OBESITY AND RISK OF MULTIPLE
MYELOMA: A CASE-CONTROL
STUDY

by

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DEDICATION

I would like to dedicate this dissertation to my loving husband, Andrew Royle, and also to my parents, Paula and Gary Amaon, my sister, Julie Amaon, and Sam Eder for their continual love and support. Thank you all for encouraging me to reach my goals. I LOVE YOU ALL!!
PREFACE

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Introduction: Several studies have reported a positive association of body mass index (BMI) with multiple myeloma; however, the period of adulthood where BMI is most important remains unclear. In addition, it is well known that body fat is associated with both sex-steroid hormone storage and with increasing insulin levels; therefore, it was hypothesized that the association between obesity and multiple myeloma may be attributed to increased aromatization of androgen in adipose tissue. Objective: The overall objective of this case-control study was to determine whether multiple myeloma cases had higher BMI and greater adult weight gain relative to healthy controls. In addition, we tested the hypothesis that hormone replacement therapy use among women will further increase the association between BMI and risk of multiple myeloma. This study used data from a pilot case-control study at M.D. Anderson Cancer Center (MDACC), entitled Etiology of multiple myeloma, directed by Dr. Sara Strom and Dr. Sergio Giralt. Methods: The pilot study recruited a total of 122 cases of histopathologically confirmed multiple myeloma from MDACC. Controls (n=183) were selected from a database of random digit dialing controls accrued in the Department of Epidemiology at MDACC and were frequency matched to the cases on age (±
5 years), gender, and race/ethnicity. Demographic and risk factor information were obtained from all participants who completed a self-administered questionnaire. Items included in the questionnaire include demographic information, height and weight at age 25, 40 and current/diagnosis, medical history, family history of cancer, smoking and alcohol use.

Statistical Analysis: Initial descriptive analysis included Student’s t-test and Pearson’s chi-squared tests. Odds ratios and 95% confidence intervals were calculated to quantify the association between the variables of interest and multiple myeloma. A multivariable model will be developed using unconditional logistic regression. Results: MM cases were 1.79 times (95% CI=0.99-3.32) more likely to have been overweight or obese (BMI > 25 kg/m$^2$) at age 25 relative to healthy controls after controlling for age, gender, race/ethnicity, education and family history of cancer. Being overweight or obese at age 40 was not significantly associated with mutliple myeloma risk (OR=1.42, 95% CI=0.86-2.34) nor was being overweight or obese at diagnosis (OR=1.43, 95% CI=0.78, 2.63). We observed a statistically significant 2-fold increased odds of multiple myeloma in individuals who gained more than 4.7 kg during between 25 and 40 years (OR=1.97, 95% CI=1.15-3.39). When assessing HRT as a modifier of the BMI and multiple myeloma association among women (N=123), no association between obesity and MM status was observed among women who have never used HRT (OR=0.60, 95% CI=0.23-1.61; n=73). Yet among women who have ever used HRT (n=50), being overweight or obese was associated with an increase in MM risk (OR=2.93, 95% CI=0.81-10.6) after adjusting for age; however, the association was not statistically significant. Significance: This study provides further evidence that increased
BMI increases the risk of multiple myeloma. Furthermore, among women, HRT use may modify risk of disease.
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INTRODUCTION

Background and Significance

Multiple myeloma is a hematologic disease characterized by the accumulation of malignant plasma cells in the bone marrow. It is a rare cancer, having an incidence rate of only 5.6 per 100,000 per year in the United States. The American Cancer Society estimates that 16,570 new cases will be diagnosed with multiple myeloma and 11,310 patients will die from the disease in the United States this year. This malignancy represents approximately 1% of all cancers in whites, and 2% of all cancers in Blacks. Prognosis tends to be poor, with only about one third of patients survive 5 or more years and 16% survive 10 years. Although research has been done to understand the etiology of multiple myeloma, crucial gaps in knowledge regarding its cause remain. Further insight into the determinants of multiple myeloma could have implications for prevention and subsequent reduction in the incidence of the disease.

Factors known to increase risk for multiple myeloma include increasing age, male gender, Black race, and a condition called monoclonal gammopathy of unknown significance (MGUS), which is believed to be a premalignant lesion to multiple myeloma. It has been suggested that multiple myeloma is associated with environmental exposures, such as ionizing radiation and agricultural occupations. In addition, there has been interest in pre-existing conditions as possible precursors of multiple myeloma, such as chronic antigenic stimulation and certain infections. The association between obesity and risk of multiple myeloma has been examined in recent studies suggesting a positive association. Current evidence suggests several mechanisms through which greater adiposity could influence
carcinogenesis of this hematopoietic malignancy. It is possible that obesity is modulating multiple myeloma risk through several biologic mechanisms, including inflammation, insulin resistance and endogenous hormone metabolism.

The World Health Organization considers obesity a disease and is defined as the condition of excess body fat to the extent that health is impaired. Over the past 20 years, the prevalence of obesity has reached epidemic levels in developed countries. In 1999-2000, 30.5 percent of the adult population in the United States was obese and 34 percent was overweight. Obesity prevalence is increasing rapidly in adults, as well as children, and it is becoming a problem even in urban areas of developing countries. Obesity is associated with several chronic diseases, including hypertension, diabetes, coronary heart disease, stroke, respiratory complications, osteoarthritis and cancer. Mounting evidence suggests that being overweight and obese are associated with the development of certain cancers, such as kidney, breast (in post-menopausal women), colon, esophagus, and endometrium. In addition, the American Cancer Society recently reported that, in both men and women, obesity was significantly associated with higher rates of death due to cancer of the esophagus, colon and rectum, liver, gallbladder, pancreas, and kidney, as well non-Hodgkin lymphoma and multiple myeloma. Lately, research has begun to look more carefully at obesity and the risk of multiple myeloma. Because obesity may be the only modifiable risk factor for multiple myeloma, further investigation is heavily warranted.

The current study allowed the examination of obesity and weight gain, throughout adulthood, and risk of multiple myeloma. Body mass index (BMI), which is calculated by dividing the body weight in kilograms by the square of the height in meters (kg/m²), is now a
widely used measurement to assess obesity with the commonly used cutoffs developed by the National Institute of Health as follows: <18.5 (underweight), 18.5-24.9 (normal), 25.0-29.9 (overweight), and ≥ 30 (obese)\(^1\). M.D. Anderson Cancer Center (MDACC) is one of the leading treatment centers for multiple myeloma in the country; however, no study on the etiology of this disease has been conducted at the institution. A pilot case-control study at MDACC was proposed to identify risk factors associated with the development of multiple myeloma. One hundred twenty-two MDACC patients diagnosed with multiple myeloma were enrolled into the study. Matched controls were selected from a database of random digit dialing controls accrued in the Department of Epidemiology at MDACC. Demographic and risk factor information was obtained. This project was supported by a NCI funded Cancer Prevention fellowship at MDACC.

**Clinical features and biology**

In order to comprehend the important factors in the etiology of multiple myeloma, it is essential to consider the biology of the disease. Multiple myeloma is a multifocal plasma cell neoplasm\(^2\). Normal plasma cells are the final products of B-cell differentiation, which synthesize and release immunoglobulins, light and heavy chain subunits of immunoglobulins, and cytokines designated as osteoclast-activating factors\(^3\). B-cells develop in the bone marrow and travel to the lymph nodes via the blood stream. Such cells may be activated, proliferate and give rise to either plasma cells (short-lived or long-lived) or memory cells; however, such activation requires contact with T-cells in the extrafollicular areas of the lymph nodes. Interaction with T-cells stimulates the B–cell to undergo isotype switching and/or differentiation into mature, short-lived plasma cells. As the origin of the primary
immune response, these short-lived plasma cells may not undergo somatic hypermutation. On the contrary, B-cells that migrate to the germinal center encounter antigens and co-stimulatory molecules to develop a secondary immune response. These long-lived plasma cells undergo somatic hypermutation and isotype switching with the generation of high-affinity molecules. They leave the lymph node via the efferent lymphatics and migrate back to the bone marrow where it produces the majority of secreted immunoglobulins in the plasma.

The exact nature of the malignant plasma cell, or myeloma cell, remains elusive. However, current evidence suggests that it is likely to be a long-lived plasma cell from the bone marrow and that has already undergone somatic hypermutation. Research has shown that myeloma cells are a result of the expansion of a single clone of an immunoglobulin-secreting malignant plasma cell. Several features of the myeloma cells, such as an abnormal localization within the bone marrow, replacement of normal bone elements, and the dysregulation of immunoglobulin secretion, are central to the clinical presentation and evolution of multiple myeloma. Multiple myeloma is characterized by a serum M-protein and skeletal destruction with osteolytic lesions, pathological fractures, bone pain, hypercalcemia and anemia. The disease involves a range of variations, from localized, smoldering (asymptomatic) and indolent myeloma, to aggressive disseminated forms with plasma cell infiltration of various organs, plasma cell leukemia, and disorders due to deposition of abnormal immunoglobulin chains in tissues. Not only do the neoplastic plasma cells cause extensive damage to the skeleton, but recurrent bacterial infections and renal insufficiency are common. A combination of pathological, radiological, and clinical
laboratory findings provides diagnostic criteria for the disease\textsuperscript{20}. The diagnosis requires the existence of at least two of three characteristics features: a paraprotein or monoclonal immunoglobulin in the blood and/or urine, bone marrow infiltration by malignant plasma cells and the presence of osteolytic bone lesions\textsuperscript{21}.

**Epidemiology**

*Obesity*

Recent literature suggests that obesity may play a role in the development of the complex disease, multiple myeloma. Since 1994, 3 case-control and 4 cohort studies assessing the relationship between obesity and multiple myeloma were published\textsuperscript{6-11,22}. An exploratory cohort study was conducted on pre-existing medical conditions as predictors of subsequent cancer in 143,574 outpatients of a health maintenance organization in California\textsuperscript{6}. An association was found between obesity (n=14,388) and the subsequent development of multiple myeloma over 21 years of follow-up (33 cases observed, 21.3 expected based on the experience of the entire cohort; standardized morbidity ratio (SMR) = 1.55, 95% CI=1.06-2.17). In the same publication, the association was further evaluated in a second cohort of 163,561 individuals who received multiple health check-ups between 1964 and 1972 and were followed for up to 24 years (177 cases)\textsuperscript{6}. The second study reported that BMI at entry examination was positively associated with the incidence of multiple myeloma in White men (RR=1.68, 95% CI=0.75-3.78, comparing the highest to the lowest quartile) after adjusting for age. This association was confirmed in Black men and women (BMI quartiles two, three, and four showed higher risk than quartile one).
In 2001, Brown et al. published a population-based case-control study examining the role of dietary and nutritional factors in the risk of multiple myeloma among blacks and whites, age 30-79, in the United States (cases: 346 white and 193 black; controls: 1086 white and 903 black)\textsuperscript{7}. A sub-analysis was performed to examine the effect of BMI on the risk of multiple myeloma while adjusting for age, geographic area, gender, and food calories. The study reported that multiple myeloma was associated with obesity in whites (OR=1.9, 95% CI=1.2-3.1) and blacks (OR=1.5, 95% CI=0.9-2.4). In contrast, a Swedish hospital-based cohort study (N=28,129) published in 2001 observed no increase in risk of multiple myeloma (n=22) in obese individuals (SIR=1.1, 95% CI=0.7-1.6) after adjusting for age, gender, and calendar-year\textsuperscript{22}. In a large cohort of hospitalized male US veterans (3,668,486 whites; 832,214 blacks), obesity was examined as a risk factor for all major cancer sites and subsites between 1969 and 1996\textsuperscript{8}. Overall, obese men were at increased risk for several major cancers as well as a number of uncommon malignancies, including multiple myeloma. For both white and black veterans, multiple myeloma risk was elevated (RR=1.22, 95% CI=1.05-1.40 for white veterans; RR=1.26, 95% CI=1.02-1.56 for black veterans) after controlling for age and calendar-year.

A Canadian, population-based case-control study of 21,022 incident cases of 19 types of cancer and 5,039 controls ages 20-76 years examined the association of obesity and the risks of various cancers (343 multiple myeloma cases)\textsuperscript{9}. This study reported a significant increased odds of multiple myeloma in overweight and obese individuals compared to those with a normal BMI (OR=1.49, 95% CI=1.14-1.95 and OR=2.06, 95% CI=1.46-2.89, respectively) after adjusting for age, sex, area of residence, education, pack-years of
smoking, alcohol use, total caloric intake, vegetable intake, dietary fiber intake, and recreational physical activity. In 2005, results from the Iowa Women’s Health Study, a population-based cohort of 37,083 postmenopausal women age 55 to 69, showed a slight association between greater BMI and multiple myeloma (overweight: OR=1.3, 95% CI=0.78-2.0, obese: OR=1.5, 95% CI 0.92-2.6) after controlling for age. Researchers recently analyzed data from a hospital-based case-control study on lymphoid neoplasms conducted in Italy between 1985 and 1997. The analysis included 141 cases of incident, histologically confirmed cases multiple myeloma age 38-79 years and 1112 hospital control subjects age 35-79. Compared to subjects of normal weight, the ORs were 1.43 (95% CI 0.92-2.24) for overweight, and 1.57 (95% CI 0.81-3.04) for obese subjects. The non-statistically significant association was consistent in both sexes, although somewhat stronger in women (1.30 in obese men and 2.26 in obese women).

Adult weight gain

To our knowledge, there has only been one exploratory study published examining the association between adult weight gain and risk of multiple myeloma. In the Friedman study, detailed above, the author showed no clear association between weight gain and risk of the disease. The association between increasing BMI as an adult and multiple myeloma seems probable given that a relationship with other cancers has also been reported, such as breast, renal cell, liver, pancreatic, and lung. Thus, it is imperative to further investigate the effects of adult weight on the risk of multiple myeloma as well.
HRT use as a modifier

To our knowledge the modifying effects of HRT use on the association between BMI and multiple myeloma has not been examined. Recent research on other cancers, specifically breast and colon cancer, has shown that HRT may modify the association between BMI and cancer risk\textsuperscript{23,24,26}. It is well known that body fat is associated with both sex-steroid hormone storage and with increasing insulin levels\textsuperscript{26}. In addition, co-regulation of sex-steroid and growth hormones such as insulin has been described in the literature\textsuperscript{27,28}. Furthermore, there is an increasing wealth of information on the association between insulin and insulin-like growth factor (IGF) and their binding proteins (IGFBP) and risk of cancer\textsuperscript{26}. However, it is unclear how sex-steroid or growth hormones, and the IGF system modify the observed association between BMI and multiple myeloma. It was hypothesized that the association between obesity and multiple myeloma may be attributed to increased aromatization of androgen in adipose tissue\textsuperscript{13}. HRT use was the only indicator of hormone status available to us for the current study; therefore, we examined its modifying effects on the relationship between obesity and multiple myeloma. However, further research on other indicators of estrogen status is necessary.

Other Risk Factors

Age is the most significant risk factor for multiple myeloma, given that the incidence of disease increases from less than 1 per 100,000 before the age of 39 to 34.2 per 100,000 by age 80\textsuperscript{3}. Rates of multiple myeloma also differ by gender. Overall, women have significantly lower incidence and mortality rates than males, a difference that has not yet been explained\textsuperscript{3}. Similarly, there is a racial disparity in the incidence and mortality. Blacks
have twice the risk of being diagnosed (11.0 per 100,000 vs. 5.1 per 100,000) and twice the risk of dying from the disease (7.4 per 100,000 vs. 3.6 per 100,000) compared to non-Hispanic whites. Several factors have been suggested to explain the racial differences in multiple myeloma, such as obesity, socio-economic status, family history and genetics. Another well known clinical risk factor is MGUS, which refers to the benign expansion of a single clone of plasma cells producing a homogenous monoclonal protein (M-protein). The prevalence of MGUS is higher in Blacks and slightly higher in females. Studies have shown that between 10%-20% of patients with MGUS will go on to develop multiple myeloma. However, the etiology of MGUS is unknown, and there is no reliable predictor of progression to multiple myeloma. Other host factors that appear to increase the risk of multiple myeloma are certain autoimmune diseases, chronic inflammatory conditions, as well as viruses that cause immunosuppression. Autoimmune disorders, such as rheumatoid arthritis (RA), polymyalgia rheumatica, pernicious anemia, and lupus erythematosus, have been linked to the etiology of multiple myeloma. In addition, cytotoxic medications frequently used in managing RA have also been linked with the hematologic malignancy; however, several studies observed an increased risk of multiple myeloma in RA patients that could not be completely explained by the use of the cytotoxic medications. Investigators have also hypothesized that repeated or chronic antigenic stimulation of the immune system may play a role in the pathogenesis of multiple myeloma. A prospective analysis of the NHANES I cohort examined the role of chronic or recurrent conditions that stimulate the immune system, such as allergies, autoimmune conditions, chronic bacterial conditions, and
inflammatory conditions, on the risk of multiple myeloma \(^\text{34}\). Bourguet and Logue reported a 2-fold increased risk for those reporting one condition compared to those reporting none, which then doubled with those that reported two or more conditions. In addition, there appears to be an association between certain viral infections and multiple myeloma. To date, this malignancy has been linked with HIV, human herpesvirus-8, and hepatitis C virus (HCV) infections \(^\text{5}\). The possible mechanism underlying the relation of certain autoimmune diseases, viral infections or other conditions with multiple myeloma risk include deregulation of cytokine interleukin-6, a potent stimulator of B-cell differentiation and promoter of myeloma cell growth \(^\text{5}\).

The role of genetics in multiple myeloma is not clear. Even though multiple myeloma occurs primarily as a sporadic disease, familial cases of multiple myeloma and MGUS have been reported \(^\text{35}\). Clustering of multiple myeloma in families implies that both shared genetic factors and/or common environmental exposure are involved in the etiology of the disease \(^\text{5}\). No specific gene has been associated with the disease; however, the literature suggests a genetic component. The role of variation in specific genes has been studied in relation to multiple myeloma risk. polymorphisms in genes regulating immune response and inflammation, including human leukocyte antigen, tumor necrosis factor alpha, interleukin-10, inhibitor protein IκBα, and cytotoxic T lymphocyte antigen-4 \(^\text{5}\). Results of these studies have been inconsistent, and significant findings have not been replicated convincingly \(^\text{31}\).

Exposure to ionizing radiation is a possible environmental risk factor for multiple myeloma. There is evidence from studies of atomic bomb survivors, occupational groups with exposure to approximately 0.05 Sv or more, and persons exposed to radiation from
therapeutic and diagnostic procedures \(^5,^36\). Several studies have provided evidence that agricultural work is also associated with multiple myeloma risk. The exposures commonly experienced by agricultural workers and that might contribute to the occurrence of the disease include pesticides, infectious organisms, and solvents \(^5,^37-^39\).

No other lifestyle factors, besides obesity, have been associated with an increased risk for multiple myeloma. Overall, examinations of alcohol use or cigarette smoking and risk of multiple myeloma found no apparent association \(^5,^31\). Although the literature on obesity and multiple myeloma suggests that energy balance may be a modifiable risk factor for the disease, recent evidence suggests that physical activity is not related to multiple myeloma \(^40\). Furthermore, while cigarette smoking has been linked to hematopoietic cancers in past epidemiologic studies \(^41\), recent publications have reported no clear association between smoking and multiple myeloma \(^41,^42\). Additionally, studies of the relationship between alcohol use and risk multiple myeloma have also found no association \(^5\). Certain dietary factors, however, have consistently shown to decrease the risk of the malignancy. Some studies reported that dietary fish and whole grain food intake are inversely associated with multiple myeloma \(^43-^45\).

**Public Health Significance**

Multiple myeloma is a treatable but rarely curable disease. With conventional therapy, only 5% of patients achieve complete response. The medial response to initial therapy remains approximately 18 months with median survival of 36 months. Recently, however, clinical trials have found high-dose chemotherapy with autologous stem cell transplant superior to conventional therapy. Complete remission rates with this therapy have
been shown to be 25-30% with a median survival exceeding 5 years. Overall, less than 50% of patients who are diagnosed with multiple myeloma survive 3 years. The insidious nature of the disease emphasizes the need for understanding the etiology of the disease, so that we can focus on prevention.

Furthermore, if obesity is involved in the etiology of multiple myeloma, we may be able to reduce the incidence of the disease by encouraging the population to lower energy intake and increase physical activity. In addition, results of the examination of the modifying effects of HRT use on the relationship between BMI and multiple myeloma will help clinicians with their decisions to prescribe HRT to women. In addition, it will be important in future research of multiple myeloma at MDACC and other institutions.

**Research Questions**

1) Is increased body mass index (BMI) associated with an increased risk of multiple myeloma?

2) Is adult weight gain during adulthood associated with an increased risk of multiple myeloma?

3) Among women, does hormone replacement therapy (HRT) modify the association between BMI and the risk of multiple myeloma?

**Objective and Hypothesis**

The overall objective of this case-control study was to determine whether multiple myeloma cases had higher BMI and greater adult weight gain relative to healthy controls and if HRT use in women modifies the association between BMI and risk of multiple myeloma. We hypothesized that multiple myeloma patients will more likely be overweight or obese and
also that patients will have gained more weight than healthy controls. In addition, we hypothesized that HRT use among women will further increase the association between BMI and risk of multiple myeloma.

Specific Aims

1) To determine the independent effect of BMI on the risk of multiple myeloma using univariate logistic regression analysis, as well as, determine the simultaneous effects of BMI controlling for potential confounding effects of age, race/ethnicity, gender, total years of education, alcohol use, cigarette smoking, family history of cancer, and history of diabetes.

2) To determine the independent effects of adult weight gain on the risk of multiple myeloma using univariate logistic regression analysis, as well as, determine the simultaneous effects of adult weight gain controlling for potential confounding effects of age, race/ethnicity, gender, total years of education, alcohol use, cigarette smoking, family history of cancer, and history of diabetes.

3) To determine whether HRT use modifies the effect of BMI on multiple myeloma risk.

METHODS

Study Design

This case-control study was conducted to examine the effects of BMI and adult weight gain on the risk of multiple myeloma. In addition, this study investigated the modifying effects of HRT use on the association between BMI and multiple myeloma in women.
Sampling Methodology

The pilot case-control study titled, *Etiology of multiple myeloma* was conducted at MDACC between January 1, 2006 and January 31, 2007. A total of 122 cases diagnosed with multiple myeloma after January 1, 2004 who visited the Bone and Marrow Transplant clinic and the Lymphoma/Myeloma clinic were enrolled. Controls (n=183) were selected from a database of random digit dialing (RDD) controls accrued in the Department of Epidemiology at MDACC (parent study *Epidemiology Controls*) and were frequency matched to the cases on age (± 5 years), gender, and race/ethnicity. Healthy controls, without a previous history of cancer (excluding non-melanoma skin cancer) were identified. This study was approved by the MDACC IRB.

Cases and Controls

**Cases.** Inclusion criteria for cases consist of MDACC patients who had a histologically confirmed diagnosis of multiple myeloma and were willing to provide a blood or buccal sample. Cases were excluded from the study if their diagnosis of multiple myeloma was prior to July 1, 2004. Cases were adults (≥18 years), of both genders and all race/ethnicities.

**Controls.** Controls consisted of willing participants between the ages of 20 and 75 identified through RDD in the Houston Metropolitan area. The exclusion criterion for controls was a previous history of cancer, excluding non-melanoma skin cancer, and individuals under the age of 18.
Case Recruitment

Eligible patients were identified from the clinic appointment listings. If possible, patients were approached during their clinic visit. Otherwise, they were contacted by telephone. If the patients could not be reached by phone, a letter was sent to their address with a stamped self-addressed post-card to return to MDACC if they were interested in participating in the study. A research interviewer was responsible for explaining the study and the consent form, and answering any questions. After informed consent was signed, the participant was asked to complete a self-administered questionnaire (see Appendix A). The participant received the questionnaire at the clinic or in the mail, along with instructions. The self-administered questionnaire was completed at their earliest convenience and returned to the Department of Epidemiology in a postage paid envelope. If the completed questionnaire was not returned within two months, the participant was follow-up with a phone call.

Control Recruitment

Population-based controls between the ages of 20 and 75 years with no prior history of invasive cancer were identified by RDD for the Epidemiology Controls parent study at MDACC. The RDD protocol that was used is based on the Waksberg procedure. Once eligible participants were identified, they were contacted by an interviewer from M. D. Anderson who explained the study, and ascertained willingness to participate and an informed consent. Each participant was interviewed by a research interviewer to obtain the same demographic and risk factor information collected from the cases. The participants in the database were then stratified by matching variables (age ± 5 years, sex and
race/ethnicity). Controls for this study were then selected from the database based on the ratio of controls needed for each strata (2 controls:1 case).

**Data Collection and Management**

**Data Collection**

Cases. Risk factor and demographic information was collected by a self-administered questionnaire. If the case participant did not return the questionnaire within 2 months, he/she was contacted by telephone and offered a phone interview.

Controls. Demographic and risk factor information was collected by a phone interview. The same information was collected for cases and controls.

**Questionnaire**

The questionnaire was designed to be easy for participants to complete, and has been used in other epidemiologic studies at MDACC. The questionnaire was available in English and Spanish. The format of the questionnaire with its predominance of close-ended questions limits error due to transcription. Upon receipt of self-administered questionnaires, they were assessed for completeness. Participants with incomplete questionnaires were called for re-query of missing information. Once complete, the questionnaire was coded using the coding manual developed for the present study. Each coded questionnaire was reviewed and edited for internal consistency before being scanned into the computer. To check for errors in the compiled dataset, existing edit check programs to verify information within each file and across files were used.
**Questionnaire Variables**

The purpose of the questionnaire was to collect information on demographic information, height and weight at age 25, 40 and current/diagnosis, medical history, family history of cancer, smoking and alcohol use.

The variables include:

a) Socio-demographic data included date and place of birth, marital status, race, ethnicity, total years of education, and income.

b) Weight and height at age 25, at age 40 and currently/at diagnosis.

c) Smoking and alcohol consumption patterns.

   1) Tobacco use, present smoking status, number of years smoked, and number of cigarettes smoked.

   2) Alcohol consumption by type and amount of beverage consumed (beer, liquor, and wine).

d) Medical history information such as immunological conditions, diabetes, hypertension, a previous history of cancer and certain medical treatments.

e) Family history information on all first-degree relatives included date of birth, death, cancer type, and date of diagnosis. The same information for second-degree relatives with cancer was also collected. No verification of self-reported cancers was planned. However, acceptable levels of accuracy for cancer reports in first-degree relatives have been reported \(^{49,50}\). The cancer type was coded to ICD-9 codes in order to categorize family history of hematologic cancers, which includes all types of leukemia, lymphoma and multiple
myeloma (ICD-9 codes: 200-208), and family history of multiple myeloma (ICD-9 code: 203.0) \textsuperscript{51}.

\textit{Data Collection Instrument}

The questionnaire was previously validated and has been used for many years in the Department of Epidemiology at MDACC \textsuperscript{52}. This report validated several demographic and clinical variables (e.g. weight, height, age, marital status, previous medical and surgical procedures, previous cancers and radiotherapy) using medical records as the gold standard, showing excellent agreement. Self-administered questionnaire data were compared with data from phone interviews to determine reliability of the instrument. Agreement rates were high, especially among categorical data.

\textit{Data Management, Data Quality Assurance, and Confidentiality}

Once all the data was collected, all identifying characteristics were removed and a separate dataset was created to be used in the data analysis. All paper copies of the dataset were kept in a locked desk when not in use. In addition, all electronic files of the dataset were secured in a password-protected computer. Confidentially was rigorously maintained. All personnel were aware of the importance of keeping all information concerning the study subjects confidential and were trained in the protection of confidentiality. Participants were assured that all information obtained will be kept confidential. The dataset did not contain personal identifiers.

\textit{Statistical Analysis}

Statistical analysis was performed on the total sample of 122 cases and 186 controls using the STATA software program (StataCorp, College Station, TX) \textsuperscript{54}. Student’s t-tests
and Pearson’s chi-squared tests were used to describe relevant variables such as age, gender, race/ethnicity, BMI, adult weight gain, education, smoking history and alcohol use, family history of cancer, history of diabetes, and history of HRT-use. Standard statistical methods for the analysis of data from a frequency matched case-control study were applied.

**Statistical analysis to address specific aims**

**Aim 1 and 2-BMI and weight gain.** Using univariate logistic regression, odds ratios (ORs) and 95% confidence intervals were calculated to quantify the association between BMI/weight gain and multiple myeloma. We assessed the data for potential confounders, such as total years of education, alcohol use, family history of cancer, family history of hematologic cancers and history of diabetes. Variables found to be significantly associated with increased risk of multiple myeloma (p-value ≤ 0.20) were modeled using backwards stepwise unconditional logistic regression. Matching variables, age, race/ethnicity and gender, were also included in the model to control for residual confounding. Multivariable modeling simultaneously adjusts for the effects of all variables in the constructed model.

**Aim 3-Modifying effects of HRT use.** The associations between BMI and multiple myeloma by HRT use were assessed by stratified analysis and an interaction term in the main effects model. For the stratified analysis, ORs and 95% confidence intervals were calculated while adjusting for age. In addition, crude and adjusted ORs and 95% confidence intervals were calculated for the main effects and interaction term adjusting for age only. Due to the small sample size of women, age was the only confounder considered.
Definition of Study Variables

BMI was categorized according to the National Institute of Health guidelines (1998) as follows: \( \leq 24.9 \text{ kg/m}^2 \) (referent), 25.0-29.9 kg/m\(^2\) (overweight), and \( \geq 30 \text{ kg/m}^2 \) (obese) \(^{19}\). It was based on self-reported height and weight at age 25 and age 40 for both cases and control. Those who were younger than 40 years (n=12) were excluded from the analysis for BMI at age 40. BMI at interview for controls was based on self-report as well. For cases, BMI at diagnosis was based on height and weight recorded in MDACC medical records. This measurement was used because some patients were interviewed after diagnosis. Due to the fact that some cases reported severe weight loss before diagnosis and weight gain due to treatment prior to MDACC, BMI at diagnosis was adjusted taking into consideration patient’s reported weight loss or gain prior to diagnosis as indicated in the medical record. All charts were reviewed to determine if severe weight loss or weight gain had occurred and how much. The reported weight loss or gain was then subtracted or added to the measured weight, respectively, to be used in the calculation of BMI. Those that reported weight gain/loss but did not report how much were excluded from the analysis (n=4). To gain power in the multivariable analysis, the overweight and obese categories were combined (\( \geq 25 \text{ kg/m}^2 \)). Weight gain between age 25 and 40 years was calculated using weight (kg) at age 40 subtracted by weight (kg) at age 25 years. Those who were younger than 40 years were excluded from this analysis (n=12). This time period was chosen because it was a 15-year period that was equal among all participants and there was little concern about weight loss due prior to disease diagnosis since the mean age at diagnosis in this population was 61. Categories were created using the tertile distribution in the controls: <4.7 kg (referent), 4.7-
11 kg, and >11 kg. However, in the multivariable analysis, the upper tertiles were combined and compared to the <4.7 kg referent group. HRT use was based on self-reported use of HRT. The HRT exposure variable was be categorized dichotomously (never use vs. ever use). Age was modeled as a continuous variable and race/ethnicity was categorized as non-Hispanic White, non-Hispanic Black, Hispanic White or Asian. All other variables were dichotomized, sex (male vs. female), education (high school or less vs. more than high school), cigarette smoking (never vs. ever), alcohol use (never vs. ever), family history of cancer (yes vs. no), family history of hematologic cancer (yes vs. no), history of multiple myeloma (yes vs. no), and history of diabetes (yes vs. no).

RESULTS

Of the 173 eligible multiple myeloma cases identified at MDACC, 122 cases completed the questionnaire, 18% of cases never returned the questionnaire despite multiple follow-ups, 4.5% of cases refused to participate, or 7% of cases were deceased or too sick to participate. The overall participation rate was 70.5%. There were no differences in the distributions of gender, race/ethnicity, Texas residency, diagnosis year, or diagnostic age between the completed cases and those lost to follow up. For the population-based controls, the overall response rate for was 71%.

The final study sample included 122 MDACC multiple myeloma cases and 186 population controls. Table 1 shows the distribution of major characteristics among cases and controls. Ages of the population range, for cases, from 33-83 years, and, for controls, from 28-86 years. Because controls were frequency matched to cases on age, gender and race/ethnicity we did not expect nor did we observe differences in cases and controls by these
three factors. Compared to controls, cases tended to be less educated ($P=0.007$), but not significantly different according to cigarette smoking or alcohol use. More than controls, cases reported having a first degree relative with cancer ($P=0.027$). Family history of hematologic cancer and family history of multiple myeloma were not significantly different between cases and controls. Cases were also more likely to have reported diabetes ($P=0.020$). Among women ($n=124$), cases and controls had similar proportions of HRT use ($P=0.692$).

Table 2 presents the distribution of the BMI exposure variables among cases and controls. The distribution of BMI (continuous or categorical) was similar among cases and controls; however, BMI at diagnosis (categorical) was borderline significantly different ($P=0.078$). The distribution of adult weight gain was significantly different between cases and controls ($P=0.034$) with cases having gained more weight. Among cases, 73% gained more than 4.7 kg between age 25 and 40 as compared to 61.8% of controls.

**Specific Aim 1 and 2**

Using logistic regression, the effects of BMI and weight gain on the risk of multiple myeloma were analyzed. For Aims 1 and 2, the Hosmer-Lemeshow method was used to build the logistic regression models. First, univariate logistic regression was performed. Table 3 presents the crude odds ratios (ORs), 95% confidence intervals (CIs) and p-values for multiple myeloma and factors of interest. Variables found to have a p-value$<0.20$ were considered for the multivariable model, along with clinically significant variables. For all BMI variables (Aim 1), a BMI $<25$ kg/m$^2$ was chosen as the reference group. For Aim 2, weight gain of less than 4.7 kg was used as the reference group. All other variables were
dichotomized: education (≤ High school diploma/>High school diploma), family history of cancer (yes/no), family history of hematologic cancer (yes/no), family history of multiple myeloma (yes/no), and history of diabetes (yes/no). For education, less than a high school diploma was selected as the reference group. The absence of all other factors (no) was used as the reference group the univariate logistic regression. Education, family history of cancer, family history of hematopoietic cancers and history of diabetes all had a p-value<0.20 and were considered for the multivariable model.

A stepwise unconditional logistic regression was used to develop a multivariable model for the association between BMI at age 25, 40 and diagnosis and adult weight gain and multiple myeloma (Table 4 and 5). The three matching variables (age, race/ethnicity, and sex) were included in all 4 multivariable logistic regression models as confounders. Education and family history of cancer were also included in the model. No other confounding factors materially affected the odds ratio for BMI or weight gain and multiple myeloma.

Table 4 presents the 3 logistic regression models for for multiple myeloma and BMI at age 25, age 40, and diagnosis(#1, #2, and #3 respectively). The table includes the crude and adjusted odds ratios (ORs) and 95% confidence intervals (CIs) for each model. After adjusting for confounders, being overweight or obese (BMI > 25 kg/m²) at age 25 was associated with an odds ratio of 1.79 (95% CI=0.98-3.20). A 42% increased risk was associated with having a BMI > 25 kg/m² at age 40 (OR=1.42, 95% CI=0.86-2.34); however, this association was not statistically significant. A BMI > 25 kg/m² at diagnosis associated
with a 43% increased risk of multiple myeloma (OR=1.43, 95% CI=0.78, 2.63; although, this association was also not statistically significant.

The association between adult weight gain between the ages of 25 years and 40 years is shown in Table 5. We observed a statistically significant 2-fold increased risk of multiple myeloma in individuals who gained more than 4.7 kg during the 15 year period (OR=1.97, 95% CI=1.15-3.39) after adjusting for age, gender, race/ethnicity, education, and family history of cancer.

**Specific Aim 3**

The modifying effects of HRT use on the association between BMI and multiple myeloma in women was also evaluated using two different methods: stratified analysis and main effects model with an interaction term. Table 6 shows the results for the stratified analysis. After stratifying by HRT use (never vs. ever), we observed an effect modification of the association between BMI and multiple myeloma. No association between obesity and MM status was observed among women who have never used HRT (OR=0.60, 95% CI=0.23-1.61; n=73). Yet among women who have ever used HRT (n=50), being overweight or obese was associated with an increase in MM risk (OR=2.93, 95% CI=0.81-10.6) after adjusting for age; however, the association was not statistically significant. The test for homogeneity for the crude model was marginally significant ($P=0.082$). Table 7 shows similar results as the stratified analysis. No significant association was observed in women who have never used HRT and have a BMI > 25 kg/m$^2$ (OR=0.62, 95% CI=0.23, 1.65) after adjusting for age. Conversely, the joint effect of being overweight and obese and using HRT had nearly a four-fold increase in odds (OR=3.93, 95% CI=0.86, 17.8). The
significance of the interaction term was tested using the likelihood ratio test, which was approaching significance ($p=0.076$).
Table 1. Descriptive characteristics of the study population.

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>No. of cases (%)</th>
<th>No. of controls (%)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td><strong>N=122</strong></td>
<td><strong>N=186</strong></td>
<td></td>
</tr>
<tr>
<td>Age (years) (range)</td>
<td>33-83</td>
<td>28-86</td>
<td></td>
</tr>
<tr>
<td>≤ 45</td>
<td>8 (6.6)</td>
<td>13 (7.0)</td>
<td></td>
</tr>
<tr>
<td>44-50</td>
<td>11 (9.0)</td>
<td>19 (10.2)</td>
<td></td>
</tr>
<tr>
<td>51-55</td>
<td>12 (9.8)</td>
<td>31 (16.7)</td>
<td></td>
</tr>
<tr>
<td>56-60</td>
<td>23 (18.9)</td>
<td>43 (23.1)</td>
<td></td>
</tr>
<tr>
<td>61-65</td>
<td>26 (21.3)</td>
<td>37 (19.9)</td>
<td></td>
</tr>
<tr>
<td>66-70</td>
<td>12 (9.8)</td>
<td>23 (12.4)</td>
<td></td>
</tr>
<tr>
<td>71-75</td>
<td>14 (11.5)</td>
<td>18 (9.7)</td>
<td></td>
</tr>
<tr>
<td>&gt;75</td>
<td>12 (8.3)</td>
<td>6 (3.2)</td>
<td>0.074</td>
</tr>
<tr>
<td>Gender</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>75 (61.5)</td>
<td>109 (58.6)</td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>47 (38.5)</td>
<td>77 (41.4)</td>
<td>0.615</td>
</tr>
<tr>
<td>Race</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Non-Hispanic White</td>
<td>81 (66.4)</td>
<td>137 (73.7)</td>
<td></td>
</tr>
<tr>
<td>Black</td>
<td>20 (16.4)</td>
<td>28 (15.1)</td>
<td></td>
</tr>
<tr>
<td>Hispanic White</td>
<td>18 (14.8)</td>
<td>17 (9.1)</td>
<td></td>
</tr>
<tr>
<td>Asian</td>
<td>3 (2.4)</td>
<td>4 (2.1)</td>
<td>0.439</td>
</tr>
<tr>
<td>Education</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤ High School</td>
<td>32 (26.2)</td>
<td>26 (14.0)</td>
<td>0.007</td>
</tr>
<tr>
<td>&gt; High School</td>
<td>90 (73.8)</td>
<td>160 (86.0)</td>
<td></td>
</tr>
<tr>
<td>Cigarette smoking</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Never</td>
<td>65 (53.3)</td>
<td>102 (54.8)</td>
<td></td>
</tr>
<tr>
<td>Ever</td>
<td>57 (46.7)</td>
<td>84 (45.2)</td>
<td>0.788</td>
</tr>
<tr>
<td>Alcohol</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Never</td>
<td>51 (41.8)</td>
<td>82 (44.1)</td>
<td></td>
</tr>
<tr>
<td>Ever</td>
<td>71 (58.2)</td>
<td>104 (55.9)</td>
<td>0.692</td>
</tr>
<tr>
<td>Family history of cancer §</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>46 (37.7)</td>
<td>94 (50.5)</td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>76 (62.3)</td>
<td>92 (49.5)</td>
<td>0.027</td>
</tr>
<tr>
<td>Family history of hematologic cancer §</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>113 (92.6)</td>
<td>178 (95.7)</td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>9 (7.4)</td>
<td>8 (4.3)</td>
<td>0.248</td>
</tr>
<tr>
<td>Family history of multiple myeloma §</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>117 (95.9)</td>
<td>184 (98.9)</td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>5 (4.1)</td>
<td>2 (1.1)</td>
<td>0.082</td>
</tr>
<tr>
<td>History of diabetes</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>99 (81.1)</td>
<td>168 (90.3)</td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>23 (18.9)</td>
<td>18 (9.7)</td>
<td>0.020</td>
</tr>
<tr>
<td>HRT use in women</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Never</td>
<td>27 (57.4)</td>
<td>47 (61.0)</td>
<td></td>
</tr>
<tr>
<td>Ever</td>
<td>20 (42.6)</td>
<td>30 (39.0)</td>
<td>0.692</td>
</tr>
</tbody>
</table>

*Family history of cancer in 1st degree relative excluding non-melanoma skin cancer*
Table 2. Distribution of BMI at 25 years, 40 years, and diagnosis and adult weight gain among cases and controls.

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>No. of cases</th>
<th>No. of controls</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N=122 (%)</td>
<td>N=186 (%)</td>
<td></td>
</tr>
<tr>
<td>BMI at 25 years</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean kg/m^2 (SD)</td>
<td>23.3 (3.23)</td>
<td>22.6 (3.63)</td>
<td>0.156</td>
</tr>
<tr>
<td>By group</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Normal</td>
<td>90 (73.8)</td>
<td>153 (82.3)</td>
<td></td>
</tr>
<tr>
<td>Overweight</td>
<td>27 (22.1)</td>
<td>25 (13.4)</td>
<td></td>
</tr>
<tr>
<td>Obese</td>
<td>5 (4.1)</td>
<td>8 (4.3)</td>
<td>0.137</td>
</tr>
<tr>
<td>BMI at 40 years*</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean kg/m^2 (SD)</td>
<td>26.2 (4.1)</td>
<td>25.9 (5.7)</td>
<td>0.563</td>
</tr>
<tr>
<td>By group</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Normal</td>
<td>52 (42.6)</td>
<td>88 (47.3)</td>
<td></td>
</tr>
<tr>
<td>Overweight</td>
<td>50 (41.0)</td>
<td>68 (36.5)</td>
<td></td>
</tr>
<tr>
<td>Obese</td>
<td>18 (14.7)</td>
<td>22 (11.2)</td>
<td></td>
</tr>
<tr>
<td>BMI at diagnosis ε</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean kg/m^2 (SD)</td>
<td>29.1 (5.8)</td>
<td>28.2 (5.5)</td>
<td>0.198</td>
</tr>
<tr>
<td>By group</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Normal</td>
<td>24 (20.3)</td>
<td>46 (24.7)</td>
<td></td>
</tr>
<tr>
<td>Overweight</td>
<td>47 (39.8)</td>
<td>89 (47.8)</td>
<td></td>
</tr>
<tr>
<td>Obese</td>
<td>47 (39.8)</td>
<td>51 (27.4)</td>
<td>0.078</td>
</tr>
<tr>
<td>Weight gain (kg) from 25 to 40 yrs of age*</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&gt; 4.7</td>
<td>32 (26.7)</td>
<td>68 (38.2)</td>
<td></td>
</tr>
<tr>
<td>4.7-11</td>
<td>49 (40.8)</td>
<td>49 (27.5)</td>
<td></td>
</tr>
<tr>
<td>&gt; 11</td>
<td>39 (32.5)</td>
<td>61 (34.3)</td>
<td>0.034</td>
</tr>
</tbody>
</table>

* Two cases and 8 controls were excluded due to ages being less than 40.  
εFour cases were excluded due to undetermined weight gain or loss.
Table 3. Univariate logistic regression analysis.

<table>
<thead>
<tr>
<th>Risk factor</th>
<th>Crude Odds Ratio (95% CI)</th>
<th>p-value</th>
<th>Trend p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>BMI at 25 years (kg/m²)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Normal</td>
<td>1.00</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Overweight</td>
<td>1.79 (0.98, 3.25)</td>
<td>0.057</td>
<td></td>
</tr>
<tr>
<td>Obese</td>
<td>1.08 (0.34, 3.39)</td>
<td>0.900</td>
<td>0.177</td>
</tr>
<tr>
<td><strong>BMI at 40 years (kg/m²)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Normal</td>
<td>1.00</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Overweight</td>
<td>1.24 (0.75, 2.05)</td>
<td>0.392</td>
<td></td>
</tr>
<tr>
<td>Obese</td>
<td>1.38 (0.68, 2.82)</td>
<td>0.370</td>
<td>0.292</td>
</tr>
<tr>
<td><strong>BMI at diagnosis (kg/m²)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Normal</td>
<td>1.00</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Overweight</td>
<td>1.01 (0.55, 1.86)</td>
<td>0.969</td>
<td></td>
</tr>
<tr>
<td>Obese</td>
<td>1.77 (0.94, 3.33)</td>
<td>0.078</td>
<td>0.054</td>
</tr>
<tr>
<td><strong>Adult weight gain between age 25 and 40 years (kg)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&gt; 4.7</td>
<td>1.00</td>
<td></td>
<td></td>
</tr>
<tr>
<td>4.7-11</td>
<td>2.13 (1.20, 3.77)</td>
<td>0.010</td>
<td></td>
</tr>
<tr>
<td>&gt; 11</td>
<td>1.35 (0.75, 2.41)</td>
<td>0.319</td>
<td>0.313</td>
</tr>
<tr>
<td><strong>Education</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;= High school</td>
<td>1.00</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&gt; High school</td>
<td>0.46 (0.26, 0.81)</td>
<td>0.008</td>
<td></td>
</tr>
<tr>
<td><strong>Family history of cancer</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>1.00</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>1.69 (1.06, 2.69)</td>
<td>0.027</td>
<td></td>
</tr>
<tr>
<td><strong>Family history of hematologic cancer</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>1.00</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>1.77 (0.66, 4.73)</td>
<td>0.253</td>
<td></td>
</tr>
<tr>
<td><strong>Family history of multiple myeloma</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>1.00</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>3.93 (0.75, 20.6)</td>
<td>0.105</td>
<td></td>
</tr>
<tr>
<td><strong>History of diabetes</strong></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>1.00</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>2.17 (1.12, 4.21)</td>
<td>0.023</td>
<td></td>
</tr>
</tbody>
</table>

* Two cases and 8 controls were excluded due to ages being less than 40.
† Four cases were excluded due to undetermined weight gain or loss.
§ Family history of cancer in 1st degree relative excluding non-melanoma skin cancer.
Table 4. Crude and adjusted odds ratios for BMI associated with multiple myeloma risk.

<table>
<thead>
<tr>
<th>BMI (kg/m²)</th>
<th>Cases n (%)</th>
<th>Controls n (%)</th>
<th>Crude OR (95% CI)</th>
<th>p-value</th>
<th>Adjusted OR§ (95% CI)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>#1. BMI at age 25</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt; 25</td>
<td>90 (73.8)</td>
<td>153 (82.3)</td>
<td>1.00</td>
<td>1.00</td>
<td></td>
<td>1.00</td>
</tr>
<tr>
<td>≥ 25</td>
<td>32 (26.2)</td>
<td>33 (17.7)</td>
<td>1.65 (0.95, 2.86)</td>
<td>0.076</td>
<td>1.79 (0.98, 3.20)</td>
<td>0.054</td>
</tr>
<tr>
<td>#2. BMI at age 40*</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt; 25</td>
<td>52 (42.6)</td>
<td>88 (47.3)</td>
<td>1.00</td>
<td>1.00</td>
<td></td>
<td>1.00</td>
</tr>
<tr>
<td>≥ 25</td>
<td>68 (55.7)</td>
<td>90 (49.1)</td>
<td>1.28 (0.80, 2.04)</td>
<td>0.301</td>
<td>1.42 (0.86, 2.34)</td>
<td>0.174</td>
</tr>
<tr>
<td>#3. BMI at diagnosis £</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt; 25</td>
<td>24 (22.9)</td>
<td>46 (24.7)</td>
<td>1.00</td>
<td>1.00</td>
<td></td>
<td>1.00</td>
</tr>
<tr>
<td>≥ 25</td>
<td>94 (79.7)</td>
<td>140 (75.3)</td>
<td>1.32 (0.76, 2.31)</td>
<td>0.323</td>
<td>1.43 (0.78, 2.63)</td>
<td>0.245</td>
</tr>
</tbody>
</table>

§ Adjusted for sex, race/ethnicity, age, education, and family history of cancer.
* Two cases and 8 controls were excluded due to ages being less than 40.
£ Four cases were excluded due to undetermined weight gain or loss.

Table 5. Crude and adjusted odds ratios for weight gain between age 25 and 40 years associated with multiple myeloma risk.

<table>
<thead>
<tr>
<th>Weight gain between age 25 and 40 years (kg)*</th>
<th>Cases n (%)</th>
<th>Controls n (%)</th>
<th>Crude OR (95% CI)</th>
<th>p-value</th>
<th>Adjusted OR§ (95% CI)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 4.7</td>
<td>32 (26.2)</td>
<td>68 (36.5)</td>
<td>1.00</td>
<td>1.00</td>
<td></td>
<td>1.00</td>
</tr>
<tr>
<td>≥ 4.7</td>
<td>88 (72.1)</td>
<td>110 (59.1)</td>
<td>1.70 (1.03, 2.82)</td>
<td>0.039</td>
<td>1.97 (1.15, 3.39)</td>
<td>0.014</td>
</tr>
</tbody>
</table>

* Two cases and 8 controls were excluded due to ages being less than 40.
§ Adjusted for sex, race/ethnicity, age, education and family history of cancer.
Table 6. Crude and adjusted odds ratio for BMI (at age 40) associated with multiple myeloma risk by HRT-use status.

<table>
<thead>
<tr>
<th>BMI at 40 (kg/m²)</th>
<th>Cases</th>
<th>Controls</th>
<th>Crude OR (95% CI)</th>
<th>p-value</th>
<th>Adjusted OR§ (95% OR)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Ever HRT-use</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>BMI &lt; 25</td>
<td>9 (45.0)</td>
<td>19 (63.3)</td>
<td>1.00</td>
<td>1.00</td>
<td>1.00</td>
<td>1.00</td>
</tr>
<tr>
<td>BMI ≥ 25</td>
<td>11 (55.0)</td>
<td>11 (36.7)</td>
<td>2.11 (0.67, 6.68)</td>
<td>0.204</td>
<td>2.93 (0.81, 10.6)</td>
<td>0.103</td>
</tr>
<tr>
<td><strong>Never HRT-use</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>BMI &lt; 25</td>
<td>15 (55.5)</td>
<td>19 (41.3)</td>
<td>1.00</td>
<td>1.00</td>
<td>1.00</td>
<td>1.00</td>
</tr>
<tr>
<td>BMI ≥ 25</td>
<td>12 (44.5)</td>
<td>27 (58.7)</td>
<td>0.56 (0.21, 1.47)</td>
<td>0.241</td>
<td>0.60 (0.23, 1.61)</td>
<td>0.313</td>
</tr>
<tr>
<td>Test of homogeneity</td>
<td></td>
<td></td>
<td></td>
<td>0.082</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

§Adjusted for age.

Table 7. Main effects model with interaction term.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Crude OR (95% CI)</th>
<th>P-value</th>
<th>Adjusted OR§ (95% CI)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>BMI at age 40 (&lt; 25 vs ≥25)</td>
<td>0.56 (0.22, 1.47)</td>
<td>0.241</td>
<td>0.62 (0.23, 1.65)</td>
<td>0.342</td>
</tr>
<tr>
<td>HRT use (ever vs never)</td>
<td>0.60 (0.21, 1.70)</td>
<td>0.337</td>
<td>0.50 (0.17, 1.49)</td>
<td>0.215</td>
</tr>
<tr>
<td>BMI at age 40 x HRT use</td>
<td>3.75 (0.84, 16.8)</td>
<td>0.084</td>
<td>3.93 (0.86, 17.8)</td>
<td>0.076</td>
</tr>
</tbody>
</table>

§Adjusted for age.
DISCUSSION

This pilot case-control study evaluated the risk of multiple myeloma in relation to BMI and adult weight gain as well as whether HRT use in women modifies the association between multiple myeloma and BMI. Our study found that overweight and obese individuals (BMI $\geq 25$ kg/m$^2$) had an increased risk of developing multiple myeloma. Due to a small sample size, these elevated risks are not statistically significant. Gaining more than 4.7 kg (about 10 lbs) between the ages of 25 and 40 may also increase the risk. For women, our data suggests that the HRT use modulates the association between BMI and multiple myeloma; although, this association is also not statistically significant. To the best of our knowledge, our study is the first to look at three measurements for height and weight at different ages throughout adult life, weight gain during adulthood, as well as, the modifying effects of HRT-use in women, in relation to multiple myeloma.

The elevated risk we observed with increased BMI is consistent with the relationship reported in the multiple myeloma literature $^6$-$^{11}$. These studies have shown that obesity increases the risk of multiple myeloma, risk estimates ranging from 1.10 to 2.06. In addition, a recent population-based case-control study (148 cases and 116 controls) examined the role of obesity on the etiology of the disease $^5$. They demonstrated that overweight and obese individuals have a statistically significant 60% and 80% increased risk of multiple myeloma, respectively, when compared with controls with a BMI < 25 kg/m$^2$. More recently, investigators at Harvard assessed the role of body mass index and physical activity on the risk of multiple myeloma using the Nurses Health and the Health Professionals cohorts $^4$. Compared to individuals with normal BMI, the RRs were 1.3 (95% CI=0.9-2.0) for those
who were overweight and 1.5 (95% CI=0.9-2.5) for those who were obese after controlling for age, physical activity and cohort.

Larsson et al recently published meta-analysis suggesting that excess body weight is a risk factor for multiple myeloma. The meta-analysis of 11 cohort and 4 case-control studies found that compared with individuals with normal weight, the risk of multiple myeloma was statistically significantly higher among those who were overweight (cohort studies: RR=1.12, 95% CI=1.07-1.18; case-control studies: RR=1.43, 95% CI=1.23-1.68) and obese (cohort studies: RR=1.27, 95% CI=1.15-1.41; case-control studies: RR=1.82, 95% CI=1.47-2.26). Of these studies, 8 were from North America, 4 from Europe, 2 from Asia, and 1 from Australia. The association was similar among men and women and also among whites and blacks.

In our study, we observed a statistically significant 2-fold increased risk of multiple myeloma in individuals who gained more than 4.7 kg between age 25 and 40 years (OR=1.97, 95% CI=1.15-3.39). To our knowledge, this finding has not been previously reported. The positive association observed seems plausible given the literature suggests that adult weight gain is associated with increased risk of other cancers, including renal cancer, pancreatic cancer, female breast cancer, endometrial cancer, and colon adenomas. More studies assessing the role adult weight gain in multiple myeloma development we well as the identification of the mechanisms involved are needed.

The third aim of this study was to examine the modifying effects of HRT-use on the relationship between BMI and multiple myeloma in women. We found support for an interaction between HRT-use and BMI and increased risk of multiple myeloma using both
stratified analysis as well as using an interaction term in the main effects model. Using both methods, the increased risk associated with increased BMI (BMI ≥ 25 kg/m² vs. BMI < 25 kg/m²) was higher for women reporting ever HRT-use as compared to those not reporting HRT-use, after controlling for age. Unfortunately, the sample size was insufficient to adequately evaluate this observation; therefore, neither estimate was statistically significant. Still, the test for homogeneity was borderline significant, which suggests that the association between increased BMI and multiple myeloma may be modified by the use HRT use in women. We speculate that the effect is due to the direct action of estrogen from HRT use in addition to the adverse effects of excess adiposity. To our knowledge, this finding has not been previously reported in the multiple myeloma literature.

**Biologic Mechanism**

The biological mechanism underlying the association between increased BMI, weight gain, HRT-use and cancer risk is not well understood. The relationship suggests that excess energy is an important risk factor for development of cancer. Several physiological pathways have been postulated to explain the effects of energy balance and adiposity on multiple myeloma risk, including inflammation, insulin resistance and endogenous hormone metabolism.

The dysregulation of IL-6 is one of the plausible biological mechanisms underlying the association between BMI and multiple myeloma. Obese individuals have elevated levels of the proinflammatory cytokine interleukin-6 (IL-6). IL-6 expression in adipose tissue from obese individuals is 10-fold that in adipose tissue from lean individuals if normalized for the number of adipocytes present. In fact, as much as 30% of total body IL-6 may be
produced by adipocytes in obese individuals. IL-6, a pleiotropic cytokine with a wide range of biological activities, is necessary for the differentiation of immature plasmablasts into mature antibody-producing plasma cells in the bone marrow. More importantly, it has been documented to have proliferative and antiapoptotic effects on myeloma cells, as well as its levels may predict disease severity.

Insulin resistance, along with several metabolic abnormalities, has been associated with excess weight, and may lead to increased secretion of insulin from the pancreas. The effects of the chronic hyperinsulinemic state have also been demonstrated for cancers of the breast, ovary, colon-rectum, stomach, pancreas, and prostate. Chronic increased insulin concentration reduces the IGFBP and increases free IGF-1. There is evidence that suggests both insulin and IGF-1 can enhance tumor growth by stimulating cell proliferation and inhibiting apoptosis. In addition, a synergistic relationship between the IL-6 and IGF-I pathways has been suggested by in vitro experiments on multiple myeloma cell lines.

The insulin/IGF-I pathway may also affect the risk of cancers by altering the levels of sex hormones. Both insulin and IGF-1 inhibit the synthesis of the sex-hormone binding globulin (SHBP), the major carrier of testosterone and estradiol in the plasma, and consequently increase the level of free estrogens and androgen available for bioactivity. In addition, for men and postmenopausal women, adipose tissue is a major site for synthesis of estrogens from androgenic precursors. Sex hormones are known to regulate the balance between cellular differentiation, proliferation, and apoptosis, and may help the growth of preneoplastic and neoplastic cells.
Furthermore, the effects of estrogens on tumor development are mediated by estrogen receptors (ER), which induce gene transcription resulting in cell proliferation. In 2000, Otsuki et al. clearly demonstrated that anti-estrogens suppress myeloma cell growth through cytostatic and apoptotic mechanism. As a result, it was proposed that estrogen and ER may play a role in initiation and progression of multiple myeloma and that overproduction of estrogen in obese postmenopausal women may upregulate ER in plasma cells resulting in increased risk of multiple myeloma. Therefore, increasing the amount of exogenous hormones in obese women, by use of HRT, may further increase the risk of multiple myeloma in obese women.

**Strengths**

There are many strengths of this study. The proposed case-control study allowed the opportunity to investigate a rare disease such as multiple myeloma. MDACC provided us with a sufficient number of eligible patients for a pilot study with a good participation rate (71%). This participation rate is consistent with other multiple myeloma case-control studies and is mostly likely due to the rapid morbidity and mortality of the disease. We believe this is the first case-control study to evaluate BMI at three different time periods allowing assessment of temporality, as well as examine the relationship of adult weight gain and risk of the disease. The questionnaire, data collection methods and data management methods that was used in this study has also been used in numerous NCI funded protocols at MDACC. Furthermore, the questionnaire includes data on broad range of possible confounders.
Limitations

The design of case-control studies has inherent limitations. First, it is observational in nature. Although we used data to explore and develop hypotheses, we do not have the ability to test physiological mechanisms directly. In addition, recall bias was possible due to the retrospective nature of the data collection as well as dependence on self-reported data. In order to reduce recall bias, all questions were relevant to the respondent, were framed in an unambiguous way, and were stated equally to both cases and controls. Therefore, the bias introduced by this misclassification would be non-differential and towards the null. While every effort was made to maximize exposure recall in the study, there is still a possibility of missed or incorrect information.

MDACC patients are also subject to referral patterns and neither cases nor the controls were being identified through population-based registries. The identification of the controls was through RDD, a standard practice for control recruitment. A major limitation of this method is the possibility of obtaining a biased sample due to difficulties reaching minority populations \(^7\), increased cell phone usage, voicemail, and caller ID’s. In addition, the control data was collected by phone interviews and the case data was predominantly collected by self-administered questionnaires, although, a small percentage of case data was collected by phone interviews (13\%). However, as mentioned above, questions were stated equally for both cases and controls. Another limitation of the data set was asymmetry of residence for the cases and controls. The control data available for this study were exclusively recruited in the counties surrounding the Houston Medical Center; however, due to the rare nature of the disease, the cases were not restricted to those residing in this area.
(34% of cases reside outside Texas, 68% of cases reside outside Houston Metropolitan area). Unknown environmental factors that may differ between cases and controls could be influencing the results; however, since the results are consistent with the current literature, this scenario is unlikely. In addition, generalizability of these results given these data are limited; nonetheless, this study is necessary to test the feasibility in preparation for future multi-center studies.

CONCLUSIONS

In summary, our case-control study suggests that being overweight or obese at ages 25, 40 and at diagnosis increases the risk of developing multiple myeloma. In women, this association may be modulated by HRT use. In addition, adult weight gain also increases the risk of developing multiple myeloma. These results support our original hypothesis. Therefore, we may be able to reduce the incidence of multiple myeloma and other diseases associated with obesity by encouraging the population to maintain a healthy weight. It is possible that obesity and weight gain may alter multiple myeloma risk through the IL-6, insulin/IGF-1, or sex-hormone pathways. Additional research to clarify the underlying biological mechanisms as well as to examine other environmental and genetic risk factors will be valuable toward the interpretation of these findings and development of effective strategies to prevent this disease.

FUTURE DIRECTION

Effective strategies to cancer prevention have become a critical task of public health in the U.S. The investigation of the roles of BMI, weight gain and HRT use in the development of multiple myeloma is just one piece of the puzzle. The association with
obesity is becoming established within the multiple myeloma literature; however, it is necessary to clarify its underlying biologic mechanism. However, the findings of adult weight gain as a risk factor for multiple myeloma as well as the modifying effect of HRT-use should be replicated and confirmed by multi-institutional studies. Advances in the field of molecular biology have allowed recent investigation of the role of genetic susceptibility in multiple myeloma risk. An association with family history and the racial disparity of the disease strongly suggests a role of genetic factors. Genes of interest that may be interacting with obesity on risk of multiple myeloma include those involved in immune function and inflammation. Altogether, this suggests the need for larger and more comprehensive studies that analyze genetic susceptibility in conjunction with demographic, lifestyle, environmental, and clinical information.
LITERATURE CITED


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VITA

Jill Amaon was born in Houston, Texas on July 20, 1979 to parents Gary and Paula Amaon. Gary, a retired attorney, worked for the Nature Conservancy as the Edward’s Plateau Eco-regional Manager until recently retiring in June 2007. Paula, a retired dentist, spends her time volunteering for Planned Parenthood and medical-dental mission trips in Guatemala and Africa. Jill was recently married to Andrew Royle, a Chevron geophysicist originally from Newfoundland, Canada. She graduated from St. John’s School in 1997 and began her undergraduate work at Trinity University in San Antonio, Texas. In 2001, she received a B.S. in Biology from Trinity University. Jill received her Master of Public Health at the University of Texas School of Public Health in 2004. She worked closely with Dr. Herbert Dupont on her thesis titled *Study of nosocomial and Clostridium difficile-associated diarrhea at St. Luke’s hospital*. During this time she wanted to further her education in epidemiology and decided to pursue a Doctor of Philosophy at the University of Texas School of Public Health. She was awarded an R25 pre-doctoral fellowship in Cancer Prevention at M.D. Anderson Cancer Center, which supported her dissertation research. At M. D. Anderson, Jill worked closely with her mentor, Dr. Sara Strom, in the Department of Epidemiology.