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Research Article

Intestinal Parasitosis and CD4 Levels among Cancer Patients in Calabar, Nigeria

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ABSTRACT

Cancer is a public health menace with high rate of mortality, especially in developing countries. The condition as well as its therapy may negatively affect the immune system of its patients thereby predisposing them to opportunistic infections, including parasitic diseases with management problems. To investigate the intestinal parasite status and CD4 levels of cancer patients visiting a Tertiary Hospital, in Calabar, Nigeria, hence proffer solution to the cancer management problems. A cross sectional [study design was employed with 317 stool and blood samples, each collected from 186 confirmed cancer and 131 non-cancer patients (apparently healthy individuals). Direct microscopy and formol ether concentration techniques were employed for the examination and identification of stool parasites. BD-fascount technique for CD4 count. Data were analyzed with statistical package for social sciences (SPSS) version 25.0 using Chi-square and t-test, respectively at $P < 0.05$ and 95% confidence interval. The overall prevalence of intestinal parasites in this study was 87(27.44%) with significantly higher prevalence seen in cancer 65(34.9%) than in non-cancer subjects 22(16.8%), (X^2=12.72, P<0.001). Subjects with choriocarcinoma recorded the highest occurrence of intestinal parasites. Mean CD4 level was significantly lower in cancer patients (589.30±333.83) than in non-cancer subjects (703.37±290.86) (t=3.157, P=0.002). Parasite infected cancer subjects had significantly lower mean CD4 counts than their non-infected counterpart (543.86±299.41 versus 617.79±349.11 cells/ul), respectively (t = 1.445, P = 0.001). Parasite species detected in the study in order of their frequencies were hookworm 27(40.3%), Ascaris lumbricoides (34.3%), Trichuris trchiura (9.0%), Taenia spp (6.0%), Entamoeba histolytica/dispar (6.0%) and Strongyloides (4.5%). This study has confirmed that cancer lowers its host's CD4 level either alone or in combination with intestinal parasites which may play etiologic or enhancement role in cancer development, with complications and management problems. Management of cancer cases should include parasitological diagnosis and treatment.

Keywords: *Cancer, CD4, Immunity, Parasites, Infection*

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INTRODUCTION

Globally, estimated 3.5 billion people are affected with 450 million falling ill due to intestinal parasitic infections (Garcia, 2001; Behnam *et al.*, 2017). These infections are caused by the helminths and protozoan that inhabit the gastro-intestinal tracts of humans and animals from where they may invade other parts of the body and tissues (Loukopoulos *et al.*, 2007) and are acquired through fecal- oral route by ingestion of the infective forms in contaminated food and water, under cooked meat or larval penetration of the skin (Harpham, 2002). Factors such as low economy, inadequate sanitation, lack of portable water and education, a hot and humid, tropical climate, as seen in Nigeria, promote infection with intestinal parasites (Houweling *et al.*, 2003; Bundy *et al.*, 2009).

The immune system performs a critical role in the establishment of infections, disease control, reducing severity and spread of disease as well as controlling and clearing of parasitic infections (Behnam *et al.*, 2017). In immunocompromised individuals, as in HIV/AIDS and cancer, the intensity and severity of infections including parasitic diseases are elevated. The quest for providing means of longevity and productivity of live among this group of patients, especially cancer patients, through therapy has been a major problem to the host's natural immunity in handling infections thereby increasing the risk of opportunistic infections. Cancer patients are more vulnerable to infections,

and diseases become severe on establishment (Bina *et al.,* 1999).

According to reports, the rate of parasitic infections in recent years is on the increase with increasing immunosuppressive therapies (Marcos *et al.,* 2013; Bora *et al.,* 2016). The species of parasites implicated in low immunity as well as having oncogenic properties are *Toxoplasma gondii*, *Schistosoma haematobium*, *Strongyloides stercoralis* (Khurana *et al.,* 2005), *Giardia intestinalis, Entamoeba histolytica, Cryptosporidium parvum, Cyclospora cayeatanensis, Isospora belli, Microsporidia* spp, *Blastocystis hominis* and *Ascaris. lumbricoides* (Menon *et al.,* 1999; Babady, 2016; Behnam *et al.,*2017).

Existing literature reveals that most malignancies as well as anti-cancer therapy are implicated in immunosuppression resulting in reduced effectiveness of both natural and adaptive immune responses. This immunosuppressive effect is seen in the rapid destruction of newly proliferating cells, (the myeloid and lymphoid cells) thereby facilitating pre-disposition to infection (O'Brien *et al.,* 2003; Madu *et al.,* 2013;). Lymphocytes and neutrophils as well as CD4 lymphocytes are greatly reduced in cancer patients and have been associated with untimely death among patients undergoing chemotherapy (Sharma & Lokeshwar, 2005). With regards to the increasing rate of cancer in developing countries and the use of cytotoxic agents with immunosuppressive effects for the treatment of patients, the destructive role of parasites on hematologic system, digestion and nutrition (malnutrition) and complications arising from anemia, it becomes pertinent to determine the association of cancer with intestinal parasites infection and CD4 cells (immune) levels among cancer subjects.

Cancer is a leading cause of death worldwide, accounting for nearly 10 million deaths in 2020 (Ferlay *et al*., 2020). It has a rapid spreading capacity where nearby as well as distance cells and organs can be reached causing life threatening complications in humans if not handled with alacrity (Miller *et al.,* 1993). Its ability to spread to isolated sites and the circulation militates against the normal body defense mechanism, rendering patients susceptible to secondary infections. Pathogens would thrive well in a broken immune system with cancer inclusive. Secondary infections such as parasitic, viral, fungal, gram negative and gram-positive bacterial infections have been implicated in cases of malignancies more seriously in those associated with blood and immune cells (Menon *et al.,* 1999; Babady, 2016).

An estimated 15% worldwide malignancies of about 1.2 million cases per annum are caused by infectious organisms with a greater proportion from developing countries (Pisani *et al*., 1997). Parasites with oncogenic potentials are predominant within host population. As they remain in their host, removing them may lead to tumor establishment (Kuper *et al*., 2000).

There is little or no information on the cases and effect of cancer in Nigeria probably resulting from inadequate statistics and in Calabar, data on cancer are scanty. The association between cancers, intestinal parasitic infection, and immune status has also not been established. This study was aimed to investigate intestinal parasitosis prevalence, its relationship with the immune cells (CD4 T cells) levels among cancer subjects in Calabar, Nigeria

MATERIALS AND METHODS

Study area: The study was conducted in the University of Calabar Teaching Hospital in Calabar, the capital city of Cross River State in Southern Nigeria. Calabar is comprised majorly 2 local government areas viz: Calabar Municipality and Calabar South. Calabar covers an area of 402 sq. Km with an elevation of 32 km. It has a population of 371,022 as of the 2006 national population census (Ottong *et al*., 2010). It lies between latitude 4°57'0" N and longitude 8°19'30" E. The University of Calabar Teaching Hospital is a major government hospital where cancer patients from other government hospitals and private clinics are referred to.

Study Design: This design was a cross sectional type.

Ethical Considerations and Informed Consent: An ethical clearance was obtained from the Health Research Ethical Committee, of the study hospital. The letter was presented to heads of Units/Department **f**or their permission to interact with and enroll the patients for the study. Consent was obtained from participants as well as care givers in a one-on-one interaction.

Inclusion Criteria: Only individuals for clinical/medical check-ups or in admission with a known condition, both (cancer and non-cancer) within the hospital and had their consent given were considered.

Exclusion Criteria: Persons without defined disease conditions, who were not patients in the selected hospital and without an informed consent obtained, were excluded.

Administration of Questionnaires: With the aid of the care givers, a structured, interviewer-administered questionnaires were used to collect socio-demographic information from the participants. Such information included age, gender, type of cancer, type and duration of treatment, etc.

Sampling Technique and Sample Collection: A purposive sampling technique was employed in which only available persons who gave their consent at the time of the study were enrolled for sample collection.Stool and blood samples were collected from 317 (186 cancer and 131 non-cancer (apparently healthy)) subjects, including males and females of all ages.

Four milliliters of venous blood sample was collected from each of the subjects into a 5ml vacutainer, well labeled bottle for evaluation of CD4 level.

A clean, wide-mouthed, leak-proof universal container, fully labeled with subjects' details was issued to each subject, after being guided, for stool sample collection. Samples were immediately moved to the laboratory for parasitological studies. Samples not processed immediately after collection were preserved in the refrigerator after the addition of 10% formol-saline.

Laboratory Processing of Stool Samples

Macroscopy: Stool samples were examined macroscopically for color, consistency, presence of blood, mucus, and adult worms or their segments.

Microscopy

Direct Smear: About a gram of the stool sample was homogenized in 5ml of normal saline in a separate universal container. A drop of the homogenate was placed centrally on each of two grease-free microscope slides; a drop of saline was added to the smear on one slide and Lugol's iodine to that on the other slide. These preparations were mixed, cover-slipped and examined microscopically with 10x and 40x objectives, respectively for parasites (Arora and Arora, 2010).

Formol-ether Concentration Technique: Half a tea spoonful of fecal sample was mixed with 10 ml of water in a separate but clean sample container and filtered via bi-layered mesh gauze in a funnel. The filtrate was spurned at 2000 rpm for 2 minutes; supernatant was discarded, sediment re-suspended in normal saline and again spurned and the supernatant discarded. Sediments was then re-suspended in 7 ml of formol saline, allowed for 10 minutes fixation and 3 ml of ether was added. Tubes were covered and shaken to mix thoroughly. Tubes were again centrifuged at 2000 rpm for 2 minutes. These tubes were allowed for 2 minutes to reveal four layers. The contents of the layers in descending order were ether, plug of debris, a clear layer of formal saline, and a layer of sediments. Layer of debris was detached from the side and liquid removed with small amount of formal saline left for re-suspension of sediment. Drops of sediments were placed on a clean glass slide, cover-slipped and examined microscopically as described in direct examination (Arora and Arora, 2010).

Analysis of whole blood for CD4 using BD fascount technique: Following collection and transportation of samples to the laboratory, BD Facscount reagent tubes were labeled with subjects' laboratory numbers and prepared as directed by the "**Becton, Dickinson** and **Company, BD Fascount, BB Bioscience**". Each reagent tube impregnated with CD4 PE/CD14 PE-Cy™5/CD15 PE-Cy5, fluorescent nuclear dye, and reference beads were mixed upside down for 5 seconds and then upright. Whole blood samples were mixed by inversion for about 5 minutes. From each mixed whole blood sample, 50µl was pipetted into the different reagent tubes. The mixture of blood and reagent in the tubes were then capped and vortexed for 5 seconds, covered, protected from light and incubated at room temperature (20-25^{0}c) for 60-120 minutes in the dark. Following incubation for about 2 hours, sample tubes were uncapped and 50µl of fixative solution (PBS) were added which were recapped and vortexed for 5 seconds. Sample tubes were uncapped and placed in a run position on the fascount machine and ran within 48 hours of preparation. After completion of analysis by fascount, CD4 tubes (sample tubes) were removed and reagent discarded appropriately. The result (CD4 count) was printed out from the fascount machine on completing the analysis (Ledbetter *et al*., 1981; Engleman *et al*., 1981).

Statistical Analysis:
Data obtained from the study were analyzed using Statistical Package for Social Science (SPSS), version 25.0 (IBM SPSS v.25 Inc., Chicago Il, USA) using chi-square and independent sample t-test, respectively at $P < 0.05$ and 95% confidence interval.

RESULTS

An overall prevalence of intestinal parasites in both study groups was 87(27.44%) with cancer subjects having statistically significant higher prevalence 65(34.95%) than non-cancer subjects 22(16.79%) (X^2=12.719, df= 1, P<0.001). Helminths ova were more frequently detected 76(23.97%) than protozoan cysts 2(0.63%) with 9(2.84%) of the subjects having mixed helminths and protozoan infection (Table 1).

Table 1:
Overall Prevalence of Intestinal Parasites among Cancer and Non-Cancer Subjects

Subjects	No. examined	No. (%) with parasite			Total
		Helminths	Protozoa	Helminths/ Protozoa	
Cancer	186	57 (30.65)	2 (1.08)	6 (3.23)	65 (34.95
Non-cancer	131	19 (14.50)	0 (0.00)	3 (2.29)	22 (16.79)
Total	317	76 (23.97)	2 (0.63)	9 (2.84)	87 (27.44)

Table 2:
Distribution of Intestinal Parasites by Cancer Type

Cancer Type	No. Examined	No. (%) Positive for Parasites
Prostate	37(19.89)	11(29.73)
Ovarian	31(16.67)	9(29.03)
Breast	30(16.13)	10(33.33)
Cervical	27(14.52)	11(40.74)
*CA of GIT	10(5.37)	5(50.00)
Endometrial	9(4.84)	5(55.56)
Oral	8(4.30)	1(12.50)
Lungs	6(3.23)	1(16.67)
Choriocarcinoma	7(3.76)	4(57.14)
Vulva	5(2.69)	2(40.00)
*Others	16(8.60)	6(37.50)
Total	186(100)	65(34.95)

**Cancer of Git include: Colon, billiary cancer.*
**Others include: Cancer of Skin & subcutaneous tissues, phylloid, renal, bladder, neuroblastoma and hematologic malignancy*

Table 2 is on the distribution of intestinal parasites by cancer type. Subjects with choriocarcinoma had the highest prevalence of intestinal parasites 4(57.14%). This was followed by those with endometrial cancer 5(55.56%) while oral cancer subjects scored the least 1(12.50%). However, no association was observed between intestinal parasitosis and type of cancer (X^2=8.29, P=0.601).

Comparison of mean CD4+ levels of cancer and non-cancer subjects is given in Table 3. Mean CD4+ cell count was

significantly lower in cancer subjects than in their non-cancer counterpart, 589.30±333.83 cells/µl vs 703.37±290.86 cells/µl, respectively (t=3.157, P=0.002).

The comparison of mean CD4 of cancer and non- cancer subjects with and without intestinal parasite infections is shown in table 4. Parasite infected cancer subjects had significantly lower mean CD4 counts than their non-parasite infected counterpart (543.86±299.41 cells/µl vs 617.79±349.11 cells/µl, respectively, t = 1.445, P = 0.001). Also, non-cancer subjects with parasites recorded significantly lower mean CD4 counts than those without parasites (592.86±220.29 cells/µl vs 725.68±299.01 cells/µl, respectively, t = 1.97, P= 0.050).

Table 5 shows the frequency of parasite species detected in the study. Parasite species detected in the study in order of their frequencies were hookworm 27(40.3%), *Ascaris lumbricoides* (34.3%), *Trichuris trchiura* (9.0%), *Taenia* spp (6.0%), *Entamoeba histolytica/dispar* (6.0%) and *Strongyloides* (4.5%).

Table 3:
Comparison of Mean CD4 Levels of Cancer and Non-Cancer Subjects

Subjects	No. Examined	Mean CD4+ cells/µl
Cancer	186	589.30±333.83
Non- Cancer	131	703.37±290.86

Table 4:
Comparison of Mean CD4 Levels of Cancer and Non-Cancer Subjects with and without Parasites

Subjects	With Parasites		Without Parasites	
	n	Mean CD4+ cells/µl	n	Mean CD4+ cells/µl
Cancer	65	543.86±299.41	121	617.79±349.11
Non- Cancer	22	592.86±220.29	109	725.68±299.01

Table 5:
Frequency of parasite species detected in the study

Parasite species	Frequency (%)		All
	Cancer	Non-Cancer	
Ascaris	11(39.29)	12(30.77)	23(34.32)
Hookworm	10(35.71)	17(43.59)	27(40.29)
Trichuris	3(10.71)	3(7.69)	6(8.96)
Taenia	1(3.57)	3(7.69)	4(5.97)
Srongyloides	1(3.57)	2(5.13)	3(4.48)
Entamoeba histolytica/dispar	2(7.14)	2(5.13)	4(5.97)
Total	28(100)	39(100)	67(100)

DISCUSSION

The 27.44% prevalence of intestinal parasites reported in this study is considerably higher than 10.0% reported among patients with malignancy in Ardabil Province, Northwest Iran (Behnam *et al.,* 2017) but much lower than 61.6% in South Brazil, 80% in Northeast India and 42.0% in Malaysia (Menon *et al.,* 1999; Bora *et al.,* 2016; Jeske *et al.,* 2018). The lower prevalence compared to the later could probably be linked to subject's composition as children who have been reported to have increasing records of intestinal parasitosis formed a greater proportion of their study populations but were outnumbered in this present study. Helminths ova being more frequently detected (23.97%) than protozoan cysts (0.63%) in this study is clear indication of poor sanitation/hygiene and poverty.

Parasite species detected in the study in order of their frequencies were hookworm 27(40.3%), *Ascaris lumbricoides* (34.3%), *Trichuris trchiura* (9.0%), *Taenia* spp (6.0%), *Entamoeba histolytica/dispar* (6.0%) and *Strongyloides* (4.5%).

These findings, however, suggests the continuous predominance of intestinal parasites and increased health risk on individuals within and outside Calabar irrespective of interventions by government and non-governmental organizations, hence, a call for intensification of intervention strategies with emphasis on diagnosis and treatment of positive cases and proper hygiene practices which are key to controlling parasitic diseases.

The higher prevalence of intestinal parasites among cancer than non-cancer subjects in this study (34.95% vs 16.79%, X^2=12.719, P<0.001) suggests their aetiologic and/or enhancement role in cancer development as records have shown intestinal parasitosis for example, ascariasis, strongyloidiasis and amebiasis to be associated with colon, lungs, hepatobiliary, periampullary, pancreatic malignancies as well as adenocarcinoma and cholangiocarcinoma (Sahel *et al.,* 1987; Kedar & Malde, 1993; Gupta *et al.,* 1995; Arulprakash *et al.,* 2015; Tanaka *et al.,* 2016). The effect of parasitic infection may not be limited to just its possible involvement in carcinogenesis but may, as reported elsewhere, result in other complications including anemia (Otu-Bassey *et al*., 2017) which may aggravate the health problems of the victims.

The higher prevalence of intestinal parasites in this study and its negative effect on CD4 cells of cancer and non-cancer subjects alike suggests their role in the suppression of their hosts' immunity, with greater health risk to the already immunocompromised cancer patients.

Apart from the involvement of parasites in cancer development, cancers as a condition and its treatment have played roles in the enhancement of parasitic infections in patients. The increasing occurrence of parasitic infection possibly leads to further complications and subsequently management problems. Cancer has been identified as having a significant influence on the immune system by either spreading to marrows which make the blood cells that help in fighting infection or by directly attacking the blood component as in the case of leukemia. When blood cells or the precursors are damaged or compromised, there is usually increased vulnerability to pathogens and opportunistic infections which doubles the level of destruction to the immune system.

Infections in all senses can promote carcinogenesis through the following conditions; first, delayed inflammation resulting from persistent agents within host where phagocytes at sites of injury liberate reactive radicals with the capacity of causing damage to biological molecules such as proteins,

deoxyribonucleic acids, and cell membranes, redirect enzymatic functions and gene expressions and possibly inducing cancer development. The second mechanism involves, the inclusion by inserting active cancer genes into the host genomes in which these genes may be turning off the activity of tumor suppressor genes or directly stimulating mitosis as seen in oncogenic viruses. Lastly, infections can initiate carcinogenesis through reduced immunosurveillance due to immunosuppression which in all cases the risk of developing tumor is usually increased in all forms of immunodeficiency (Brooks *et al.*,1998).

The low immune levels (low CD4+ count) observed in this study among cancer compared to non-cancer subjects is suggestive of the negative role played by different types of malignancies on the immune system of sufferers. This reduced CD4 counts of cancer patients may result in increased vulnerability to infections including parasitic infections as well as other opportunistic disease-causing agents which thrive well in immunocompromised individuals, if not monitored; perhaps, this may be suggestive of the higher prevalence of intestinal parasites among cancer subjects than their non-cancer counterparts in the present study.

In conclusion, reduced immunity (low $CD4^+$ count) increases parasite prevalence among cancer patients. From the findings in this study, the relationship between malignancy and parasitic infections as well as reduced immunity based on $CD4^+$cell enumeration is outstanding and not negligible. Considering the negative effects of intestinal parasites on human immune cells and their involvement in other health complications, health care providers should consider periodic stool examination and de-worming exercise for cancer patients as part of combating parasites burdens in Nigeria and the world at large. Furthermore, we recommend a pre- and post-treatment evaluation of intestinal parasites burden on cancer patients to distinguish between the intrinsic roles of malignancies on parasitic infection from treatment-associated effects.

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