasonal changes and to determine if a disparity exists between Alaska Natives and non-Natives. The design of this study is a non-randomized, review of 25(OH)D levels obtained over a three-year time period. A thorough review of literature was conducted to identify research designs similar to those of this study. Evaluation of the body of vitamin D research was also conducted to provide a foundational understanding of the factors that may play a role in vitamin D status in rural populations in southwest Alaska including latitude, ethnicity, season, and dietary factors.

The design of this study is similar to a study conducted in Native Alaskans in the Ketchikan Native Indian Community in southeastern Alaska (22). The study design was a manual review of laboratory records in 83 patients with 25(OH)D levels obtained between April 1, 2005, and March 30, 2007. The population was identified as Native Alaskans, of varying tribes and degrees of Native blood. The purpose of the study was to identify the relationship between vitamin D and glucose levels. It was determined that nine out of the 83 levels of 25(OH)D were within normal limits (above 32 ng/mL [80 nmol/L]), leaving the remaining 74 levels as deficient. Furthermore, 18 values were so low that they were undetectable. There was no statistically significant correlation between 25(OH)D levels and glucose due to the very few values that were within a normal range. This study provides a foundation for further vitamin D studies within Native Alaskan populations.

The results obtained in Frost's study (22) in the southeast region of Alaska established some baseline data that indicate that hypovitaminosis D is present in Alaska Natives in southeast Alaska. The research cannot, however, be used to draw conclusions regarding vitamin D status of the populations in the southwest region. This is due to the geographic and cultural differences between the southeast and southwest regions in Alaska. The population studied in Frost's research was also completely Alaska Native and therefore does not provide information that can identify the presence of deficiency in all Alaskans (both Native and non-Native peoples).

Vitamin D Deficiency: A Global Problem

Several research studies and reviews have been conducted evaluating the factors affecting vitamin D status. One review conducted by Mithal et al. in 2009 attempted to evaluate vitamin D status across six regions throughout the world, including Asia, Europe, Middle East, Africa, Latin America, North America, and Oceania (8). Variations exist in the definition of vitamin D deficiency as well as methodology used, but 25(OH)D levels were commonly below 75 nmol/L in every region. Furthermore, levels below 25 nmol/L were common in South Asia and the Middle East. The main factors identified in the review correlating with low 25(OH)D levels include older age, winter season, darker skin pigmentation, less sunlight, dietary habits, and the absence of vitamin D fortification in foods (8).

A meta-analysis was also conducted by Hagenau et al. evaluating the status of 25(OH)D levels globally (11). A total of 394 cross-sectional studies met inclusionary criteria. The mean 25(OH)D level across all studies was 54 nmol/L and thus was insufficient. Women tended to have higher levels than men, Caucasians had higher levels than other races, and youth under 15 years old had lower levels than those over 15 years old. Interestingly, latitudinal variations were demonstrated only in Caucasians (with lower 25(OH)D levels at higher latitudes). The meta-analysis did confirm that widespread vitamin D deficiency and insufficiency were present across the globe.

Latitudinal, Seasonal and Racial Variations in Serum 25-Hydroxyvitamin D Status

The body of evidence available does appear to support the presence of latitudinal, seasonal, and racial variations in 25(OH)D in adults. Multiple research studies have evaluated one or more of these factors in relation to 25(OH)D levels. The key studies that lay the groundwork for this project are included in this evaluation.

In a review of the impact geographic location has on vitamin D synthesis, Kimlin describes the issues limiting UVB radiation above 40º latitude, including the angles of solar zenith rays (23). Solar zenith rays are the angles of the sun's rays relative to a vertical ray at a specific point. At high northern latitudes, the levels of vitamin D effective ultraviolet radiation follow a bell-shaped curve when plotted monthly from January to December, reaching peak effectiveness in July. Kimlin has also evaluated the vitamin D effective ultraviolet radiation at the equator. The levels remained fairly consistent and high throughout the year, with two subtle peaks around March and October. Low levels of vitamin D effective ultraviolet radiation at northern latitudes would explain the low production of vitamin D in the skin and thus contribute to hypovitaminosis D. Additional geographic factors affect vitamin D effective ultraviolet radiation as well, including season. It was determined that above 55º N latitude, no vitamin D effective radiation is available in the winter months (23). Furthermore, additional studies indicate that even at lower latitudes, with typical sun exposure levels, that deficiency remains common (24).

Multiple studies have evaluated seasonal changes at northern latitudes. A study conducted across seven Canadian cities evaluated seasonal changes in 25(OH)D levels at high northern latitudes (25). The centers were located in Vancouver, Calgary, Saskatoon, Toronto, Kingston, Quebec City, and Halifax (latitude range from 43.65 ºN to 52.08 ºN). The study, beyond assessing the 25(OH)D levels in adults at northern latitudes, also evaluated variables which may predict 25(OH)D status including skin pigmentation (race/color); vitamin D intake from diet, supplements, and medications; sun-related variables, and BMI. The study used <75 nmol/L to be the threshold for defining insufficiency. It was determined that 25(OH)D levels were either deficient or insufficient in 59% of participants when all seasons were averaged together. In spring, deficiency or insufficiency rates were over 75%, clearly indicating a seasonal impact on 25(OH)D levels. Other predictors of low 25(OH)D levels included BMI greater than or equal to 30, non-white ethnicity, and lower vitamin D supplementation (25).

Another study conducted in Edmonton, Alberta (latitude 53.30°N), further confirmed the high levels of vitamin D insufficiency and deficiency at high northern latitudes (26). The cross-sectional study included 1,433 patients from three clinics in the Edmonton area. 25(OH)D levels, demographic information (skin tone), and lifestyle factors (fish consumption, milk intake, sun exposure, tanning bed use, and nutritional supplementation) were evaluated by Genuis et al. (26). Sixty-eight percent of the population had some level of deficiency or insufficiency (below 80 nmol/L). A negative correlation was found between 25(OH)D levels and darker skin pigmentation. A positive correlation was found between 25(OH)D levels and fish ingestion (weekly), vitamin D supplementation, tanning bed use, and milk consumption (2 cups per day). 25(OH)D status also correlated with the seasons, consistent with other seasonal studies conducted at northern latitudes. Levels in summer and fall were higher than in winter and spring.

A study conducted by Dalgard et al. provides important information regarding 25(OH)D status at northern latitudes (9). Dalgard et al. evaluated vitamin D status in an elderly Faroese population. This study was unique as it attempted to evaluate vitamin D status of a population residing at a high northern latitude (latitude 62°N), a known risk factor for vitamin D deficiency, consuming a vitamin D-rich marine diet. The research question was whether or not the marine diet would provide adequate vitamin D to offset the decreased vitamin D synthesis in the skin anticipated at northern latitudes. Additional information gathered/assessed included dietary data using a Food Frequency Questionnaire (assessing frequency of whale blubber, whale meat and fish), body mass index (BMI), smoking status, gender, and age. Variations in 25(OH)D levels were also assessed for seasonal (monthly) variations. The study had 669 subjects, of whom only 10% had 25(OH)D levels greater than 80 nmol/L. Levels were highest in July and September, but still only 22-24% of the samples were greater than 80 nmol/L during those months. The study provides important information as to the prevalence of hypovitaminosis D at northern latitudes, even in the presence of a diet high in vitamin D. Of all of the additional factors assessed, only increased BMI correlated significantly with 25(OH)D deficiency.

Gagnon et al. assessed the prevalence and predictors of vitamin D deficiency and insufficiency in adult women living in northern latitudes (27). This cross-sectional study included 153 healthy, predominantly Caucasian women between 18 and 41 years of age. Serum 25(OH)D levels were obtained between May and September of 2006. Fifty-seven percent had their blood sample obtained in September. Researchers determined that the month in which the sample was obtained had a significant impact on 25(OH)D levels. The prevalence of vitamin D insufficiency/deficiency together was 30% in the summer months. Inversely correlative factors with 25(OH)D were elevated BMI and sunscreen use (78% of participants). Factors correlating with higher 25(OH)D levels were oral contraceptive pills, travel to a warmer climate during winter/spring, and vitamin D supplementation, which was reported in only 3% of participants (27). With the high levels of insufficiency in the summer months, the winter levels are likely to be far more deficient. This research further supports the need to assess seasonal variability at high latitudes.

A study conducted by Sullivan et al. evaluated the impact of seasonal changes on 25(OH)D levels in adolescent females in Maine (28). The study additionally evaluated dietary intake. Dietary data and 25(OH)D were obtained during the summer and winter months, along with parathyroid hormone levels and sun exposure information. The mean seasonal decrease from summer to winter of 25(OH)D was 28%, with vitamin D insufficiency in 48% of subjects despite the fact that the subjects did have dietary intake at or near the pre-2010 Adequate Intake (AI) of 200 IU/day for vitamin D. The results from this study indicate that the AI at the time, which was met or nearly met by the population, was inadequate to maintain 25(OH)D levels year-round. Although no direct application can be made from this research to the current study, as it was in adolescent females at a latitude far below that of southwest Alaska, it was a foundational study evaluating seasonal changes in 25(OH)D levels. It should be noted that the AI was raised in 2010 to 600 IU/day and became the RDA for all groups except infants.

An additional study conducted in Estonia, a country in northern Europe (latitude 59°N), evaluated seasonal changes in 25(OH)D levels (29). The study design was population-based; researchers randomly selected 367 adult participants (age 25-70 years) from health providers' registers. Researchers obtained 25(OH)D levels and parathyroid hormone levels in summer and winter. Additionally, the researchers assessed variables including age, sex, BMI, and sun-bathing habits. They identified that in winter, 73% of the participants had 25(OH)D deficiency (using 50 nmol/L as the threshold for deficiency). The mean 25(OH)D in winter was 43.7 ± 15 nmol/L and in summer was 59.3 ± 18 nmol/L, with winter levels often deficient and summer levels often insufficient. Results clearly demonstrated a seasonal difference in 25(OH)D at a high northern latitude.

Research has also evaluated the effect of skin pigmentation on 25(OH)D levels at northern latitudes (15). This cross-sectional study evaluated the correlation between ancestry and 25(OH)D levels in 107 young adults during the winter months in the Toronto area of Canada (latitude 43.65 ºN). The results revealed a staggering 93% of all participants had levels below the established sufficient level of 75 nmol/L, and nearly 75% of the population had levels below 50 nmol/L. Significant differences existed in both the dietary intake of vitamin D and the serum 25(OH)D levels of each racial group. Melanin in the skin reduces the production of vitamin D, thereby increasing risk for vitamin D deficiency. The mean 25(OH)D level of the entire sample was 39.4 +/-21 nmol/L, in Europeans the mean was 55.9 nmol/L, in East Asians the mean was 34.5 nmol/L, and in South Asians the mean was 30.5 nmol/L. The sample size of the African ancestry group was too small for analysis. The mean daily dietary vitamin D intakes for the three ancestry groups were as follows: 231 IU for the European sample, 133.4 IU for the East Asian sample, and 164.3 IU for the South Asian sample. This research study provides insight into the impact of skin pigmentation on vitamin D status at northern latitudes and also speaks to dietary influence of serum 25(OH)D. Native Alaskans were not included in the study as a population group, yet the study provides a basis to evaluate vitamin D status by ethnic/racial group in southwest Alaska. Skin pigmentation is widely variable within the Alaska Native population due to the extensive number of tribal groups and high rates of mixed ethnicity (European ancestry and Alaska Native).

Additional Factors Affecting Serum 25-Hydroxyvitamin D status in Alaskan Adults

Dietary data will not be assessed in this research study; however, the dietary impact of vitamin D rich foods plays a role in 25(OH)D status. Researchers have conducted large scale dietary studies to evaluate the dietary practices and nutrient composition of Alaska Native diets. These studies indicate that Alaska Natives consume high levels of dietary vitamin D, particularly those consuming a more traditional diet.

One such study conducted by the Center for Alaska Native Health Research (CANHR) evaluated the Alaska Native diet to address the increasing health disparities between Alaska Native and non-Native populations (30). Researchers conducted the study in the Yukon-Kuskokwim Delta region of southwest Alaska, in remote villages predominantly inhabited by Alaska Natives practicing subsistence lifestyles. Traditional foods made up an average of 22% of the daily energy intake. The more traditional diets had significantly higher levels of vitamin D. The nine categories of foods that covered the vast majority of traditional food sources included fish and fish roe, seal oil, game meat, game fowl, berries, organ meats, shellfish, animal fat, and wild greens.

Another large scale study evaluating the dietary practices of Alaska Natives was the Genetics of Coronary Artery Disease in Alaska Natives (GOCADAN) study, conducted in 2000-2003 (31). The study analyzed dietary intakes to generate recommendations to reduce cardiovascular disease. Interestingly, results indicated that Alaska Natives consumed 6 times more fish than other races within the United States. Consistent with CANHR and GOCADAN data, the traditional foods identified by Alaska Natives in those regions are the same foods Natives in the Bristol Bay region consume as well. This higher dietary vitamin D intake may help to offset the risk for 25(OH)D insufficiency or deficiency posed by reduced sun exposure, northern latitude, slightly darker skin pigmentation, and the impact of long winters experienced in the southwest region of Alaska. The higher intake, however, is not expected to maintain 25(OH)D levels in a sufficient range, in light of previous research (9).

Chapter 3

Research Design

The medical records accessed for this study are for patients who receive healthcare services at the Bristol Bay Area Health Corporation (BBAHC), a small, tribally operated health system, which provides health care throughout the southwest region of Alaska. The Bristol Bay Area Health Corporation is located in the town of Dillingham, Alaska (latitude 59.19 °N). The geographic area served by the health corporation covers 46,714 square miles (latitudes ranging from 55.91 ºN to 59.98 ºN). The region consists of Dillingham and the surrounding 34 predominantly Alaska Native villages. These rural communities are accessible only by boat or plane.

Sample Selection Criteria

The research design is a non-randomized, retrospective study including all individuals who have had 25(OH)D levels obtained by a provider from the Bristol Bay Area Health Corporation within the past 3 years (April 1, 2008-March 30, 2011). The study included adults over 18 years of age, living in the southwest region of Alaska. This study also included participants of all races. The researcher categorized participants into racial data groups based upon self-identification of race as either Alaska Native or Non- Native. The researcher classified participants who were of mixed racial descent including Alaska Native as Alaska Native.

Research Methods

The researcher obtained approval for this study prior to initiation from the Alaska Institutional Review Board, the Human Subjects Review Committee at Eastern Michigan University, and the Human Subjects Review Committee at the Bristol Bay Area Health Corporation (BBAHC).

Using VGEN, a data management system utilized by the regional health corporation, the researcher accessed the Electronic Health Record/RPMS database. The researcher compiled a panel with the search criteria including patients within the BBAHC service area that had 25(OH)D levels obtained between 04/01/2008 and 03/30/2011, date of birth, race, age, and the date drawn/result of the 25(OH)D test (see Appendix A- RPMS Data Access Sequence). The 25(OH)D samples were drawn by providers at the Bristol Bay Area Health Corporation and sent to Quest Diagnostics in Seattle, WA, for analysis.

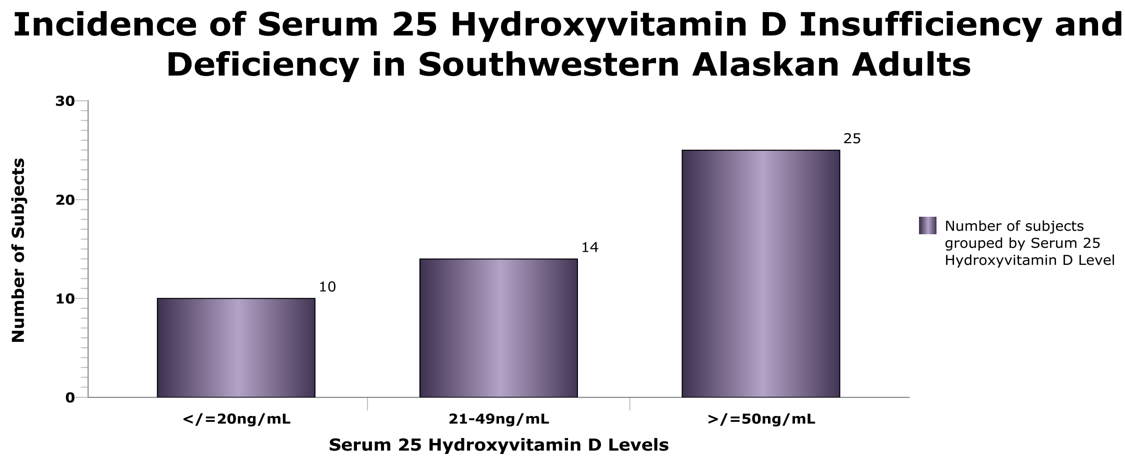
Chapter 4

Results

The results of the data collection included a panel of 49 individuals who had 25(OH)D testing conducted between 04/01/2008 and 3/30/2011 (see Appendix B: Serum 25 Hydroxyvitamin D Data by Gender, Date of Birth, Month and Ethnicity). Included in the data were 12 males and 37 females; 38 of the individuals were Alaska Native (includes one person self-identified as American Indian) and 11 were White. The average age of the individuals was 56 years. The mean 25(OH)D was 77.2 nmol/L (30.9 +/- 4.4 ng/ml) overall. The definition of 25(OH)D insufficiency was set at ≤ 75 nmol/L (30 ng/mL) and deficiency at ≤ 50nmol/L (20 ng/mL), which is supported by other research included within the field (15,25,27).

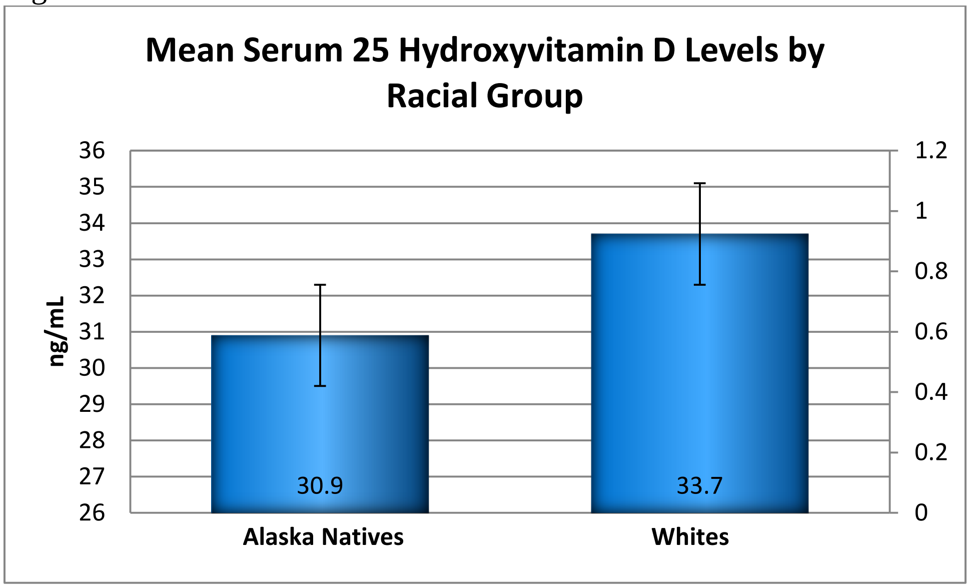
The first objective of this study was to determine the incidence of 25(OH)D insufficiency and deficiency in Alaskan adults living in rural, southwest Alaska (latitude 55.91 ºN - 59.98 ºN). Data analysis showed 49% (24/49) of the data points were ≤ 75 nmol/L (insufficiency) and 20% (10/49) were ≤ 50 nmol/L (deficiency), indicating widespread 25(OH)D insufficiency/deficiency (see Figure 1). This study has confirmed that within the study population, 25(OH)D deficiency is present in Alaskan adults living in rural, southwest Alaska.

Figure 1.



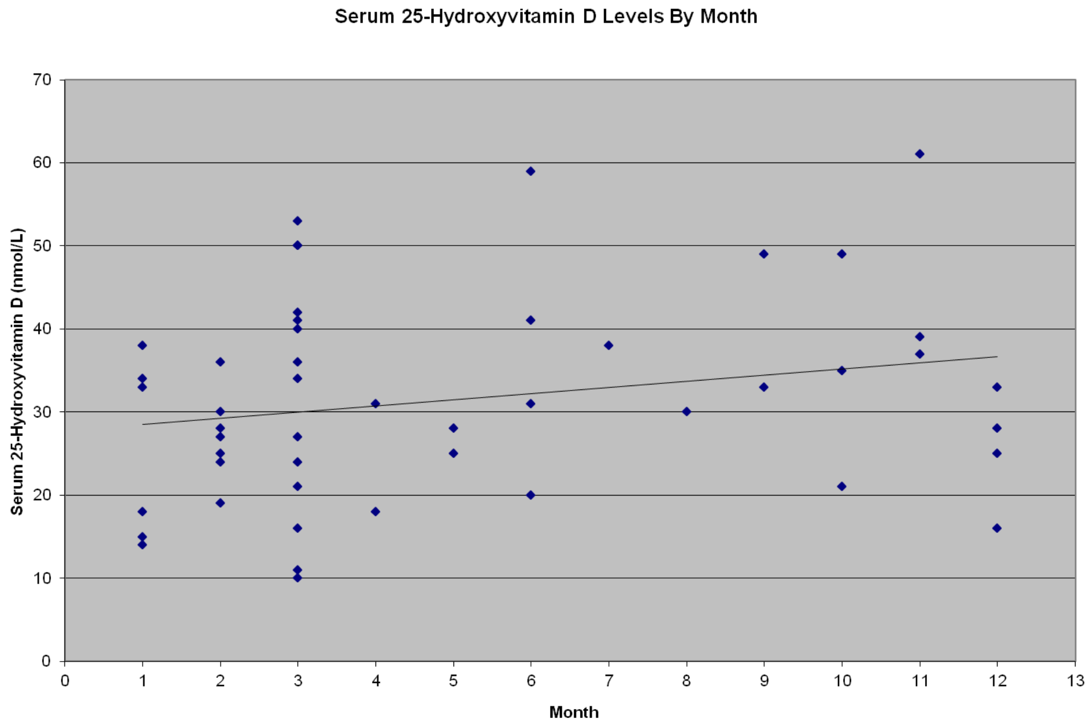
The second objective of this study was to determine if differences are present in deficiency rates between Alaska Native and non-Native participants. Using the Shapiro-Wilk Test of Normality, it was determined that 25(OH)D levels are distributed normally across the two racial groups included in the study (Alaska Native $p=0.846$ and White $p=0.694$). The researcher found no statistically significant difference between 25(OH)D levels in Alaska Natives and Whites. The average 25(OH)D in Alaska Natives was 30.9 ng/mL compared to 33.7 ng/mL in Whites ($p=0.298$) (see Figure 2). This study confirms that within this group there is no statistically significant difference between 25(OH)D levels of Alaska Native and non-Native participants, in spite of differing skin tones and suspected differences in dietary practices.

Figure 2.



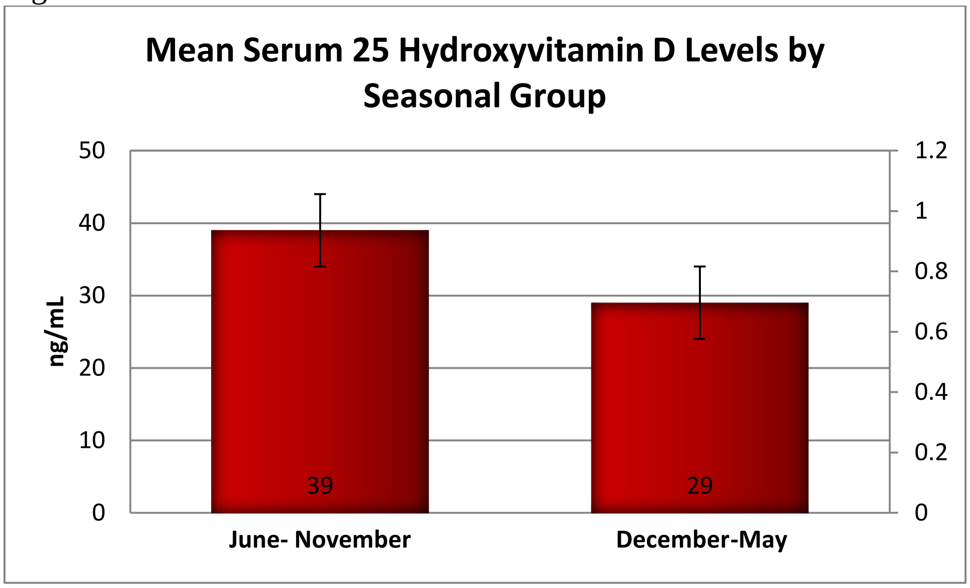
The third objective of the study was to identify seasonal trends in 25(OH)D levels in the region. Using a quadratic regression, there was a trend (p=0.075) toward lower levels from November through April, but overall the correlation between month drawn and 25(OH) levels was not statistically significant (p=0.223) (see Figure 3).

Figure 3.



When the researcher organized the data into two seasonal groups (December-May [winter/spring] and June-November [summer/fall]), the mean 25(OH)D difference was significantly different, as determined by independent samples t-test (p=0.007). The mean 25(OH)D value was 39 ng/mL in those drawn between June-November, as compared to 29 ng/mL for those drawn between December-May (see Figure 4). The data from this study do support the hypotheses that 25(OH)D insufficiency and deficiency are prevalent year-round and that statistically significant differences exist between seasons.

Figure 4.



The results of this research provide additional insight into the prevalence of 25(OH)D deficiency in rural, southwest Alaska both among Alaska Natives and Whites alike.

Study Limitations

A weakness of the study is that since the researcher did not use patient identifiers, an individual patient may have been tested more than once within the data collection period. There are two pairs of matching dates of birth included in the data set. An additional weakness of the study is that dietary intake or supplementation data were not available to correlate the vitamin D intake with serum 25(OH)D levels. Although salmon, one of the highest vitamin D food sources, is a staple food for nearly all in the region (typically eaten multiple times daily), a protective effect of eating a subsistence diet could not be identified or disproven.

Chapter 5

Research Findings as Compared to the Overall Body of Research

The findings of this research project are very interesting when compared to previously conducted research, particularly in the state of Alaska. In the laboratory record review conducted in Alaska Natives in the Ketchikan Native Indian Community of southeastern Alaska (21), 11% of those evaluated had a 25(OH)D level in a normal range (defined as 32 ng/mL) as compared to 51% of those evaluated in the Bristol Bay region in the southwestern part of the state. Although researchers selected a slightly higher threshold (by 2 ng/mL) in the Ketchikan study, the researcher noted a significantly higher 25(OH)D insufficiency/deficiency rate in that region of the state. Potential influences that may contribute to the lower 25(OH)D levels in Ketchikan may include significantly higher level of annual precipitation (leading to potentially lower exposure to UVB rays) and more diversity in the types of fish found in the region (which include salmon, halibut, yellow-eye or red snapper, ling cod, Pacific cod, and various types of rockfish, many of which contain low levels of vitamin D_3) as compared to the Bristol Bay region's lower precipitation and predominantly salmon-based diet. The researcher did not have dietary data available to further explore the vitamin D_3 intake differences between the two regions.

As compared to the other vitamin D research at high northern latitudes, results from this research project also showed higher sufficiency rates (51%) than found in other studies, which ranged in sufficient 25(OH)D levels from 7-41% of the populations studied. Of the seven key studies evaluated, three of the studies used 80 nmol/L as the threshold for sufficiency, three used 75 nmol/L and one used 50 nmol/L (9,15,22,25,26,27,28). Of the three studies with the higher threshold for sufficiency (80 nmol/L), sufficient levels of 25(OH)D were found in 10.3-31.8% of subjects (10,22,26). This is a significantly lower sufficiency rates and is not likely due to the 5 nmol.L difference in established cut off value.

Of the three studies that used the same threshold for sufficiency (75 nmol/L) as was used in this project, the rates of sufficient levels of 25(OH)D were 7% (15), 59.7% (25), and 69.3% (27) as compared to the sufficiency rate of 51% in this project (see Table 1). Some significant variations in the population groups studied were noted.

Table 1.

Research Comparison Utilizing the 75nmol/L Threshold					
Research Study:	**Latitude:**	**Gender:**	**Ethnicity:**	**Age:**	***Rate of Sufficient 25(OHO)D Levels**
Current Study	55.91-59.98˚N	12 males (25%) 36 females (75%)	Categorized by White and Alaska Native	Adults age 18 years and older (average age56 years)	51%
Gagnon et al.	45˚N	153 females (100%)	Caucasian	Adults age 18-41 years	69.3%
Greene-Finestone et al.	43.65-52.13˚N	577 males (30%) 1,335 females (70%)	Categorized by White and Other (93.1% of males and 96.4% of females were White)	Adults age 35 years and older (highest percentages of subjects were 51-70 and over 70 years)	59.7%
Gozdzik et al.	51.26˚N	49 males (46%) 58 females (54%)	Categorized by Caucasian, East Asian and South Asian	Adults age 18-30 years	7%

*Each of the studies included in the chart use the 75 nmol/L threshold to define sufficiency.

The most dramatic difference between the current study and the study with the highest sufficiency rate (27) is the month drawn. Gagnon et al. included only young females in their study. Younger individuals tend to have higher 25(OH)D levels (15), but women's levels tend to be slightly lower than males. The impact of these two factors together is not likely to have had a significant impact on overall levels in either direction. The most likely contributor to the difference in sufficiency rate between the current study and Gagnon et al. is that in the latter, 25(OH)D levels were checked only during the summer months (May-September). The majority of the levels (56.9%) were checked during September. In that study, lowest levels during the summer months were in May, when only 3.3% of the participants had their levels checked (27).

A comparison of the current study results and the study by Greene-Finestone et al. (25) showed very similar population groups. Though younger individuals were included in both studies, the majority of individuals in both studies were above 50 years of age. In the Canadian study, the gender distribution was also similar to the current study. The Canadian study also contained predominantly Caucasian individuals. The current study included both Alaska Native and White individuals, but as no statistically significant difference was found between the two, this does not present a significant variable difference between the current study and the study by Greene-Finestone et al. Monthly distribution of deficient results were shared in the Canadian study but the distribution of how many actual labs were obtained per month is unknown from the results presented. Therefore, no conclusions can be drawn about whether or not the spread of 25(OH)D levels is skewed towards any certain month/months. One strong determinant for sufficient levels is 25(OH)D supplementation. In the Canadian study, it was noted that 38.7% of males and 57.5% of females supplemented their diet with Vitamin D (25). Though the researcher did not obtain supplementation information in the current study, due to the lack of access to supplementation in most remote village settings, the researcher suspects that supplementation rates in rural Alaska are much lower than what was found in the Canadian study.

In the study conducted in Toronto by Gozdzik et al., which also used the same sufficiency cutoffs as the current study, a dramatic difference in sufficiency rate was noted (15). From the gender distribution and age of participants, it was anticipated that higher sufficiency rates would have resulted as compared to the current study. In fact, the sufficiency rates were 44% lower in the Toronto study. The significant difference in population sampled was ethnicity. In the Toronto study, melanin levels were also sampled in the 32 European, 27 East Asian, and 31 South Asian participants groups (15). The mean 25(OH)D in the European ancestry group was 55.9 nmol/L as compared with 77.5 nmol/L in the current study. The East Asian group had a mean 25(OH)D of 34.5 nmol/L, and the South Asian group had a mean 25(OH)D of 30.5. The 25(OH)D levels in the three participant groups in the Toronto study demonstrated an inverse correlation between melanin and 25(OH)D levels. Another reason for the lower levels in the Toronto study is the month in which the researchers obtained the labs: for the current study, 25(OH)D levels were taken throughout the year whereas in the Toronto study, values were obtained in February or March only−months known to have the lowest exposure to sunlight.

For the study by Sullivan et al., which defined the cutoff for sufficiency at 50nmol/L (28), interestingly, the rate of sufficient 25(OH)D levels was 52% in spite of including only lean, adolescent females at 44 ºN (much lower than the study setting of 55.91-59.98 ºN). Statistically, higher levels of 25(OH)D are found in individuals who are leaner, adolescent, and female. The one factor that may have the greatest impact− ethnicity−was not reported in the study (28).

Although no significant monthly differences in 25(OH)D were noted in this study, when months were categorized by Winter/Spring and Summer/Fall (Dec-May and June-Nov), a significant difference was noted, consistent with patterns identified in the research (9,15,23,25-27) (see Table 2).

Table 2.

Research Evaluating Serum 25-Hydroxyvitamin D Levels by Month			
Research Study:	**Month Range of Serum 25-Hydroxyvitamin D Level**	**Rate of Sufficient 25(OHO)D Levels**	**Cutoff Value Defining Sufficiency**
Current Study	All months	51%	75 nmol/L
Gagnon et al.	May-September	69.3%	75 nmol/L
Greene-Finestone et al.	All months	59.7%	75 nmol/L
Gozdzik et al.	February-March	7%	75 nmol/L
Sullivan et al.	September and March	52%	50 nmol/L
Genuis et al.	All months (but with the highest percentages of samples December-May)	23%	80 nmol/L
Dalgard et al.	All months	10.3%	80 nmol/L

A seasonal trend was noted in all studies, with the lowest levels occurring in the spring and winter months. Of the seven studies that evaluated seasonal/monthly data, the study that included only winter data had the lowest sufficiency rate (15), and the study with the highest percentage of samples drawn in winter/spring had the next lowest sufficiency rate (26). The study with all samples drawn in summer/fall months had the highest sufficiency rate (27).

In the study by Dalgard et al., researchers did not provide data by month for an indepth analysis, but they did note in the study that sufficiency rates were highest in July and September. Only 22-24% of the participants, however, had their levels drawn during those months (9). The likely reason for the significant overall difference in sufficiency rates between the Dalgard et al. and the current study is the population age. Dalgard et al. evaluated 70-74-year-olds, which is significantly older than the average age of the current study participants (56 years). Age is a known factor for 25(OH)D deficiency (11).

Conclusions and Future Work

The results of this study clearly confirm a high prevalence of 25(OH)D deficiency in the peoples of southwest Alaska throughout the year. With a host of disease states that correlate with vitamin D deficiency, the need for further studies becomes more urgent.

Future regional studies are needed to provide answers for questions such as: how does the westernization of the diet of the peoples of southwest Alaska impact 25(OH)D levels as compared to those who consume a totally subsistence diet; what levels of supplementation are effective to prevent and treat hypovitaminosis D at high northern latitudes; and are there correlations between hypovitaminosis D and diseases/conditions seen at high rates in southwest Alaska (alcoholism, depression, suicide/suicidal attempts, infection rates for tuberculosis and other infectious disease rates, and early/severe dental disease)?

The opportunities to explore further the impact of vitamin D status on health abound in southwest Alaska and can establish useful information that may be applied to other populations living at high, northern latitudes.

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Appendix A: RPMS Data Access Sequence

The specific sequence of commands required to access the report is as follows:

Select RPMS Application: VGEN

What order would you like the items displayed in? P (Predefined Order)

Select visit list from: S (Search All Visits)

Enter beginning visit date for search: 04/01/2008

Enter ending visit date for search: 03/30/2011

Do you want to use a previously defined report: N (No)

Visit Selection Menu

Select Action: S (Select Items)

Which visit item: 151 (Lab Tests)

Enter lab tests: Vitamin

Click Return to see more.

Return again.

Choose 1-15: 11 Vitamin D, 25-hydroxy Total

Enter lab tests: ^ (to exit list)

Escape twice back to Visit Selection Menu

Select Action: Q (Quit item selection)

Choose type of Report: D (Detailed visit listing)

Print Item Selection Menu

Select item: S (Select item)

Which visit items: 6 (Sex)

Enter column width for Sex:

Total report width: Enter

Select Action: S (Select item)

Which visit items: 11 (Race)

Enter column width for Race: Enter

Total report width: Enter

Select Action: S (Select item)

Which visit items: 7 (Date of Birth)

Enter column width for Race: Enter

Total report width: Enter

Select Action: S (Select item)

Which visit items: 190 (Lab Tests and Results)

Enter column width for Date of Birth: Enter

Total report width: Enter

Escape. Enter.

Do you want to print all lab tests or just those you selected?

For this item: O (Only the ones selected)

Click Return to continue.

Select Action: Q (Quit this screen)

Sort Item Selection Menu

Select Action: S (Select item)

Sort visits by which of the above: Enter (automatically sorts by visit date)

Do you want a separate page for each visit date? N (No)

Would you like a custom title for this report? N (No)

Do you wish to save this search/print/sort for future use? N (No)

Select one of the following: E (Exclude demo patients)

Do you wish to: P (Print output)

Appendix B:

Serum 25-Hydroxyvitamin D Data by Gender, Date of Birth, Month and Ethnicity

	Gender	DOB	Race	25-OHD Level	Month Drawn
1	1	10/26/1955	1	38	1
2	1	3/11/1940	1	36	2
3	2	8/8/1944	2	19	2
4	1	5/2/1972	1	25	2
5	1	4/14/1934	1	27	2
6	1	10/28/1972	1	30	2
7	1	7/29/1956	1	28	2
8	1	7/4/1950	1	42	3
9	2	12/3/1935	1	24	3
10	1	8/30/1938	1	10	3
11	1	7/11/1939	2	50	3
12	1	11/16/1938	1	50	3
13	1	8/30/1938	1	11	3
14	2	6/27/1963	1	21	3
15	1	7/30/1939	1	36	3
16	1	9/2/1985	1	34	3
17	2	10/13/1954	1	27	3
18	1	8/30/1961	1	31	4
19	1	2/9/1965	2	18	4
20	1	1/18/1954	3	28	5
21	1	11/6/1967	2	25	5
22	1	8/23/1966	1	41	6
23	1	4/23/1965	1	59	6
24	2	12/29/1954	1	20	6
25	2	11/18/1939	1	31	6
26	1	9/30/1943	2	38	7
27	1	9/1/1957	1	30	8
28	1	6/17/1943	1	33	9
29	1	7/11/1939	2	49	9
30	1	1/12/1987	2	35	10
31	1	6/12/1960	1	21	10
32	2	4/22/1966	1	49	10
33	1	1/4/1939	1	37	11
34	2	6/28/1929	2	61	11
35	1	8/28/1954	1	39	11
36	2	7/27/1953	1	25	12
37	1	11/6/1988	1	16	12
38	2	8/26/1949	1	33	12
39	1	3/20/1940	2	28	12
40	1	1/9/1964	1	15	1

41	1	9/23/1953	1	18	1
42	1	11/23/1989	1	33	1
43	1	8/26/1955	2	34	1
44	1	5/11/1965	2	14	1
45	2	6/16/1942	1	24	2
46	1	9/3/1980	1	16	3
47	1	7/4/1950	1	53	3
48	2	2/28/1948	1	41	3
49	1	7/30/1939	1	40	3
	Female=1		AK Native=1		Jan=1
	Male=2		White=2		Feb=2
			Amer Indian=3		Mar=3
					Apr=4
					May=5
					June=6
					July=7
					Aug=8
					Sept=9
					Oct=10
					Nov=11
					Dec=12