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Full Length Research Article

Statistical Modelling of Comorbidity Effect on Second Cancer

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ABSTRACT
Second cancer is a new cancer that occurs in someone who had history of cancer. The incidence of cancer is on the increase in the global scene and especially in Sub-Saharan Africa. This phenomenon constitutes huge health problems especially with comorbidity effects with other health conditions which have made the diagnosis and treatment of cancer patients a complex issue. Hence, this study determined the comorbidity effect on second cancer based on a retrospective study of 474 patients attending University of Abuja Teaching Hospital (UATH). These patients were first treated of cancer, and after one year developed another cancer or cancer free. The results revealed that the incidence of second cancer was approximately 39.5% and 41.4% of the patients with one or more other disease(s) had second cancer. Adjusted and unadjusted odds ratio from logistic regression showed that patients with history of smoking were 3.58 times more likely to develop second cancer when no adjustment was made to the model while the risk increased after adjustment. Furthermore, cormobid patients are 1.56 times more likely to develop second cancer than cancer patients without other diseases. Based on the area under the receiver characteristics curve, logistic regression model effectively distinguished between the two groups of cancer patients. Comorbidity and smoking were identified as significant factors on the incidence of second cancer among cancer patients attending UATH. Therefore, emphasis should be given to formulating policies on controlling tobacco smoking and to create health awareness on the effect of clinical factors on second cancer within the study area.

Keywords: Comorbidity, Cancer, Statistical modelling, Sensitivity, Specificity, Odd Ratio

INTRODUCTION
Cancer is the name given to a group of conditions which causes cells to grow and divide uncontrollably thereby given rise to tumours, impairments and damage immune systems. It is a deadly disease and one of the most commonly diagnosed in recent times. The global rise in cancer is alarming particularly in developing countries where socio-economic conditions are poor and inhabitants' live poverty line (World Bank, 2019). According to the WHO (2018) agency on cancer, the causes of cancer are hereditary factors and other three non-hereditary factors which are: physical carcinogen, chemical carcinogen and biological carcinogen, which has direct connection with lifestyle and genetic background. Some identifiable risk factors of cancer are use of tobacco, excessive alcohol intake, physical inactivity, unhealthy diet and some chronic infections.

Cancer is one of the leading causes of death globally and is responsible for an estimated 8.2 million deaths (WHO, 2018). There are about 32.6 million reported cancer cases globally and 14.1 million new cases documented in literature in 2012 (Salako *et al*., 2018). Global update in 2018 revealed that there were about 18.1 million new cases with about 9.6 million deaths (WHO, 2018). Following this trend, an estimated 16 million new cases per annum are expected in 2020 with over 70% of these cases expected from developing countries (Sowunmi *et al*., 2018). In Nigeria, the available records revealed that about 100,000 new cases of cancer occur every year with a high case fatality ratio. The aged standardized incidence rate of 58.3/100,000 men and 138.6/100,000 women were reported inthe Abuja cancer registry (Jedy-Agba *et al*., 2012; Sowunmi *et al*., 2018). This increased cancer

burden in recent times in Sub-Saharan Africa (SSA) and especially Nigeria constitutes health problems for the inhabitants and the government. These problems are enormous due to the comorbidity effects of other illnesses and conditions as over 70% of cancer cases have at least one comorbidity (Bellizzi and Rowland, 2007). These comorbidities, however, have made treatment of cancer patients extremely difficult with negative impact on patients' survival and quality of life.

Comorbidities can be defined as medical illnesses unconnected in aetiology or causality to the major diagnosis that co-occur with the illness of interest (Bjorgul *et al*., 2010). It is the co-occurrence of two or more disorders in the same individual at the same point in time with a primary condition. It is imperative to recognise the comorbidities of the patient, because they may interrupt diagnosis, change treatment, lead to complications, influence survival, and confound analysis of outcomes (Bjorgul *et al*., 2010). Cancer patients are likely to be comorbid which could complicate treatment and broaden management (Pule *et al*., 2019). Patient comorbidity has a significant influence on cancer stage at diagnosis; however, this influence varies significantly by cancer type (Gurney *et al*., 2015). Severe comorbidity may affect life expectancy and limiting diagnostic investigation (Salako *et al*., 2018). Studies have identified cardiovascular disease, hypertension, asthma and diabetes to behighly prevalent with cancer of the breast, cervical, prostate and colorectal cancer in Nigeria (Giovannucci *et al*., 2010; Maiyaki and Garbati, 2014).

Second cancer is a new cancer that occurs in someone who had history of cancer. It is often a new type of cancer different from the first.Causes of second cancer is not always clear; it may result from the same causative agent as the first while others may be caused by cancer treatments (American Cancer Society, (ACS), 2019) though the risk of developinga second cancer due to chemotherapy of the first cancer is rare. According to national comprehension cancer network (NCCN), there are set of patients that may likely stand the risk of second unrelated cancer due to some health related factors, which include patients who have cancer before 15 years (childhood cancer), immunodeficiency and medicine, aging and hormonal related issues (NCCN, 2020). Other identifiable risk factors could be genetic, left-over of cancer after treatment, smoking, use of alcohol, unhealthy diet, chronic infection, physical inactivity amongst others (Abdelrahman, 2010; Sharp *et al*., 2014).

Studies on the impact of comorbidities on second cancer occurrence in Nigeria are scarce and such information can influence diagnosis, prognosis, treatment outcomes and survival probability of first cancer occurrence. It is imperative therefore, to assess the effect of comorbidities on second cancer occurrence to address paucity of information on the effect of comorbidity on second cancer in Nigeria. Therefore, this study explores the comorbidity effect on second cancer using a binary logistic regression model (LRM).

MATERIALS AND METHODS

Data Collection

Data of 474 patients were obtained for this study from hospital based cancer register of patients attending University of Abuja Teaching Hospital (UATH), Abuja Nigeria, for primary diagnosis and treatment. Relevant data were collected as secondary data from cancer registry of UATH. Data collected include demographic data such as information on age at diagnosis, sex, marital status, smoking history, educational background, area of residence and clinical status which is comorbidity.

Description and Coding of Variables

Table 1 presents the coding of variables that were used for this study.

Data presentation

Descriptive statistics such as mean and standard deviation were adopted to describe continuous variable while frequency and percentage were

done to describe categorical variables. Also, cross-tabulation was performed to ascertain association between the second cancer occurrence and explanatory variables.

Logistic Regression Model

Logistic regression model is a statistical tool for modelling a binary dependent variable with one or more independent variables. It is a generalized linear regression model which uses logit as link function for the transformation of the model components. This study adopted LRM due to the fact that the response variable is dichotomous and LRM easily handles continuous covariates without discretization (Oguntade, 2018). Similarly, LRM was explored to examine the association between second cancer occurrence and socio-demographic characteristics, lifestyle and comorbidity status of cancer patients attending UATH.

Let $P(x_i)$ represents the probability of an event for the subject i, x_i are the vectors of random variables and the response variable denoted by y assumes values zero when there is non-occurrence and one when there is second cancer occurrence.The proposed model for this study is defined as:

$$\text{Logit}(P) = \log[P(x)/1-P(x)] = \beta_0 + \beta_1 X_{age} + \beta_2 X_{gender} + \beta_3 X_{comorbidity} + \beta_4 X_{smoking} + \beta_5 X_{marital\ status} + \beta_6 X_{Area}\ \beta_7 X_{Educational\ B/G}$$

$$p=\frac{e^{(\beta 0 + \beta 1\ Xage + \beta 2 Xgender + \beta 3 Xcomorbidity + \beta 4 Xsmoking + \beta 5 Xmaritalstatus + \beta 6 XArea \beta 7 XEducationalB/G)}}{1+e^{\beta 0 + \beta 1\ Xage + \beta 2 Xgender + \beta 3 Xcomorbidity + \beta 4 Xsmoking + \beta 5 Xmaritalstatus + \beta 6 XArea \beta 7 XEducationalB/G}}$$

Table 1: Description of explanatory variables, codes and citations from related studies

Variables	Codes	Description	Sources
Age at first diagnosis	Quantitative	Older age increases the chances of second cancer Immunosenescene sets in with advanced in age	Castelo-Brancoand Soveral (2014); Salako *et al*. (2018)
Gender	1 Male 0 Female	Male increases the chance of cancer	Kim *et al.* (2018);Tevfik *et al.* (2012)
Comorbidity	1 Present 0 Absent	Presence of secondary condition increases the likelihood of second cancer	Salako *et al*. (2018)
Marital status	1 Married 0 Single	Married subjects has a decreased tendency of second cancer	Swanson *et al.* (1985); Kato *et al.* (1989)
Area of Residence	1 Urban 0 Rural	Living in urban area has an increased probability of second cancer	Sharp *et al.*(2014); Meilleur *et al*. (2013)
Education	1 Educated 0 Illiterate	Literacy decreases the chance of cancer	Mouw *et al* (2008); Leuven *et al.* (2016)

Crude odd ratio method was used to ascertain individual strength of association using simple LRM while the partial adjusted or multiple LRM was performed to determine the true strength of association among the studied covariates. The classification accuracy was examined with the Receiver Operating characteristic (ROC). This showed the trade-off between the correct

classification of those that have second cancer (true positive rate) and incorrect classification of those that have second cancer (false positive rate). This was done with the plot of the probability of detecting true patients with second cancer (sensitivity) and false patients with second cancer (1-specificity) for the entire range of possible cut off points. The area under the curve revealed the average sensitivity over possible specificities for evaluation of the performance of the classifier. The closer the value of the area under the curve to 100%, the larger the sensitivity and also the specificity values, and hence, the better the performance of the classification test or function.

Ethical Consideration

The data for this study were exclusively information about anonymous human subjects from UATH. Approval was obtained from UATH prior to the commencement of this study.

RESULTS

It was observed that out of 474 patients, 191(40.3%) were male while 283 (59.7%) were females.The distribution of the result by area of residence showed that 151(31.9%) were rural dwellers while 323(68.1%) live in urban area. 17.3% were single and 82.7% were married, 33.1% of the patients have history of smoking while 66.9% were never smoked. The result by education background showed that 41.4% were never been to school and cannot read and write while 58.6% were educated (had at least primary education). In term of comorbidity status, 196 (41.4%) have other disease(s) apart from cancer and 278 (58.6%) do have only cancer. The second cancer status showed that 39.5% have second cancer while the remaining 60.5% do not have second cancer (Table 2).

Table 2: Demographic characteristics and medical history of cancer patients attending UATH

Variables	Frequency	%
Gender		
Male	191	40.3
Female	283	59.7
Residential Area		
Rural	151	31.9
Urban	323	68.1
Marital Status		
Single	82	17.3
Married	392	82.7
Smoking Status		
Yes	157	33.1
No	317	66.9
Education		
Not Educated	196	41.4
Educated	278	58.6
Comorbidity Status		
Yes	196	41.4
No	278	58.6
Second Cancer Status		
Yes	187	39.5
No	286	60.5

Table 3 shows that male patients that have second cancer is 51.1%, while 31.8% of all the females had second cancer, 40% of rural dwellers had second cancer, 39.3% those that live in urban had second cancer, 40.2% of single had second cancer, 39.4% of those that married had second cancer, 41.5% of illiterate patients had second cancer, 36.7% of educated patients had second cancer, 44.4% of patients that had one or more other disease(s) had second cancer while 36.1% of patients that had only cancer had second cancer.

Table 3: Cross-tabulation **o**f studiedcovariates and second cancer occurrence among cancer patients attending UATH

Variable	Second Cancer Status	
Gender	Yes (%)	No (%)
Male	97(51.1)	93(48.9)
Female	90(31.8)	193(68.2)
Area of		

Residence		
Rural	60(40)	90(60)
Urban	127(39.3)	196(60.7)
Marital status		
Single	33(40.2)	49(59.8)
Married	154(39.4)	237(60.6)
Smoking		
Yes	94(59.9)	63(40.1)
No	93(29.4)	223(70.6)
Education Background		
Illiterate	115(41.5)	162(58.5)
Educated	72(36.7)	124(63.3)
Comorbidity		
Yes	87(44.4)	109(55.6)
No	100(36.1)	177(63.9)

Values in parenthesis are expressed in percentages

The cross product ratios (Table 5) revealed that male patients were 2.23 times more likely to develop second cancer; patients with history of smoking were 3.58 times more likely to develop second cancer when no adjustment was made to the model or without any control variable(s). Risk of second cancer reduced among male patients after adjustment for other variables, the risk of second cancer was 4.13 times more likely among the patients with history of smoking. Also, patients who were diagnosed of other disease(s) were 1.56 times more likely to develop second cancer than cancer patients without another disease(s). Marriage reduced the risk of second cancer by 44%. Living in urban area reduced the likelihood of developing second cancer by 11%. The odds for educated to illiterates to develop second cancer are 1.36 (Tables 4, 5).

Table 4: Logistic regression model parameter estimate and its related statistics

Covariates	Coef.	Std.err	z	p>|z|	(95% CI)
Gender	-0.90	0.21	-4.27	0.001	(-1.31 -0.49)
Age	-0.02	0.01	-3.19	0.001	(-0.04 -0.09)
Area of Residence	-0.19	0.22	-0.89	0.374	(-0.620.23)
Marital Status	-0.62	0.31	-1.99	0.046	(-1.23 -0.01)
Smoking	1.35	0.21	6.37	0.001	(0.93 1.76)
Education	0.35	0.21	1.62	0.106	(-0.07 0 .76)
Comorbid	0.20	0.20	2.04	0.041	(0.020.82)

Coef.: Coefficient; Std err: Standard error; z: z-score; p>|z|: P-value; CI: Confidence interval

Table 5: Cross product ratioof studied covariates and second cancer occurrence with their associated estimatesamong cancer patients attending UATH.

Variable	Unadjusted Odds ratio	[95% CI]	Odds Ratio	[95% CI]
Gender	2.23	(1.5 3.33)	0.41	(0.27 .62)
Area of Residence	1.03	(0.69 1.56)	0.89	(0.58 1.40)
Marital status	1.04	(0.62 1.73)	0.56	(0.30 1.03)
Smoking status	3.58	(2.35 5.45)	4.13	(2.70 6.33)
Education	1.22	(0.83 1.81)	1.36	(0.88 2.08)
Comorbidity	1.41	(0.96 2.08)	1.56	(1.03 2.34)

CI: Confidence Interval

Assessment of logistic regression model of second cancer occurrence

The likelihood ratio test at 0.05 level of significance was highly significant (G = 58.1, p<0.001), which implies that at least one of the coefficients of the model is different from zero. Table 6 displays the goodness-of-fit statistic which indicated that the model was well fitted.

Table 6: Performance of a classification test of logistic regression model of second cancer occurrence

Test Statistics	Value
Number of Observations	474
Number of Covariate patterns	327
Pearson Chi2	339.06
Prob chi2	0.222
Correctly classified	67
True D definition as second cancer	0
Sensitivity Pr(+D)	48.7%
Specificity Pr(-D)	80.8%
Positive predictive value Pr(D+)	62.3%
Negative predictive value Pr(D-)	70.6%
False+rate for true~DPr(+|~D)	19.2%
False-rate for true D Pr(-| D)	51.3%
False+rate for classified+ Pr(~D| +)	37.7%
False-rate for classified- Pr(D| -)	29.4%
Correctly classified	68.1%

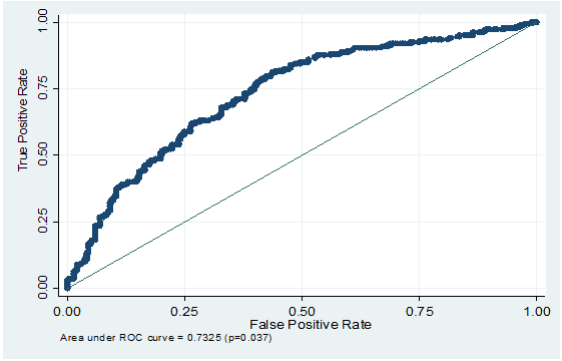

Figure 1: Receiver Operating Characteristics (ROC) curve derived from logistic regression model of second cancer occurrence

DISCUSSION

This study applied LRM to identify associated risk factors of developing second cancer. The risk factors examined span socio-demographics and clinical risks factors of patients visiting UATH for treatment. These factors include gender, age at first cancer, patient residence, marital status, education status, lifestyle which is history of smoking and the clinical risk factor (comorbidity).

Based on the result of this study, gender, smoking and comorbidity were identified as significant risk factors for second cancer occurrence. This result is in line with a related study in Lagos, Nigeria (Salako *et al*., 2018). Similarly, this study revealed that the odds ratio of present to absent of other disease(s) ranges between 1.03 times to 2.34 times with 95% confidence level. This result is consistent with earlier assertion that comorbidity may affect life expectancy and limiting diagnostic investigation (Giovannucci *et al*., 2010). Furthermore, some comorbid conditions may have a direct effect on cancer growth which invariably may lead to second cancer occurrence. Comorbidity has direct influence on prognosis, treatment outcome and survival probabilities of the patient(s) (Salako *et al*., 2018). The results of this present study also revealed that age at first cancer was indirectly related to second cancer occurrence. This implies that the earlier a patient developed the first cancer in life, the higher the chance of having a second cancer and vice versa. This is

consistent with the assertion documented in related literature on incidence of second cancer (Abdelrahman, 2010; ACS, 2019).The authors found that the age of an individual subject at the time of first treatment of cancer has a significant effect on the development of other cancer in the later years.

The area under ROC (Figure 1) indicates that logistic regression has an ability to distinguish between the two groups which support a similar finding in literature (Abdelrahman, 2010). The author noted that logistic regression has low sensitivity because of absent of clinical risk factor which was not considered.

CONCLUSION

Based on the results of the analyses carried out on the second cancer occurrence, comorbidity and smoking were found to increase the chance of second cancer occurrence within the study area and its environs. Logistic regression model has reasonable sensitivity to distinguish between 'second cancer' and 'no second cancer' groups. Therefore, emphasis should be given to formulating policies on controlling tobacco smoking and to create health awareness on the effect of clinical factors on second cancer occurrence to curb the menace of cancer within the study area and its environs.

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