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The Role of County-Level Contextual Predictors in Multiple Myeloma Mortality in the United States

By

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By

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Bachelor of Science

University of Toledo

2013

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An abstract of
A thesis submitted to the Faculty of the
Rollins School of Public Health of Emory University
in partial fulfillment of the requirements for the degree of
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Abstract

The Role of County-Level Contextual Predictors in Multiple Myeloma Mortality in the United States

By Lakshmi Radhakrishnan

Background: Myeloma is the second most common hematologic malignancy in the United States. Prior population-based studies suggest that the incidence and mortality of black patients is two times higher compared to the whites and others (American Indian/AK Native, Asian/Pacific Islander). While some studies point to underlying biological mechanisms for this observed difference, others suggest the role of individual socioeconomic disparities as the cause. To our knowledge, no studies have analyzed the independent association of county-level contextual variables on myeloma mortality.

Methods: I used Surveillance, Epidemiology and End Results (SEER) data from 18 registries across the United States to examine racial differences in mortality from 1973-2011 for 83,903 myeloma patients. International Classification of Disease for Oncology, 3rd Edition (ICD-O-3) and morphologic (9732/3) codes were used to identify cases. Analysis was done on two levels: individual-level (using race, sex and age of diagnosis) and county-level (high school education, poverty line and unemployment). Crude incidence and mortality rates and regression models were used for analysis.

Results: Blacks were more likely to be diagnosed at a younger age (median age of diagnosis: 66 years), and live in Middle and Low socioeconomic status (SES) counties as compared to whites. These counties were characterized by populations more likely to not have received a high school education, to live below poverty-line and to be unemployed (all $p<0.0001$). Blacks had higher crude incidence and mortality rates compared to whites. However, after controlling for county-level contextual variables of SES, high-school education, poverty-line and unemployment, blacks had a lower odds of mortality compared to whites (p-value<0.0001). Additionally, regression models revealed increasing mortality with decreasing county SES (p-value<0.001).

Conclusions: Black patients have higher crude mortality rates compared to whites and other myeloma patients. The opposite becomes true after controlling for county-level contextual variables (SES, high-school education, poverty and unemployment); signifying their role as confounders in the causal pathway between race and myeloma mortality. Further population-based studies examining both, the biological variants of this disease in conjunction with race, as well as the socio-contextual factors surrounding these populations are needed, to reduce the racial disparity in myeloma mortality.

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Background

Multiple myeloma is the second most common hematological malignancy accounting for 10% of all hematologic malignancies (1, 2). It is caused by uncontrolled proliferation of clonal plasma cells in the bone marrow, leading to end organ damage presenting as hypercalcemia, renal failure, and anemia or bone lesions (3, 4). Over the past two decades the incidence of myeloma has been gradually increasing in the United States (1). For the year 2015, the estimated incidence of myeloma is approximately 26,850 cases (14,090 in men and 12,760 in women), with an anticipated mortality of 11,240 persons (6,240 in men and 5,000 in women) (5, 6). The incidence of myeloma is higher in men than women; and twice as common in blacks as compared to whites (7-9). Despite major clinical research in the field of myeloma, a decisive explanation to account for the higher incidence of myeloma among men and blacks has not been realized (10). Myeloma is a disease continuum and is mostly preceded by monoclonal gammopathy of undetermined significance (MGUS), followed by a state of smoldering myeloma, slowly progressing to symptomatic myeloma (9-12). Numerous primary and secondary genetic events play a part in this disease progression. Although the etiology of MGUS is unclear, it has a higher prevalence among blacks, suggesting a reason for increased incidence of myeloma in blacks (10, 11).

The risk factors for multiple myeloma have not been well elaborated due to the difficulty in conducting such prospective studies. Nevertheless, some retrospective analyses have identified certain uniform risk-factors across these studies. One such factor is race. Notwithstanding advances in technology and increasing clinical trials, there remains a differential overall survival rate between blacks and whites. Nonetheless, this difference is not completely attributable to genetic variations between the two groups (2,

13, 14). Prior population based studies that showed higher incidence and mortality rates for blacks with myeloma (2, 11, 13, 15-17), also established that this difference does not persist after controlling for treatment (1, 18-20). This implies the influence of extraneous socio-contextual factors, such as socioeconomic status (21), education and income on racial differences in survival (21-25).

The value of socio-contextual variables, both individual and community-level, is immense in determining mortality (25). Meta-analyses from the year 2000 demonstrate that mortality attributable to community-level social factors are comparable to deaths by actual pathopsychological and behavioral causes. For the same year, Galea et al. proved that deaths attributed to low educational attainment, racial segregation, area-level poverty, and income inequality, all put together, matched estimates of deaths due to actual psychological and psychological causes (23).

In the same vein, several analyses have studied the independent associations of individual-level variable with mortality. Most contextual predictors are inter-linked through different pathways; clumping them together to measure their singular effect might actually suppress their independent associations with the outcome (22). Fiala et al. showed that individuals with low SES are at increased risk for myeloma. Conversely, patients with higher SES are less likely to develop comorbidities as compared to individuals with middle and lower SES (P-value = 0.007) (1). However, the exact causal pathway linking the two is yet to be clarified. The association could be due to many reasons; decreased access to medical care that accompanies lower SES; absence of health insurance or poor health insurance, and lack of awareness to seek medical care, all of which increase propensity for poor health outcomes. Furthermore, studies have shown the risk of myeloma to be

significantly higher in the lowest categories of occupation, education and income (24, 26). Although some of these differences in risk could be attributed to the resulting differences in lifestyles and diet, as well as higher levels of obesity in blacks, it is important to further examine these differences (12, 27). We can see that both individual and community-level social predictors are associated with mortality and survival outcomes.

Accordingly, based on our understanding of the various levels of social factors involved in myeloma mortality pathways, we decided to use county-level predictors of mortality in our study. These are: median household income, percentage of persons with less than high school education, percentage of persons living below poverty line and percentage of persons unemployed as the county-level predictors of mortality for our study. There have not been many large population-based disparity studies in multiple myeloma outcomes that have explored the relationship between racial differences in mortality and county-level contextual factors. Using data from eighteen registries of the Surveillance Epidemiology and End Results database (SEER), this paper seeks to uncover the role of county-level variables in myeloma mortality from 1973-2011 in the United States (28).

Through this population-based study, we propose to test two hypothesis. First, black crude mortality rates are higher than white crude mortality rates throughout the period of study. Second, this racial difference in mortality is attenuated after adjusting for county-level contextual variables. Using data stratified on individual level variables (race, sex, and age of diagnosis), we will provide crude mortality rates to map existing patterns of myeloma mortality. Thereafter, to assess the effect of county-level variables in mortality, we will run regression analysis controlling for county-level contextual variables (median household income, percentage of persons with less than high-school education, percentage

of persons living below poverty line, percentage of persons unemployed). The analysis hopes to (a) elucidate the reasons behind differential mortality rates for myeloma between the stratified populations, if existent; (b) reinforce the need for disparity studies focused on myeloma outcomes; and (c) provide further understanding to reduce health disparities and improve myeloma survival outcomes.

The Role of County-Level Contextual Predictors in Multiple Myeloma Mortality in the United States

By Lakshmi Radhakrishnan

Background: Myeloma is the second most common hematologic malignancy in the United States. Prior population-based studies suggest that the incidence and mortality of black patients is two times higher compared to the whites and others (American Indian/AK Native, Asian/Pacific Islander). While some studies point to underlying biological mechanisms for this observed difference, others suggest the role of individual socioeconomic disparities as the cause. To our knowledge, no studies have analyzed the independent association of county-level contextual variables on myeloma mortality.

Methods: I used Surveillance, Epidemiology and End Results (SEER) data from 18 registries across the United States to examine racial differences in mortality from 1973-2011 for 83,903 myeloma patients. International Classification of Disease for Oncology, 3rd Edition (ICD-O-3) and morphologic (9732/3) codes were used to identify cases. Analysis was done on two levels: individual-level (using race, sex and age of diagnosis) and county-level (high school education, poverty line and unemployment). Crude incidence and mortality rates and regression models were used for analysis.

Results: Blacks were more likely to be diagnosed at a younger age (median age of diagnosis: 66 years), and live in Middle and Low socioeconomic status (SES) counties as compared to whites. These counties were characterized by populations more likely to not have received a high school education, to live below poverty-line and to be unemployed (all $p<0.0001$). Blacks had higher crude incidence and mortality rates compared to whites. However, after controlling for county-level contextual variables of SES, high-school education, poverty-line and unemployment, blacks had a lower odds of mortality compared to whites (p-value<0.0001). Additionally, regression models revealed increasing mortality with decreasing county SES (p-value<0.001).

Conclusions: Black patients have higher crude mortality rates compared to whites and other myeloma patients. The opposite becomes true after controlling for county-level contextual variables (SES, high-school education, poverty and unemployment); signifying their role as confounders in the causal pathway between race and myeloma mortality. Further population-based studies examining both, the biological variants of this disease in conjunction with race, as well as the socio-contextual factors surrounding these populations are needed, to reduce the racial disparity in myeloma mortality.

Introduction

Multiple myeloma accounts for over 10% of all hematologic malignancies, making it the second most common hematologic malignancies (1, 2). Over the past two decades, the incidence of myeloma has been gradually increasing in the United States, with an estimation of 26,850 cases (14,090 in men and 12,760 in women), and an anticipated mortality of 11,240 persons (6,240 in men and 5,000 in women) for the year 2015 (5, 6). Myeloma is a disease continuum, is mostly preceded by monocloncal gammopathy of undetermined significance, followed by a state of smoldering myeloma, slowly progressing to symptomatic myeloma. Numerous primary and secondary genetic events play a part in this disease progression (9-12).

Risk factors for myeloma have not been well elaborated due to the difficulty in conducting such prospective studies. Nevertheless, some retrospective analyses have identified certain uniform risk-factors across these studies; race being one such risk factor. Despite major clinical research in the field of myeloma, there is no conclusive explanation to account for the higher incidence of myeloma among men and blacks (2, 13, 14). However, this difference ceases to persist after controlling for treatment, suggesting the influence of extraneous socio-contextual factors, such as socioeconomic status, on overall survival. Both individual and county-level socio-economic status is a risk factor for mortality, particularly low SES (1). Patients with higher SES are less likely to develop comorbidities as compared to individuals with middle and lower SES. Similar studies have also elucidated the compelling associations of county-level predictors such as education, poverty-line, income inequality and unemployment with all-cause mortality outcomes (22-25).

In keeping with our understanding of individual-level and county-level risk factors for myeloma, we decided to elucidate the role of county-level predictors with myeloma mortality. Many of the recent public health campaigns targeting health disparities have not sufficiently addressed myeloma and other hematologic malignancies. To our knowledge, this a novel study comparing crude mortality rates to mortality rates after controlling for county-level variables. We herein utilize data from eighteen registries of the Surveillance Epidemiology and End Results (28) to understand the role of county-level variables in relative mortality rates for multiple myeloma from 1973-2011 in the US. We propose to test two hypothesis. First, black crude mortality rates are higher than white crude mortality rates throughout the period of study. Second, black mortality rates are less than white mortality rates after adjusting for county-level contextual variables. Stratifying our data on individual level variables (race, sex, and age of diagnosis), we will provide crude mortality rates to map existing patterns of myeloma mortality. Thereafter, to assess the effect of county-level variables in mortality, we will run regression analysis controlling for county-level contextual variables (median household income, percentage of persons with less than high-school education, percentage of persons living below poverty line, percentage of persons unemployed). We seek to elucidate the cause for such disparities and provide a direction for future disparity studies in myeloma.

Methods

Data Sources

Population-based myeloma incidence and mortality was obtained from the Surveillance, Epidemiology and End Results (28) program (SEER) at the National Cancer Institute. Cases were diagnosed from January 1973 through December 2011. For our analysis, we

used data based on November 2013 submissions from both, SEER-9 and SEER-18 registries. The SEER-9 database accounts for nearly 10% of the U.S population. It contains incidence data compiled since 1973, from the original nine population based registries (Atlanta, Connecticut, Detroit, Hawaii, Iowa, New Mexico, San Francisco-Oakland, Seattle-Puget Sound, and Utah) (28). SEER expanded twice thereafter; first in 1992, to include Los Angeles and San Jose-Monterey, Rural Georgia and the Alaska Native Tumor Registry, and later in 2000; this time including Greater California, Kentucky, Louisiana, New Jersey, and Greater Georgia (29). The final SEER-18 registry accounts for 28% of the US population. Despite the slight overrepresentation of urban and foreign populations in the SEER registries, they are comparable to the general US population (30).

Study Cohort

Myeloma was defined using International Classification of Disease for Oncology, 3rd Edition (ICD-O-3) and morphology (9732/3) codes. Figure 1 depicts the selection of myeloma cases from the SEER-18 registries. Cases with unknown age (n=9) and race (n=578) were excluded from the analysis. Cases with known race were grouped into white, black, and other (American Indian/AK Native, Asian/Pacific Islander). Patients whose disease status was based on a death certificate or autopsy only, and patients who were not actively followed-up, were excluded from the regression models (n=1570), resulting in a final study cohort of 83,903 cases. Patients were divided into eras based on year of diagnosis: 1973-1980, 1981-1985, 1986-1990, 1991-1995, 1996-2000, 2001-2005, and 2006-2011.

Study Variables

The primary aim of our study was to understand the relationship between race and multiple myeloma mortality. Therefore, our main exposure variable was race itself. Our secondary

aim was to explicate the differences in the effects of individual-level variables and county-level variables, on multiple myeloma mortality.

Individual-level variables included: race, sex and year of diagnosis. Values for crude standard mortality rates, using these variables, were obtained from the SEER-9 registry as per the above mentioned study eras.

We also used additional independent variables to ascertain the effect of county-level variables on myeloma mortality. The vales for these variables were calculated using the Census 2000 summary files (SF), and extracted from the SEER-18 registry. These variables were: median household income (MHI), percentage of persons with less than high school education, percentage of persons living below poverty and percentage of persons unemployed. To understand the effect of varying county-level attributes on myeloma survival outcome, we divided our education, employment and poverty variables into quartiles and labelled these Low, Middle, Upper and High, respectively. SEER registries do not contain patient reported socio-economic status (21). In the absence of this variable, median household income (MHI) was used to proxy SES. Patients were divided into tertiles based on MHI, and classified as Low, Middle and High. These county-level variables were used in our regression analysis to ascertain their varying effect on mortality.

Calculation and Presentation of Rates and Ratios

We used SEER-9 data to calculate our crude age-adjusted incidence rates (IR), standard mortality rates (MR) and rate ratios (31). IR and MR were expressed as new cases per 100,000 person-years, and age-adjusted to the 2000 US standard population and compared across our individual-level variables of race and sex (32). Additionally, using white male

as the reference, mortality rate ratios (MRR) with 95% confidence intervals (95%CI) were also used to compare mortality rates across race and sex.

We also calculated the ratio of crude IR to MR, over the various study eras, using white male as reference. This ratio provides a value of the number of deaths per person diagnosed, and gives us an understanding of the extent of mortality as relative to incidence. We tracked these ratios over time and created a graph to visually represent the changes in mortality per incidence over the period of study.

For our descriptive analysis, we used data from SEER-18 registries. Differences in baseline characteristics at diagnosis across racial groups were analyzed using t-tests and ANOVA tests. To determine the mortality rates using our county-level variables, we further created Cox regression models using case listings from the same registry. We created separate three models: a full model with all study variables and two smaller models to tease out the effect of individual-level versus county-level variables. The variables in the individual-level model are: race, sex and year of diagnosis. Variables used in the county-level model include: SES, percentage of persons with less than high school education, percentage of persons below poverty and percentage of persons unemployed.

A level of significance (α) of .05 was considered statistically significant. We do not attribute the values of our county-level to individual cases in our study sample, to avoid the ecologic fallacy. All statistics were computed using the National Cancer Institute SEER*Stat software, version 8.2.0. (www.seer.cancer.gov/ seerstat) and SAS software, version 9.4 (SAS Institute Inc, Cary, NC)

Results

Population Baseline Characteristics

During the period, 1973-2011, 86,051 cases of multiple myeloma were diagnosed among the residents of the 18 SEER registries. Exclusion of cases with unknown age at diagnosis (n=9), unknown /unspecified race (n=578) and loss of follow-up (n=1,570) resulted in a study population of 83,903 cases: 64,474 white, 15,036 black and 4,393 others (Table 1). The population contained slightly higher number of males (44,862) as compared to females (39,041). The median age at diagnosis was found to be 70 years (range 20-100 years) for the overall population; with a lowest median age of diagnosis for blacks at 66 years; followed by whites at 71 years, and others at 69 years (all $P<0.01$). Similarly, the median age of diagnosis was lower for males (69 years) as compared to females (71 years), all $P<0.01$).

Contextual Variables

Contextual variables in our study were obtained from the Census 2000 SF. These were county-level variables used to ascertain the effect of contextual characteristics, on multiple myeloma mortality between races. Median household income, percentage of persons with less than high-school education, percentage of persons below poverty and percentage of persons unemployed were the four variables analyzed in this study. Median household income for our study sample was $46,120.00 (range: $15,810- $79,890). For the purpose of our analysis, MHI was divided into tertiles and used as a proxy for socio-economic status (21). ANOVA results showed that SES varied significantly with race (P-value<0.0001). The remaining contextual variables were split into quartiles of Low, Middle, Upper and High, and analyzed accordingly. Similar ANOVA tests for these variables show a higher proportion of blacks (3.3% of the total 17.92%) and others (1.03% of the total 5.22%), to be less likely to have received a high school education, as compared to whites (11.56% of

the total 76.84%). Likewise black and other race was significantly associated with living below poverty line (1.17% and 0.13% compared to 2.54%, P-value<0.0001); and unemployment, as opposed to white race (6.46% and 2.23% compared to 24.63%, P-value<0.0001).

When interpreting these results, it is important to distinguish that these are not individual-level variables. Therefore, these numbers are not a direct representation of the cases within our study; rather these contextual variables are proportion estimates of the value of the variable with respect to the population of the respective county. In other words, even if a black female in our study, resides within a Low SES county, it does not mean that she herself belongs to that Low SES category. Rather, it indicates that a higher proportion of people in her county are from the low SES category.

Incidence Rates

In the study, blacks were found to have the highest age-adjusted incidence rate per 100,000; 11.7 (95%CI 11.4, 12.0, P-value<0.05); over twice as compared to whites, 5.1 (95%CI 5.0, 5.1) and over thrice as compared to others, 3.7 (95%CI 3.5, 3.8). Within this population, the incidence rate was highest for black males, 14.0 (95%CI 13.5, 14.4) followed by black females, 10.2 (95%CI 9.9, 10.5, P-value<0.05). Table 2 proves additional incidence rates across all three racial groups.

Mortality Rates

Overall mortality rates in the study revealed blacks to have the highest mortality rate per 100,000; 10.1 (95%CI 9.9, 10.4, p<0.05), followed by whites, 4.3 (95%CI 4.3, 4.4) and then others, 3.0 (95%CI 2.9, 3.1). Females had a lower mortality rate over all three races (Table 3), with black females reporting the highest within the females, 8.5 (95%CI 8.2, 8.8). Standard mortality ratios, using white males as reference, revealed black males to

have over twice the mortality of white males at 2.25 (95%CI = 2.16, 2.35); followed by black females at 1.5 (95%CI = 1.44, 1.56). Comparatively, white females, other males and other females had a reduced risk of mortality (Table 4). Mortality rates over the study eras (Figure 3) show blacks to have consistently higher mortality across the period of study; increasing from 8.3 to 13.5 per 100,000 for black males and 5.4 to 8.5 per 100,000 for black females. Additional five-year mortality rates over the three racial groups have been provided in Table 5.

To understand the magnitude of mortality per case diagnosed, we calculated the ratio of crude incidence rate to crude mortality rate for all groups over the various study eras. Using white male as reference, IR: MR was similar, from 1973-1980, for white and other males (1.37 and 1.35 respectively), compared to a much higher ratio for black males (1.48). We found a different relationship in women, with all women, white, black and other, expressing similar ratios in 1973-1980 (1.52, 1.59 and 1.53 respectively). We also noticed trends in ratios over 1973-2011, with the highest decrease in IR: MR for black males (1.48 to 1.12), followed by black females (1.59 to 1.33) and then other females (1.53 to 1.28). The complete listing of ratio is provided in Table 6.

Regression Analysis

A regression analysis with only variables: sex, race and year of diagnosis, was conducted to determine the singular effects of individual-level variables (Table 7). We found all variables to be significantly associated with a reduced mortality. Males were at lower odds or mortality compared to females (HR = 0.98, P-value = 0.0401). Black race and others were also significantly associated with a decreased odds ratio, as compared to white (HR = 0.884 and 0.944 respectively, P-value<0.0001).

A second multivariate model, this time with all our study variables showed sex, race, county-level SES and year of diagnosis to be independently associated with myeloma mortality. The racial disparities in mortality were additionally reduced after multivariable adjustment for individual and county-level risk factors. After adjustment, blacks showed reduced mortality (HR = 0.872, P-value<0.0001) as compared to whites. Conversely, Middle and Low SES counties were significantly associated with higher mortality compared to High SES counties (HR = 1.078 and 1.182, respectively, all P <0.0001). The remaining results of the model are summarized in Table 8.

Thereafter, we assessed a regression model containing only county-level traits, to understand whether these effects were different than those of individual traits. We found that county-level variables to be independently associated with multiple myeloma mortality. There was an increasing odds of mortality associated with decreasing SES (Middle SES HR = 1.139, Low SES HR = 1.257, P-value>0.0001). High level poverty was also associated with increased mortality (HR = 1.398, P-value = 0.0064). Surprisingly, reduced education was associated with decreasing odds of mortality; for Middle (HR = 0.955, P-value = 0.955) and Upper (HR = 0.915, P-value = 0.0001) quartiles of those without a high school education. Similarly, Upper level of unemployment was also associated with decreased mortality (HR = 0.86, P-value = 0.0001). The complete list of results can be accessed in Table 9.

Discussion

Despite a higher crude incidence and crude mortality rate for myeloma among Black Americans, few studies have actually studied the cause of this disparity in mortality (1, 2, 17, 26). Through our large study of patients with multiple myeloma, specially examining

disparities in myeloma mortality by race, we discovered: 1) As previously noted, blacks have higher crude mortality rates as compared to whites; 2) in contrast, blacks have a lower mortality rate after controlling for county-level contextual variables, and 3) the county-level variables (SES, high-school education, poverty-live and unemployment) are independently associated with multiple myeloma mortality.

We found that blacks present with myeloma at a lower age, 66 years, with over twice an incidence rate as compared to whites, and over thrice the rate compared to others. Although, risk factors for myeloma have not been agreed upon, evidence of familial aggregation of MGUS myeloma within black families is well evidenced (2, 8, 33-35). However, acceptance of genetic factors as a clear reason for differential incidence needs more research, not just on the basis of affirming evidence (i.e. clustering of MGUS), but research specifically focused on the racial variations in gene expression and disease presentation between blacks and whites. Unfortunately, such analysis was outside the purview of our research. A difference in risk-behaviors (for example: alcohol consumption and smoking), along with independent environmental exposures (such as long-term pesticide exposure) could also be related to differential incidence (36-38). Additional prospective studies are needed to examine the effect of lifetime exposures on myeloma incidence.

Similarly, we found blacks to have over twice the mortality compared to whites, and over thrice the mortality of others. This trend was consistent across the various study variables throughout the period of study. An analysis of the mortality rate ratio showed similar trends; with black men having over twice the mortality of the reference white males, and black females coming in second with just under twice the mortality of the white males.

Mortality is dependent on incidence, i.e. disease diagnosis. Therefore, in order to discover the existence of racial disparity in mortality outcome, it is important to understand mortality with respect to incidence. To do this, we obtained a ratio of the incidence rate to mortality rate for all racial sub-groups throughout the eras of our study. This ratio gave us the mortality per case diagnosed for each race and sex sub-group. We found that throughout the period of study, black males have the poorest ratio (0.36 unit drop from 1973-2011), followed by black females (0.26 unit drop from 1973-2011), as compared to white males (0.12 unit drop from 1973-2011). This suggests that blacks have a disproportionately higher crude mortality as compared to whites that cannot be solely attributed to previously existing higher rates of crude incidence within blacks. This suggests the involvement of extraneous factors responsible for the differential mortality between races.

Our multivariate model with only individual traits showed some very interesting results. The most surprising was the reduced odds of mortality for males (2%), black race (11.6%) and other race (5.6%). This is the opposite of what was evidenced by the crude mortality rates, where blacks had higher mortality over all individual-level variables throughout the period of study. Furthermore, our complete multivariable model that controlled for both individual-level and county-level variables, gave us altered mortality risk ratios for black race. There was an additional reduction in mortality risk; 12.8% reduction in the odds of myeloma mortality associated with black race (P-value<0.0001). Furthermore, this (full) regression model also found males to have a 3% higher overall survival for myeloma as compared to females (P-value = 0.025). Low and Middle SES were significantly associated with 18.2% and 7% increased mortality as compared to persons in High SES. Additionally, we also observed 4.2% increased odds of mortality in

the Upper quartiles of those with less than high school education. These results point to the important confounding role played by county-level variables, in the causal pathway, between race and multiple myeloma mortality.

Similarly, the reduced regression model with only county-level traits showed a significantly increasing risk of mortality with decreasing SES (Middle SES, 13.9% and Low SES, 25%) and increasing levels of poverty (High, 39.8%). Surprisingly, we noticed decreasing trends of mortality for decreasing levels of high school education (Middle, 4.5% and Upper, 8.5%), and unemployment (Upper, 14%). The results indicate a clear independent and opposite association between county-level contextual variables and mortality. However, care must be taken before generalizing these results to every patient hailing from these counties, as these are not patient-reported numbers, but proportions indicative of the contextual conditions in those respective counties. One could make general inferences of the overall state of deprivation and infrastructure in said county, but one cannot directly attribute these traits to individual cases, or else we would succumb to the ecologic fallacy. These models have explicated the need to integrate biological differences in myeloma presentation along with lifetime exposure variation to reduce racial health disparities. More studies are needed to tease out the exact associations between these indicators and myeloma mortality.

The overarching goal of this study was to uncover the role of county-level variables in the causal pathway, if any, between race and mortality. This study has several strengths: its large sample size, population-based design, inclusion of county-level contextual predictors of survival (poverty, employment status, and education), and racial, geographic and socioeconomic diversity in the study sample. In addition, rigorous statistical methods

were employed to demonstrate racial disparity patterns, adding power to our results. The study is limited by lack of patient-reported SES measures; forcing us to use a surrogate variable instead. This is common in clinical studies because most medical records do not contain direct information pertaining to SES. Additionally, lack of patient reports on the remaining county-level variables force us to use county-level proportions from the Census SF. When making interpretations, it is important to not succumb to the ecologic fallacy, and attribute the traits of the county-level characteristics to specific cases within out study. These variables do not represent specific cases, rather give us a broader sense of neighborhood characteristics shared by the cases in our study. The use of both, SEER-9 and SEER-18, registries for data analysis also potentially reduced external validity and study power. Missing data on age, race and active follow up in the SEER registries also lead to some missing variables. However, SEER registries account for missing data by rigorous evaluation for data totality, creating over 98% case ascertainment registry-wide (39).

In conclusion, our findings allow us to accept our initial null hypothesis that county-level contextual factors do in fact confound the causal relationship between race and mortality. We found that blacks as a race, have higher crude incidence and mortality rates, compared to the general populations. However, after controlling for county-level contextual variables, blacks have lower mortality when compared to the general population. These county-level contextual variables are also independently associated with multiple myeloma mortality. Secondarily, Blacks living in high poverty and Middle or Low SES conditions are independently at risk of poor outcomes. Further prospective studies, accounting for both; biological differences in disease presentation as well as differential

contextual exposure, need to be conducted to effectively understand their role in myeloma mortality.

Many of the recent public health campaigns targeting health disparities have not sufficiently addressed myeloma and other hematologic malignancies. Our study highlights the need for further such studies examining both, the biological variants of this disease in conjunction with race, as well as socio-contextual factors surrounding these populations, to eliminate hematologic disparities based on race and SES.

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Tables

Table 1: Descriptive Characteristics of the Study Population (SEER-18), 1973-2011

	White	**Black**	**Other**	**P-value**
Total - n (%)	64,474 (76.84%)	15,036 (17.92%)	4393 (5.22%)	
Male	35,115 (41.85%)	7,447(8.88%)	2,300(2.74%)	
Female	29,359 (34.99%)	7,589(9.04%)	2,093(2.49%)	
Median Age of Diagnosis – n (Range)	71 (20-100)	66 (20-100)	69 (24-99)	p<0.01
SES - n (%)				p<0.0001
High	16,789(20.01%)	3,023 (3.6%)	1,377(1.64%)	
Middle	33,781(40.26%)	8,875(10.58%)	2,676(3.19%)	
Low	13,904(16.57%)	3,138(3.74%)	340(0.41%)	
Percentage of Persons With Less than High School Education – n (%)				p<0.0001
Low	30,457 (36.30%)	4216 (5.02%)	2268 (2.70%)	
Middle	24,317 (28.98%)	8,052 (9.60%)	1,261 (1.50%)	
Upper	9,548 (11.38%)	2,742 (3.27%)	864 (1.03%)	
High	152 (0.18%)	26 (0.03%)	0 (0%)	
Percentage of Persons Below Poverty – n (%)				p<0.0001
Low	40,346 (48.09%)	5,555 (6.62%)	2935 (3.50%)	
Middle	21,999 (26.22%)	8,502 (10.13%)	1,349 (1.61%)	
Upper	1,963 (2.34%)	955 (1.14%)	59 (0.07%)	
High	166 (0.20%)	24 (0.03%)	50 (0.06%)	
Percentage of Persons Unemployed – n (%)				p<0.0001
Low	29,535 (35.20%)	3,082 (3.67%)	1,444 (1.72%)	
Middle	14,277 (17.02%)	6,531 (7.78%)	1,079 (1.29%)	
Upper	3,170 (3.78%)	1,404 (1.67%)	137 (0.16%)	
High	17,492 (20.85%)	4,019 (4.79%)	1,733 (2.07%	

Table 2: Age-Adjusted Incidence Rates by Race and Sex (SEER-9)

	White		**Black**		**Other**	
	Count	*IR (95%CI)*	*Count*	*IR (95% CI)*	*Count*	*IR (95% CI)*
Total	36, 784	5.1 (5.0, 5.1)	7,854	11.7* (11.4, 12.0)	2,527	3.7* (3.5, 3.8)
Male	19,664	6.4 (6.3, 6.5)	3,879	14.0* (13.5, 14.4)	1,339	4.4* (4.1, 4.6)
Female	17,120	4.1 (4.1, 4.2)	3,975	10.2* (9.9, 10.5)	1,188	3.1* (3.0, 3.3)

* = the rate ratio indicates that the rate is significantly different than the rate for White ($p<0.05$)

Table 3: Standard Mortality Rates by Race and Sex (SEER-9), 1973-2011

	White		**Black**		**Other**	
	Count	*MR (95% CI)*	*Count*	*MR (95% CI)*	*Count*	*MR (95% CI)*
Total	30912	4.3 (4.3, 4.4)	6287	10.1*(9.9, 0.4)	1946	3.0*(2.9, 3.1)
Male	16435	5.7 (5.6, 5.7)	3142	12.8*(12.3,13.3)	1044	3.7*(3.4, 3.9)
Female	14477	3.4 (3.4, 3.5)	3145	8.5*(8.2, 8.8)	902	2.5*(2.3, 2.7)

* = the rate ratio indicates that the rate is significantly different than the rate for White ($p<0.05$)

Table 4: Mortality Rate Ratios by Race and Sex (SEER-9), 1973-2011

Mortality Rate Ratio (using White Male as reference)			
Subgroups	**Rate Ratio**	**Upper CI**	**Lower CI**
White Male	1.00		
White Female	0.6056	0.592	0.6195
Black Male	2.2553	2.1643	2.3492
Black Female	1.5001	1.4427	1.5594
Other Male	0.6475	0.6065	0.6905
Other Female	0.4394	0.4102	0.4702

Table 5: Mortality Rates in by Study Eras (SEER-9), 1973-2011

Mortality Rates (per 100,000)				
Sex	**Years**	**White**	**Black**	**Other**
Male	*1973-1980*	4.1 (3.9, 4.3)	8.3 (7.2, 9.5)	3.4 (2.7, 4.3)
	1981-1985	5.4 (5.2, 5.7)	12.4 (11.0, 14.0)	3.8 (3.0, 4.7)
	1986-1990	6.0 (5.7, 6.3)	12.3 (10.9, 13.7)	3.3 (2.6, 4.7)
	1991-1995	6.1 (5.9, 6.4)	14.7 (13.3, 16.2)	4.0 (3.3, 4.7)
	1996-2000	6.0 (5.8, 6.3)	13.9 (12.6, 15.2)	3.7 (3.2, 4.3)
	2001-2005	6.2 (6.0, 6.5)	12.9 (11.7, 14.1)	3.6 (3.1, 4.1)
	2006-2011	5.6 (5.5, 5.8)	13.5 (12.5, 14.6)	3.7 (3.3, 4.2)
Female	*1973-1980*	2.5 (2.4, 2.6)	5.4 (4.7, 6.1)	1.9 (1.4, 2.5)
	1981-1985	3.5 (3.4, 3.7)	8.0 (7.1 (9.0)	2.0 (1.5, 2.7)
	1986-1990	3.8 (3.6, 3.9)	8.1 (7.3, 9.1)	2.8 (1.5, 2.7)
	1991-1995	3.9 (3.7, 4.0)	9.4 (8.5, 10.3)	2.6 (2.2, 3.2)
	1996-2000	3.8 (3.6, 4.0)	10.2 (9.3, 11.0)	2.6 (2.2, 3.0)
	2001-2005	3.6 (3.5, 3.8)	9.0 (8.3, 9.8)	2.5 (2.2, 2.9)
	2006-2011	3.1 (3.0, 3.3)	8.5 (7.9, 9.2)	2.5 (2.2, 2.8)

Table 6: Ratio of Incidence Rate to Mortality Rate over Study Eras (SEER-9), 1973.2011

IR: MR							
Subgroups	**‘73-‘80**	**’81-‘85**	**‘86-‘90**	**‘91-‘95**	**‘96-‘00**	**‘01-‘05**	**‘06-‘11**
White Male	1.37	1.09	1.03	1.07	1.10	1.10	1.25
White Female	1.52	1.17	1.08	1.08	1.13	1.17	1.39
Black Male	1.48	1.19	1.03	1.00	0.94	1.11	1.12
Black Female	1.59	1.13	1.20	1.12	1.08	1.11	1.33
Other Male	1.35	1.11	1.09	1.15	1.14	1.19	1.27
Other Female	1.53	1.40	1.25	1.12	1.19	0.88	1.28

Table 7: Multivariate Model with Only Individual-Level Traits (SEER-18), 1973-2011

Individual-Level Variables Only				
	Hazard Ratio	**Upper CI**	**Lower CI**	**P-value**
Sex				
Female	1			
Male	0.98	0.961	0.999	0.0401
Race				
White	1			
Black	0.884	0.861	0.908	<.0001
Other	0.944	0.902	0.988	0.0127
Year of Diagnosis	0.980	0.979	0.980	<.0001

Table 8: Multivariate Model with All Predictors of Mortality for Multiple Myeloma (SEER-18), 1973-2011

Full Cox Model				
	Hazard Ratio	**Upper CI**	**Lower CI**	**P-value**
Sex				
Female	1			
Male	0.974	0.952	0.997	0.0258
Race				
White	1			
Black	0.872	0.844	0.902	<.0001
Other	0.96	0.905	1.018	0.1715
SES				
High	1			
Middle	1.078	1.043	1.113	<.0001
Low	1.182	1.135	1.231	<.0001
Year of Diagnosis	0.978	0.977	0.979	<.0001
Percentage of Persons With Less than High School Education				
Low	1			
Middle	1.013	0.982	1.045	0.423
Upper	1.042	0.996	1.09	0.072
High	0.988	0.751	1.3	0.9309
Percentage of Persons Below Poverty				
Low	1			
Middle	1.003	0.945	1.065	0.9175
Upper	1.013	0.917	1.12	0.7976
High	1.224	0.96	1.562	0.1033
Percentage of Persons Unemployed				
Low	1			
Middle	1.011	0.951	1.074	0.7357
Upper	1.033	0.953	1.12	0.4282
High	1.051	0.866	1.274	0.6149

Table 9: Multivariate Model with Only County-Level Traits, 1973-2011

County-Level Variables Only				
	Hazard Ratio	**Upper CI**	**Lower CI**	**P-value**
SES				
High	1			
Middle	1.139	1.103	1.177	<.0001
Low	1.257	1.207	1.309	<.0001
Percentage of Persons With Less than High School Education				
Low	1			
Middle	0.955	0.926	0.985	0.0039
Upper	0.915	0.876	0.956	<.0001
High	0.83	0.629	1.093	0.1845
Percentage of Persons Below Poverty				
Low	1			
Middle	1.026	0.969	1.088	0.3769
Upper	1.039	0.943	1.146	0.4401
High	1.398	1.099	1.779	0.0064
Percentage of Persons Unemployed				
Low	1			
Middle	0.956	0.902	1.014	0.1347
Upper	0.86	0.796	0.93	0.0001
High	0.951	0.787	1.149	0.6052

Figures

Figure 1: Selection of study cohort (SEER-18)

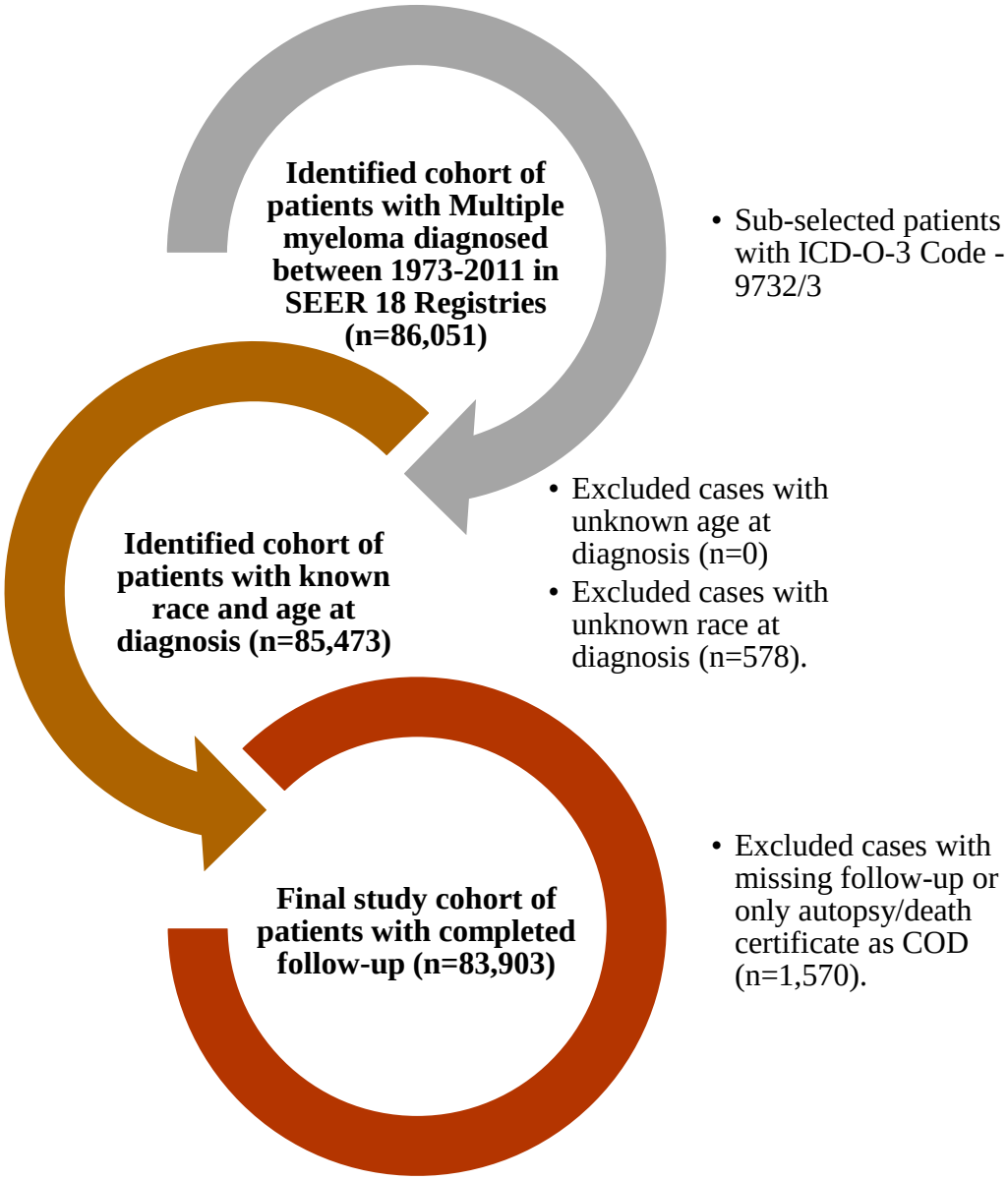


Figure 2: Consolidated Mortality Rates Varying by Sex and Race (SEER-9), 1973-2011

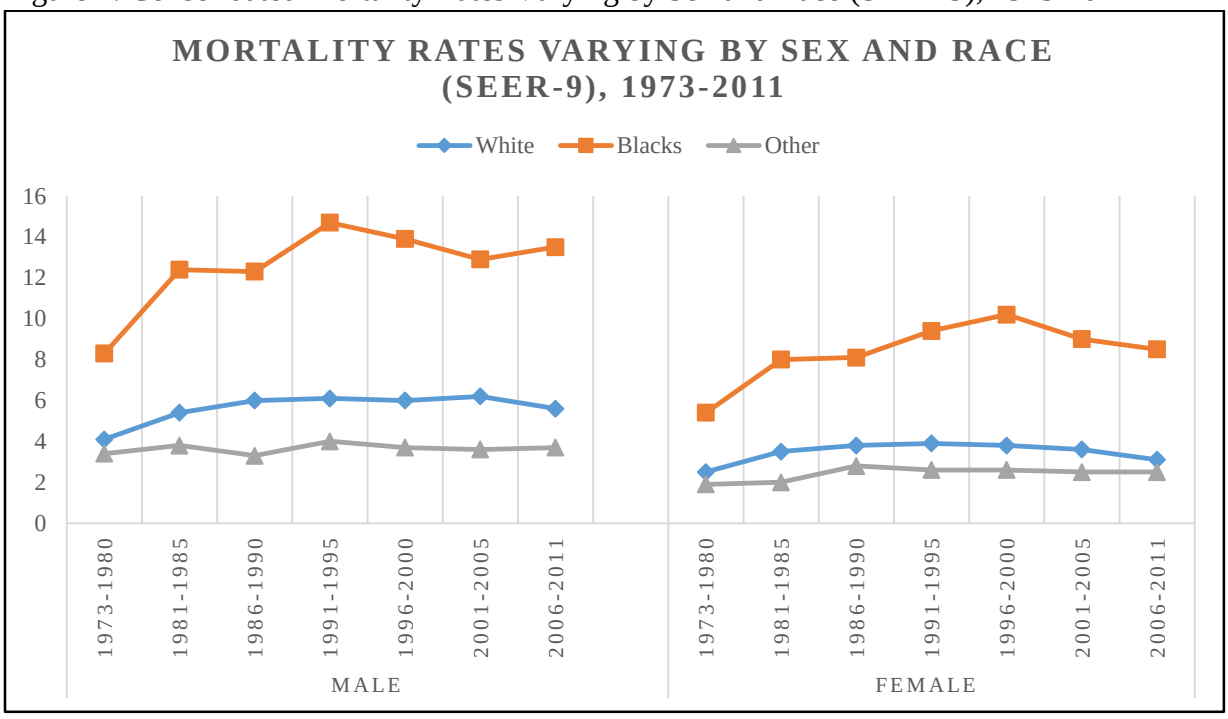
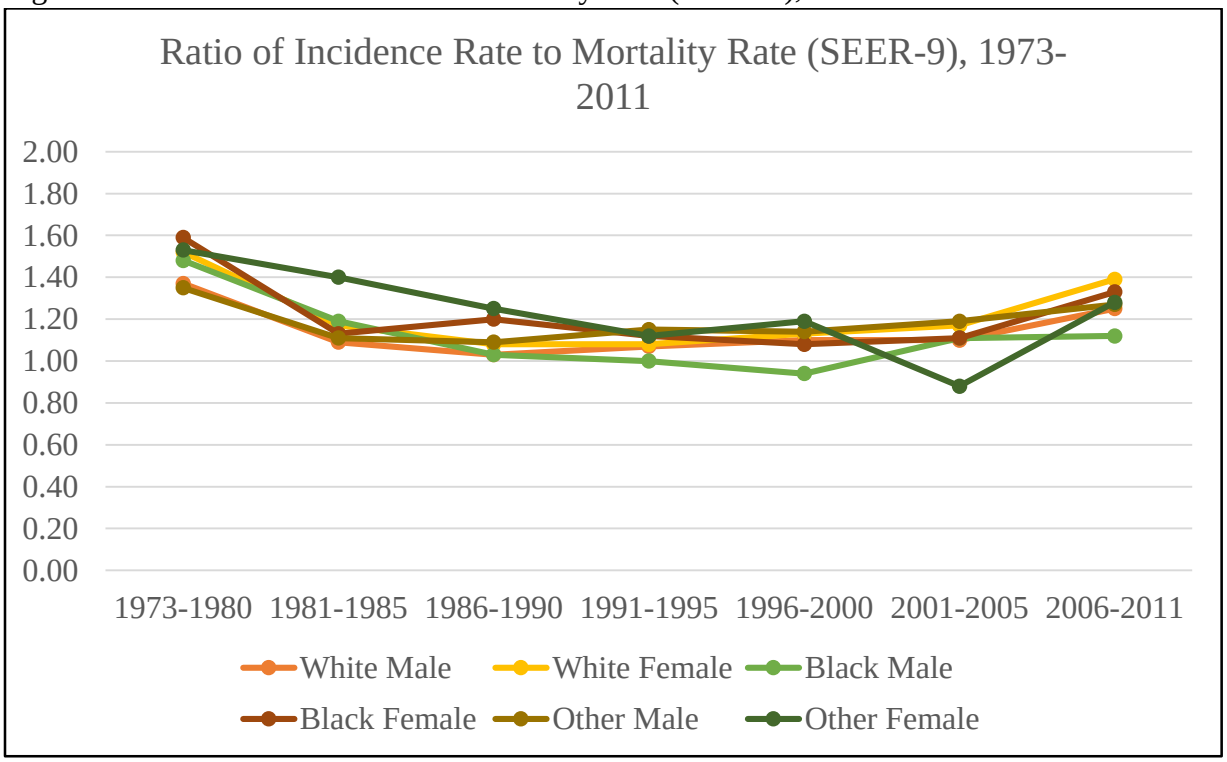


Figure 3: Ratio of Incidence Rate to Mortality Rate (SEER-9), 1973-2011



Summary

We found that blacks have over thrice the crude incidence and mortality of whites. Using incidence to mortality ratios, we elucidated this this disparity in mortality as due to differences outside of genomic. Upon examination of individual versus county-level characteristics, we found that both have significant and independent impacts on mortality. Only considering individual-level variables put blacks at a higher risk of mortality. However, the opposite was seen after controlling for county-level contextual variables. Race, sex, SES, level of education, poverty and unemployment were all significantly associated with survival at varying levels. To truly understand cause of mortality holistically, we believe that future studies should focus on pre-existing socioeconomic differences between black and white patients, as a means to explain differential health outcomes and mortality.

Public Health Implications

This study has identified that black race is at risk of higher incidence and mortality rates. The study also identified the confounding role played by county-level contextual factors; particularly middle and low socioeconomic status, decreasing education, increasing unemployment and poverty, as risk factors for increased mortality. These are novel findings, as they elucidate the presence of not just a biological difference in the presentation of myeloma between races, but also the independent association between these county-level variables and myeloma mortality. This study highlights the need for more disparity studies specifically focused on socio-contextual exposures of myeloma patients. Place and built characteristics of the patient might have a higher impact on mortality and survival outcome that we realize. Study designs specifically focusing on measuring these characteristics will be useful. By holistically understanding the differential incidence and

mortality rates, public health professionals and clinicians can better target interventions with the ultimate goal of eliminating disparities in care.

Future Directions

A future direction for this study would be to examine both differential biology, along with life exposure between black and white races, as an explanation for higher mortality. Population-based studies including patient reported measures of social deprivation should also be explored, as a means to explain differential mortality in races. Lastly, studies that incorporate patient-reported contextual measures, are needed, to explicate the intermingling of biological and psychosocial pathways, that together result in disease manifestation.