Evaluation of hormone quantification as an orientation screening in the diagnosis of hormone-dependent breast cancers in women in Abidjan, Côte d'Ivoire.

Abstract

Aim: Estrogens and progesterone play an important role in the regulation of various physiological processes in women. Although they are essential for breast development, paradoxically they promote the development of certain cancers, in particular breast cancer, through the stimulation and proliferation of cells by the action of hormone receptors. In Côte d'Ivoire, more than half of all diagnosed cases of breast cancer are hormone-dependent. Because of the link between female hormones and breast cancer, the consideration of certain factors, such as the period of influence of hormones (estrogen and progesterone) as well as their quantification, could be considered in orientation screening for hormone-dependent breast cancer.[too long and does not reflect the AIM]

Methodology: A case-control study conducted at the Cancerology Department of the Treichville University Hospital, the National Blood Transfusion Centre, and the Pasteur Institute of Côte d'Ivoire recruited 85 participants, including 39 cases and 46 non-menopausal and menopausal controls. Socio-demographic information and the participants' clinical status were collected through a questionnaire and consultation of the medical file. Blood samples were taken in dry red tubes with a coagulation activator on the day of inclusion for postmenopausal women and during the follicular phase for non-menopausal women (between days 4 and 7 of the menstrual cycle). The quantification of hormones (estrogen, progesterone, FSH, and LH) was performed by immunoassay on the Cobas e411 Analyser®.

Results: Postmenopausal cases had early menarche (13 years) and late menopause (52.46 years) compared to controls and also had slightly higher mean plasma oestradiol 2 and progesterone levels (P=0.04; P=0.017). Among these cases, those with ER+ tumors had slightly higher mean plasma oestradiol-2 levels (15.28 pg/mL) than those with ER- tumors (9.20 pg/mL) (P=0.03).

Conclusion: The epidemiological investigation and the quantification of hormones in the participants' blood plasma revealed a positive association between the period of influence of these hormones, their concentrations, and hormone-dependent breast cancer in postmenopausal women.

Keywords: Breast cancer; estradiol-2; progesterone; hormone receptors; immunohistochemistry; biomarker.

1 . Introduction

In all countries of the world, regardless of their state of economic development, the breast is the most common site of cancer in women (1). Globally, it accounts for 24.5% of all incident female cancers, with the highest rates in North America, Western Europe, and Australia (2,3). Breast cancer is the leading cause of cancer death in women in almost all countries with 2.2 million cases and an estimated 685,000 deaths in 2020 (3). Several types of breast cancer have been described depending on the status of the hormone receptors expressed by the cancer cells. These are referred to as hormone-dependent or non-hormone-dependent cancers whose growth may or may not be stimulated by female hormones. The majority of breast cancer is hormone-dependent, i.e. the cancer cells contain hormone receptors for estrogen (ER) and sometimes for progesterone (PgR) (4). Estrogen and progesterone play an important role in the regulation of various physiological processes in women (5). They are mainly produced in the ovaries in women before menopause, while they are produced mainly by tissues such as fat after menopause (6). However, prolonged exposure to estrogen is a factor in the development of certain cancers, particularly breast cancer (7,8). Although estrogen is produced by the female body and is essential for breast development, paradoxically it is also involved in the development of breast cancer through stimulation and cell proliferation (9,10) by the action of hormone receptors overexpressed by cancer cells in patients with hormone-dependent breast cancer

(11). High concentrations of steroid hormones (estrogen and progesterone) bind to receptors on the cancer cells and promote the development of the tumor mass. The longer estrogen circulates in a woman's body, the higher her risk of developing breast cancer (12). Relatively high levels of oestradiol are thought to increase the risk of breast cancer, especially in post-menopausal women where the level is normally low.

In Côte d'Ivoire, breast cancer ranks first among women's cancers before cervical cancer. According to data from the Abidjan cancer registry, the standardized incidence rate was 44.7 per 100,000 women, of which approximately 74% were in the late stages (III and IV), with 1,785 deaths with a mortality rate in 2020 of 25.3 per 100,000 women, and in more than half of diagnosed cases of SC, the cells express estrogen receptors (13,14).

The therapeutic management of breast cancer recommends, among other things, an immunohistochemical examination of biopsies or surgical specimens. The result of this examination provides information on the presence or absence of hormone receptors in cancer cells. Thus, the presence or absence of hormone receptors is a prognostic factor but above all predictive of the therapeutic response (15). In the Ivorian context, the cost of this examination is still quite high, and the time taken to obtain the results is long (between 1 and 2 months) given that the technical facilities for carrying it out are only available in a few references health centers, which nevertheless remain insufficient for the Ivorian population.

However, because of the link between female hormones and breast cancer, the consideration of certain factors, such as the period of influence of the hormones (estrogen and progesterone) as well as their quantification, could be envisaged in orientation screening for hormone-dependent breast cancer.

2. Materials and methods

2.1 Materials

2.1.1 Recruitment of women

This case-control study took place from May 2020 to September 2021 at the Cancerology Department of the University Hospital of Treichville for the recruitment of cases, at the collection department of the National Blood Transfusion Centre of Treichville as well as at the Reception, Reception, and Sampling Unit of the Pasteur Institute of Cote d'Ivoire for the recruitment of controls. Two groups of women were included in the study, a first group of non-menopausal and menopausal women with breast cancer (cases) and a second group of non-menopausal and menopausal women without the disease (controls). For cases, women of any age diagnosed with breast cancer at any stage were included in the study, and for controls, women of any age with a normal ultrasound mammogram of less than one year old were included in the study. Not included in the study for all groups were women who were pregnant or had a history of hormone use in the 6 months before inclusion or had started chemotherapy. Informed consent was obtained from each participant before the interview and sampling. The study protocol was approved by the National Ethics Committee for Life Sciences and Health under the number IRB000111917.

2.1.2 Biological material

The biological material consisted of venous whole blood samples.

2.2 Methods

2.2.1. Questionnaire and data collection

Sociodemographic information, clinical status, age of menarche, age of first pregnancy, age of menopause, parity, body mass index (BMI), use of hormonal contraception, family history of breast cancer, and immunohistochemical status of the patient’s tumors were collected using a questionnaire and consultation of the medical records.

2.2.2. Sample collection and storage

Blood samples were taken in dry red tubes with a coagulation activator (Vacutest kima®, Italy) on the day of inclusion for postmenopausal women and during the follicular phase for non-menopausal women (between days 4 and 7 of the menstrual cycle). For each participant, two 4 ml tubes were

collected. The blood samples were then placed on a rack at room temperature for approximately one hour for coagulation. Serum separation was performed by centrifuging the clotted blood samples at 3000 rpm for 10 minutes. The serum was collected in a 2 ml cryotube and stored at -20 °C for further analysis.

2.2.3. Hormone quantification

The different hormones, namely estradiol 2 (E2), progesterone, follicle-stimulating hormone (FSH), and luteinizing hormone (LH) were quantified by the electrochemiluminescence immunoassay (ECLIA) method using the Elecsys Estradiol III, Elecsys Progesterone III, Elecsys FSH and Elecsys LH kits on the Cobas e 411Analyser® (Roche, Germany) according to the manufacturer's recommendations (16).

2.2.4. Statistical analyses

Data were collected using EPI info™ (CDC) software version 7.2.4.0 and extracted to Excel. Statistical analyses were performed using R Studio version 2022 software. Statistical differences between cases and controls were investigated by Student's t-test for variables following the normal distribution and by the Wilcoxon-Mann-Whitney test for variables not following the normal distribution. For binary variables such as the family history of breast cancer and use of hormonal contraception, the significance of differences between cases and controls was investigated by the Chi-square test for a significance level $\alpha = 0.05$.

3. Results

3.1 Epidemiological characteristics of the women

A total of 85 women were included in this study, i.e., 39 cases and 46 controls distributed in 4 subgroups according to menopausal status (**Table I**). The mean age of the cases was 53.7 (± 12) years, but in the postmenopausal cases, it was 60 (± 7) years with extremes of 48-72 years and 36 (± 5) years with extremes of 26-44 years in the non-menopausal cases. By analyzing the mean age of menarche and menopause, the menopausal cases had early menarche (13 years) (*P<0.0001*) and late menopause (52.46 years) (*P=0.01*) compared to the controls of the same group (**Table II**). The postmenopausal cases were therefore under the influence of hormones for longer than the controls in the same group. In the non-menopausal women, there were no significant differences between cases and controls for variables such as age at menarche, age at first pregnancy, parity, BMI, family history of breast cancer, and use of hormonal contraception (**Table II**).
The histological type observed in all cases was non-specific infiltrating carcinoma (NSIC) and the majority of them (38%) did not attend school (**Figure 1**).

Table I: Distribution of women by menopausal status

	Case (n)	*Controls (n)*	*Total*
Non-menopausal	*11*	*18*	***29***
Menopausal	*28*	*28*	***56***
Total	***39***	***46***	***85***

Table II: Epidemiological characteristics of women

	Cases (n)	*Controls (n)*	*p-value*
Non-menopausal women	11	18	
Age in years, mean (standard deviation)	36.09 (5.30)	37.5 (7.45)	***0.58***
Age at menarche in years, mean (standard deviation)	12.63 (1.74)	12.72 (1.17)	***0.87***
Age at first pregnancy in years, mean (standard deviation)	25.18 (7.05)	23.13 (4.50)	***0.37***
Parity (n), mean, (standard deviation)	2.18 (1.47)	2.11 (1.99)	***0.71***
BMI (kg/m^2), mean (standard deviation	27.15 (6.41)	26.15 (2.87)	***0.9***
Family history of breast cancer (%)	9.09	5.55	***1***
Hormonal contraceptive use (%)	90.90	72.22	***0.22***
Menopausal women	28	28	
Age in years, mean (standard deviation)	60.71 (6.88)	59.42 (6.63)	***0.48***
Age at menarche in years, mean (standard deviation)	13 (1.15)	14.10 (1.61)	***<0.0001***
Age at first pregnancy in years, mean (standard deviation)	22.14 (5.89)	19.60 (2.74)	***0.14***
Age at menopause in years, mean (standard deviation)	52.46 (3.52)	49.85 (2.90)	***0.01***
Parity (n), mean (standard deviation)	4.89 (3.2)	3.71 (1.6)	***0.18***
BMI (kg/m^2) mean (standard deviation)	28.54 (4.29)	27.58 (4.43)	***0.41***
Family history of breast cancer (%)	32.14	28.57	***0.77***
Hormonal contraceptive use (%)	53.57	53.57	***1***

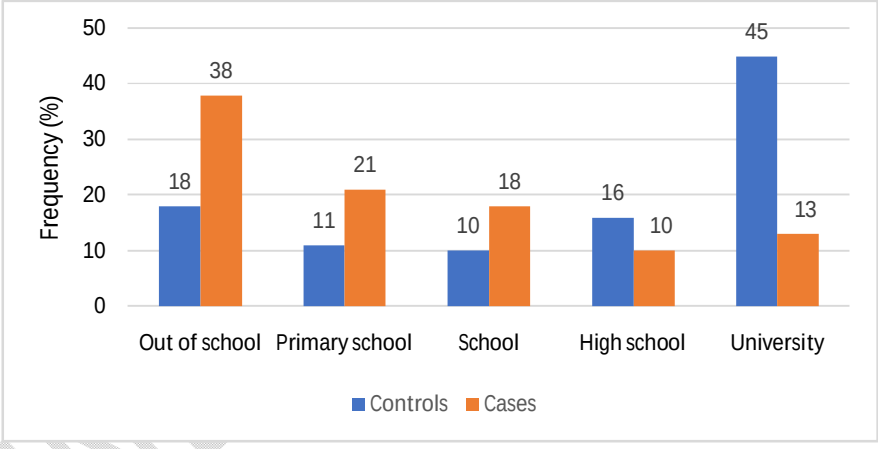

Figure 1 : Women's educational level

3.2 Plasma estradiol-2 and progesterone levels

In non-menopausal women

In cases, the mean estradiol-2 value was 50.58 pg/mL with a minimum of 29.6 pg/mL and a maximum of 86.84 pg/mL, while in controls it ranged from 32.73 pg/mL to 247 pg/mL with a mean of 110.47 pg/mL. In these women, the mean plasma level of estradiol-2 was higher in the controls than in the cases (P=0.001), while there were no differences between the two groups in progesterone (Table III).

In postmenopausal women

Estradiol-2 levels ranged from less than 5 pg/mL to 38.07 pg/mL with a mean of 13.54 pg/mL in cases and from less than 5 pg/mL to 16.5 pg/mL with a mean of 9.45 pg/mL in controls. For progesterone measurements, the mean was 0.186 ng/mL in cases with a range of 0.073 ng/mL to 0.720 ng/mL.

Postmenopausal cases had slightly higher mean plasma estradiol-2 and progesterone levels than controls (P=0.04; P=0.017) (**Table III**).

Table III: Plasma concentration of E2, progesterone, FSH, and LH in women

	Cases (n)	***Controls (n)***	***p-value***
Non-menopausal women	11	18	
Estradiol 2 (pg/mL) mean, standard deviation	50,58(22,24)	110,47 (19,98)	***0,001***
Progesterone (ng/mL) mean, standard deviation	0,211 (0,082)	0,188 (0,096)	***0,509***
FSH (mIU/mL) mean, standard deviation	24,63 (44,28)	7,51 (1,35)	***0,11***
LH (mIU/mL) mean, standard deviation	9,30 (11,81)	6,87 (1,71)	***0,49***
Menopausal women	28	28	
Estradiol 2 (pg/mL) mean, standard deviation	13,54 (7,95)	9,45 (3,68)	***0,04***
Progesterone (ng/mL) mean, standard deviation	0,186 (0,127)	0,130 (0,059)	***0,017***
FSH (mIU/mL) mean, standard deviation	74,5 (27,06)	62,92 (24,09)	***0,138***
LH (mIU/mL) mean, standard deviation	39,03 (13,78)	33,79 (13,79)	***0,07***

3.3 Immunohistochemical status of tumors and plasma E2 concentration in cases

Analysis of the immunohistochemical status of the tumors showed that in about 72% of the cases, the tumors expressed estrogen receptors (ER+), and in 67% of the cases they expressed both estrogen receptors (ER+) and progesterone receptors (PgR+), and in about 65% of the cases, there was the presence of distant metastases (**Table IV**). Postmenopausal cases with ER+ tumors had a significantly higher mean plasma oestradiol 2 level (15.28 pg/mL) than postmenopausal cases with ER- tumors (9.20 pg/mL) (P<0.05). However, no difference was observed in non-menopausal cases (**Figure 2**).

Table IV: Immunohistochemical status of tumors

	Numbers	Percent (%)
ER status		
Positive	28	71.79
Negative	11	28.20
PgR status		
Positive	26	66.66
Negative	13	33.33
ER / PgR status		
ER +, PgR +	26	66.66
ER+ PgR -	2	5.12
ER- / PgR-	8	20.51
Distant metastases		
Yes	25	61.4
No	14	39.9

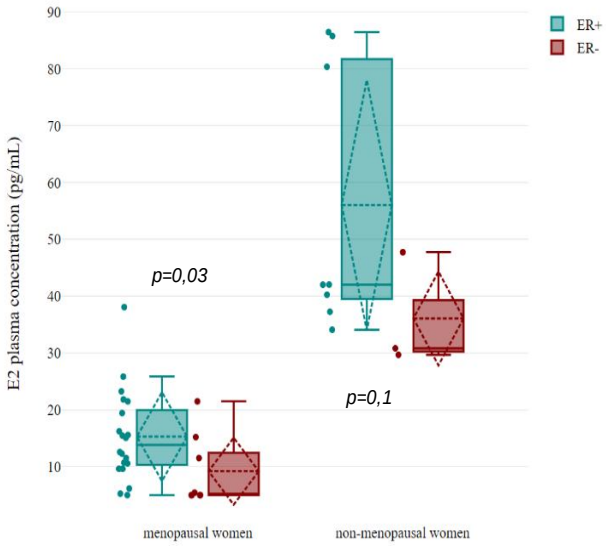

Figure 2: Plasma E2 concentration in cases with RE+ and RE- tumours

ER+: Estrogen Receptor positive
ER-: Estrogen Receptor negative
PgR+: Progesterone Receptor positive
PgR-: Progesterone Receptor negative

4. Discussion

In our study, the mean age of cases at diagnosis was 52.7 years. This result is in agreement with that of an African meta-analysis which showed a mean age at diagnosis that varied between 46 and 60 years (17). However, this result is different from those of industrialized countries where the average age of onset of breast cancer has been increasing in recent years (18-20) and is around 67 years in France for example. This difference could be explained by the fact that in developing countries, populations are adopting an increasingly westernized lifestyle with an increase in risk factors, while populations in developed countries are returning to a much healthier lifestyle as a result of awareness-raising policies among at-risk populations.

Menopausal cases had early menarche (13 years) and late menopause (52.46 years) compared to controls in the same group. This observation has been made by several authors (21,22). Indeed, these risk factors may influence the risk of developing breast cancer through long-term effects on sex hormone levels in postmenopausal women, through long-lasting changes in breast tissue (23,24). In a meta-analysis of 13 case-control studies in postmenopausal women, circulating estradiol-2 levels were 6% lower in women who menstruated at 14 years or older than in women who menstruated before 12 years (25).

Our study did not find an association between risk factors such as parity, BMI, family history of breast cancer, and use of hormonal contraceptive methods in the different groups. Although some of these risk factors have been reported in African American women (26,27), in Tanzanian women, the study by Akoko et al did not find evidence of these factors and breast cancer (28). Further studies on these risk factors need to be carried out in sub-Saharan women.

The histological type observed in all cases was non-specific infiltrating carcinoma (NSIC). Our results are similar to those of the Ivorian study which found 82% (247/302) and 90.44% of NSIC (29,30).

In our study, the average circulating estradiol-2 level in non-menopausal cases was (50.58 pg/mL). Some authors have obtained similar results (48 pg/mL) (31) in a similar population. In addition, in the non-menopausal controls in our study, we recorded a mean level of 110.47 pg/mL which was higher

than in the patients. Sturgeon et al reported similar results in a case-control study in non-menopausal women during the late follicular phase (32). Indeed, the interpretation of hormone quantification results in premenopausal women can be complex due to intra-subject variation in the cycle involving considerable variation during the follicular phase (31). This differentiation during the follicular phase was not performed in our study.

Postmenopausal cases had slightly higher mean plasma levels of estradiol-2 (13.54 pg/mL) and progesterone (0.186 ng/mL) than controls. These results are comparable to those of Zhang et al, who showed that higher estradiol-2 and progesterone levels were associated with an increased risk of ER+/PgR+ tumors (33). In addition, the distribution of postmenopausal cases according to hormone receptor status and mean plasma estrogen level showed that patients with ER+ tumors had a slightly higher mean oestradiol-2 level compared to cases with ER tumors. This phenomenon was observed in a meta-analysis of 9 prospective studies on hormonal risk factors for breast cancer in postmenopausal women (34). In view of these results, the quantification of estradiol-2 could be used in the orientation screening of immunohistochemistry in postmenopausal women.

The proportion of cases with tumors expressing estrogen receptors (ER+) was higher than that of patients expressing progesterone receptors (PgR+). Similar results have been obtained by several authors in Africa (35,36) and America (37).

Furthermore, our study showed that in 65% of the cases diagnosed, there was the presence of distant metastases, which could be explained by the fact that the diagnosis of breast cancer is late in the Ivorian socio-economic context. Indeed, the majority of cases had a low economic level and did not attend school, which can be added stigma, lack of information, fear, and the use of traditional medicine which could be factors favoring a late diagnosis of the disease. These results are in line with those of Ivorian studies which showed that patients had a very low economic level and that very few had access to diagnostic means (30,38).

Conclusion

Prolonged exposure to female sex hormones is a factor that favors the development of hormone-dependent breast cancer, especially in postmenopausal women in Côte d'Ivoire. Hormone quantification allowed us to demonstrate a positive association between the serum level of estradiol-2 and the presence of estrogen receptors in cancer cells in postmenopausal women. The quantification of estradiol-2 in these women could be used as a guideline screening for immunohistochemistry. This study presents us with avenues to consider, however, it would be interesting to extend it to a larger study population to gain a better understanding.

Limitations of the study

Although we used rigorous sampling methods to select our sample, we are aware that the small size of our sample and the non-distribution of non-menopausal women by early and late follicular phase may limit the statistical power of our results.

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