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RESEARCH ARTICLE

SOME HORMONAL CONTRACEPTIVES, HORMONE-RELATED REPRODUCTIVE BREAST CANCER RISK FACTORS AMONG WOMEN IN PORT HARCOURT: A CASE-CONTROL STUDY.

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Abstract

Aim: To determine the association between hormonal contraceptives / other hormonal-related reproductive risk factors and breast cancer among women in Port Harcourt.

Background: Despite the known benefits of hormonal contraceptive agents and other well established non-contraceptive benefits, they have been associated with risk of breast cancer among women. In addition to hormonal agents, some other factors have been associated with the risk of breast cancer.

Materials and Methods: The study was carried out among patients with clinically and histologically confirmed breast cancer (as cases) and patients without any known cancer (as controls) in the out-patient clinics and wards of the public (and some private) tertiary hospitals in Port Harcourt. All histologically confirmed breast cancer patients were recruited for the study and the controls were individually matched based on age with a matching ratio of 1:1.

Results: The mean age for the case control study was 44.67±13.41 (cases) and 46.11±13.76 respectively. The odds of developing breast cancer among the women using oral contraceptive pills was similar to that of women who were not using oral contraceptive pills. The odds of developing breast cancer among the women using injectable hormonal agents was 1.26 times higher among women with breast cancer (OR = 1.26, 95% CI=0.74-2.16), although, the relationship was not significant (P>0.05). Those that were 18 years old at first pregnancy were less likely to develop breast cancer compared to women greater than 18 years old at first pregnancy, the relationship was significant.

Conclusion: Injectable contraceptives in this study were associated with higher odds of developing breast cancer among cases than controls though the relationship was not significant. Pregnancy before 18 years of age reduces the odds of breast cancer significantly.

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Introduction:-

Globally, breast cancer is the commonest cancer among women (Forbes, 1997; Parkin et al., 1999; Ferlay et al., 2010; Agbo et al., 2013) and yearly, an estimate of 1.38 million new cases (at 2008) and 1.7 million new cases (in 2012) diagnosed (Parkin et al., 2005; Jemal et al., 2011; Amadou et al., 2013; WHO IARC, 2013). National governments and international governmental and non-governmental organizations have therefore invested in preventive advocacy and in the care of breast cancer patients. The Breast Health Global Initiative (BHGI 2014) in projecting the future burden of breast cancer reported that there would be about 19.7 million new cases in the next ten years out of which 10.6 million cases will occur in less developed countries. The study in summary determined the risk relationship between hormonal risk factors and breast cancer among Nigerian women in Port Harcourt comparing findings with of the international community.

Any hormonal agent whose mechanism involves interfering with ovulation, fertilization and implantation is a hormonal contraceptive and six classes of hormonal contraceptive agents had earlier been highlighted as reported by Gupta et al. (2008): oral contraceptive pills; combined hormonal patch; trans-vaginal agents; injectable hormonal agents; intrauterine (levo-norgestrel-impregnated) device; and levo-norgestrel implants.

Findings on the role of hormonal contraceptives on breast cancer have not been consistent (Black et al., 2004). Using combined oral contraceptive pills as a prototype, earlier study did not find any association with breast cancer (CDC & NICHHD, 1986; Black et al., 2004); however, a collaborative group (CGHFBC, 1996) found a significant association though not when the pills have been stopped for more than 10years. The risk of breast cancer among users of oral contraceptive pills with mutations in BRCA1 and BRCA2 genes is higher (Black et al., 2004; Narod et al., 2002; Ursin et al., 1997; Heimdal et al., 2002).

Kumle et al. (2002) reported that use of Progestin-only pill increases breast cancer risk to similar level as the combined oral contraceptive pills does, highlighting also that recent use of OCPs is associated with breast cancer risk. This finding is partly supported by Bethea et al. (2015) who stressed that prolonged use of oral contraceptives is associated with estrogen receptor positive (ER+) and estrogen receptor positive (ER-) breast cancer.

Exposure of beagle to Depo-Medroxy-progesterone Acetate (DMPA) in 1970 was associated with development of breast cancer (Frank et al., 1979; Jordan, 1994). This seemed to have set the stage for further studies. Works done by some other researchers (McDaniel & Pardthaisong, 1973; Liang et al., 1983; Greenspan et al., 1980) did not confirm such association. Also a WHO based study (WHO, 1991) did not find any association. On the contrary, Strom et al. (2004) found some reduced risk of breast cancer with use of DMPA. The International Collaborative Post-Marketing Surveillance of Norplant (2001) reported a slightly increased risk of breast cancer with the Norplant levonorgestrel implant system; whereas Backman et al. (2005) found no increased risk with the levonorgestrel-intrauterine system.

It seems that larger studies done among western population (Vessey & Yeates, 2013; Hannaford et al., 2007; Hankinson et al., 1997; Marchbanks et al., 2002) did not establish association between breast cancer and hormonal contraceptives/risk factors, whereas smaller studies (Assi et al., 2013; Danaei et al., 2005) appear to point in the direction of a correlation.

Sighoko et al. (2015) found no significant risk of breast cancer in African women after first full term pregnancy compared to that observed among western women.

Breast cancer in Nigeria accounts for 29.7% of all cancers among women; the incidence in Nigeria is known to have double from 15 per 100,000 to 33 per 100,000 over a period of 16 years, with a male to female ratio of 1:99 and peak incidence occurring between 35 and 45 years in women (Oluyemi, 2015). The age standardized incidence rates of breast cancer in females in Nigeria was reported to be 52.0 per 100, 000 for Ibadan cancer registry and 64.4 per 100, 000 for Abuja cancer registry since no complete national registry exist (Jedy-Agba et al., 2012; Ebughe et al., 2016).

Methods:-

Study Sites:-

The study was carried out in the out-patient clinics of public tertiary health care facilities and private hospitals providing cancer treatment and care in Port Harcourt, Rivers State.

Research Design:-

A Case-control study in which the cases were breast cancer patients and the controls were patients without any known cancer.

Study Population:-

The study was carried out among women with histologically confirmed breast cancer (as cases) and non-cancer patients (as controls) in the out-patient clinics and wards of the health facilities.

Inclusion Criteria:-

Female patients aged 20 years and above with clinically and histologically confirmed breast cancer in the health facilities chosen (cases). Matched patients were of similar age who, were non-cancer patients in the out-patient clinics of the selected hospitals (controls).

Exclusion Criteria:-

Patients who are unable to communicate or are too ill to provide information. Patients who are depressed about their condition and are unwilling to talk or participate in the study

Sample Size Determination:-

The sample size was 213 participants. Formula for Sample Size Calculation for Case-Control Studies (Charan & Biswas, 2013):

$$\mathbf{n} = \left(\frac{r+1}{r}\right)\frac{(\bar{P})(1-\bar{P})(Z_{\beta}+Z_{\alpha/2})^2}{(P1-P2)^2}$$

Sampling Techniques:-

All histologically confirmed breast cancer patients (cases) in the health facilities who gave consent were recruited for the study and patients without any known cancer (as controls) in the out-patient clinics and wards of the public (and some private) tertiary hospitals in Port Harcourt. All histologically confirmed breast cancer patients were recruited for the study and the controls were individually matched based on age with a matching ratio of 1:1.

Methods of Data Analysis:-

Data was analyzed using Statistical Package for Social Sciences (SPSS 2.0) and presented as tables. Descriptive analysis was carried out for demographic characterization; logistic regression was performed for categorical variables. Bivariate logistic regression analysis and Mantel-Haenszel Chi Square test was done to test for risk of association between the dependent variable (breast cancer) and the independent variables.

Validity/Reliability of Instrument:-

The study instrument was pre-tested among similar group of cases and control (at Federal Medical Centre, Yenagoa and The Niger Delta University Teaching Hospital, Okolobiri), and necessary corrections made before use.

Ethical Considerations:-

The approval of the ethical committee of all health facilities used and informed consent was obtained from all participants.

Results:-

Presented in the tables below are the results of responses from respondents on possible risk factors of breast cancer in both cases and controls.

Table 1:- Socio-demographic characteristics among cases and controls (Age) This table shows the age distribution of participants for both cases and control

Variables	Cases (%) (n=213)	Control (%) (n=213)	Total
Age(years)			
20-29(Adolescent)	25 (11.74)	23 (10.80)	48 (11.27)
30-39(Young Adult)	68 (31.92)	56 (26.29)	124 (29.11)
40-49(Early Mid. Age)	47 (22.07)	57 (26.76)	104 (24.41)
50-59(Late Mid. Age)	37 (17.37)	37 (17.37)	74 (17.37)
60-69(Elderly)	24 (11.27)	28 (13.15)	52 (12.21)
≥70(Aged)	12 (5.63)	12 (5.63)	24 (5.63)
Mean age	44.67±13.41	46.11±13.76	

The age range with the highest number (31.92) of cases was 30-39years; and the age range with the least number of cases was ≥70years as reflected in table 4.2(a). The mean age for cases was 44.67±13.41 and that for the control group was 46.11±13.76.

Table 2:- Socio-demographic characteristics among cases and controls (Education) This table shows the educational level of participants for both cases and control

Education	Cases (%) (n = 213)	Control (%) (n = 213)	Total
None	0 (0.0)	1 (0.47)	1 (0.23)
Primary	36 (16.90)	48 (22.54)	84 (19.72)
Secondary	63 (29.58)	60 (28.17)	123 (28.87)
Tertiary	114 (53.52)	104 (48.83)	218 (51.17)

The table 2 shows that only one participant in the control group had no formal education, otherwise all others had at least a primary education. In all those with tertiary education appear to be in the majority in both the cases and control group, followed by participants with secondary education.

Table 3:- Socio-demographic characteristics among cases and controls (Religion and Marital Status) This Table shows the distribution of religious affiliations of participants in the study and their marital status

Variables	Cases (%) (n = 213)	Control (%) (n = 213)	Total
Religion			
Christianity	203 (95.31)	205 (96.24)	408 (95.77)
Islam	10 (4.69)	8 (3.76)	18 (4.23)
Marital Status			
Single	34 (15.28)	35 (16.43)	69 (16.20)
Married	167 (78.40)	156 (73.24)	323 (75.82)
Separated	5 (2.35)	13 (6.10)	18 (4.23)
Widow	0 (0.0)	1 (0.47)	1 (0.23)
Divorced	7 (3.29)	8 (3.76)	15 (3.52)

The dominant religion of participants in the study was Christianity amounting to over 200 (95.31% for cases and 96.24% for controls), with Islam being 10 (4.69%) for cases and 8 (3.76%) persons for the control group.

Most participants were married (78.40% for cases and 73.24% for the control group), followed by the singles (15.28% for cases and 16.43% for controls).

Table 4:- Socio-demographic characteristics among cases and controls (Occupation) This table presents the occupational distribution of the participants for cases and control

Characteristics	Cases (%) n=213	Control (%) n=213	Total
Occupation			
Accountant	2 (0.94)	5 (2.35)	7 (1.64)
Business	78 (36.62)	83 (38.97)	161 (37.79)
Civil servant	58 (27.23)	51 (23.94)	109 (25.59)
Farmer	7 (3.29)	9 (4.23)	16 (3.76)
Fishing	0 (0.0)	3 (1.41)	3 (0.70)
Health worker	14 (6.57)	11 (5.16)	25 (5.87)
House-Keeping	7 (3.29)	7 (3.29)	14 (3.29)
Law Practice	1 (0.47)	2 (0.94)	3 (0.70)
Retired C/S	3 (1.41)	4 (1.88)	7 (1.64)
Self employed	5 (2.35)	7 (3.29)	12 (2.82)
Students	35 (16.43)	27 (12.68)	62 (14.55)
Unemployed	3 (1.41)	4 (1.88)	7 (1.64)

The participants in the study as shown in table 4 belonged to twelve different occupations, with about 36.62% (cases) and 38.97% (controls) being business women. Civil servants were the next common among the cases (27.23%) and controls (23.94%). The least group was fishing for cases (0.00%) and law practice for controls (0.94%). The unemployed among the cases were 3(1.41%) and 4(1.88%).

Table 5:- Socio-demographic characteristics among cases and controls (State of Origin 1) This table shows the state of origin of the participants for both cases and control.

State of Origin Characteristics	Cases (%) n = 213	Control (%) n = 213	Total
Abia	17 (7.98)	23 (10.80)	40 (9.39)
Adamawa	2 (0.94)	0 (0.0)	2 (0.47)
Akwa-ibom	11 (5.16)	9 (4.23)	20 (4.69)
Anambra	5 (2.35)	4 (1.88)	9 (2.11)
Bayelsa	11 (5.16)	9 (4.23)	20 (4.69)
Benue	2 (0.94)	0 (0.0)	2 (0.47)
Borno	1 (0.47)	0 (0.0)	1 (0.23)
Cross river	6 (2.82)	7 (3.29)	13 (3.05)
Delta	15 (7.04)	11 (5.16)	26 (6.10)
Ebonyi	2 (0.94)	1 (0.47)	3 (0.70)
Edo	6 (2.82)	5 (2.35)	11 (2.58)
Ekiti	1 (0.47)	1 (0.47)	2 (0.47)
Enugu	9 (4.23)	7 (3.29)	16 (3.76)
Imo	37 (17.37)	32 (15.02)	69 (16.20)
Kaduna	2 (0.94)	0 (0.0)	2 (0.47)
Kano	0 (0.0)	1 (0.47)	1 (0.23)
Kogi	0 (0.0)	4 (1.88)	4 (0.94)

Table 6:- Socio-demographic characteristics among cases and controls (State of Origin 2) This table shows the remaining state of origin of the participants for both cases and control.

Characteristics (State of Origin)	Cases (%) n = 213	Control (%) n = 213	Total
Kwara	1 (0.47)	0 (0.0)	1 (0.23)
Lagos	0 (0.0)	1 (0.47)	1 (0.23)

Ogun	2 (0.94)	0 (0.0)	2 (0.47)
Ondo	1 (0.47)	3 (1.41)	4 (0.94)
Osun	0 (0.0)	1 (0.47)	1 (0.23)
Oyo	1 (0.47)	1 (0.47)	2 (0.47)
Plateau	1 (0.47)	0 (0.0)	1 (0.23)
Rivers	80 (37.56)	91 (42.72)	171 (40.14)
Taraba	0 (0.0)	2 (0.94)	2 (0.47)

In this study done in Port Harcourt, the respondents were indigenes of 25 different state of the federation, out of which 171 (40.14%) were of Rivers State origin {80 (37.56%) for cases and 91 (42.72%) for controls} as illustrated in table 4.2(e) and (f).

Table 7:- Some Hormonal contraceptives risk factors among cases and controls (OCPs, Injectable contraceptives) This table illustrates the odd ratio, 95% Confidence interval and p-value for oral contraceptive pills; and injectable contraceptives for both cases and controls.

Risk Factors/Variables	Cases	Control	Total	Odd ratio (Mantel-Haenszel (X^2))	95% Confidence Interval (CI)	p-value
Oral contraceptive pills						
Yes	81	80	161	1	0.66-1.51	0.932
No	129	127	256	(0.00)		
Total	**210**	**207**	**417**			
Injectable hormonal agents						
Yes	40	33	73	1.26	0.74-2.16	0.439
No	170	177	347	(0.81)		
Total	**210**	**210**	**420**			

Table 7 presented the hormonal contraceptives risk factors of breast cancer among the women respondents in Port Harcourt. The odds of developing breast cancer among the women using oral contraceptive pills was similar to that of women who were not using oral contraceptive pills. Hence, no significant relationship exists between use of oral contraceptive and breast cancer development. (Odds ratio, OR = 1.0, 95% CI=0.66-1.51). The odds of developing breast cancer among the women using injectable hormonal agents was 1.26 times higher than the women who were not using injectable hormonal contraceptive (OR = 1.26, 95% CI=0.74-2.16), although, the relationship was not significant (P>0.05).

Table 8:- Hormone-related reproductive risk factors among cases and controls 1 This table illustrates the odd ratio, 95% Confidence interval and p-value for breast feeding; frequency of breast feeding; regularity of menstruation and age at first pregnancy for both cases and controls.

Risk Factors/Variables	Cases	Control	Total	Odd ratio (Mantel-Haenszel (X^2))	95% Confidence Interval (CI)	p-value
Breast feeding						
Yes	151	162	313	0.73	0.45-1.18	0.217
No	56	56	100	(0.10)		
Total	**207**	**206**	**413**			
Frequency of Breast Feeding						
<6 months	38	46	84	0.83	0.49-1.42	0.562
≥ 6 months	110	111	221	(0.50)		
Total	**148**	**157**	**305**			
Regularity of Menstruation						
Irregular	31	36	67	0.79	0.45-1.39	0.466
Regular	145	133	278	(0.75)		
Total	**176**	**169**	**345**			
Age at first pregnancy						

<18	50	63	113	0.39	0.24-0.61	0.001*
≥18	106	112	218	(0.57)		
Total	**156**	**175**	**331**			

Table 9:- Hormone-related reproductive risk factors among cases and controls 2 This table illustrates the odd ratio, 95% Confidence interval and p-value for breast feeding; frequency of number of past deliveries; abortion and its frequency; and menstrual status for both cases and controls.

Risk Factors/Variables	Cases	Control	Total	Odd ratio (Mantel-Haenszel (X^2))	95% Confidence Interval (CI)	p-value
Number of past deliveries						
Multi-parity	131	145	276	0.71	0.45-1.14	0.167
Nulli-parity	62	49	111	(2.22)		
Total	**193**	**194**	**387**			
Any Abortion						
Yes	82	96	178	0.75	0.50-1.13	0.184
No	127	112	239	(2.04)		
Total	**209**	**208**	**417**			
Frequency of abortion						
>3	29	29	58	1.33	0.67-2.67	0.476
≤3	45	60	105	(0.76)		
Total	**74**	**89**	**163**			
Menopausal Status						
Pre-menopausal	176	169	345	1.19	0.70-2.02	0.579
Post-menopausal	35	40	175	(0.46)		
Total	**211**	**209**	**420**			

*Statistically significant ($p<0.05$)

Tables 8 and 9 presented the hormone-related reproductive risk factors of breast cancer among the respondents in Port Harcourt. The odds of women that is breast feeding developing breast cancer was less than women that were not breast feeding (Odds ratio, OR = 0.73, 95% CI=0.45-1.18). Hence, breastfeeding is a protective factor of having breast cancer, although this relationship was not significant (P>0.05). The odds of women that breastfed for less than 6 months developing breast cancer was less than women that breastfed greater than 6 months. The odds of developing breast cancer was found to be 0.79 (95% CI=0.45-1.39) times among women with irregular menstruation compared to women that has regular menstruation. Those with irregular menstruation are less likely to develop breast cancer.

The odds of developing breast cancer was found to be 0.39 (95% CI=0.24-0.61) times among women less than 18 years old at first pregnancy. Hence, those that were 18 years old at first pregnancy were less likely to develop breast cancer compared to women greater than 18 years old at first pregnancy, the relationship was statistically significant (P<0.005). The odds of developing breast cancer was found to be 0.71 (95% CI=0.45-1.14) times among multi-parity women. Hence, women with two or more deliveries were less likely to develop breast cancer compared to women who never has any delivery, although, the relationship was not statistically significant (P>0.005). Women who had more than three abortions showed increased risk of developing breast cancer (OR=1.33, 95% CI=0.67-2.67) compared to those who had less than three or no cases of abortion. While those who has ever had menopause showed an increased risk of breast cancer but was not statistically significant (OR=1.19, 95% CI=0.70-2.02).

Discussion:-

Association between exposures to hormonal contraceptives and risk of breast cancer:-

This study sought to identify hormonal contraceptives and other risk factors of breast cancer among women in Port Harcourt, Rivers State, Nigeria. Hormonal contraceptive use is a known risk factor (Weir, 2007). Current study revealed that oral contraceptive pill had no effect on breast cancer. In other words, there was no significant relationship between use of oral contraceptive and breast cancer development. However, there was a slight increased risk of developing breast cancer among the women using injectable hormonal agents compared to women not using

the injectable hormonal agents, although, the relationship was not significant (P>0.05). Though, Kuru et al. (2002) found hormonal contraceptive use to be a risk factor of developing breast cancer among Turkish women, this study findings is similar to some studies conducted among Italian (Talamini et al., 1985), United States women (Malone, 1993) and Bangladesh women (Zannat et.al., (2015). They reported no risk between hormonal contraceptive use and development of breast cancer.

Exposures to hormone-related reproductive factors and risk of breast cancer:-

It is well documented that breast feeding practice decreases risk of breast cancer (Kuru et al., 2002; Kim et al., 2007; Ozmen et al., 2009). This study showed that the odd ratio of the relationship between breast feeding, frequency of breast feeding and risk of developing breast cancer was less than one, hence, breast feeding may be a protective factor of breast cancer, although the relationship was not significant (P>0.05). Similarly, Zannat et al., (2015) in a study on risk factors for breast cancer among women in selected hospitals in Bangladesh reported that there was no risk of breast cancer associated with breast feeding or frequency of breast feeding.

Age at first full-term pregnancy has been considered important to the risk of developing breast cancer by previous studies (Tavani et al., 1997; Kuru et al., 2002). In this study, the odds of developing breast cancer were found to be 0.39 times among women less than 18 years old at first pregnancy. Hence, those that were 18 years old at first pregnancy were less likely to develop breast cancer compared to women greater than 18 years old at first pregnancy, and this relationship was statistically significant (P<0.005). However, this study was not in tandem with Zannat et al., (2015) who reported that early marriage, first pregnancy before 20 years have no effect on breast cancer among their study participants.

Current study revealed that the odds of developing breast cancer were found to be 0.71 among multi-parity women. Hence, women with two or more deliveries were less likely to develop breast cancer compared to women who never has any delivery, although, the relationship was not statistically significant (P>0.005). Similarly, Tavani et al. (1997) and Ebrahimi et al. (2002) reported that breast cancer risk decreases with high parity. However, some studies of meta-analysis in Nordic countries and study conducted in Nigeria (Ewertz et al., 1990; Adebamowo and Adekunle, 1999), reported that no association was reported between risk of developing breast cancer and number of past deliveries among women studied.

Women who had more than three abortions showed increased risk of developing breast cancer (OR=1.33) compared to those who had less than three or no cases of abortion. While those who has ever had menopause showed an increased risk of breast cancer but was not statistically significant (P>0.05).

Conclusion:-

This study also added that higher age at first pregnancy; use of injectable hormonal agents; women who had more than three abortions; were associated with higher breast cancer risk. More studies with bigger sample sizes conducted in similar settings are required. Besides, future research on this subject should favor population based data and analytical study designs that will produce better evidence, in terms of generalization and ability to demonstrate causality.

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