Oncology
and Radiotherapy ©
1 (46) 2019: 084-089 • REVIEW ARTICLE

Risk factors versus causal inferences: the implications on multiple myeloma in developed versus developing countries

Ogbonna C. Nwabuko[1,2,3], Ifeanyi C. Nnezianya[4], Uche B. Aguocha[4]

[1] Department of Haematology and Blood Transfusion, Federal Medical Centre, Umuahia, Abia State, Nigeria
[2] Department of Haematology, College of Health Science, Abia State University, Aba Campus, Abia State, Nigeria
[3] Department of Public Health Sciences, Walden University, Baltimore, USA
[4] Department of Surgery, Federal Medical Centre, Umuahia, Abia State, Nigeria

SUMMARY

Multiple myelomas (MM) is a cancer of the bone marrow. It is a non-communicable disease of public health importance. It is currently the second most popular hematological malignancy (after non-Hodgkins lymphoma) which targets the middle-aged and elderly population, especially those of the black race. It is a disease known for its ability to cause skeletal complications (i.e., chronic bone pain, osteoporosis and pathological fracture) at an advanced stage. One of the greatest challenges in the diagnosis and management of MM especially in low-income countries is difficulty identifying the potential hazards and/or proximate causes of the disease both environmentally and biologically.

This study aims to highlight some of the potential risk factors of multiple myeloma and their possible stratification based on the hazard risk levels.

Methods: This was an evidence-based review essay of 29 references related to the descriptive epidemiology of MM, risk factors of the disease and their possible implications (clear links) to the disease control approximately over the past two decades (2001-2018). Two keywords: (MM and Risk factors/ Descriptive epidemiology in developed and developing countries) were used as a search strategy to identify answers to research questions. PubMed, Medline, Google Scholar, African Journal Online (AJOL) were the search database reviewed.

The risk assessment was categorized broadly into environmental (i.e., lifestyle) and biological (cytogenetic karyotypes). Each of these groups is stratified into three sub-divisions of low (standard)-, Intermediate- and High risk- level sub-divisions.

The identification of risk factors of MM helps in risk management. The risk management is a-two-way-approach (i.e., preventive and cure) which includes the public health safety measures to prevent exposure to the potential hazards and the clinical approach which uses therapeutic interventions (individualized therapy) in disease control. These strategies could be useful in navigating the course, prognosis and disease outcome both in the developed and developing countries.

Key words: mm, risk factors, causal inference, risk assessment, risk management, developed and developing countries

Address for correspondence:

Ogbonna Collins Nwabuko, Department of Haematology, Federal Medical Centre, Aba Road, PMB 7001, Umuahia, Abia State, Nigeria, email: ogbollins2002@yahoo.com

Word count: 4487 **Tables:** 03 **Figures:** 01 **References:** 31

Received: - 09 July, 2019

Accepted: - 24 August, 2019

Published: - 30 August, 2019

INTRODUCTION

According to the American Heritage Dictionary (2000) definition, a cause is that which produces an effect, result or consequence. On the other hand, modern epidemiologists have re-defined cause as an event, condition, or characteristic that preceded the disease onset and that, had the event, condition or characteristic been different, the disease would not have occurred at all or would not have occurred until some later time [1]. "Cause" has been shown to have key attributes like association, time order, directionality including host and environmental factors. It may be active or passive and positive (i.e., when its presence induces a disease) or negative (i.e., when its presence is preventive or protective. A typical example of a cause is the Human Papillomavirus (HPV) which causes cancer of the cervix.

However, risk factors are those factors used by epidemiologists which are not direct causes, but rather serve to identify more proximate causes of disease. They are otherwise known as the predisposing factors or factors a few steps away from the true cause of the disease. Incidentally, the cause of most non-communicable diseases is unknown, hence, they fall under this category of causation known as risk or predisposing factors. Multiple causations (also known as a web of causation model), are the backbone of the contemporary epidemiology [1].

The Non-communicable disease of importance to be discussed in this section is Multiple myelomas. Multiple myelomas, otherwise known as plasma cell myeloma, is a cancer of the bone marrow with profound morbidity and mortality. It is hematological malignancy which is characterised by proliferation of abnormal plasma cells in the bone marrow, leading to chronic waist pain, anaemia, skeletal-related events (such as osteoporosis, pathological fracture, and vertebral collapse), chronic renal failure and other end-organ-organ failures [2]. The target audience includes middle to the elderly aged population. This target group who present commonly with features suggestive of MM is termed the "perceived susceptible group". In Nigeria, they make up to 12.7% (about 21 million based on 2006 population census) of the total population. Previous studies are in keeping with the above target group as the high-risk group for MM [3].

Tab. 1. Predisposing risk factors of MM

	Environmental	Biological
Potentially Etiologic Risk Factors [1]	[+]All predisposing factors with Hazard Ratios ≥ 3.0	• Age (>65 years) [1] • Male Gender [1] • Black Race [1] • Obesity [8] • Family History (Genetics) :HLA-Cw2, HLA-Cw5 [10] • Abnormal Karyotypes (Hyerdiploidy and Hypodiploid) [11] • MGUS [1, 6, 7] • SMM [1, 6, 7]
Diet	Low fish consumption • Low green vegetable consumption [7]	
Infectious disease [10]	• Herpes zoster • Kaposi Sarcoma Herpes Virus (KSHV) [10] • Hepatitis C Virus • Ebstein-Bar Virus • Mutated CMV • HIV/AIDS	
Suspected Risk Factors (no consistent evidence of causal relationship)	• Smoking • Alcohol • GVHD • Organophosphates (Pesticides and Herbicides) • Organic solvent (PMS, Paint, Benzene) • Radiations • Asbestos[+] (HR 3.7) • Allergic conditions	
Occupational Hazards/ lifestyle [1, 10]	• Petrochemical workers[+] (HR 3.7) • Painters • Nuclear workers • Occupational therapist • Food processing industrial workers • Use of hair dye>20 years • Laxatives[+] (HR 3.7)	

Basically, the risk factors of MM can be categorized broadly into environmental (i.e., lifestyle) and biological (i.e., cytogenetic karyotypes) factors (Table 1).

Most biologic risk factors are ''potentially etiologic factors of MM," while the environmental risk factors include diet, infectious diseases, occupational hazards and other suspected/presumed factors with no consistent evidence of the causal relationship

(Table 1). The biologic risk factors such as cytogenetic abnormalities, which are made after diagnosis are stratified into three sub-divisions of low (standard), Intermediate and High-risk karyotypes (Table 2).

Although a systematic review of the global burden of multiple myeloma showed its incidence to be higher in North America such as the United States of America, it is popularly known as a black man cancer based on the epidemiological history of the disease [2]. The known predisposing factors of MM include black race (i.e., commoner in African-American than their white counterparts), male gender disparity, elderly age group, environmental exposures to hydrocarbons, ionizing radiations, pesticides, herbicides, hair dyes, viral infections such as Karposi sarcoma herpes virus, Hepatitis C virus, Ebstein-Barr virus, mutated cytomegalovirus and immunosuppressive conditions such as HIV/AIDS, graft-versus-host diseases occasioned by stem cell and organ transplantations [3-11].

MM is a haematological disease of public health importance because of its negative impact on the health indices of its target population, both in developed and in developing countries.

DESCRIPTIVE EPIDEMIOLOGY AND RISK FACTORS OF MM

Multiple myelomas is one of the hematological malignancies of public health importance globally. It accounts for about 1% of all cancers and 15% of lymphoproliferative malignancies [12]. It also accounts for 27% of all lymphohaemopoietic deaths and 0.9%-2% of cancer-related mortalities globally [12]. Like any other cancer, the etiology of multiple myeloma is unknown. However, factors implicated as potentially aetiologic for multiple myeloma have been identified [4]. They include gender disparity-it is commoner in elderly males than the female counterparts with a Male to Female ratio of about 2:1. It is twice commoner in black than white with a median age between 60-65 years and relatively rare before the forties in developed countries. There is a familial tendency for multiple myeloma in about 3-5% of the American population with more reports in first-degree family members with Human Leucocytic Antigen HLA-Cw2 and Cw5 [10]. Other potentially aetiologic factors include the hypothesized precursors of multiple myeloma such as Monoclonal Gammopathy of Undetermined Significance (MGUS) and Smouldering Multiple Myeloma (SMM). Both MGUS and SMM are premalignant plasma cell disorders. However, the previous study by Landgren et al. has shown that MGUS and SMM have 1% and 10%-20% risks of progression to multiple myeloma per year respectively (Table 1) [8].

Tab. 2. Tabular illustration of MM campaign theory [3]

Serial No	Perception	Target Intervention
1	Perceived susceptibility	Educating targeted group about multiple myeloma, the clinical presentation such as chronic back or bone pain (>1 month), anaemia, pathological fracture or weight loss.
2.	Perceived severity	The complications of multiple myeloma such as transfusion-dependent anaemia, chronic renal failure requiring dialysis or kidney transplant, pathological fracture requiring orthopedic intervention, osteoporosis, the burden of treatment of the disease and death.
3.	Perceived Benefits	Early screening will give rise to: i) Early detection (diagnosis) and disease prevention ii) Early therapy iii) Complication prevention iv) Improved QOL and overall survival interval v) Improved life expectancy of the target group
4.	Perceived Barrier	a) Institutionalizing periodic screening test for myeloma of the target group in all health centres in Nigeria (Policy). b) Use of social marketing theory as a strategy of health promotion for multiple myeloma screening in Nigeria. c) Use of public relations as a strategy to appeal to the targeted group.

Other risk factors include environmental agents such as cumulative exposure to certain chemicals such as dioxin, herbicides, pesticides and ionizing radiation. There is a hypothesis that these specific pesticides are causatively linked to myelomatogenesis through the hypothesized precursors of multiple myeloma such as essential monoclonal gamopathy (MGUS) and Smouldering Multiple Myeloma [13, 14]. Ionizing radiation is another presumed risk factor of MM-about 29 out of 129 survivors of bombing of Nagasaki in 1945 died of multiple myeloma signifying a causal link between ionizing radiation and the disease [10].

Generally, the relative risk RR of people exposed to agriculture, food processing, and chemical industries to having multiple myeloma has increased to 1.8. It is even higher for those exposed to asbestos and laxatives. The highest risk of having multiple myeloma is exposure to petrochemicals (RR=3.7). According to the American cancer society prospective mortality study, prolonged use of dye for greater than twenty years is a high-risk factor for multiple myeloma [10, 11].

Other suspected risk factors with no provided consistent evidence of causal inference include exposure to smoking, alcoholism, obesity, low fish consumption, low green vegetable consumption and previous history of viral infections (Table 1) [6, 7].

Multiple myelomas is a non-communicable disease and fall within the groups of diseases with multi-factorial predisposing factors. Hence, the web of causation model will be useful in identifying the causal inference. In this model, some of the predisposing factors may indirectly cause the disease through the formation of intermediary factors that will ultimately give rise to the disease, while others may directly lead to the disease. However, it is worthy of note that the established risk factors in myelomatogenesis include genetic or hereditary, environmental, immunological, viral and host factors [10-11]. These risk factors can cause hypermutation and immunoglobin gene recombination of the post-germinal centre plasma cells leading to their aberrations and immortalization to form long-lived plasma cells known as multiple myeloma [15-17]. There is always a temporality and time order showing that the associated factors always precede the disease [1, 18]. Because it has an insidious onset, it may be presumed that the time order may be prolonged before the disease emergence.

In developing countries such as Nigeria, multiple myeloma poses a diagnostic dilemma to the surgeon, especially orthopaedic surgeon and physician as a result of poor case ascertainment in developing countries such as Nigeria [19]. This leads to late presentation and frequent skeletal manifestations. Orthopaedic complications such as chronic back pain, pathological fracture and osteoporosis are the common clinical markers of multiple myeloma that bring target patients to the hospital in Nigeria [9]. Unfortunately, they are usually misdiagnosed as having orthopaedic disease as primary pathology and kept under their care, only to be diagnosed by haematologist long after further complications must have set in [3]. These complications, coupled with poor therapeutic interventions available for the disease led to poor prognosis and survival outcomes of people living with multiple myeloma in the region [19, 20].

A recent study showed that about 7.6% of diagnosed multiple myeloma patients survive up to five years post-diagnosis [19]. This was significantly below five years post-diagnosis period survival of 44.9% by Surveillance Epidemiological End-Results (SEER) cancer statistics review of 1975-2007 in the United States of America [21]. By this analysis, the implication is that the United State of America is well ahead of Nigeria by over fifty years in the management of multiple myeloma as of the year 2007. It becomes more worrisome now with the current SEER statistics which has risen from 44.9% to 50.7% (an additional 5.8%) [22].

The United States of America is one of the countries in Northern America with the highest age-standardized incidence rate of multiple myeloma (3.6-6.3 per 100,000), while most countries within sub-Saharan Africa are within 0.4-1.2 per 100,000. The current death of people with multiple myeloma is 3.3 per 100,000 for both men and women. The Age-standardized incidence rate in males is 6.7 per 100,000 while that for females is 3.3 per 100,000 [2]. There were an estimated 124,733 people living with MM in the USA in 2015. Approximately 0.8 percent of men and women will be diagnosed with MM at some point during their life in the United States [22].

In Nigeria, Africa's most populous nation with an estimated population size of over 200 million people and an annual growth rate of 3%, it is estimated that multiple myeloma accounts for about 1021 out of 102,100 of newly diagnosed cancers annually [23]. However, while the Case Fatality Index (CFI) of people living

with MM in the USA is about 59.5 percent, their counterparts in Nigeria is about 93.1%.

The lesson to be drawn from this epidemiological data is that though multiple myeloma is twice commoner in black than white, its prevalence is commoner in the United States of America compared to the sub-Saharan African countries. This is understandable because of dearth in data and case ascertainment in the region. It is probable that with proper surveillance and good epidemiological and clinical knowledge of the disease, the correct statistics of the disease will be realized in the region [3].

Anti-myeloma chemotherapy regimens and stem cell transplantation (Autologous Stem-Cell Transplantation (ASCT)) are the standard definitive interventions for people living with MM. The anti-myeloma chemotherapeutic regimens have undergone a series of transformation and evolution over the years. The current anti-myeloma therapeutic agents have changed the paradigm in the management of the disease. These agents have the best effect on improving the quality of life and overall survival intervals of MM patients. They have positively changed the course of the disease especially in high-income countries such as the United State of America where they are more readily available [24].

The consensus standard of treatment of MM is yet to be achieved in many developing countries [25]. Unlike in developed countries where treatment is beginning to be customized based on mapping of patient's genome, most low and middle-income countries are yet to offer their patients such options. In Nigeria, the major anti-myeloma chemotherapy drug is the old conventional alkylating agent known as melphalan (M) which is usually combined with a steroid (i.e. Prednisolone, P) as a double or triple-only combination regimen. MP is still the most commonly accessible combination regimen used for treating MM patients because of the cost and availability, long after it has been phased out for treating MM patients in most developed countries. About 84% of newly diagnosed MM patients in some low-income countries still depend on MP doublet combination regimen [8]. This is contrary to the standard triple regimen accepted worldwide as the current treatment of choice for MM. A very few patients could afford a bortezomib-based or Immuno-modulatory agent IMiD-based combination regimens of MP (i.e., bortezomib-melphalan-prednisolone VMP (7.7%) and Thalidomide-melphalan-prednisolone TMP (19.7%) respectively)). These triple-only combination regimens are partially standard. "Partial" in this context connotes a combination of a target (novel) therapy with an old conventional regimen (i.e., MP in this case). The consensus standard anti-myeloma therapy (i.e., bortezomib-lenalidomide-dexamethasone VRD) has a better median overall survival (OS), Progressive Free Survival (PFS) and Overall Response Rate (ORR) compared to the partially standard therapy [25, 26]. But, again, this is bad news for many developing countries as less than 20% of MM patients in the region could access the partially standard anti-myeloma regimen [20]. The remaining 16% constitute the MM patients who are either on unclassified (i.e. neither known old conventional nor new novel therapy) anti-myeloma regimens (such as vincristine, Adriamycin, dexamethasone VAD) or not on any cytotoxic chemotherapy [25].

IMPLICATIONS OF RISK FACTORS TO RISK ASSESSMENT

Multiple myelomas is an incurable disease. However, with good knowledge of the disease and better diagnostic and therapeutic interventions, the quality of life of people living with multiple myeloma could be improved. When the overall survival of the target population is improved, their average life expectancy from birth invariably increases [3, 27].

High-income countries such as the United States of America have attained a significant milestone in the care of people living with multiple myeloma. This is based on a better understanding of the knowledge of the epidemiology and biology of the disease. Based on the risk assessment and causal inference, the United States of America, through their public health department could come up with a public health approach of creating awareness and prevention of multiple myeloma. This is achievable through information dissemination to the target audience on the possible predisposing factors to multiple myeloma. This approach makes use of a behavioral framework to effect the desired change.

The health believes model framework theory uses four perceptive mechanisms in its evaluation of the target interventions. They are the Perceived Susceptibility, Perceived Severity, Perceived Benefit and Perceived Barrier (Table 2) [3, 27].

Perceived susceptibility involves educating the targeted group about multiple myeloma using the clinical presentation such as chronic back or bone pain (>1 month), anaemia, pathological fracture or weight loss. In perceived severity, the intervention is to emotionally appeal to the target audience about the complications of multiple myeloma such as transfusion-dependent anaemia, chronic renal failure requiring dialysis or kidney transplant, pathological fracture requiring orthopaedic intervention, osteoporosis and other burdens of disease treatment and death.

In perceived benefits, the public health specialist should educate the target audience on the benefits of early screening for multiple myeloma including early detection (diagnosis) and disease prevention, early therapy commencement, prevention of complications, improvement of overall survival interval and average life expectancy of the target group.

The perceived barrier in public health campaign involves institutionalizing periodic screening test for myeloma in the target group in all health centres. (Policy-making); the use of social marketing theory as a strategy of health promotion for multiple myeloma screening and the use of public relations as a mechanism to appeal to the targeted group.

Most high-income countries have identified possible risk factors of MM up to the extent of stratification of risk levels of the disease based on cytogenetic analysis of the karyotypes. This is demonstrably using the Mayo stratification for Myeloma and risk-dependent therapy (mSMART) and International Myeloma Working Group Risk stratification [28, 29]. The biologic risk factors such as cytogenetic abnormalities, which are made after diagnosis are stratified into three sub-divisions of low (standard)-, Intermediate- and High risk- karyotypes (Table 3).

These strategic leadership approaches have gone a long way in improving case ascertainment, characterizing the disease

Tab. 3. Biologic risk stratification of mm based on cytogenetic abnormalities [28, 29]

Standard-Risk Karyotype	Intermediate-Risk Karyotype	High-Risk Karyotype
All others including • Trisomies • t(11;14)(q13;q32) • t(6;1)	FISH • t(4;14)(p16.3;q32) • 1q gain • High PC S-phase	FISH • Del 17p • t(14;16)(q32;q23) • t(14;20) • GEP • High risk signature

and individualizing therapy for the target population. This has translated to a better therapeutic intervention for improving the survival interval and the average life expectancy of people living with multiple myeloma [24]. This is evidenced by the low value of the case fatality rate of MM in the USA (55%) compared to the high value (>90%) recorded in Nigeria, which is understandable because of inadequate therapeutic interventions for the management of multiple myeloma in Nigeria. Therefore, most of the people living with MM in sub- Saharan Africa die before their 5th year of diagnosis.

The hazard identification (risk factor) is the first step in the risk assessment of MM. Risk assessment entails constant identification, assessment and management of population at health risk [30]. It is an integral part of health protection. The 4 basic steps of risk assessment process include hazard identification (i.e., what health problems are caused by the pollutant?), dose-response assessment (what are the health hazards at different exposures?), exposure assessment (how much of the pollutant are people exposed to during a specific time period?) and risk characterization (what is the extra risk of health problems in the exposed population?) (Figure 1) [31].

In order to justify the causal-relationship of the potential hazards of MM, they must be subjected to a risk assessment test to establish their impact on the target population in causing MM. It is the risk assessment that gives rise to hazard ratio HR (or risk ratio RR).

Once a risk has been established, as evidenced by a high HR, the next line of action is to control the potential hazard. Risk management is the process of controlling the incidence of disease by primarily preventing or treating (cure) the disease condition. In the case of MM, risk management is a-two-way-approach (i.e., preventive and curative) which include the public health safety measures to prevent exposure to the potential hazards and the clinical approach which uses therapeutic interventions (individualized therapy) in the disease control.

In high-income countries, the risk assessment mechanism is robust enough to identify the potential hazards of MM and to set-up safety measures to prevent exposure to such hazards. They also have the best therapeutic treatment against MM leading to improved survival outcomes of people living with MM compared to their counterparts in low-income countries.

CONCLUSION

Risk identification in MM is the first strategic approach towards its holistic management. The role of epidemiology in risk stratification, policymaking, diagnosis, and treatment of people living with multiple myeloma cannot be over-emphasized. Prevalence of 1%-2% attributed to multiple myeloma from the USA SEER cancer statistics will help in prudent allocation of funds for the management and researches on the disease in the region. These strategies could be useful in navigating the course, prognosis and disease outcome both in the developed and developing countries. Epidemiology remains the only public health approach towards the prevention of the disease in the target population.

REFERENCES

1. Aschengrau A, Seage, GR. Essentials of epidemiology in public health. Third edition. Burlington, MA: Jones and Bartlett. 2014.
2. Cowan AJ, Allen C, Barac A, Basaleem H, Fitzmaurice C. A Global burden of multiple myeloma-A systematic analysis for the global burden of disease study 2016. JAMA Oncol. 2018:E1-E7.
3. Nwabuko OC, Igbigbi EE, Ejele OA. Public health approach on multiple myeloma prevention in Nigeria. J Blood Lymph. 2018;8:229.
4. Alexander DD, Mink PJ, Adami H, Cole P, Mandel JS, et al. Multiple myeloma: a review of the epidemiological literature. Int J Cancer. 2007;120:40-61.
5. Ries LAG, Eisner MP, Kosary CL. SEER cancer statistics review, 1975-2002. Bethesda, MD: National Cancer Institute. 2005.
6. Blair CK, Cerhan JR, Folsom AR, Ross JA. Anthropometric characteristics and risk of multiple myeloma. Epidemiology. 2015;16:691-694.
7. Brown LM, Gridley G, Pottem LM. Diet and nutrition as risk factors for multiple myeloma among blacks and whites in the United States. Cancer Causes Control. 2001;12:117-125.
8. Landgren O, Kyle RA, Pfeiffer RM, Katzmann JA, Caporaso NE, et al. Monoclonal gammopathy of undetermined significance (MGUS) consistently precedes multiple myeloma. A prospective study. Blood. 2009;113:5412-5417.
9. Nwabuko OC, Igbigbi EE, Okoh DA. Plasma cell myeloma: challenges in diagnosis in sub-saharan Africa. Jokull J. 2015;65:254-266.
10. Terpos E, Rahemtulla A. Myeloma. In: Hoffbrand AV, Catovsky D, Tuddenham EG (eds). Postgraduate Haematology. 5th edition. London: Blackwell, 2005:681-702.
11. Litchen MA, Kaushansky K, Prchal JT, Marcel ML, Burns JL, et al. Myeloma. In: Armitago JO (eds). William Manual of Hematology. 9th edition. New York: McGraw-Hill Education, 2017:634-662.
12. Parkin DM, Bray F, Ferlay J, Pisani P. Global cancer statistics, 2002. CA Cancer J Clin. 2005;55:74-108.
13. Landgren O, Kyle RA, Hoppin JA, Beane Freeman LE, Cerhan JR, et al. Pesticide exposure and risk of monoclonal gammopathy of undetermined significance (MGUS) in the agricultural health study. Blood. 2009;113:6386-6391.
14. Rajkumar SV, Larson D, Kyle RA. Diagnosis of smouldering multiple myeloma. N Engl J Med. 2011;365:474-475.
15. Bergsagel PL, Kuehl WM. Molecular pathogenesis and a consequent classification of multiple myeloma. J Clin Oncol. 2005;23:6333-6338.
16. Kuehl WM, Bergsagel PL. Molecular pathogenesis of multiple myeloma and its premalignant precursor. The J Clin Invest. 2012;122:3456-3463.
17. Prideaux SM, O'Brien EC, Chevassut TJ. The genetic architecture of multiple myeloma. Adv Hematol. 2014;2014:864058.
18. Rothman KJ, Greenland S. Causation and causal inference in epidemiology. Am J Public Health. 2005;95:S144-150.

19. Nwabuko OC, Igbigbi EE, Chukwuonye II, Nnoli MA. Multiple myeloma in Niger Delta, Nigeria: complications and the outcome of palliative interventions. Cancer Manag Res. 2017:9:189-196.

20. Nwabuko OC, Nnoli MA, Okoh DA, John ER, Chukwuonye II. Survival outcome of multiple myeloma patients on chemotherapeutic regimens in the niger-delta Nigeria. Int J Recent Sci Res. 2015;6:4889-4893.

21. Altekruse SF, Kosary CL, Krapcho M. SEER Cancer Statistics Review. 1975-2007. 2017.

22. Howlader N, Noone AM, Krapcho M. SEER Cancer Statistics Review, 1975-2014. 2016.

23. Ferlay J, Shin HR, Bray F, Forman D, Mathers C, et al. Estimates of worldwide burden of cancer in 2008. GLOBOCAN 2008. Int J Cancer. 2010;127:2893-2917.

24. Hideshima T, Mitsiades C, Tonon G, Richardson PG, Anderson KC. Understanding multiple myeloma pathogenesis in the bone marrow to identify new therapeutic targets. Nat Rev Cancer. 2007;7:585-598.

25. Nwabuko OC. Management of multiple myeloma in developing countries. IntechOpen. 2018.

26. Durie BG, Hoering A, Abidi MH, Rajkumar SV, Epstein J, et al. Bortezomib with lenalidomide and dexamethasone versus lenalidomide and dexamethasone alone in patients with newly diagnosed myeloma without intent for immediate autologous stem-cell transplant (SWOG SO777): a randomized, open-label, phase 3 trial. Lancet. 2017;389:519-527.

27. Nwabuko OC, Igbigbi E, Ejele OA. Promoting public health campaign on awareness and screening for multiple myeloma in Nigeria. Arch Hematolo Blood Dis. 2018;1:15-20.

28. Mikhael JR, Dingli D, Roy V, Reeder CB, Buadi FK, et al. Management of newly diagnosed symptomatic multiple myeloma: updated mayo stratification of myeloma and risk-adapted therapy (msmart) consensus guidelines Mayo Clin Proc. 2013;88:360-376.

29. Chng WJ, Dispenzieri A, Chim CS, Fonseca R, Goldschmidt H, et al. IMWG consensus on risk stratification in multiple myeloma. Leukemia. 2014;28:269-277.

30. Suckling R, Ferris M, Price C. Risk identification, assessment and management in public health practice: a practical approach in one public health department. J Public Health. 2003;25:138-143.

31. US Environmental Protection Agency. Conducting a human health risk assessment. US EPA. 2014.).