Risk Factors for Osteoporosis in Alaska Native Women: A Cross-Sectional Survey

A Thesis

By

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Précis

Mitch Greenlick likes to say that a thesis should be a journey. This thesis certainly has been a journey, and a circuitous one at that. My first exposure to osteoporosis was about six years ago, while I was still working at the Reed College nuclear reactor. I got a call from Eric Orwoll asking me to test the calcium levels of mice that had been fed a special diet, and I spent several months stuffing frozen dead mice into the reactor to measure calcium levels. That experience ended my promising career as an animal researcher.

A few years later, Kelly Krohn emailed all medical students looking for someone to go to Alaska and study osteoporosis. Osteoporosis still interested me and this project didn't involve dead mice, so off I went. Like any small student project, it was unfunded at the start. Fortunately, Dr. Krohn and I were able to find enough funds to launch the project and sustain it to completion.

The original plan was for a small summer research project. I was to learn about field epidemiology, travel, and, I hoped, publish my research in a scientific journal. I visited some incredibly remote and beautiful places and met a lot of wonderful people. And, at the end of the summer I had some viable data.

A researcher can always collect more data. I found a high level of interest in both the health care providers and the patients I saw. The project kept growing and I returned to Alaska. This document describes my work and reports my findings. I hope it will prove useful in guiding the development of osteoporosis prevention programs for Alaska Natives.

Acknowledgements

Solo epidemiological research projects seldom happen now, and I am extremely grateful to the many people who helped me with this one. Unfortunately, it is not possible to list everyone individually. I apologize to those whose names I have omitted.

The nurses, health aides, and clerical staff at all of the clinics cited in this report deserve special recognition for their help in recruiting people to interview, finding space for me to talk with them, and making me welcome at the clinics. I am most indebted to the people in the communities I visited, both for their hospitality and also for participating in my study.

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Abstract

Objective: To estimate the prevalence of risk factors for osteoporosis in Alaska Native women.

Methods: This study is a cross-sectional convenience sample of patients from 17 clinics in Alaska. I interviewed subjects regarding dietary calcium, demographics, and risk factors for osteoporosis. I measured subjects' calcaneal bone density using quantitative ultrasound.

Results: I collected data from 452 women, 316 of whom were Alaska Natives. Risk factors for osteoporosis were highly prevalent. Many Alaska Natives were current smokers (45%) or former smokers (32%), and 45% had low bone density (t-score < -1.0). Total dietary calcium intake was lower than recommended (median=379 mg/day). Both current smokers (Odds Ratio (OR)=3.9, 95% Confidence Interval (95% C.I.)=1.8-8.4) and former smokers (OR=2.8, 95% C.I.=1.3-6.2) were significantly more likely to have low bone density than subjects who have never smoked. Chronic users of oral steroids were also significantly more likely (OR=4.7, 95% C.I.=1.8-12.0) to have low bone density than non-users of oral steroids.

Conclusions: Risk factors for low bone density and osteoporosis are prevalent in Alaska Native women. The number of Alaska Native women at risk for osteoporosis will increase during the next decade as the population ages. A comprehensive prevention program to reduce the prevalence of modifiable risk factors in this population is warranted.

Chapter 1 – Introduction

I examined the relationship between risk factors for low bone density and bone density measurements in Alaska Native women, and implemented a cross-sectional survey to evaluate a convenience sample of Alaska Native and non-native women age 20 years and over.

Osteoporosis

Osteoporosis is a disease in which the normal architecture of bone is disrupted and the matrix of bone is demineralized. In a healthy adult, two cell types with opposite functions are active in bone remodeling. Osteoblasts synthesize the organic components of the bone matrix; over time this matrix mineralizes. Osteoclasts, by contrast, break down or resorb bone (Junqueira, 1995). When this process is under normal homeostatic control, the amount of bone resorbed is roughly equal to the amount of new matrix formed. In osteoporosis, this balance is disturbed and osteoclasts resorb bone faster than osteoblasts can replace it. This disruption of remodeling eventually leads to lower bone mass and a change in bone architecture. These abnormalities reduce bone strength. As a result, people with osteoporosis are at increased risk for fractures. Most medical therapies for osteoporosis attempt to restore the balance between osteoclasts and osteoblasts by inhibiting the osteoclasts. More detailed discussions of the basic science of bone metabolism can be found in other sources (Favus, 1996; Riggs, 1995).

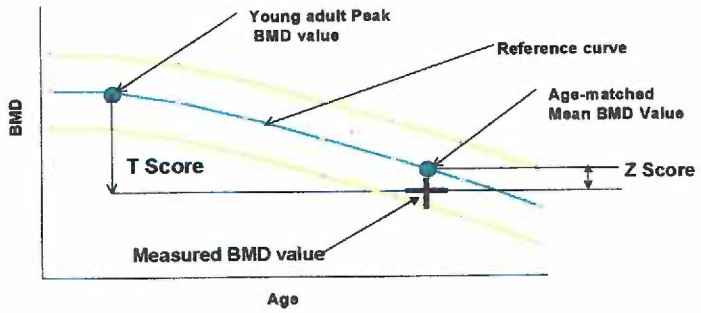
There are two categories of osteoporosis, primary and secondary (Rosenberg, 1994). Primary osteoporosis is associated with aging and becomes more prevalent at menopause. Secondary osteoporosis is caused by a factor other than age or menopause. Causes of secondary osteoporosis include Cushing's syndrome, Type 1 diabetes, alcohol abuse, lithium, anticonvulsants, malabsorption, and multiple myeloma.

Bone density changes with age in a characteristic pattern (Figure 1-1). Bone progressively increases in density from a state of minimal ossification in a newborn infant to peak density at

approximately thirty years of age. After age thirty, bone mass begins a slow and steady decline until menopause. After menopause, bone mass declines rapidly (Hansen, 1995). This postmenopausal bone loss is the reason osteoporosis prevention efforts are often focused on women at or just past menopause.

Osteoporosis is technically a histologic diagnosis made using a biopsy sample. A biopsy can detect both a decrease in ossification and interruptions in the normal cross-linked structural network of bone (Recker, 1996). In practice, biopsy is very rarely used to make a diagnosis; various bone density measurement techniques are used instead. Bone density measurements are non-invasive and are almost as accurate as more invasive techniques in detecting osteoporosis.

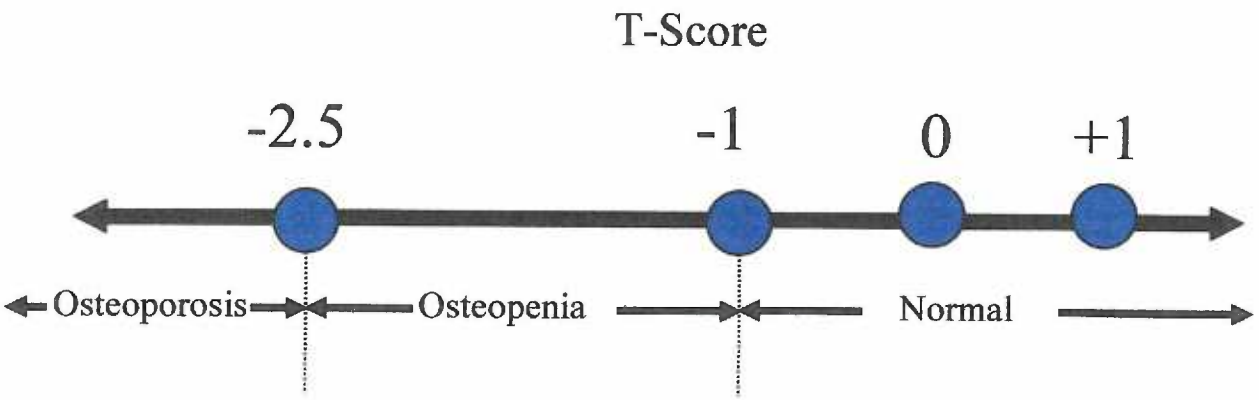
Figure 1-1 Population Mean Bone Density vs. Age with 2.5 Standard Deviation Confidence Limits



Bone density measurements are interpreted in three ways, as g/cm^2, as a t-score, and as a z-score. A t-score is the number of standard deviations from the mean density of young, normal, sex-matched individuals. A z-score is the number of standard deviations from the mean density for sex and age-matched individuals. The World Health Organization (W.H.O.) developed the most widely accepted criteria for classifying t-scores based on measurements taken at the femoral neck or lumbar spine (Kanis, 1994). Under W.H.O. criteria (Figure 1-2), a t-score greater than -1.0 is normal. A t-score between -1.0 and -2.5 is classified as osteopenia, or low bone density.

A score of less than -2.5 is classified as osteoporosis. These criteria apply only to measurements taken at the femoral neck or lumbar spine.

Figure 1-2 Graphical Depiction of World Health Organization Classification of T-scores



The major health consequence of osteoporosis is increased risk of fracture. A consensus panel study estimated that 90% of hip and spine fractures in elderly white women are attributable to osteoporosis (Melton, 1997). Hip and vertebral compression fractures are the most important morbidities associated with osteoporosis, but many other types of fractures are associated with this disease. A national study using Medicare data found 5.3 discharges per 10,000 person-years with a diagnosis of vertebral fracture for 65-year olds, and 47.8 discharges per 10,000 person-years with a diagnosis of vertebral fracture for 90-year olds (Jacobsen, 1992). Hip and vertebral fractures have enormous health and financial costs. One study estimated the annual U.S. expenditures to treat osteoporotic fractures to be $13.8 billion in 1995 (Ray, 1997). Hip fractures are associated with significant mortality. One study found 8% mortality at 3 months post-fracture (Cree, 2000). A nested-case control study found 20% mortality at one year for hip fracture patients at least 70 years old, with a crude relative risk of 2.4 compared to age-matched controls (Wolinsky, 1997). Hip fracture patients were also hospitalized or institutionalized more frequently after their fracture than age-matched controls. In addition to traditional outcome measures, all of these fractures can affect quality of life, activities of daily living, and body image.

Age-associated bone degeneration does not affect all women equally. The list of known and putative risk factors for osteoporosis is quite long. Risk factors identified by the National Osteoporosis Foundation are shown in Table 1-1 (National Osteoporosis Foundation, 1999). Other putative risk factors for osteoporosis are under investigation (Melton, 1996). More risk factors are likely to be identified in the future.

Table 1-1 Selected Risk Factors for Osteoporotic Fractures According to the National Osteoporosis Foundation

Non-modifiable Risk Factors	**Potentially Modifiable Risk Factors**
History of Fracture as an Adult History of Fracture as an Adult in a First Degree Relative Caucasian Race Female Sex Dementia Poor Health/Fragility	Current Cigarette Smoking Low Body Weight (<127 lb.) Estrogen Deficiency: -Early Menopause or Bilateral Oophorectomy -Premenopausal Amenorrhea (>1 year) Lifelong Low Calcium Intake Alcoholism Recurrent Falls Inadequate Physical Activity Impaired Eyesight Despite Adequate Correction

Motivation

The term "Alaska Natives" includes three culturally, linguistically, and genetically distinct groups: Eskimos, Indians, and Aleuts. These groups traditionally inhabited different regions of Alaska (Figure 1-3). Within each of these broad ethnic classifications exists substantial linguistic and cultural heterogeneity. The diversity of indigenous Alaskan people limits the value in attempting to make generalizations. Yet studying each subgroup also presents challenges because of the large number of subgroups and small population in some of the subgroups.

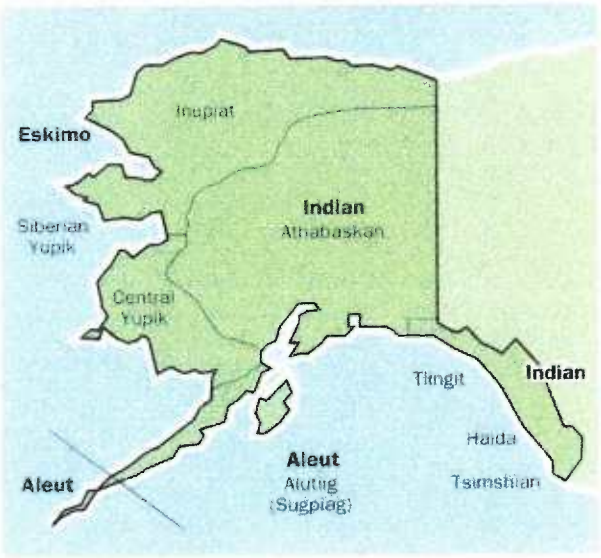
Health care resources for Alaska Natives have traditionally focused on treating acute medical conditions. Infectious diseases receive a high level of attention, an appropriate response to their high incidence. Botulism, for example, has an incidence of 10.7 per 100,000 person-years in Alaska, substantially higher than in any other state (Beller, 1998).

Chronic diseases are beginning to receive more attention as we recognize their increasing impact on Alaskan Natives. More Alaska Natives are living to the older ages associated with many chronic diseases. Osteoporosis is one such chronic disease that is likely to be increasing among Alaskan Natives, but few reports have been published on the subject. A keyword search of MEDLINE using *Alaska Natives* and *osteoporosis* or *bone density* for 1965 through 1999 records yields fewer than twenty articles. Specialized references also yield a small number of articles (Fortuine, 1993).

Some evidence suggests that Alaska Natives may have lower bone density than Caucasians. A study published by the International Biological Perspective found that Eskimo people had lower bone density than Caucasians and this was more pronounced in the elderly (Mazess, 1978). A small study by the same investigator found that Aleutian Islanders also have lower bone density than Caucasians (Mazess, 1985).

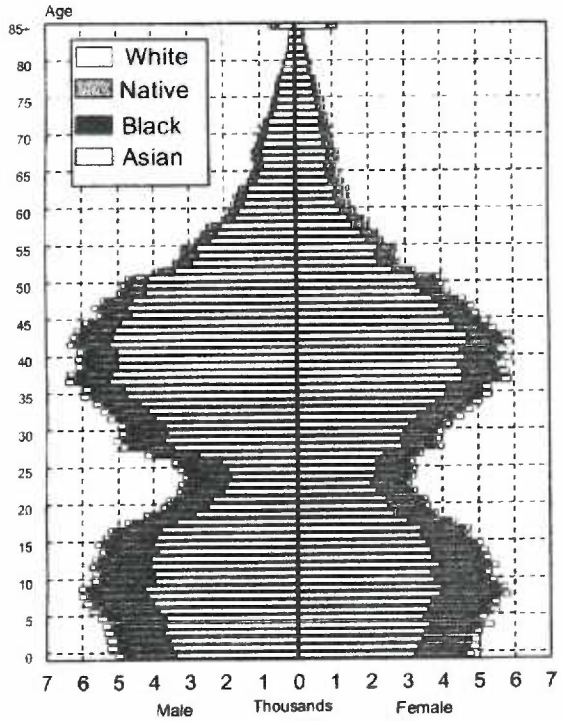
A large proportion of female Alaska Natives of the "baby boom" generation is nearing menopause. Figure 1-4 shows the age structure of the population of Alaska subdivided by race. Since osteoporosis is primarily a disease of postmenopausal women, osteoporosis will become an important issue in Alaska Native health care as life expectancy of Alaska Natives increases. Information about the distribution of risk factors in this population will be useful in planning prevention and intervention programs. My goal for this project was to provide an estimate of the prevalence of low bone density and the risk factors for low bone density in Alaska Natives.

Figure 1-3 Geographical Distribution of Alaska Natives by Tribal Grouping



Source: Wainwright, 1996

Figure 1-4 Alaska Population: Age and Sex Distribution by Race



Source: Alaska Department of Labor, Research and Analysis Section, Demographics Unit.

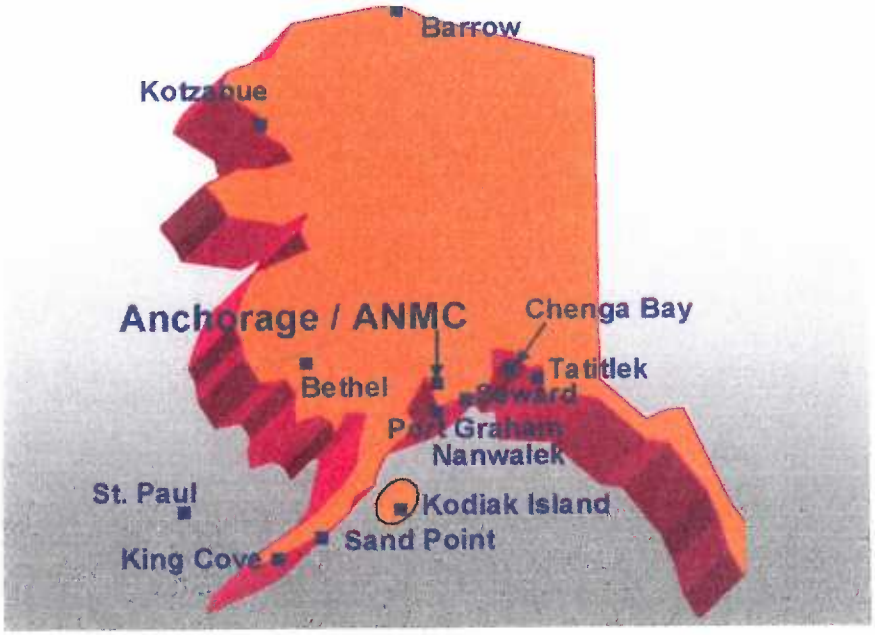
Chapter 2 – Methods

This study is a cross-sectional prevalence survey of Alaska Native women based on a convenience sample of patients at 13 sites in Alaska and data collected in Alaska from July 7, 1998 to August 31, 1998 and from August 4, 1998 to September 21, 1999.

Subject Recruitment

I recruited subjects at a total of 17 Indian Health Service (I.H.S.) and tribal clinics in 13 municipalities (Figure 2-1). Clinics were selected as a convenience sample, rather than a random sample. I chose clinics using the following four criteria: 1) approval of local tribal authority, 2) willingness of at least one health care provider to follow up on patients at that clinic, 3) the availability of space at the clinic for subject interviews, and 4) the costs associated with the clinic visit were within the study budget. I attempted to maximize the geographical diversity of study sites as permitted by the site selection criteria. I recruited subjects among patients receiving care from the following clinics: five clinics at the Alaska Native Medical Center (ANMC) (Family Medicine, Diabetes, Internal Medicine, Orthopedic, and Women's Health) and clinics at King

Figure 2-1 Locations of Study Sites in Alaska



Cove, Kodiak, Sand Point, Tatitlek, Nanwalek, Port Graham, St. Paul, Seward, Chenega Bay, Barrow, Bethel, and Kotzabue. I also recruited subjects among the Alaska Native and non-native staff of each clinic. Staff members were recruited either by email (ANMC) or by word of mouth.

I included only females who were at least 20 years old. Potential subjects were excluded if they failed to complete the study protocol or if no valid density measurement could be taken. Clinic staff conducted the initial recruitment of subjects, either face-to-face or by telephone. At one village, the local radio station broadcast a public service announcement to recruit subjects. All recruiters explained that participation in the study was entirely voluntary and that there was no cost to the subject. No record was kept of the number of potential subjects who declined to participate at initial recruitment. When subjects presented themselves for the study interview, I again explained the voluntary nature of the study and offered to answer questions about the study. I gave subjects still willing to participate in the study a consent form (Appendix A). For those who refused to participate at the interview stage, I recorded the reason for refusal.

Data Collection Methods

After obtaining consent, I interviewed all of the subjects using a closed-response questionnaire (Appendix B) at 15 of the clinics. At two clinics (Port Graham and Nanwalek) the subjects completed the questionnaire themselves.

During the interview, I entered the subject responses directly into database software (Epi Info 6.04b, CDC, Atlanta, GA) using a portable computer. Due to time constraints, subjects in Nanwalek and in Port Graham filled out paper versions of the questionnaire while waiting to see me. In these cases, I verified the answers for a sample of questions during the interview. These paper questionnaires were entered into the database at a later time. With each subject, I obtained questionnaire data before the bone density measurement was taken.

I used the questionnaire data to estimate dietary calcium. During the interview, I asked subjects how many servings per week in the last year on average they ate a given food item. Estimating a serving size for each food, I determined the amount of calcium per serving from tables of nutrient values (Appendix C) and used these values to calculate calcium intake. The calcium measures are described in the Definitions section of this chapter.

I measured calcaneal bone density using a Sahara Clinical Bone Sonometer (Hologic, Inc., Waltham, MA), following the recommendations of the manufacturer for the use of this device (Appendix D). The right calcaneus was measured unless the subject had a history of any injury to the right foot or ankle (except sprains, bunions, or fracture of the metatarsals or phalanges). If the first measurement was not satisfactory, I repeated the measurement up to four times. If none of these repeated measurements passed an automated reliability test, the mean of the multiple measurements was used as that subject's bone density for the statistical analysis. In some cases, no numerical value for the measurement was obtainable from the subject; these subjects were excluded from the analysis (n=6). At the end of the study visit, I provided the subjects with reports of their density results (Appendix E) and encouraged them to discuss the results with their health-care provider.

I completed a standard Indian Health Service Form 803 ambulatory encounter record for every study visit. This record included the subject's t-score, estimated bone density, broadband ultrasound attenuation, speed of sound through bone, and appropriate notations to aid the interpretation of the results. Records completed in 1999 were coded as a telephone visit to prevent inadvertent billing for participation in the study by the hospital. My supervising physician at each clinic read and signed the encounter records, which I placed in the subject's medical chart along with a photocopy of the signed consent form.

Data Security and Quality Control

I verified the questionnaire responses by comparing selected response variables with the data in individual electronic medical records. Records for most subjects were available via direct dial-up access to the computer system at the Alaska Native Medical Center. I determined from the medication record which subjects were taking the following drugs: alendronate, etidronate, estrogen, estrogen/progesterone mixtures, calcium supplements, corticosteroids, calcitonin, raloxefene, tamoxifen, phenobarbital, phenytoin, and carbamazepine. Birth date and diabetes diagnosis were also confirmed by electronic medical record.

I encrypted data files containing identifying information during the course of this study when they were not in use. Identifying information such as name and medical record number were stripped from the electronic data files at the end of the data analysis to prevent any accidental disclosure of confidential information.

Definitions

The following definitions were used for the purposes of this study:

Alaska Native: Any person who identified herself as an Alaska Native or American Indian. This included American Indians living in Alaska but originally from other states.

Clinic staff: Any person who worked at the clinic or hospital, including cleaning and kitchen staff.

Salpingo-oophorectomy: Any subject who stated that 1) both of her ovaries were removed, 2) one ovary was removed, or 3) a hysterectomy had been performed but the subject was uncertain if her ovaries were still intact was considered to have had a salpingo-oophorectomy.

Calcium Supplement: Any dietary supplement containing calcium, including multivitamins containing calcium.

Diabetic: Any person who identified herself as a diabetic. Gestational diabetes mellitus and insulin resistance were not considered diabetes for this study. Subject's diabetes status was confirmed as part of the review of the electronic medical record.

Menopause: Any woman who stated that she had started or completed menopause was considered to have started menopause. Also, any woman who stated she had surgical menopause was considered to have started menopause.

Total Daily Dietary Calcium: The number of servings consumed per week of each food multiplied by the amount of calcium per serving of that food and divided by seven.

Total Daily Dairy Calcium: The number of servings consumed per week of each dairy food multiplied by the amount of calcium per serving of that food and divided by seven.

Total Daily Calcium from Supplements: The number of days per week supplements were used multiplied by the dose of calcium and divided by seven.

Total Daily Calcium Intake: The sum of total dietary calcium and daily calcium from supplements. (This was the primary calcium measure used in the statistical analysis.)

Statistical Methods

Power Analysis

I performed an estimated power analysis using an estimated prevalence of osteopenia in each group. The minimum odds ratio to be detected was assumed to be 2.0, alpha was set to 0.05, and power (1-Beta) to 90% (see Table 2-1). Calculations were performed using the method described by Fleiss (1981) using Epi Info. The comparison group consists of non-native people served by the Indian Health Service and/or the native corporations, which serve relatively few non-natives. The non-natives they do serve are mostly clinic staff and their dependants. Given the small number of non-native people served by the I.H.S. and the focus of this investigation on

Alaska Natives, I assumed that 1/3 of the subjects would be non-natives. These results led me to choose a t-score of –1.0 as the cutoff for normal bone density.

Table 2-1 Estimated Sample Size Given Different Assumptions of Prevalence and Bone Density Cut Point for Alaska Natives vs. Non-Natives

Criteria	# Non-Native: #Native	Native Prevalence	Non-Native Prevalence	Estimated # Native	Estimated #Non-Native	Total Subjects
t-score <= -1.0	1:2	0.44	0.21	129	64	193
t-score <= -2.5 low prevalence	1:2	0.10	0.005	85	170	255
t-score <= -2.5 high prevalence	1:2	0.10	0.05	368	735	1,103

Assumptions: Alpha = 0.05, Beta = 0.10, Minimum detectable odds ratio change = 2.0

Univariate Analysis

I used SPSS 9.0 (SPSS, Inc., Chicago, IL) and Excel 97 (Microsoft, Inc., Redmond, WA) to perform the statistical analysis. The major variables of interest are shown in Table 2-2. Bone density was dichotomized into low density (t-score <-1.0) and high density (t-score ≥ -1.0). Dichotomous variables were examined by cross-tabulation with normal vs. abnormal bone density. Likelihood ratio Chi square statistics and odds ratios (ORs) were calculated for each of these variables. For continuous variables, I generated descriptive statistics and histograms. In some cases, I assessed the normality of continuous variables with a Kolmogorov-Smirnov test. I used the Mann-Whitney U test to compare pack years of smoking between Alaska Natives and non-natives.

Regression Modeling

I developed a set of logistic regression models that dichotomized subjects by bone density to high density and low density using the same criteria used in the univariate analysis. I used a method, modeled after that of Hosmer and Lemeshow (1989), to select variables for the multivariate analysis. The univariate likelihood ratio Chi squared results were used to screen

potential variables in the model. The p-value for these tests had to be 0.25 or less unless the variable was known from other sources to have a relationship with osteoporosis. These potential variables are shown in Table 2-2. I used the gamma statistic (Agresti, 1990) to measure the relatedness of binary variables with one another. Interactions were tested using both forward and backward stepwise likelihood ratio procedures. I assessed the fit of the model by plotting the predicted probabilities from the final models against Cook's distance and separately plotting predicted probabilities against the Pearson residuals (Appendix C). Three individual cases that were outliers on these plots and that changed the estimated odds ratios of the model were removed from the final analysis. I also used the Hosmer and Lemeshow goodness of fit test and Nagelkerke R^2 as formal tests of goodness of fit.

I developed two sets of models using the above procedures; one set using the data from Alaska Natives only and one set using the data from all study subjects.

Table 2-2 Candidate Predictor Variables and Variable Type, Tested for Use as Covariates in the Statistical Multivariate Analysis

Predictor	**Variable Type (units)**
Dietary Calcium Intake from Dairy Products and Supplements	Continuous (mg/day)
Calcium Supplementation	Dichotomous
Clinic Staff vs. Non-Staff	Dichotomous
Native vs. Non-Native	Dichotomous
History of Ankle Fracture	Dichotomous
Physical Exercise of at Least Twenty Minutes per Day 3x per Week	Dichotomous
Oral Corticosteroids for at Least Six Weeks at Any Time in Their Life	Dichotomous
Ever Having Smoked Tobacco, Currently Smoking Tobacco, Not Ever Smoking Tobacco	Dichotomous
Cigarette Consumption History	Continuous (packs/day and pack years)
The Use of Hormone Replacement Therapy	Dichotomous
The Use of Oral Contraceptive Pills	Dichotomous
Presence of Diabetes	Dichotomous
Anchorage vs. Other Sites	Dichotomous
Age at Time of Study Measurement	Continuous (years)

Chapter 3 – Results

Subjects took 15-60 minutes to complete the study interview and density measurement. I interviewed and measured a total of 483 potential subjects; of those 452 (94%) met all inclusion criteria and provided complete data for the purposes of statistical analysis. The geographical distribution of study subjects is shown in Table 3-1. Sixteen persons declined to participate in the study. Three persons declined because they felt they were too young to have a bone density measurement, three others declined because they did not want to answer study questions, three did not want to find out if they had cancer, and two did not wish to potentially lose their insurance coverage. The remaining five declined to give a reason for not participating in the study.

I reviewed the medical records of 401 (89%) subjects approximately nine months after the last study visit. Two persons were deceased at the time of the review. There were 17 errors in birth dates found in the 401 birth dates reviewed. I personally entered all of the data, so my error "rate" per keystroke, at 6 keystrokes per birth date, was 0.8%. Only five of these erroneous birth dates differed by a year or more from the correct birth date. The medical record agreed closely with the questionnaire data. The study questionnaire identified diabetics correctly 98% of the time, oral steroid users 93% of the time, and hormone replacement therapy users 82% of the time. Three subjects were taking alendronate, four, tamoxifen, and one, calcitonin.

The primary study analysis considered risk factors for low bone mass in Alaska Natives (N=316). Risk factors for osteoporosis were prevalent in the study population (Table 3-2). Smokers made up 35% of all subjects and 45% of Alaska Natives. Nearly one in five Alaska Natives reported having broken a foot or ankle at some time in their lives. Ex-smokers comprised 30% of all subjects and 32% of Alaska Natives. The median tobacco consumption history was eight pack-years. Most Alaska Native participants (60%) had started menopause and 9% had taken at least one six-week course of oral steroids during their lifetimes. Some protective factors

were also prevalent in the study population. Approximately one-third of the Alaska Natives were taking hormone replacement therapy, and 49% of Alaska Natives and 61% of non-natives stated that they exercised at least three times a week for 20 minutes or more per day.

The median total calcium intake of Alaska Natives was 379 mg/day, and 63% of Alaska Natives reported that they took some type of dietary supplement containing calcium. The calcium consumption of all subjects combined was higher (Table 3-3) than that of Alaska Natives alone. This was due to much higher calcium consumption by non-native study participants.

Low bone density was highly prevalent in the study population with 45% of Alaska Natives and 22% of non-natives having a t-score less than -1.0. The mean t-score of Alaska Natives was -0.9 compared to an average t-score of +0.2 for non-natives (Table 3-4).

Many of the risk factors were significantly associated with low bone density in the univariate analysis. Crude odds ratios for Alaska Natives and for all subjects appear in Table 3-5. Fracture history, steroid use, menopause, hormone replacement therapy, current smoking, former smoking, and age were all positively associated with low bone density for Alaska Natives. Exercising three times per week for at least 20 minutes was negatively associated with low bone mass. Variables, which did not pass the screening criteria for the multivariate model, were 1) clinic staff vs. non-staff, 2) diabetics vs. non-diabetics, and 3) Anchorage vs. all other sites.

Gamma coefficients for selected variables are shown in Tables 3-6 and 3-7. Diabetes was strongly associated with the subject having started menopause (gamma=0.68). The use of hormone replacement therapy was also strongly related with menopausal status (gamma=1.0). No other variables were strongly related with one another.

Several risk factors were significantly associated with low bone density in the multivariate model (Table 3-8). In the analysis of Alaska Natives, both current smokers and

former smokers were more likely to have low bone density compared to those who had never smoked. Oral steroid use was also associated with low bone density (Table 3-8).

The multivariate analysis of all subjects combined showed similar results (Table 3-9). Smoking history and oral steroid use were less strongly associated with low bone density than in univariate models. A composite variable created by combining history of hip, ankle, or foot fracture and history of osteoporosis diagnosis was significantly associated with low bone density. Alaska Natives were almost twice as likely to have low bone density than non-natives (Table 3-9).

I eliminated several variables from the multivariate analyses during statistical screening. Variables were screened to test a theoretical relationship with bone density and to test for a confounding effect. Diabetes was evaluated because several of the field visits were made with the diabetes team. As a result, diabetics were over-represented in the study. Diabetic status did not meet the statistical screening criteria for inclusion in the model; I concluded it was not an important source of confounding and eliminated it from the multivariate analysis. Two other variables were eliminated from the multivariate analysis by this process; being a health care worker versus all other subjects and being a subject in Anchorage versus other sites. Hip fracture, foot fracture, and history of osteoporosis diagnosis were rare enough events that I chose to combine them into a single variable in the primary analysis.

The variables that passed the initial screening were included in the initial multivariate logistic regression models. I included several theoretically important variables in the final multivariate model even though they were not statistically significant in that model. Hormone replacement therapy use and menopause were highly related. When two strongly correlated variables are included in the same multivariate statistical model they will often dilute each other's association with the dependant variable. Normally two variables that are this strongly correlated would not be placed in the same multivariate model. In this case, they are both important factors

in explaining the risk for low bone density. Hormone replacement is positively associated with low bone mass in the univariate analysis. This is true in the multivariate analysis until age and/or menopause are added to the model.

Results from the final logistic regression model for Alaska Natives are shown in Table 3-8. All of the variables in this model were tested for interactions with age. The age-steroid interaction was significant. The age-smoking and age-history of fracture interactions approached significance. I performed fit diagnostics, as described in the methods section, on a model with all of the variables in Table 3-9, and the age-steroid interaction term. I removed three cases that were highly influential. With the removal of these cases, the age-steroid term became unambiguously non-significant ($p=0.4$) and the age-smoking term became statistically significant. Goodness of fit diagnostics with the age-smoking term was not as satisfactory. The Pearson residuals demonstrated greater variance (Figure A-4). I decided that the best fit and most interpretable model was a model without interaction terms. It is likely that effect modification exists between two or more variables in the model, but the study sample was too small to draw meaningful conclusions about the existence of specific relationships. Estimated odds ratios for specific age groups calculated using the logistic regression model shown in Table 3-8 appear in Table 3-10.

Table 3-1 Frequency Distribution of Study Subjects by Study Site, Percent of Total Number of Subjects from Each Site and Percent of Population Sampled at a Given Site

Site	Number of Subjects	Percent of Total Subjects	Population[1]	Percent Population Sampled
Anchorage	184	41	258,752	0.07
Barrow	38	8	4,397	0.86
Bethel	3	1	5,463	0.05
Chenega Bay	10	2	35	29
King Cove	7	2	703	1
Kodiak	23	5	6,859	0.34
Kotzabue	21	5	2,964	0.71
Nanwalek	20	4	180	11
Port Graham	31	7	190	16
Sand Point	18	4	830	2
Seward	64	14	3,040	2
St. Paul	19	4	761	3
Tatitlek	14	3	110	13
Total	452	100	284,284	0.16

[1]Estimate from Williams, 1999

Table 3-2 Percent of Alaska Native and Non-Native Subjects with Selected Characteristics

Characteristic	All Subjects N=452	Native N=316	Non-Native N=136	P-value[1]
Current Smokers	35.2%	45.3%	11.8%	<0.001*
Former Smokers	30.3%	31.6%	27.2%	0.343
History of Ankle or Foot Fracture	18.4%	19.0%	16.9%	0.599
Oral Steroid Use	8.2%	8.9%	7.4%	0.592
Started Menopause	58.9%	60.4%	55.2%	0.295
Hormone Replacement Therapy	33.8%	31.3%	39.7%	0.086
Exercise 3x/Week>=20 min.	52.8%	49.4%	61.0%	0.022*
Diabetic	10.0%	10.4%	5.9%	0.108
History of Hip Fracture	1.5%	1.9%	0.7%	0.325
Clinic Staff	35.2%	20.3%	69.9%	<0.001*
Low Bone Density	30.3%	45.3%	22.1%	<0.001*
Calcium Supplement Use	58.0%	56.0%	62.5%	0.198
History of Hip, Ankle, or Foot Fracture, or Osteoporosis Diagnosis	24.6%	26.0%	21.3%	0.290

*Significant for $p<0.05$

[1]Native compared with non-native using likelihood ratio Chi squared test

Table 3-3 Descriptive Statistics of Dietary Calcium Intake Estimates for All Subjects and for Alaska Natives

Calcium Measure	All Subjects Mean Median (25-75 percentile)	Alaska Natives Mean Median (25-75 percentile)	p-value[1]
Dairy Calcium (mg/day)	231 140 (39-359)	185 107 (24-278)	<0.001*
Total Dietary Calcium (mg/day)	360 272 (110-529)	306 198 (94-441)	<0.001*
Calcium from Supplements (mg/day)	309 0 (0-257)	298 0 (0-200)	0.028*
Total Calcium Intake (mg/day)	669 471 (191-916)	604 379 (161-746)	<0.001*

* $p<0.05$
[1]Mann-Whitney U test, Alaska Natives vs. Non-Natives

Table 3-4 Summary Statistics of Age, T-score, Estimated Bone Density Characteristics and Pack Years of Smoking for Study Subjects

Characteristic	All Subjects	Alaska Natives	Non-native	p-value
Age[1] (years)	49±12	50±13	51±9	0.209[2]
t-score	-0.6±1.2	-0.9±1.2	0.2±1.2	<0.001*[2]
Bone Mineral Density (g/cm^2)	0.507±0.136	0.483±0.137	0.595±0.133	<0.001*[2]
Median Pack-Year Smoking History	4	8	0	<0.001*[3]

* $p<0.05$
[1]Age ± standard deviation
[2]Independent samples t-test
[3]Mann-Whitney U test

Table 3-5 Univariate Analysis of Subject Characteristics Tabulated by Abnormal vs. Normal Bone Density[1]

Variable	All Subjects Crude OR	All Subjects 2 sided p-value	Alaska Native Crude OR	Alaska Native 2 sided p-value
Alaska Native vs. Non-Native	2.9 (1.8-4.6)	<0.001*	N/A	N/A
History of Foot or Ankle Fracture	1.7 (1.0-2.7)	0.042*	2.3 (1.3-4.1)	0.005*
Exercise at Least 3x per Week	0.5 (0.4-0.8)	0.001*	0.6 (0.4-1.0)	0.016*
Diabetic	1.4 (0.8-2.7)	0.270	1.3 (0.6-2.7)	0.446
Oral Steroid Use	1.9 (1.0-3.7)	0.061*	2.8 (1.2-6.4)	0.012*
Started Menopause	3.7 (2.4-5.6)	<0.001*	4.3 (2.7-7.0)	<0.001*
Hormone Replacement Therapy	1.4 (1.0-2.1)	0.085*	1.8 (1.1-3.0)	0.013*
Calcium Supplement Use	1.1 (0.8-1.6)	0.593	1.4 (0.9-2.3)	0.174*
History of Hip Fracture	10.0 (1.2-84.0)	0.009*	6.2 (0.8-54.0)	0.051*
Clinic Staff vs. Non-Staff	0.6 (0.4-0.8)	0.002*	0.8 (0.5-1.4)	0.404
Current Smoker vs. Never Smoker	2.6 (1.7-4.3)	<0.001*	2.3 (1.3-4.3)	0.005*
Former Smoker vs. Never Smoker	2.1 (1.3-3.4)	0.004*	2.2 (1.2-4.2)	0.012*
History of Osteoporosis Diagnosis	3.4 (1.4-8.3)	0.004*	2.8 (1.0-7.5)	0.036*
History of Hip, Ankle, Foot Fracture, or Osteoporosis Diagnosis	2.3 (1.5-3.5)	<0.001*	2.7 (1.6-4.6)	<0.001*
Anchorage vs. All Other Sites	1.2 (0.8-1.8)	0.383	1.0 (0.6-1.6)	0.969
Age in 5-Year Intervals[2]	1.4 (1.3-1.5)	<0.001*	1.4 (1.3-1.6)	<0.001*
Calcium Intake in mg	1.0 (1.0-1.0)	0.438	1.0 (1.0-1.0)	0.061*
Pack-Years of Smoking History	1.3 (1.2-1.4)	<0.001*	1.3 (1.1-1.4)	<0.001*

*$p \leq 0.250$ screening level for the multivariate model
[1]Abnomal bone density is defined as a t-score of –1.0 or less by calcaneal ultrasound
[2]Age is modeled as the number of 5-year intervals from age 30

Table 3-6 Gamma[1] Coefficients among Selected Study Variables as an Evaluation of Relatedness of Candidate Predictor Variables in a Multivariate Analysis for Alaska Native Subjects Only

Variable	Started Menopause Gamma (p-value)	Smoking Status[2] Gamma (p-value)	Hormone Replacement Therapy Gamma (p-value)
Started Menopause	N/A	0.062 (0.525)	1.0 (<0.001)*[3]
Hormone Replacement Therapy	1.0 (<0.001)*[3]	0.054 (0.577)	N/A
Oral Steroid Use	0.006 (0.975)	-0.159 (0.348)	0.268 (0.204)
Exercise at Least 3x per Week	0.076 (0.491)	-0.034 (0.701)	0.250 (0.029)
Smoking Status[2]	0.062 (0.525)	N/A	0.054 (0.577)
Clinic Staff vs. Non-Staff	0.013 (0.928)	-0.343 (0.002)	0.172 (0.250)
History of Hip, Ankle, Foot Fracture, or Osteoporosis Diagnosis	0.499 (<0.001)	0.219 (0.044)	0.296 (0.028)
Diabetes	0.688 (<0.001)*	-0.312 (0.018)	0.264 (0.178)
Calcium Supplement Use	0.160 (0.164)	0.078 (0.412)	0.166 (0.171)
Anchorage vs. All Other Sites	-0.224 (0.065)	0.293 (0.002)	-0.227 (0.075)

*Highly related (gamma > 0.6)
[1]Gamma is used to compare the relatedness of binary variables and is interpreted like a correlation coefficient
[2]Smoking status coded as an ordinal variable; 0=Never Smoker, 1=Former Smoker, 2=Current Smoker
[3]2x2 Table has one empty cell because no premenopausal women were taking hormone replacement therapy

Table 3-7 Gamma[1] Coefficients among Selected Study Variables as an Evaluation of Relatedness of Candidate Predictor Variables in a Multivariate Analysis for All Study Subjects

Variable	**Started Menopause Gamma (p-value)**	**Smoking Status[2] Gamma (p-value)**	**Hormone Replacement Therapy Gamma (p-value)**
Started Menopause	N/A	0.126 (0.108)	1.00 (<0.001)*[3]
Hormone Replacement Therapy	1.00 (<0.001)*[3]	-0.010 (0.896)	N/A
Oral Steroid Use	0.038 (0.825)	-0.120 (0.401)	0.301 (0.089)
Exercise at Least 3x per Week	-0.194 (0.040)	-0.186 (0.014)	-0.097 (0.330)
Smoking Status[2]	0.126 (0.108)	N/A	-0.10 (0.896)
Clinic Staff vs. Non-Staff	-0.051 (0.608)	-0.507 (<0.001)	-0.305 (0.002)
History of Hip, Ankle, Foot Fracture, or Osteoporosis Diagnosis	0.362 (0.001)	0.120 (0.191)	0.239 (0.036)
Alaska Native vs. Non-Native	0.108 (0.297)	0.646 (<0.001)*	-0.181 (0.091)
Diabetes	0.639 (<0.001)*	-0.085 (0.440)	0.282 (0.099)
Calcium Supplement Use	0.127 (0.188)	-0.051 (0.513)	0.149 (0.137)
Anchorage vs. All Other Sites	-0.221 (0.021)	0.302 (<0.001)	-0.214 (0.310)

*Highly Related (gamma > 0.6)

[1]Gamma is used to compare the relatedness of binary variables and is interpreted like a correlation coefficient

[2]Smoking status coded as an ordinal variable; 0=Never Smoker, 1=Former Smoker, 2=Current Smoker

[3]2x2 Table has one empty cell because no premenopausal women were taking hormone replacement therapy

Table 3-8 Predictors of Low Bone Density from a Multiple Logistic Regression Model for Alaska Native Subjects Only

Variable	Adjusted OR[1]	p-value[2]
Current Smoker vs. Never Smoker	3.9 (1.8-8.4)	<0.001*
Former Smoker vs. Never Smoker	2.8 (1.3-6.2)	0.010*
History of Hip, Ankle, Foot Fracture, or Osteoporosis Diagnosis	1.7 (1.0-3.1)	0.082
Age (5-year Increase)[3]	1.5 (1.3-1.8)	<0.001*
Hormone Replacement Therapy	0.6 (0.3-1.1)	0.119
Started Menopause	1.4 (0.6-3.1)	0.442
Oral Steroid Use	4.7 (1.8-12)	0.001*
Exercise at Least 3x per Week	0.7 (0.4-1.2)	0.184

*p<0.05
[1]All variables listed in the table are included in the multiple logistic regression model
[2]p-value by Wald Test
[3]Age is modeled as the number of 5-year intervals from age 30

Table 3-9 Predictors of Low Bone Density from a Multiple Logistic Regression Model for Non-Native and Alaska Native Study Subjects

Variable	Adjusted OR[1]	p-value[2]
Current Smoker vs. Never Smoker	2.3 (1.3-4.2)	0.004*
Former Smoker vs. Never Smoker	1.6 (1.0-2.9)	0.103
History of Hip, Ankle, Foot Fracture, or Osteoporosis Diagnosis	1.7 (1.0-2.8)	0.043*
Age (5-year Increase)[3]	1.4 (1.2-1.6)	<0.001*
Hormone Replacement Therapy	0.6 (0.3-1.0)	0.051
Started Menopause	1.7 (0.8-3.3)	0.148
Oral Steroid Use	2.2 (1.1-4.8)	0.037*
Exercise at Least 3x per Week	0.7 (0.4-1.0)	0.056
Alaska Native vs. Non-native	1.8 (1.1-3.1)	0.024*

*p<0.05
[1]All variables listed in the table are included in the multiple logistic regression model
[2]p-value by Wald Test
[3]Age is modeled as the number of 5-year intervals from age 30

Table 3-10 Estimated Odds Ratios for Low Bone Density by Age Group for Alaska Natives, Based on the Alaska Natives only Multiple Logistic Regression Model

Age group (Years)	Adjusted OR[1]
20-24	0.4
25-29	0.7
30-34[2]	1.0
35-39	1.5
40-44	2.3
45-49	3.4
50-54	5.1
55-59	7.8
60-64	12.0
65-69	18.0

[1]Adjusted for smoking history, exercise, menopausal status, hormone replacement therapy usage, oral steroid use, and fracture history
[2]Reference group age 30-34 years

Chapter 4 – Discussion

Osteoporosis is a debilitating degenerative disease associated with aging. Environmental, behavioral, and genetic factors act to either decrease or increase the risk of osteoporosis. Several factors suggest that Alaska Natives may have a different risk profile for osteoporosis than the United States population as a whole. Changing behavior patterns among Alaska Natives combined with an increasing life expectancy make this an important and interesting population to evaluate for osteoporosis risk.

Alaska is exposed to considerably less sunlight than other parts of the United States. Sunlight is required for the conversion of 7-dehydrocholesterol to previtamin D3, an essential component for calcium absorption (Marcus, 1996). This conversion process is less efficient in the elderly, adding to their risk for osteoporosis and fractures (Heaney, 1996). Inefficient conversion combined with low exposure to sunlight may have a profound effect on elderly Alaska Natives. The changing diet of Alaska Native peoples may also increase their risk for osteoporosis. The diet of indigenous peoples has changed dramatically in the last thirty years (Whiting, 1998). The effect of these dietary changes on calcium intake is not well characterized. Informally, I found that Alaska Native women consume smaller quantities of milk and other dairy products than the United States average. This low consumption is due to the high prevalence of lactose intolerance, high cost, and limited availability of these foods. Lactose intolerance is a special problem because the major food items fortified with vitamin D are dairy foods. This combination of reduced dietary vitamin D intake and low exposure to sunlight may lower bone density.

I measured an average calcium intake lower than reported by other researchers. Nobmann and colleagues (Nobmann, 1992) found a mean dietary intake, excluding dietary supplements, of 516 mg/day in Alaska Native females and 597 mg/day for Caucasian females in the National

Health and Nutrition Examination Survey II (NHANES II). In this survey Alaska Natives consumed 306 mg/day on average. When I included dietary supplements in my sample, the discrepancy between my measurement and the value reported by Nobmann et al. disappeared. Cummings and colleagues (Cummings, 1995) reported a higher mean calcium intake, excluding supplements, of 713 mg/day in a sample of 9,516 Caucasian women. This informal comparison supports the hypothesis that Alaska Natives have lower calcium intake than Caucasian women. All of these estimates are lower than the recommended dietary intake (1200 mg/day) (National Osteoporosis Foundation, 1999). The differences between my results and the work of others may be due to the use of different dietary measures. My dietary survey did not include all high-calcium foods. Notably absent from the measurement was cheese, which can be a major source of dietary calcium. It is unlikely, but possible, that including cheese could raise the mean daily intake to the recommended level. The large difference between measured and recommended intakes suggests that Alaska Natives are not consuming recommended levels of calcium.

Hormone replacement therapy and menopause were related to one another and to low bone density. This confounding relationship is easily explained. Women taking hormone replacement therapy are older than the study population as a whole. When either menopausal status or age is added to the statistical model, this confounding with age is eliminated, and hormone replacement therapy is then negatively associated with low bone density. An additional complication is that premenopausal women do not take hormone replacement therapy, almost by definition. This fact made it impossible for me to test for statistical interactions between these two important variables using conventional statistical techniques.

Issues with Ultrasound Bone Density Technology

The diagnosis of osteoporosis is most often made with a bone density measurement. While the interpretation of these tests seems simple, several technical issues complicate their interpretation.

A variety of bone density measurement techniques are available (Lang, 1991). The most widely accepted technique is Dual Energy X-ray Absorptiometry (DEXA). DEXA uses an X-ray source to generate two photon beams of known intensities and energies. The beams are directed at a specific anatomic site. A detector on the opposite side of the site measures the amount of radiation that passes through the tissue. The absorption of radiation roughly follows Beer's law (Barrow, 1988). Since the intensity of the X-ray beam is known, it is an easy calculation to determine how much radiation the bone absorbs. Denser bone absorbs more radiation. The use of two photon energies with different absorption characteristics allows the device to correct for the amount of soft tissue surrounding the bone. This correction allows accurate measurements of relatively deep anatomic sites such, as the femoral neck and lumbar vertebrae.

Ultrasound is a relatively new technology for bone density measurements. Ultrasound methods pass high frequency sound waves through the anatomic site of interest. Unlike DEXA, ultrasound cannot correct for the amount of soft tissue around deep anatomic skeletal sites. Instead of the femoral neck or lumbar vertebrae, shallow anatomic sites are measured. The most common measurement sites are the patella, metacarpals, and the calcaneus. Even when measuring at shallow sites, edema can affect the measurement (Johansen, 1997). Ultrasound densitometry most commonly takes advantage of two physical properties to make its measurements, attenuation and speed of sound (Njeh, 1997). Broadband ultrasound attenuation (BUA) is a measure of the absorption of sound by bone and is analogous to X-ray absorption used by DEXA. Speed of sound through the bone is often measured as well. Denser, healthier bone allows sound waves to propagate at a higher speed than in lower density bone.

DEXA and ultrasound densitometry are strongly correlated measurements of bone density. Greenspan and colleagues found correlation coefficients between DEXA at the calcaneus and several ultrasound units of 0.79-0.86. The relationship was slightly weaker between DEXA of the femoral neck and ultrasound at the calcaneus (r=0.7-0.8) (Greenspan, 1997).

While ultrasound is a valid technique, it has limitations. Ultrasound is a less precise measurement technique than DEXA; therefore it has a larger standard deviation. A t-score of -1.0 obtained by ultrasound is a lower density than a t-score of -1.0 obtained by DEXA. This results in systematic underdiagnoses of osteoporosis by ultrasound using W.H.O. criteria (Faulkner, 1999).

The differences between DEXA and ultrasound are the reason I did not use the ultrasound results as a diagnostic marker for osteoporosis. If the W.H.O. t-score cut point of -2.5 for osteoporosis is applied to ultrasound results, most persons with osteoporosis are misclassified as non-osteoporotic. Theoretically, I could use a different cut point that adjusts for the differences between ultrasound and DEXA. No widely accepted method for this adjustment exists. I opted instead to use a cutoff of -1.0 to define an abnormal result. This is an accepted W.H.O. criterion for low bone density or osteopenia. Using this criterion, almost all persons who have osteoporosis will have an abnormal test result. The disadvantage of this method is that some persons with low bone mass by DEXA will be misclassified as having normal bone mass. The cut off of –1.0 strikes a reasonable balance between detecting persons at high risk of low bone density and avoiding large numbers of false positive results.

Limitations

This study was a cross-sectional study, so no information about the temporal relationship between risk factors and bone density was gathered. I selected subjects for the study by convenience sampling. Subjects are persons using the health care system, and many of the

subjects have reasons to be concerned about osteoporosis. For example, several subjects were referred to the study because of long-term corticosteroid use.

Communities were selected based on the level of support from the local health care system and tribal corporations. These communities may differ from the Alaska Native population as a whole in terms of availability of health care resources or other factors that may affect risk factor distribution. I did not visit any sites in Southeast Alaska, and I did not obtain enough data from northern communities to test for a relationship between average daylight exposure and bone density.

The calcium measure I used was, at best, a good estimate of dietary sources of calcium. The instrument relied heavily on dairy products to estimate calcium intake. This may not be appropriate because dairy products are only recently widely available in rural Alaska and are expensive. Many of the study subjects reported that they were lactose intolerant. These factors imply that dairy calcium makes up a smaller proportion of total dietary calcium than it does in the general United States population. The dietary measure also did not account for the significant seasonal variation in the diet of Alaska Natives (Nobmann, 1992). Foods like salmon, herring eggs, and salmon berries are available only during a short period during the summer, although some are preserved and consumed throughout the year. Exercise is also a seasonal activity in Alaska. The exercise habits of subjects across the seasons were not assessed in this study.

Misclassification of ethnicity is a concern in this study. I determined the ethnicity of subjects by self-report. I did not identify blood quantum. Some non-native subjects were possibly misclassified as Alaska Natives. This leads to difficult questions about the definition of an Alaska Native, because intermarriage between different tribes, and with Caucasians, is quite common. I do not believe that this limitation seriously compromises my results, because all subjects were recruited from I.H.S. facilities. Patients at these facilities must demonstrate some Alaska Native or American Indian heritage to receive care.

Alcohol abuse is a risk factor for osteoporosis that I did not attempt to measure. Accurately assessing alcohol consumption is quite difficult and complicates the patient interview. I decided that these difficulties outweighed the benefits of collecting information about alcohol consumption.

In this study, I used the odds ratio as my measure of association. This measure is statistically valid, but the odds ratio does not approximate the relative risk in this case because of the high prevalence of low bone density in this population.

I personally interviewed the subjects. It is possible that I asked the questions in such a manner as to bias the results. To minimize this bias I followed the questionnaire closely and always performed the bone density test after I completed the interview.

The sample size, while adequate to test for many main effects, was too small to detect a statistically significant effect for exercise. A larger sample would make it possible to more reliably test for effect modification between age and the variables whose interaction terms approached significance.

Future Studies

Several changes to this study design should be incorporated into future work. A larger sample, with better representation of Southeast Alaska and of native peoples living above the Arctic Circle, would allow richer statistical models to be constructed. Measurement of body mass index, serum vitamin D, and better assessment of comorbidities such as rheumatoid arthritis, cancer, and seizure disorders would make it possible to adjust statistically for these important factors. A large enough sample with broad representation would allow for the development of a reference database of bone densities for this population. A measurement of the prevalence of lactose intolerant persons would be useful. A further improvement would be to follow subjects as a cohort to determine the rate of osteoporotic fractures in this population.

Conclusions

Osteoporosis is a growing problem for Alaska Native women. My work indicates that several risk factors for osteoporosis exist in this population. The magnitude of the associations between risk factors is similar to that seen by other investigators in cohort studies (Forsen, 1998; Cummings, 1995).

The total calcium consumption of Alaska Natives in this study is lower than the USDA recommended level. Given the high prevalence of other risk factors this is a cause for concern. These results suggest that a population-based dietary intervention is worthwhile. The dietary intervention should not focus only on calcium intake; instead it should be a comprehensive intervention that emphasizes a low fat and high fiber diet.

Other modifiable risk factors should also be addressed in a prevention program. Clearly, a high priority should be given to smoking cessation programs. The high prevalence of exercise in the study population is encouraging and suggests that indoor community centers that facilitate exercise during the winter will be utilized if built. Programs for the elderly to prevent falls should also be implemented where feasible. Prevention programs in Alaska need to account for the large seasonal variation in diet and activity level.

The Alaska Native population is aging and becoming more at risk for osteoporosis. Interventions exist that can decrease the risks of developing osteoporosis for individuals and for whole populations. Effective treatments for osteoporosis are available. Right now we have a golden opportunity to implement a systematic program to prevent osteoporosis and fractures. If we take advantage of this opportunity we can avoid a significant amount of morbidity and mortality in Alaska Natives.

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Appendix A – Consent Form

Title: Assessment of Risk Factors for Osteoporosis among Alaska Natives
Principle Investigators: Kelly Krohn, M.D. (503) 494-8963
Joshua Filner, Medical Student (907) 729-1126
Co-investigator: Jane Kelly, M.D. (907) 729-1126

Purpose: You have been invited to participate in this research study because you are a woman over the age of twenty. The purpose of this research is to learn about the risks Alaska Native women have for osteoporosis, often called brittle bone disease. Participation takes about 15 minutes.

Procedures: If you decide to participate in this research study we will ask you questions about what foods you eat and some medical conditions which are known to affect the risk of getting osteoporosis. Afterwards we will measure how strong your bones are using a machine approved by the Food and Drug Administration. This machine uses ultrasound, not x-rays. It takes a few minutes to set up and about 10 seconds to measure your bone strength. You will feel the machine buzz while it is working. You will be given a copy of the results and a copy of this form to take home with you. A doctor or other health care practitioner will discuss any unusual results with you. A copy of your results will be put in your medical record. We will also check your medical record to see if you have taken certain medicines or have certain illnesses known to affect the risk of osteoporosis.

Risks and Discomforts: There are no known risks associated with the use of this or any ultrasound. The bone measurement is painless. Some ultrasound gel will get on your foot. The information we will collect could affect your insurability.

Benefits: You may or may not be personally helped by participating in this study. By participating in this study you are helping us to understand who will get osteoporosis and help develop programs to prevent it. You also get a free ultrasound measurement of your bones which will tell you something about your chances of getting osteoporosis.

Alternatives: You may choose not to participate in this study.

Confidentiality: Neither your name nor your identity will be used for publication or publicity purposes.

Costs: There is no cost for participation in this study.

Liability: The Oregon Health Sciences University, as a public corporation, is subject to The Oregon Tort Claims Act, and self-insured for liability claims. If you suffer any injury from this research project compensation would be offered to you only if you establish that the injury occured through the fault of the University, its officers or employees. However, you have not waived any legal rights by signing this form. If you have further questions, please call the Oregon Health Sciences University Medical Services Director at (503) 494-6020 or Dr. David Barrett of the Alaska Native Medical

Center at (907)229-2062. It is not the policy of the U.S. Department of Health and Human Services, or any federal funding the research project in which you are participating to compensate or provide medical treatment for human subjects in the event the research results in physical injury.

Participation: Dr. Kelly Krohn (503) 494-8963 has offered to answer any other questions you may have about this study. If you have questions regarding your rights as a research subject you may contact the Oregon Health Sciences University Institutional Review Board at (503) 494-7887 or Dr. David Barrett of the Alaska Native Medical Center Institutional Review Board at (907) 229-2062. You may refuse to participate or you may withdraw from this study without affecting your relationship with or treatment at this clinic, Alaska Native Medical Center, or Oregon Health Sciences University. Your signature below indicates that you have read the foregoing and agree to participate in this study.

Study Participant	Date
Investigator	Date

Appendix B – The Study Questionnaire

Native Alaskan Bone Mineral Density Pilot Project

IDENTIFYING INFORMATION

Id. Number <idnum> Date of Interview <mm/dd> Date Entered <today/yy>
Last name <A > First name & initial <A >
City or town _____ ZIP #####
Site # (1= Anchorage 2= Sandpoint 3=Kodiak)
Date of Birth <mm/dd/yy> Age ### years Sex <A> (M/F)
Native American <Y> Tribe1_____ Tribe2 _____
Have you ever broken your ankle or foot or had pins placed in them?
<Y>
BMD #.### T-Score ##.# BUA ##.# SOS ####.#

Dietary Questionnaire
Will Multiply servings/week by 4 for monthly

Food	Do you eat	Average Servings/week
Milk,fresh (1 cup)	<Y>	##.#
Milk, Evaporated(1/4 cup)	<Y>	##.#
Milk, powdered (1/3 cup powder w/1 cup water = 1 cup milk)	<Y>	##.#
Coffee w/milk or cream (1 Tbsp.)	<Y>	##.#
Yogurt, Plain 1 cup	<Y>	##.#
Ice Cream (1/2 cup=scoop)	<Y>	##.#
Canned Salmon w/bones (1/4 cup)	<Y>	##.#
Sardines (1 can)	<Y>	##.#
Fish Head soup (2 cups)	<Y>	##.#
Stinkfish? (SERVING SIZE?)	<Y>	##.#
Kelp w/herring eggs (1 cup)	<Y>	##.#
Small blackfish w/bones (3 oz.)	<Y>	##.#
Dried Salmon, Sockeye or Red(3 oz.)	<Y>	##.#
Whole Needlefish (3 oz.)	<Y>	##.#
Juices w/Calcium (1 cup)	<Y>	##.#
Fishheads (2 heads)	<Y>	##.#
Dark Green Leafy Vegetables (1 cup)	<Y>	##.#
Broccoli (2 spears)	<Y>	##.#
Cold Cereal (1 1/2 cup)	<Y>	##.#
Hot Cereal (1 cup)	<Y>	##.#
Egg (1)	<Y>	##.#

Do you take Ca supplements (e.g. tums, Oscal)? <Y>
If so how often/week # Dose #####
Do you do physical labor at home or as part of a paid job? <Y>
Do you exercise at least 3 times a week for 20 minutes or more? <Y>

Has a healthcare provider suggested exercise in the last year or last visit? <Y>
Have you ever broken your hip? <Y>
Has a health care provider ever told you you have osteoporosis? <Y>
Do you have diabetes? <Y>
Are you taking or have you taken steroids(longer than 6 wks.)? <Y>
Do you or have you ever smoked tobacco? <Y> If so for how long?(years) ##.#
How many packs per day? #.#
Has any healthcare provider suggested quitting in the last year? <Y>
For women only:
Have you started menopause (have your periods stopped)? <Y>
Are you taking hormone replacement therapy? <Y>
Are you taking or have you ever taken birth control pills? <Y>
If so for how long?(Years) ##.#

Comments

Appendix C – Methods Notes

Table A-1 Site Specific Recruitment Notes

Anchorage	In 1998, the investigator worked at several different clinics (Family Medicine, Internal Medicine, Women's Health, and Orthopedics). Subjects were referred directly by providers working at that clinic. In 1999, to fill a shortage of non-native subjects and make more efficient use of clinic time, appointments were scheduled in advance for many study subjects in addition to the 1998 methodology. Due to space constraints and organizational changes, subjects were recruited only from the Orthopedics and the Women's Health clinics.
Bethel	Very few subjects met the local institutional requirements for referral to the study. All subjects had a high degree of suspicion for osteoporosis (1998 only).
Kotzabue **Barrow**	A traveling rheumatologist referred many of the subjects to the study (1999 only).
Sand Point **Kodiak**	At these sites walk-in patients were recruited for the study; no phone calls were made for recruitment. These visits were made in conjunction with the diabetes team (1998 only).
Seward **Tatitlek** **Nanwalek** **Chenega Bay** **Port Graham** **King Cove**	At these sites the majority of subjects were recruited via telephone calls from the local providers and had appointments scheduled in advance. Walk-in subjects were also inducted into the study. (Seward 1998 and 1999, Others 1998 only)

Table A-2 Elemental Calcium Content of Food Items per Serving Used in Calculations of Dietary Calcium Intake[1]

Food	Calcium Content per Serving
Milk (unknown % fat)	297 mg
Evaporated Milk	164 mg
Powdered Milk	210 mg
Coffee + Cream	22 mg
Yogurt	447 mg
Ice Cream (unknown % fat)	84 mg
Cooked Greens	131 mg
Broccoli	36 mg
Cold Cereal	26 mg
Hot Cereal	24 mg
1 Egg	24 mg
Calcium-Fortified Juice	289 mg
Sardines	351 mg
Canned Salmon	60 mg
Fish Head Soup	168 mg
Kelp w/ Herring Eggs	161 mg
Small Black Fish	236 mg
Dried Salmon	84 mg
Whole Needlefish	93 mg

[1]Calcium Values from Nobmann (1993) and using Nutrition Data System Version 3.2 (Nutrition Coordinating Center of the University of Minnesota, St. Paul, MN)

Figure A-1 Predicted Values vs. Cook's Distance from the Final Logistic Regression Model, for All Natives

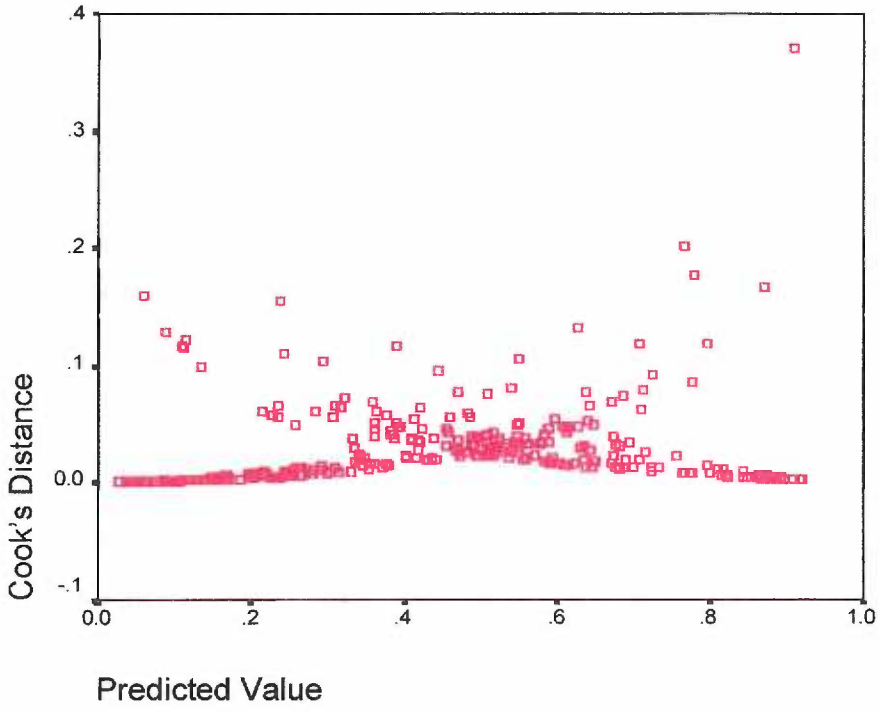


Figure A-2 Predicted Values vs. Pearson Residuals from the Final Logistic Regression Model, for All Natives

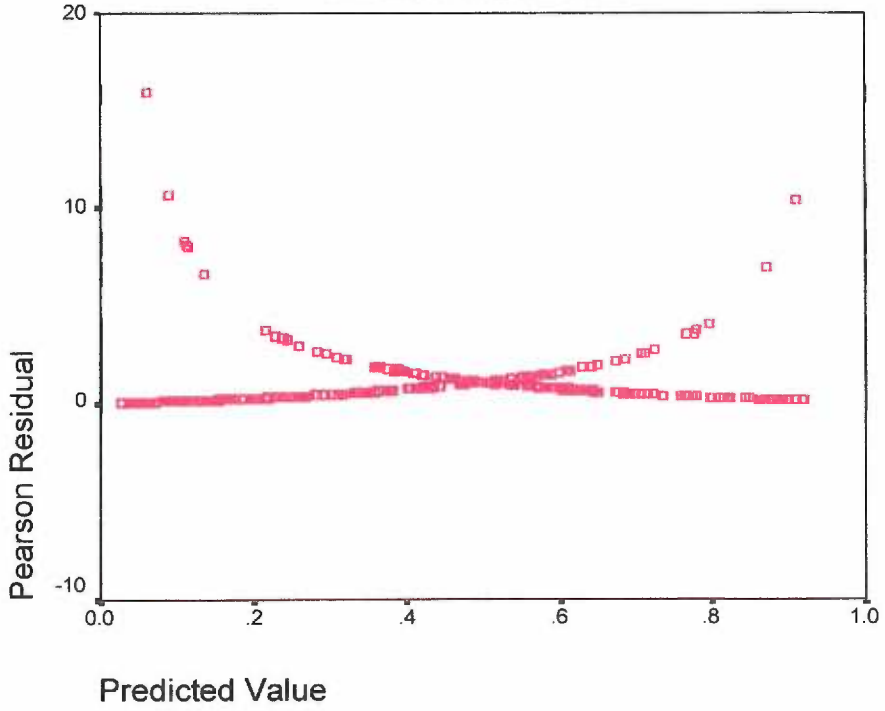


Figure A-3 Predicted Values vs. Cook's Distance from a Logistic Regression Model for All Variables Shown in Table 3-9 and an Age-Smoking Interaction Term, for All Natives

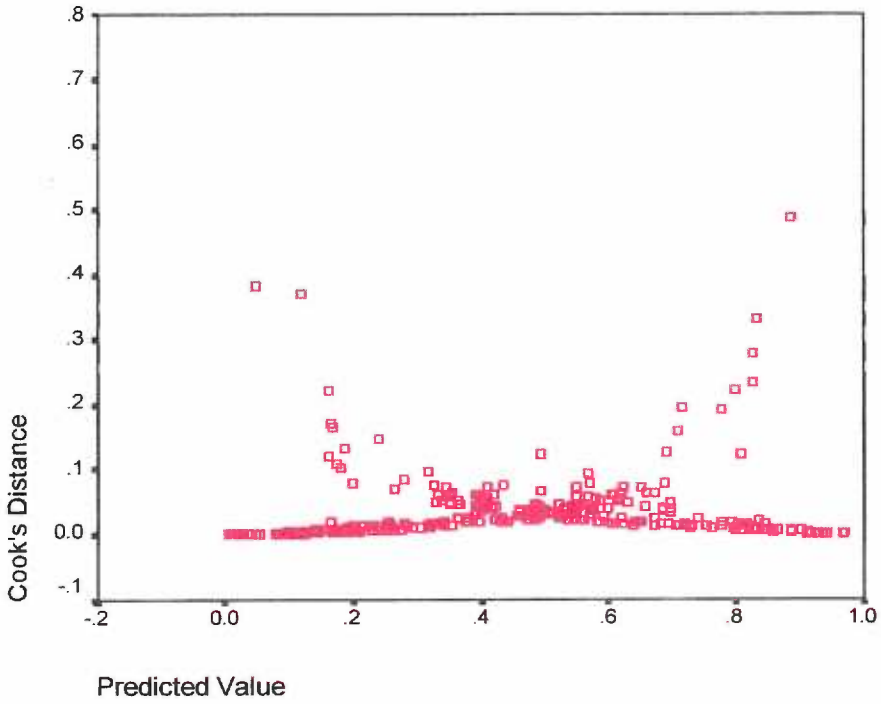
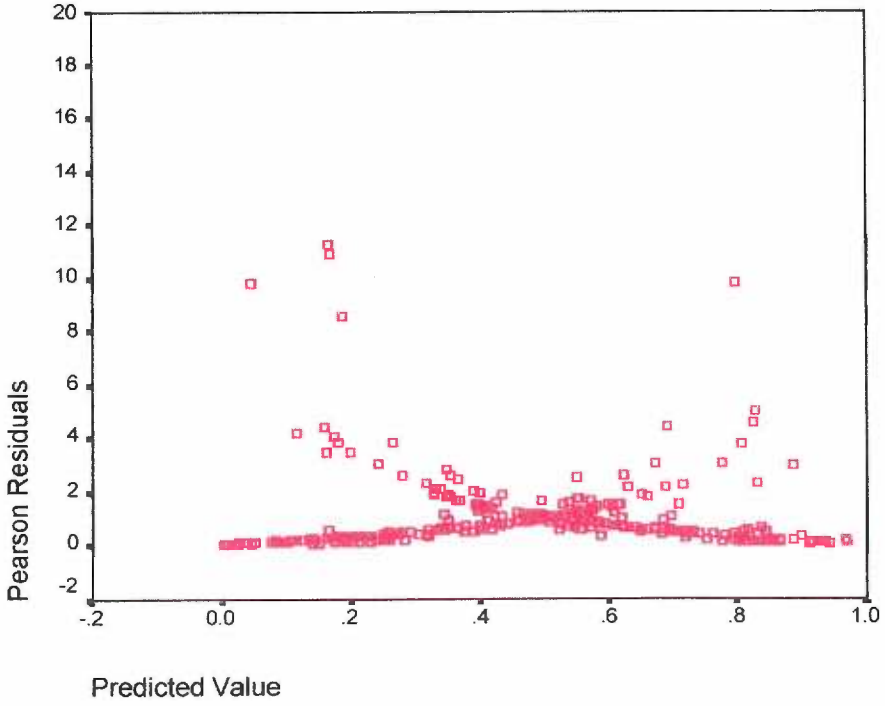


Figure A-4 Predicted Values vs. Pearson Residuals from a Logistic Regression Model for All Variables Shown in Table 3-9 and an Age-Smoking Interaction Term, for All Natives



Appendix D – Ultrasound Methods

Calcaneal density was measured using a Sahara Clinical Bone sonometer (Hologic, Inc., Waltham, MA). The recommendations of the manufacturer were followed for the use of the sonometer. This procedure included wiping the foot with either an alcohol wipe or baby wipe and putting special oil-based ultrasound coupling gel onto the sonometer's transducer. The foot was then positioned carefully in the sonometer and then the density measurement was made. The right calcaneus was measured unless the subject gave a history of any injury to the right foot or ankle (except sprains, bunions, or fracture of the metatarsals or phalanges). If the sonometer indicated the result was not reliable, that result was recorded in the comments section of the database and the measurement was repeated after repositioning the foot. In most cases after three attempts at a stable measurement the subject was allowed to leave.

At the beginning of each day when study measurements were made, the quality control phantom supplied with the ultrasound machine was measured. No study measurements were made unless a normal result within two standard deviations of the mean was measured from the phantom. Results for the 1999 measurements are shown in Figure A-5 and Figure A-6.

Figure A-5 Ultrasound Quality Control Log for August 1999

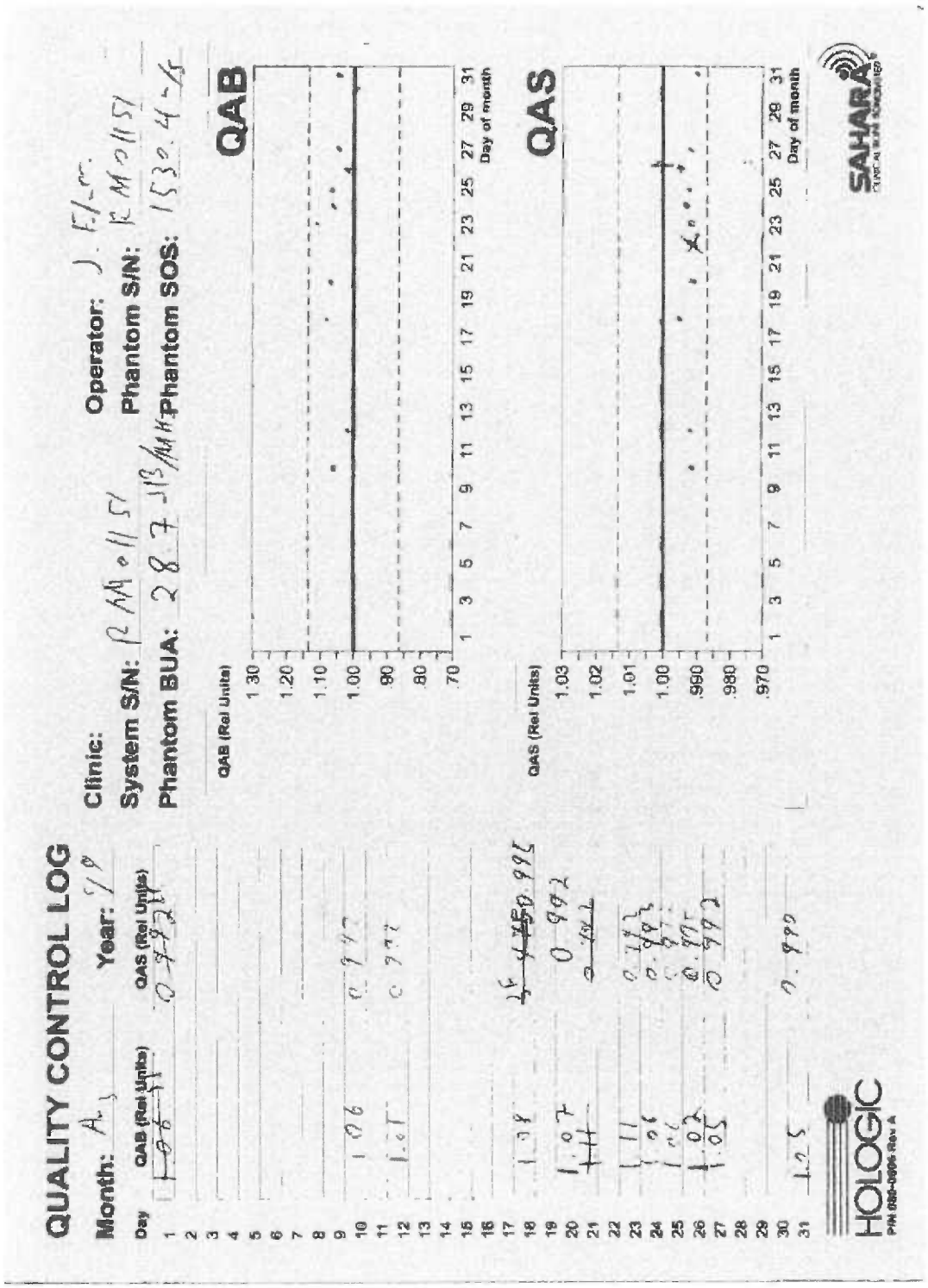
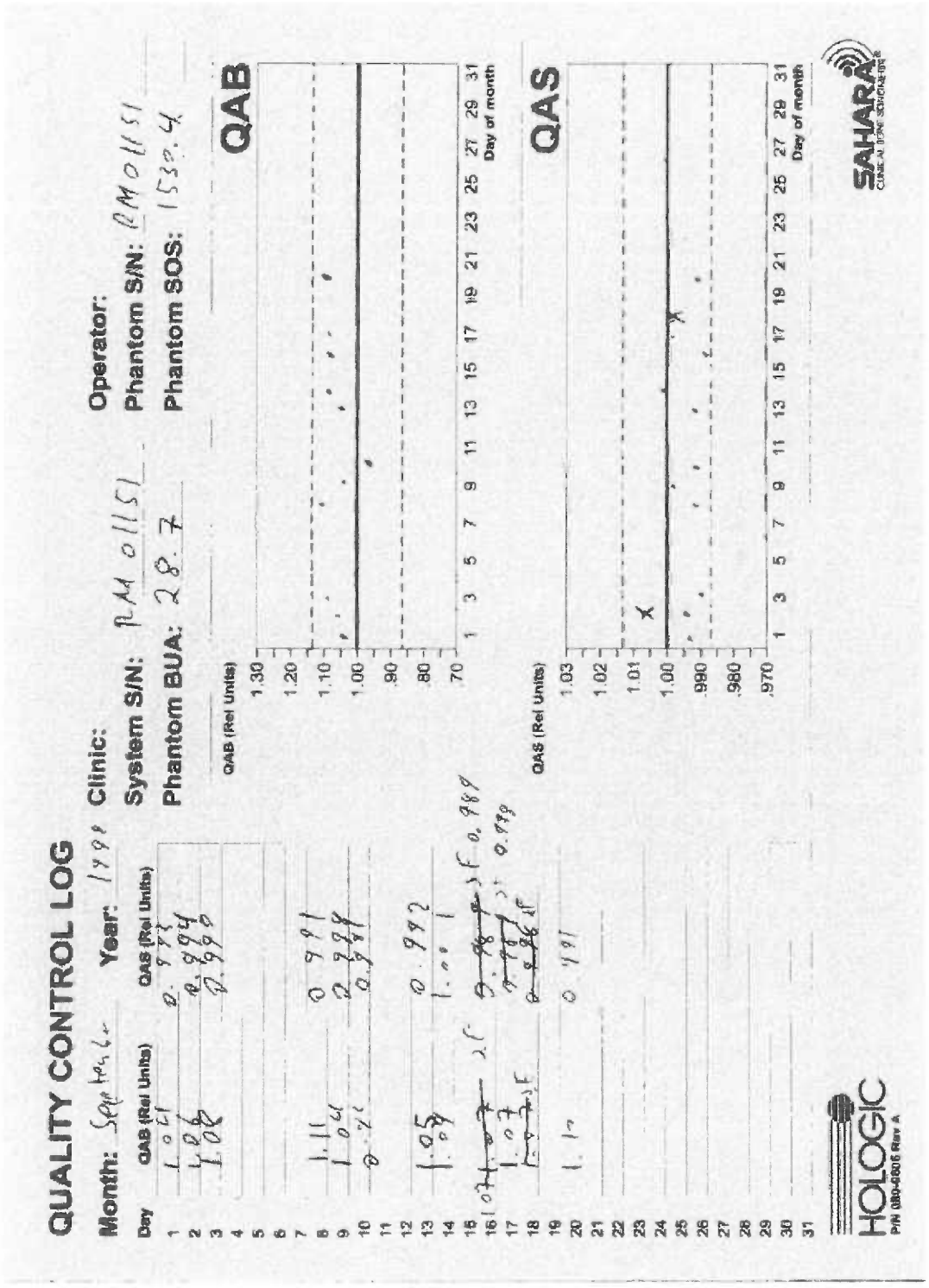


Figure A-6 Ultrasound Quality Control Log for September 1999



Appendix E – Subject T-Score Report

What patients need to know about Ultrasound Bone Scans:

Ultrasound Bone Scans do not involve the use of x-rays. Rather the scan is done using sound waves.

Ultrasound Bone Scans are used as a fracture risk assessment tool. The heel (calcaneus) is a good site to measure since the heel is similar to other areas (spine, hip) and seems to be a good indicator of fracture risk.

Over the last several years, quantitative ultrasound (QUS) measurements, like the one done on your heel, have been applied by researchers to the assessment of bone status and risk for fracture. A database of normal women has been compiled that allows comparisons of measurements made on individuals to a reference population. From this comparison, fracture risk can be estimated. Normal reference ranges have not been collected on men or on other ethnic groups at this time.

What is a T-Score?

T-score compares your bone mass to that of healthy young women – those that have the best bone mass. Bone mass in young women is referred to as PEAK because that's the stage of life when bone mass is highest. A T-score (or standard deviation from the average) can be either a + (plus) or a - (minus) number. The usual range for T-scores is -1.0 to + 2.0. If the score is +, then you are above average compared to young women. If the score is - then you are below average. The National Osteoporosis Foundation suggests that values below -1.0 are of some concern and that those below -2.0 may suggest the need for active therapy.

T-Score: _____

- ❑ **Your value is normal. We recommend that you continue with practices for preventing osteoporosis (adequate dietary calcium intake, daily physical exercise, and postmenopausal hormone replacement therapy).**
- ❑ **Your value suggests an increase in fracture risk. We recommend that you discuss these results with your physician.**

Provided by: The Assessment of Risk Factors For Osteoporosis among Alaska Natives Study Contact Dr. Kelly Krohn 503-494-8963 with questions or concerns regarding this measurement.