Meta-Analysis: Assessing the Role of High Fat Diet as a Risk Factor for Prostate Cancer

Okobi Tobechukwu Joseph.[1], *, Iyevhobu Kenneth Oshiokhayamhe.[2,] Obodo Basil Nnaemeka.[2], Uhomoibhi Oserefuamen Trinitas.[3], Usoro Edidiong Raphael.[4], Irobonosen Osaze Israel.[5]

[1]Biology Department, Georgetown University, Washington D.C., USA.
[2]Department of Medical Laboratory Science, Ambrose Alli University, Ekpoma, Nigeria
[3]Department of Social Science and Mathematics, University of the District of Columbia, Maryland, DC., USA
[4]Department of Biomedical Sciences, Augusta University, Augusta Georgia, USA.
[5]Center for Infectious Disease Control, 161 Nigerian Airforce Hospital, Makurdi, Nigeria
[6]Department of Microbiology, College of Biosciences, Federal University of Agriculture, Abeokuta, Nigeria
[7]Department of Community Medicine, Ahmadu Bello University Teaching Hospital (ABUTH), Zaria, Nigeria.

Abstract- Dietary intake has been implicated as one of the factors associated with prostate cancer. This study is aimed at assessing the role of high fat diet as a risk factor for prostate cancer. Articles were reviewed which included case control studies, cohort studies or randomized clinical controlled trials published between 1997 and 2017 that focused on the role of high fat diet as a risk factor for prostate cancer in humans. Ten (10) articles were then selected based on the relevance to the research topic and most recent of the articles. Out of the ten articles selected and reviewed, four were prospective cohort studies with sample sizes ranging from 525 to 10,564 participants, while six were case control studies with sample size ranging from 90 to 932 participants. The meta-analysis was performed by using multivariable adjusted HR, OR or RR and forest plots were created for all studies reviewed. The results revealed that most of the studies showed a strong association between high fat diet and prostate cancer incidence and mortality with statistically significant results ($p<0.05$). However, two of the articles did not find any significant association ($p>0.05$) between high fat diet and prostate cancer risk. The results of this study provided evidence to prove that there is a statistically significant association with the role of high fat diet implicated as a risk factor for prostate cancer.

Index Terms- Prostate Cancer, Meta-analysis, High Fat Diet, Risk Factor, Mortality

I. Introduction

Prostate cancer is a major cause of cancer related deaths in the U.S. It is the world's second most diagnosed cancer and the fifth leading cause of cancer deaths in males [1]. In the United States, it is the second most common cancer in males and the 6th leading cause of cancer death [2]. It is estimated that 1 out of every 11 men will be diagnosed with prostate cancer at some point in their lifetime with the likelihood of this number increasing with advancing age. Over 3 million men were estimated to be living with prostate cancer in 2018 with 174,650 estimated new cases and 31,620 estimated deaths reported in 2019 [2]. Despite the overall decline in mortality rates in recent decades due to early

diagnosis with screening measures such as prostate specific antigen (PSA), digital rectal examination (DRE) and improved treatment modalities, prostate cancer remains a major source of concern among men [3]. Several risk factors predispose to prostate cancer. According to the American Cancer Society, race/ethnicity, age and family history of prostate cancer are the only established risk factors of prostate cancer [4].

A wide range of additional risk factors have been examined as potential risk factors for prostate cancer although evidence around the association is still a work in progress [5]. Dietary fat is a fundamental contributor to obesity and of the many lifestyle factors; high fat diet is considered a risk factor for prostate cancer [6]. Obesity share a complex relationship with prostate cancer through signaling pathways that alter cell proliferation and angiogenesis [6]. According to Discacciati, [7], it is also associated with increased incidence of high-risk and aggressive prostate cancer. Lifestyle changes in dietary fat intake may therefore help ameliorate some of the negative outcomes associated with prostate cancer and survivorship [7]. Considering the various roles of high fat diet on the incidence of prostate cancer, this study is aimed at determining the role of high fat diet as a risk factor for prostate cancer. This will help inform healthy dietary patterns to decrease the incidence and mortality from prostate cancer.

II. Methods

A PubMed search for the topic 'high fat diet risk factor for prostate cancer yielded an initial 172 results. The meSH search terms were 'prostatic neoplasm, diet, high fat diet, and risk factors. Filters were subsequently applied to focus on the most relevant articles.
2.1 Eligibility Criteria

Articles reviewed included case control studies, cohort studies or randomized clinical controlled trials that focused on the role of high fat diet as a risk factor for prostate cancer in humans. Articles between 1997 to present were included while meta-analysis or systematic review articles were excluded. Articles with titles and abstracts that were not relevant to this paper were also excluded. Ten (10) articles were then selected based on the following criteria; relevance to the research topic and most recent

of the 147 articles. Figure 1 below shows a flow diagram for the inclusion and exclusion of studies.

2.2 Data analysis

The meta-analysis was performed by using multivariable adjusted HR, OR or RR as provided in the studies. The specific software used to create the forest plot was evidence partners (https://www.evidencepartners.com/resources/forest-plot). Forest plots were created for all studies reviewed. Plots for the cohort studies and case control studies were also created to make comparative analysis using the subgroups.
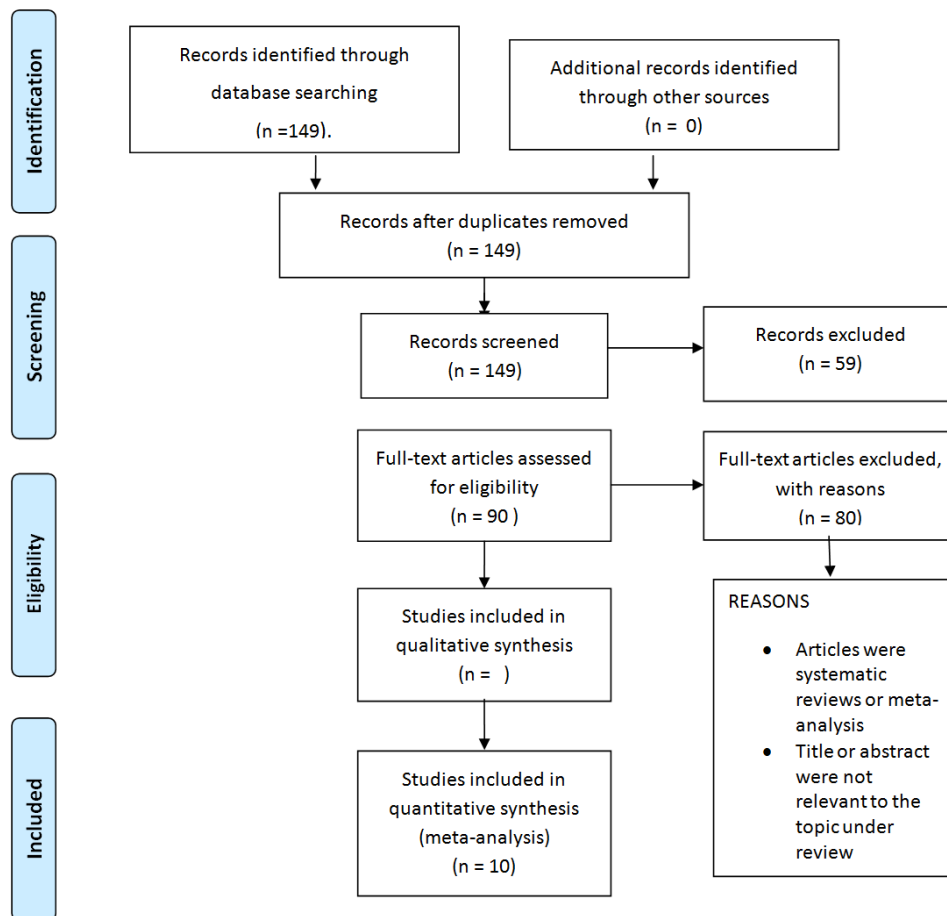

Figure 1. Flow Diagram for the inclusion and Exclusion of Studies.

III.   RESULTS

Ten (10) studies were reviewed for this meta-analysis. These were studies from different countries published between 1997 and 2017. Of these studies, four were prospective cohort studies with sample sizes ranging from 525 to 10,564 participants, while six were case control studies with sample size ranging from 90 to 932 participants. The prostate cancer cases were histologically confirmed cases and their dietary pattern was assessed using a self- administered food frequency questionnaire to determine their intake of high fat diets compared with other diets. The hazard ratio (HR), odd ratio (OR) or relative risk of these studies were extracted from the papers and these were adjusted for age, race, total energy intake, body mass index (BMI), alcohol, smoking, family history of prostate cancer, tumor grading, primary treatment and other factors, using the multivariable adjustment model. While most of the studies showed a strong association between high fat diet and prostate cancer incidence and mortality with statistically significant results (p<0.05), Yang *et al* [8] showed some association between high fat diet and prostate cancer which was however not statistically significant (p>0.05). Two others [8, 9] did not find any association between high fat diet and prostate cancer risk. The table below summarizes the articles analyzed.

Table 1. Summary of Articles Analyzed.

Article	First author's last name	Year of publication	Location	Type of study	Sample size	Method of Assessment of the Health Condition	Methods of Asessment of the Risk Factor	Adjusted OR or RR and their 95% CI
Diary intake in relation to prostate cancer survival	Downer [10]	Feb 22, 2017	Orebro County, Sweden	cohort	525 prostate cancer patients	Patients diagnosed following prostate-related symptoms and confirmed with histology by study pathologist with tumor stage assigned according to WHO TNM classification system	Self-administered food frequency questionnaire	HR- 6.10, 95% CI: 2.14-17.37 P-value= 0.001, multivariate-adjusted model (adjusted for age at diagnosis, calendar year at diagnosis, non-alcohol energy intake, height, BMI, smoking status, alcohol consumption, tumor grade, family history, primary treatment, low fat and high-fat milk).
Milk and other dairy foods in relation to prostate cancer recurrence: Data from the cancer of the prostate strategic urologic research endeavor (CaPSURE)	Tat [9]	Nov 6, 2017	United states	Prospective study (cohort)	1334 men with non-metastatic prostate cancer	Biopsy-proven prostatic adenocarcinoma	Validated semi-quantitative Food frequency questionnaire	HR: 2.96; 95% CI:1.58-5.54, P-value <0.001 multivariate adjusted model (adjusted for age at diagnosis, daily calories, years from diagnosis to FFQ, pretreatment CAPRA score, smoking status, BMI, walking pace, primary treatment
Dairy intake after prostate cancer diagnosis in relation to disease-specific and total mortality	Yang [8]	Nov 15, 2016	United states	Prospective study (cohort)	926 men with non-metastatic prostate cancer patients	Biopsy-confirmed prostate cancer patients	Food frequency questionnaire	RR: 2.41, 95% CI:0.96-6.02. P value=0.04 multivariable adjusted model (adjusted for BMI, smoking status, vigorous exercise, time interval between diagnosis and completion of FFQ, Gleason score, clinical T stage, PSA levels at diagnosis, initial treatment, family history of prostate cancer, data-derived dietary patterns
Diet, lifestyles, family history, and Prostate Cancer Incidence in an East Algerian Patient Group	Lassed [13]	Oct 19, 2016	East Algeria	Case-control	90 patients and 190 controls	Histologically confirmed prostate cancer	Questionnaire	RR: 3.02, 95% CI 2.17-4.20. P value <0.0001
Dietary fat and early-onset prostate cancer risk	Lophatananon [14]	January 19, 2010	United Kingdom	Case control	512 cases and 838 controls	Histologically confirmed prostate cancer patients	Self-administered Food frequency questionnaire	OR:2.53, 95% CI: 1.72-3.74. P value <0.001 multivariable adjusted model (energy adjustment, age, one or more first-degree relatives with prostate cancer, and baldness in the 4th decade of life.

Association of energy, fat, calcium, and vitamin D with prostate cancer risk	Kristal [15]	Aug 11, 2002	King County, Washington	Case-control	605 cases and 592 controls	Histologically confirmed prostate cancer cases identified from Seattle-Puget Sound SEER cancer registry	Self-administered food frequency questionnaire	OR: 2.01, 95% CI: 1.03-3.92. multivariable adjusted model (age, race, family history of prostate cancer, education, BMI, number of screening PSA tests within 5years before reference date, total energy intake, nonfat sources of energy.
Dietary factors and risks for prostate cancer among blacks and whites in the United States	Hayes [16]	Jan 8, 1999	United States	Case-control	932 cases and 1201 controls	Pathologically confirmed prostate cancer cases	Food frequency questionnaire	OR: 2.8, 95% CI: 1.3-5.9. P value= 0.04. multivariable adjusted model.
A prospective study on dietary fat and incidence of prostate cancer	Wallström [17]	August 29, 2007	Malmo, Sweden	Cohort study	10,564 individuals	Ascertained by record linkage with the national Cancer Register	A seven-day menu book, a questionnaire, a 45-min complementary interview	RR: 0.92, 95% CI: 0.74-1.14. Multivariable adjusted model (adjusted for total energy intake, age, diabetes, BMI)
A case-control study of diet and prostate cancer	Key [18]	1997	Oxford shire, West Berkshire and Leeds	Case-control	328 cases and 328 controls	Biopsy-confirmed prostate cancer cases	Dietary questionnaire adapted from the food frequency questionnaire	OR: 1.00, 95% CI: 0.69-1.45. Adjusted for social class
Case-control study of diet and prostate cancer in China	Lee [19]	1998	China	Case-control	133 cases and 265 controls	Histopathologically confirmed prostate cancer cases	Questionnaire	OR: 3.6, 95% CI 1.8-7.2. P value <0.01. multivariable adjusted model

3.1 Meta-Analysis of the Studies

The multivariate adjusted HR, RR or OR and 95% confidence intervals (95% CI) based on the study, were used for the meta-analysis. The forest plot was arranged in a chronological order from the most recent of the studies analyzed to the oldest. The sizes of the square were made proportional to the sample size of each study. Of the 10 studies analyzed, 7 showed statistically significant association between high fat diets as a risk factor for prostate cancer. Although Yang et al [8] showed an association between high fat diet and prostate cancer, this was found not to be statistically significant. However, 2 other studies [8, 9] found no statistically significant association between prostate cancer risk and high fat diet. The diagram below shows a forest plot of the studies analyzed.
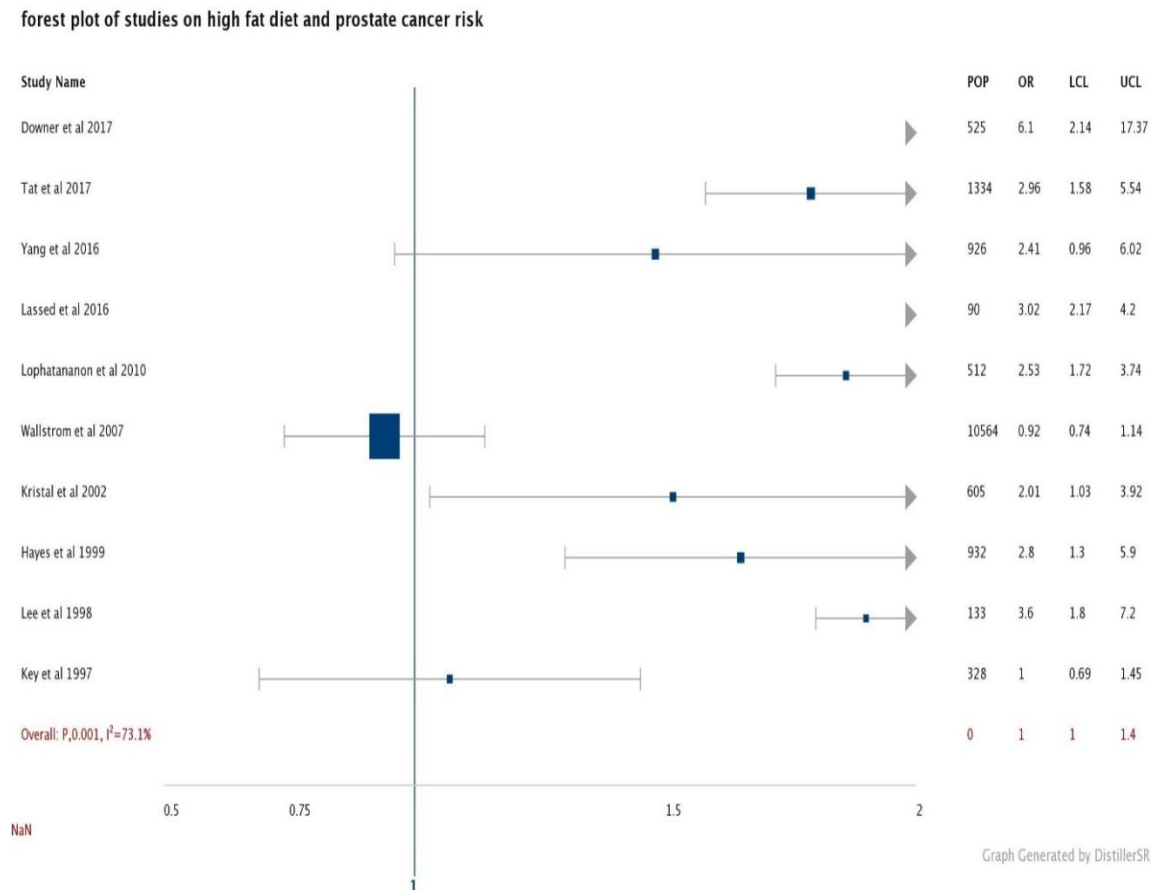

Figure 2. Forest Plot of Studies on High Fat Diet and Prostate Cancer Risk.

A subset analysis was done to compare the studies based on study type; case-control studies and cohort studies.

3.2 Based on study type

The studies were stratified into case-control studies and cohort studies. Six (6) of the studies analyzed were case-control studies while the other 4 were cohort studies. The association between high fat diet and prostate cancer appeared to be stronger with the case control studies compared to the cohort studies as 5 out of the 6 case-control studies showed a statistically significant association unlike the cohort studies in which only 2 out of the 4 studies showed a statistically significant association. However, significant difference existed in the sample sizes when comparing both groups as the case-control group appeared to have smaller sample size compared to the cohort group. Notably, the study with the largest sample size which was a cohort study did not support an association between high fat diet and prostate cancer risk. Figure 3 and 4 show forest plots of the two subgroups.

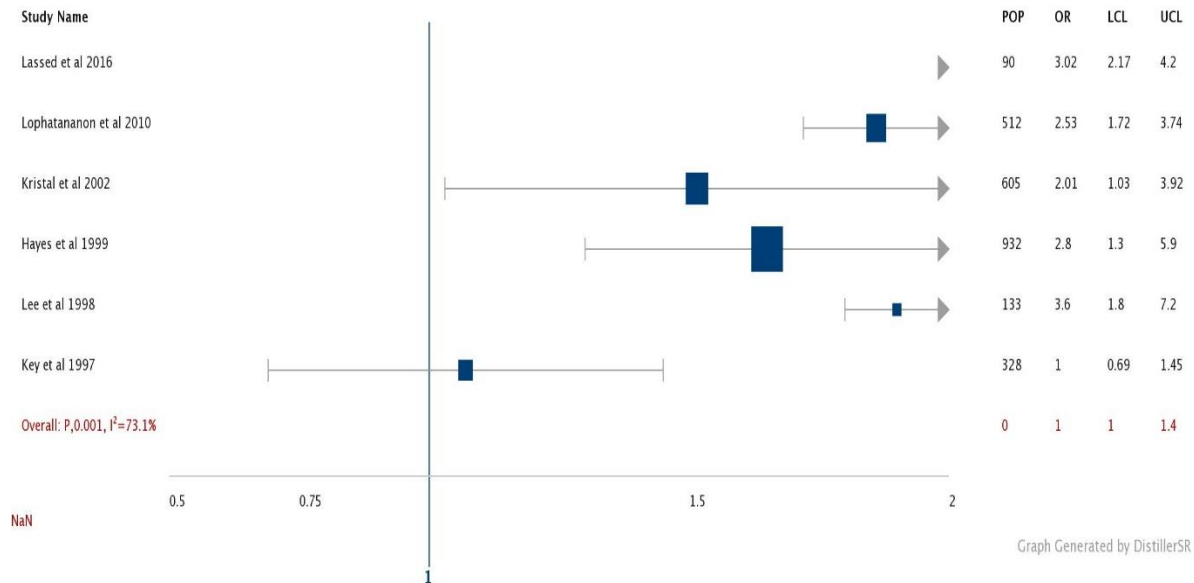forest plot of case-control studies on high fat diet and prostate cancer risk

Study Name	POP	OR	LCL	UCL
Lassed et al 2016	90	3.02	2.17	4.2
Lophatananon et al 2010	512	2.53	1.72	3.74
Kristal et al 2002	605	2.01	1.03	3.92
Hayes et al 1999	932	2.8	1.3	5.9
Lee et al 1998	133	3.6	1.8	7.2
Key et al 1997	328	1	0.69	1.45
Overall: P,0.001, I²=73.1%	0	1	1	1.4

0.5   0.75   1.5   2
NaN

Graph Generated by DistillerSR

Figure 3. Forest Plot of Case-Control Studies on High Fat Diet and Prostate Cancer Risk.

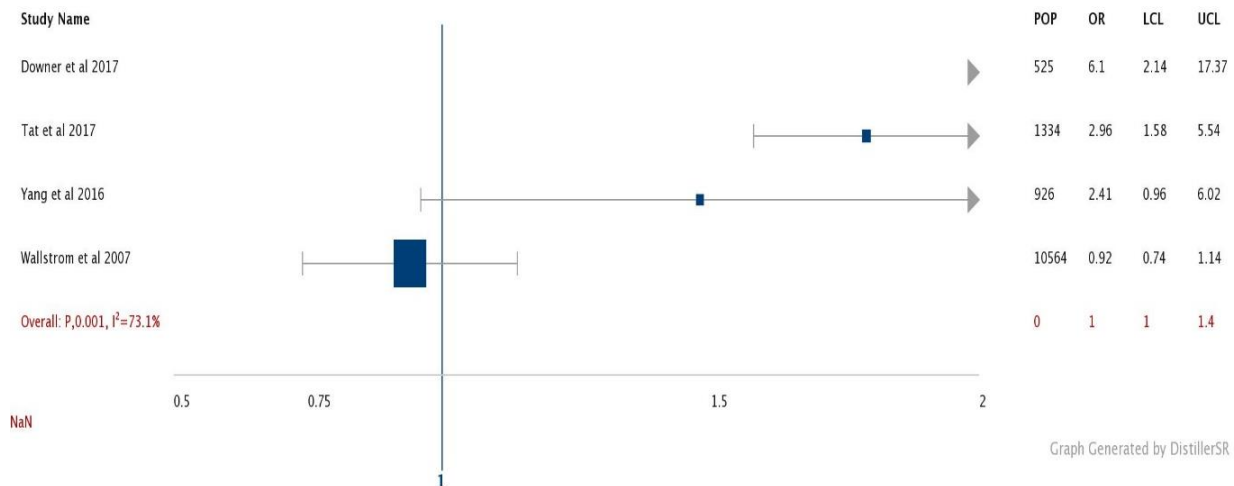forest plot of cohort studies on high fat diet and prostate cancer risk

Study Name	POP	OR	LCL	UCL
Downer et al 2017	525	6.1	2.14	17.37
Tat et al 2017	1334	2.96	1.58	5.54
Yang et al 2016	926	2.41	0.96	6.02
Wallstrom et al 2007	10564	0.92	0.74	1.14
Overall: P,0.001, I²=73.1%	0	1	1	1.4

0.5   0.75   1.5   2
NaN

Graph Generated by DistillerSR

Figure 4. Forest Plot of Cohort Studies on High Fat Diet and Prostate Cancer Risk.

IV. DISCUSSION

The relationship between high fat diet and the onset of prostate cancer has been previously discussed and reported [8]. Several other studies have strongly agreed that dietary habits are the most implicated factor that is related to cancer [10].

The results of that revealed a strong association between high fat diet and prostate cancer incidence and mortality with statistically significant results. This is in line with the study of Downer *et al*., [10] where they reported that dietary fat such as butter was associated with increased levels of prostate cancer mortality. Also, the reports of the Health Professionals Follow-up Study (HPFS) and the Physicians' Health Study (PHS) supported the claims of this study. They observed that increased milk intake was associated with increase in prostate cancer progression [11]. Investigations by Pettersson *et al.* [12] revealed that dietary fats increased the risk of chronic prostate cancers. However, the associations of high fat diet with increased prostate cancer progression have also been reported among men with chronic prostate cancer. This is however attributed to be due to increased levels of circulating IGF-1 which may promote cancer onset [10]. The outcome of the meta analysis conducted by this study agreed with the result of where significant association was found between high fat diet and prostate cancer [9, 10, 13], while other studies conducted by Yang *et al*., [8] revealed an association between dietary fats and prostate cancer, though this observation was not significant. The discrepancies in the results could be attributed to methods of evaluation, variations in the type of evaluation used by the researchers and the state of wellbeing. Also, variations could also be attributed to the period of review, the search methods and type of analysis.

In line with the above, it is important to note that this study involved reviews of ten articles that are relevant to the research topic and analyzed to provide significant correlation between high fat diet and onset of prostate cancer. This study will serve a general purpose in the future wherein conclusions from this study will be further used to make useful prognosis and monitoring of prostate cancer progression which has in turn contributed to existing knowledge.

Although studies have established the role of obesity in carcinogenesis, researches on the role of high fat diet as a risk factor for prostate cancer are yet to reach a consensus [3, 10]. Some results show that there are statistically significant association between high fat diet and prostate cancer risk, while others do not. This meta-analysis of studies on the research question was done to determine what opinion is favored based on scientific validation. While differences in results still exist in the articles reviewed, most of the articles show a statistically significant association with the role of high fat diet as a risk factor for prostate cancer.

The strength of these studies in making this association include that patients used for these studies were histologically diagnosed and confirmed cases and not relying on prostate specific antigen (PSA) or digital rectal examination (DRE) which may identify false positive cases. Also, cofounders that may affect results were adjusted for in these studies. The risk assessment used for all the studies were validated food frequency questionnaires that were designed to suit the peculiarities on the environment were these studies were done. However, this may also be a limitation of these studies as the subjectivity in filling out these questionnaires may not favor an objective result. Also, these questionnaires accessed dietary intake for a limited period making the assessment of dietary patterns of intake over time, difficult. Recall bias may have affected the results as patients with prostate cancer may tend to make more association with high fat meal as a way of making an explanation for the disease. Most of these studies also focused on particular population limiting the generalizability of these results. The case-control studies which made most of the statistically significant association had used smaller sample sizes compared to the cohort studies. Future direction that research could ideally take to more conclusively answer the question would be to use more objective ways to determine high fat intake in addition to the food frequency questionnaire such as blood tests. In addition, larger scale studies involving larger sample size may also help in making a more generalizable conclusion.

V. CONCLUSION

This meta-analysis has gone on to show a statistically significant association between high fat diet and prostate cancer risk. While there is still room for more research to validate this claim, these results are substantial enough to encourage healthy diets low in fat content as a preventive measure for prostate cancer.

REFERENCES

[1] GLOBOCAN. (2018). http://gco.iarc.fr/today/online-analysis-table..

[2] SEER. (2019). https://seer.cancer.gov/report_to_nation/prostate.html.

[3] Williams H, P. I. (2009). Epidemiology, pathology, and genetics of prostate cancer among African Americans compared with other ethnicities. *Methods Mol Biol.,* 47.

[4] Society., A. C. (2009). *Cancer facts.* Atlanta: American cancer society.

[5] ED, C. (2003). Epidemiology of prostate cancer. *Urology*, 62:3–12.

[6] Bray G. A., P. B. (1998). Dietary fat intake does affect obesity. *Am. J. Clin. Nutr.*, 68:1157-1173.

[7] Discacciati A., O. N. (2012). Body Mass Index and Incidence of localized and advanced prostate cancer- a dose-response meta-analysis of prospective studies. *Ann. Oncol*, 23:1665-1671.

[8] Yang, M., Kenfield, S. A., Van Blarigan, E. L., Wilson, K. M., Batista, J. L., Sesso, H. D., Ma, J., Stampfer, M. J. and Chavarro, J. E. (2015). Dairy intake after prostate cancer diagnosis inrelation to disease-specific and total mortality. *Int J Cancer,* 15;137(10):2462-2469. doi: 10.1002/ijc.29608.

[9] Tat, D., Kenfield, S. A., Cowan, J. E., Broering, J. M., Carroll, P. R., Van Blarigan, E. L. and Chan, J. M. (2018). Milk and other dairy foods in relation to prostate cancer recurrence: Data from the cancer of the prostate strategic urologic research endeavor. *Prostate*, 2018 Jan; 78(1):32-39. doi: 10.1002/pros.23441.

[10] Downer, M. K., Batista, J. L., Mucci, L. A., Stampfer, M. J., Epstein, M. M., Håkansson, N., Wolk, A., Johansson, J. E., Andrén, O., Fall, K. and Andersson, S. O. (2017). Dairy intake in relation toprostate cancer survival. *Int J Cancer,* 1;140(9):2060-2069. doi:10.1002/ijc.30642.

[11] Chan, J. M., Gann, P. H. and Giovannucci, E. L. (2005). Role of diet in prostate cancer development and progression. *J Clin Oncol*, 23:8152–8160.

[12] Pettersson, A., Kasperzyk, J. L. and Kenfield, S. A. (2012). Milk and dairy consumption among men with prostate cancer and risk of metastases and prostate cancer death. *Cancer Epidemiol Biomarkers Prev,* 21:428–436.

[13] Lassed, S., Deus, C. M., Lourenço, N., Dahdouh, A., Rizvanov, A. A., Oliveira, P. J. and Zama, D. (2016). Diet, Lifestyles, Family History, and Prostate Cancer Incidence in an EastAlgerian Patient Group. *Biomed Res Int*., 2016:5730569.

[14] Lophatananon, Z., O'Brien, L., Wilkinson, R.A., Hall, A.L., Sawyer, E., Page, E., Liu, J.F., Barratt, S., and Rahman, A.A. (2010). UK Genetic Prostate Cancer Study Collaborators; British Association ofUrological Surgeons' Section of Oncology, Eeles R, Muir K. Dietary fat and early-onset prostate cancer risk. *Br J Nutr*. 103(9):1375-1380. doi:10.1017/S0007114509993291.

[15] Kristal, A. R., Cohen, J. H., Qu, P. and Stanford, J. L. (2002). Associations of energy, fat, calcium, and vitamin D with prostate cancer risk. *Cancer Epidemiol Biomarkers Prev*. 11(8):719-25. PubMed PMID: 12163324.

[16] Hayes, R. B., Ziegler, R. G. and Gridley, G. (1999). Dietary factors and risks for prostate cancer among blacks and whites in the United States. *Cancer Epidemiol Biomarkers Prev*. 8(1):25-34.

[17] Wallström, P., Bjartell, A., Gullberg, B., Olsson, H. and Wirfält, E. (2007). A prospective study on dietary fat and incidence of prostate cancer (Malmö, Sweden). *Cancer Causes Control*, 18(10):1107-1121. PubMed PMID: 17726648.

[18] Key, T. J., Silcocks, P. B., Davey, G. K., Appleby, P. N. and Bishop, D. T. (1997). A case-control study of diet and prostate cancer. *Br J Cancer*. 76(5):678-687. PubMed PMID: 9303371; PubMed Central PMCID: PMC2228001.

[19] Lee, M. M., Wang, R. T., Hsing, A. W., Gu, F. L., Wang, T. and Spitz, M. (1998). Case-control study of diet and prostate cancer in China. Cancer Causes Control. 9(6):545-552. PubMedPMID: 10189039.

AUTHORS

First Author – Okobi Tobechukwu Joseph, Biology Department, Georgetown University, Washington D.C., USA., kennylamai@yahoo.com

Second Author – Iyevhobu Kenneth Oshiokhayamhe, Department of Medical Laboratory Science, Ambrose Alli University, Ekpoma, Nigeria

Third Author – Obodo Basil Nnaemeka, Department of Medical Laboratory Science, Ambrose Alli University, Ekpoma, Nigeria

Fourth Author – Uhomoibhi Oserefuamen Trinitas, Department of Social Science and Mathematics, University of the District of Columbia, Maryland, DC., USA

Fifth Author – Usoro Edidiong Raphael, Department of Biomedical Sciences, Augusta University, Augusta Georgia, USA.

Sixth Author – Irobonosen Osaze Israel, Center for Infectious Disease Control, 161 Nigerian Airforce Hospital, Makurdi, Nigeria