International Journal of Medicine and Medical Sciences Vol. 4(4), pp. 103-109, April 2012
Available online at http://www.academicjournals.org/IJMMS
DOI: 10.5897/IJMMS12.028
ISSN 2006-9723 ©2012 Academic Journals

Full Length Research Paper

Biological evolution of tryptophan and phenylalanine in the occurrence of breast cancer in Senegalese women

Fatimata Mbaye[1,3]*, Malick Fall[1], Ahmadou Dem[2] and Mbacké Sembène[1,3]

[1]Faculty of Science and Technology, University Cheikh Anta Diop, P. O. Box 5005 Dakar, Senegal.
[2]Faculty of Medicine, Pharmacy and Odonto-Stomatology, University Cheikh Anta Diop, Institute of cancer, Dakar, Senegal.
[3]Laboratory of Biology Animals Populations Sahelo-sudanian, IRD, CBGP, Bel Air BP.1386 Dakar.

Accepted 3 April, 2012

The reports provided by OMS in 2011 revealed that cancer is a major cause of death worldwide, causing 7.6 million deaths in 2008. Breast cancer represents in the world, the most common malignancy of women, and it seems that the low penetrance genes, frequently mutated in the general population would play an important role in the development of this cancer. The purpose of this study is to evaluate the involvement of the protein diversity of cytochrome B (mitochondrial gene) in the occurrence of breast cancer in Senegalese women. We analyzed by PCR-sequencing cytochrome B variability in thirty Senegalese patients suffering from breast cancer. The nucleotide sequences obtained were transformed into amino acid sequences with BioEdit software version 7.0.8. Changes of one or more tryptophan to other amino acids, ranging normal tissue to cancerous tissue, are noted in some individuals with a penetrance of 72.41%. Our results also show a significant increase (79.3%) in the rate of phenylalanine in cancerous tissues with very different proportions between individuals. Any increase in the rate of tryptophan and phenylalanine in cancerous tissues could be correlated with an increased risk of developing breast cancer.

Key words: Cytochrome B, tryptophan, phenylalanine, breast, cancer, Senegal.

INTRODUCTION

The reports provided by OMS in 2011 showed that cancer is a major cause of death worldwide, causing 7.6 million deaths in 2008, about 13% of global mortality. It therefore represents a major public health problem. Cancer is the emergence of a cell clone that proliferates, invades, and metastasizes, despite the different levels of control of the body. It is a dogma that the last 30 years of research have continued to check (Stoppa-Lyonnet et al., 2010). Once considered a disease of the rich, it is now found among the poor in Senegal. Most cancer patients die from lack of means to support this costly disease in terms of drug costs, resulting from the level of living. Recent advances in molecular biology have allowed passing mathematical models proposed in the fifties to a biological reality. We now know that cancer is a disease of DNA resulting from the accumulation of successive mutational events: The acquired or germline mutations alter the normal function of some genes (Sobol and Eisinger, 2004). The discovery of oncogenes and their return, the tumor suppressor genes, established the pattern of cancer forming and progressing, following the onset of spontaneous somatic mutations. We now know that the genomes of tumors undergo many changes that disrupt profoundly affect the structure and functioning (Theillet, 2010). Most mutations are acquired (somatic) in tumor transformation. However, some are present from conception (the constitutional changes, or germ) and explain the genetic predisposition to cancer (Stoppa-Lyonnet et al., 2010). In nearly 25 years, more than 70 genes predisposing to cancer have been identified (Futreal et al., 2004).

Breast cancer is in the world, the most common malignancy of women; causes approximately 30% of

*Corresponding author. E-mail: mbaye_fatimasy@yahoo.fr. Tel: 00 (221) 773665998.

cancers and about 16% of cancer deaths in women (D'hondt et al., 2008). It is the second most common cancer in women in Sub-Saharan Africa after that of the cervix (Ly et al., 2011), particularly in Senegal (Dem et al., 2008).

It occurs in young women with a mean age at diagnosis between 42 and 53 years depending on the region, and is most often diagnosed at a late stage. These are mainly invasive ductal carcinoma with features of aggressive tumors (high SBR grade [grade III], low expression of hormone receptors and HER2). Under the new classification of breast cancers, some studies show that 16 to 55% of these tumors belong to the sub-group known as the triple negative (Ly et al., 2011). One of the problems the Curie Institute in Dakar faces is the resurgence of the disease in young women. In the literature, breast cancer in young women occurs at either the age of 35, sometimes less than 40 years, or sometimes less than 50 years (Espié and Cottu, 2003). Here, we will stick to the third option.

The objective of this work is to study the diversity of protein cytochrome B (Cyt. B), between healthy tissue and cancer, to determine the penetrance of the mitochondrial gene encoding breast cancer in Senegalese women, especially women who are received at the Institute Joliot Curie in Hospital Aristide Le Dantec.

PATIENTS AND METHODS

One of the first stages of this study is to obtain and collect samples necessary for its implementation. Sampling was done following a number of parameters, given in Table 1. From each patient, a perfectly healthy tissue sample and a sample of cancerous tissue are removed. Samples are taken in their interventions, by Prof. Ahmadou DEM Institute Joliot Curie in Hospital Aristide Le Dantec and colleagues. They are immediately forwarded to the Joint Laboratory IRD-ISRA-UCAD Molecular Biology of the Center for Biology and Population Management (CBGP) IRD Bel-Air, where the various stages of analysis are carried out. The samples are preserved in alcohol 96°C.

Currently, biological samples representing different stages of tumor progression: normal breast tissue, benign tumors, malignant tumors, and samples of special interest (tumors of the young woman) are available in the laboratory. The analysis focuses on 30 patients, all black. A portion of these biopsies was extracted nucleic acid (DNA).

Total genomic DNA was extracted from 25 mg to healthy tissue and cancerous (approximately 2 mm × 2 mm) using standard Qiagen method (Qiagen Dneasy Tissue Kit). Once the DNA was extracted, a portion of Cyt.B of great interest was amplified and sequenced. The Cyt.B has an area of over a thousand base pairs of the mitochondrial genome, located at positions 14201 and 15341 in the human sequence (Anderson et al., 1981), has a low recombination rate (related to the maternal inheritance only) and has a relatively high variability although it is a coding sequence, which justifies the choice of this marker. Primers used to amplify Cyt.B were as described previously (Montgelard et al., 2002). The 50 µl PCR reaction mixture contained 28.9 µl water, 5 µl enzyme buffer supplied by the manufacturer, 2 µl dNTP, 5.10^{-6} pmol of each primer H6 (5'TCT-CCA-TTT-CTG-GTT-TAC-AAG-AC 3') and L7 (5' ACC-AAT-GAC-ATG-AAT-AAA-CAT-GGT-T 3'), 0.1 µl of Taq polymerase and 4 µl of DNA extract. PCR conditions were 94°C for 3 min, followed by 40 cycles (92°C for 45 s, 50°C for 1 min, 72°C for 1 min 30 s), and a final elongation at 72°C for 10 min.

Table 1. Parameters sampling.

Patient	Age (years)	Tumor seat
1	50	Right breast
2	21	Left breast
3	46	Left breast
4	32	Right breast
5	40	Left breast
6	34	Right breast
7	35	Right breast
8	19	Right breast
9	50	Left breast
10	52	Left breast
11	60	Right breast
12	70	Right breast
13	42	Undefined
14	46	Right breast
15	57	Right breast
16	38	Left breast
17	73	Right breast
18	35	Right breast
19	44	Left breast
20	28	Right breast
21	49	Left breast
22	45	Right breast
23	52	Left breast
24	54	Right breast
25	40	Right breast
26	73	Right breast
27	35	Undefined
28	38	Undefined
29	48	Left breast
30	73	Left breast

Sequencing was performed by Macrogen in South Korea. A portion of the mitochondrial Cytochrome B gene was sequenced. The sequences of Cyt.B, healthy and cancerous tissue are carefully checked, adjusted and aligned with BioEdit software version 7.0.8 (www.mbio.nscu.edu/BioEdit/bioedit.html). Each healthy tissue is aligned next to the cancerous tissue to visualize and locate the mutations. The standard indices of genetic variation: genetic distances intra-healthy tissue, intra-cancerous tissues and between tissues, as well as genetic distances correlated on the one hand, at the age of the patients and secondly, the location of tumors (right breast or left breast) are explained with the software MEGA 4 (Evolutionary Molecular Genetics Analysis 4) (Tamura et al., 2007). The mtDNA coding is used. This allows you to convert nucleotide sequences into protein sequences using different reading frames possible. The reading frame is the sequence of triplets along a portion of mRNA. For a ribonucleotide sequence data, there are three different reading frames. The transformation into amino acid sequences was performed with the BioEdit editor. At this level, firstly, we try to establish a correlation between the rate of mutated

amino acids and age of the patients according to the Pearson coefficient correlation note (r), and secondly to look for mutations of interests within a single individual between cancerous and healthy tissue:

$$r = \frac{\sum (X - \overline{X}).(Y - \overline{Y})}{\sqrt{\sum (X - \overline{X})^2} \times \sqrt{\sum (Y - \overline{Y})^2}}$$

RESULTS

Alignment and genetic distance of cytochrome B

A portion of Cyt.B cells cancerous was sequenced in 30 individuals. The results are compared with those obtained from matched non-cancerous breast tissue, derived from the same patients. The sequences obtained are in number 60. Following a careful correction, we are left with 58 sequences, with a maximum length of 806 base pairs. The individual No 13 was eliminated because of a high genetic diversity. Analyses of genetic diversity and protein therefore focused on 29 individuals.

A comparison of nucleotide sequences at the intra and inter-individual variability shows strong Cyt.B. Strong disruption of normal tissue is observed in cancer tissue. The value of genetic distance (0.400) in healthy tissue is higher than cancerous tissue (0.281). Between the two groups, the genetic distance is 0.340. Young women represented 63.3% of our study population; the genetic distance within the tissue (0.461) is higher than that observed in healthy tissue of older women (0.310). By against, the genetic distance within the cancerous tissue of younger women (0.275) is lower than the intra-cancerous tissue of older women (0.291). The genetic distance between cancerous and normal tissues of young women (0.364) is higher than that observed between healthy and cancerous tissues of older women (0.297). In our study population, 53.3% of patients had a tumor that is located in the right breast, 36.7% in the left breast and the rest is not defined in the cards collection. The genetic distance intra-healthy tissue located at the right sound (0.461) is much higher than intra-healthy tissue located in the healthy left (0.249). The opposite effect is observed at the intra-cancerous tissue. The genetic distance between cancerous and healthy tissue located in the right breast (0.366) is higher than that observed between healthy and cancerous tissue of the left breast (0.255). In general, the results show that the genetic distance intra-healthy tissue is higher than intra-cancerous tissues regardless of the hierarchical level compared (the age of the patients and the right breast). For cons, the opposite is found in the left breast.

Protein diversity of cytochrome B

The protein sequences were obtained following transformation of the nucleotide sequences into amino acid sequences. After a test phase on three individuals, it was agreed that the second reading frame was by far the most appropriate, because it had the least stop codon. The total percentage of mutated amino acids in our patients was 36.47%. The correlation index R amino acid levels mutated versus age of patients was 0.0385. The correlation is shown in Figure 1. Changes of one more Trp to other amino acids from healthy tissues to cancerous tissues are noted in some individuals with a penetration of 72.41%. Among these individuals, mutations lead to 47.62% in truncated proteins. Meanwhile, an increasing number of Trp in 68.97% of cases is noted in the cancerous tissue. Our results also show a significant increase (79.3%) in the number of phenylalanine in cancerous tissues, with very different proportions. The results are given in Tables 2 and 3.

DISCUSSION

The objective of this work is to study the Cyt.B diversity of protein between healthy and cancer tissue, and to determine the penetrance of the mitochondrial gene encoding the breast cancer in Senegalese women. The choice to study mitochondrial DNA, fell on the Cyt.B because of the work done in laboratories; suggesting that the Cyt.B had a relatively high variability, although it is a gene. We analyzed by PCR-sequencing variability Cyt.B in 30 Senegalese patients suffering from breast cancer, a total of 60 sequences. The results are compared not in terms of epidemiology but in terms of mutational changes. The risk factors of breast cancer, which included previous exposure to hormone therapy, family history, obesity, ethnicity, were not taken in to account in our data processing. Only the patient age and tumor localization (left breast or right breast) were considered.

Genetic diversity of cytochrome B

The Americans, in their project "Cancer Genome Atlas'' found 189 genes whose mutations are involved in the onset or development of tumors. Only two of these genes are common to breast and colon cancer, all others differ. The researchers posited that each type of cancer is a very specific disease, requiring a specific treatment. Going further, they explain that each patient is different from the other. Our results show a high variability of nucleotide at both intra and inter-individual. This could be explained on the one hand, by the peculiarities of the mitochondrial genome: heteroplasmy and mitotic segregation. The heteroplasmy is the coexistence in the same cell of two species of mitochondrial DNA. During cell division, mitochondria of a cell are not distributed homogeneously in the daughter cells. Thus, from a cell with two types of mitochondrial populations, the daughter

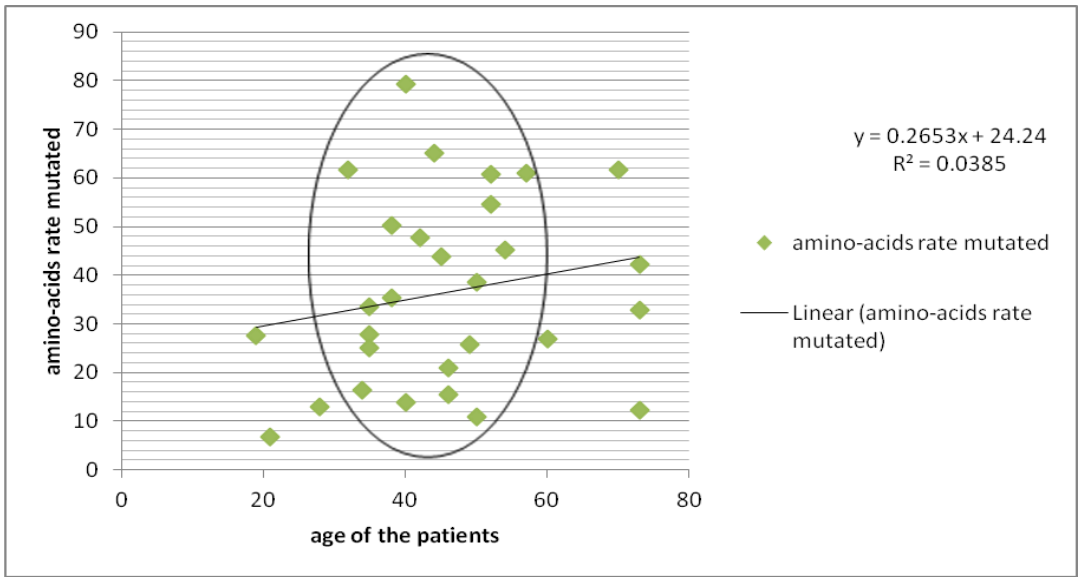

Figure 1. Curve of correlation of the rate of mutated amino acids at the age of the patients.

Table 2. Summary of changes in individuals with tryptophan.

Patient	Substitutions of Trp to TS-TC	Amino acid substitution of Trp to TS- TC
1	Cys	Gly ; His ; Cys
2	_ _ _ _	Gly
3	End ; Met	2 (Arg) ; End ; Cys
4	Met ; End ; Phe	Pro ; End
5	_ _ _ _	End
6	Arg	End ; His
7	_ _ _ _	Phe ; Gly
8	Gln ; End	Phe ; Cys ; Pro
9	Gly	Leu
10	End ; Lys ; Ile ; Lys	End
11	Cys	_ _ _ _
12	Val ; Arg ; End	His ; End ; Arg ; Phe
15	Thr ; Cys ; Arg	2 (End)
16	Glu	End
17	Gly ; Val ; Arg	2 (Gly) ; Arg ; Phe
18	Cys	_ _ _ _
19	End	End ; Gly
20	_ _ _ _	Gly
21	Cys	_ _ _ _
22	End ; Gly	_ _ _ _
23	End ; Gly	_ _ _ _
24	Arg ; Phe ; Gly	_ _ _ _
25	Lys ; leu	End ; 2 (Phe) ; Gly
26	End	End
27	_ _ _ _	Phe
28	_ _ _ _	2(Phe)
30	End ; Cys	_ _ _ _

- - - -, No modification.

Table 3. Summary table of individuals with a greater number of Phe in cancerous tissues.

Patient	Mutated amino-acids to Phe TS, TC	Nature of mutation
1	End, Glu	
2	Val	
3	2 (Leu), 3 (Tyr)	
4	Ser, 2 (Gly), Asp, His, Tyr, 2 (Leu), Trp	
5	Leu	
6	Glu, Ile	
7	His, Cys, Tyr	
8	2 (Ser), Cys, Leu	
10	End, Arg, Ser, Cys, Glu, Val, Ala, Leu	
11	End, 2 (Ile), 3 (Ser), Pro	
12	2(Leu), His	
14	Ile, Leu	Missense mutation
15	End, Ile, 2 (Cys), Glu, Ser	
16	Ser, 2 (Leu), Cys	
17	Leu, His	
19	Pro	
20	Leu	
22	End, Ser, Val, Gly	
23	End, Gln, 3 (Gly), Val, Leu, Ile	
24	End, 2 (Leu), Glu, Trp, Ile, Val, Ser, Gly	
27	Gly, Leu, Ile, Ser	
28	Pro, Ile	
30	End, 2 (Val)	

cells with variable rates of each of the two populations can be obtained. The phenomenon called mitotic segregation explains that from an egg containing a given proportion of normal and mutated mitochondrial DNA, an individual can have highly variable sex normal DNA / DNA mutated in its various tissues and organs. Associated with the threshold effect, this phenomenon explains the heterogeneity of clinical expression of diseases associated with mitochondrial DNA (DiMauro and Schon, 2001). On the other hand, this inter-individual variability observed could be due to mutations in precancerous especially as the samples are from the same breast. Indeed, Palacios et al. (2008) have shown that loss of heterozygosity observed in 90% of tumors BRCA1/2, are also present in preneoplastic lesions: carcinoma *in situ* of these patients, but also in non-tumor tissue. These results suggest that non-tumor tissues have a certain degree of genetic alterations that are predispose to neoplastic transformation.

The genetic distance within the normal tissue compared with intra-cancerous tissue, reveals a genetic differentiation. The proliferation of normal cells appears to be much faster. This shows that the main characteristic of the cancer cell is that its proliferation is no longer under control of the regulatory mechanisms of the body, and instead it evolves at a pace of its own. Thus, it does not necessarily divide faster than normal cell from which it derives, but its proliferation is no longer understood as meeting the unique needs of the organization, it escapes the different levels of its control. The high genetic distance observed between healthy and cancerous tissues could be explained by the fact that the mammary gland is constantly changing during the life of a woman.

The genetic distance correlated with patient age, which reveals that the genetic distance observed at the intra-healthy tissue of younger women is higher than the genetic distance of intra-healthy tissue of older women. This shows that genetic differentiation is related to the age of the patients. The proliferation of normal cells is faster in younger women. For cons, the genetic distance within the cancerous tissue is higher in older women; thus, we are told that the rate of proliferation of the cancer cell increases with age. The activity of repair genes in cell division decreases. This would explain the fact that cancer is a disease of aging. The genetic distance inter-healthy tissue and cancerous higher among young, could explain the large tumors observed in them during sampling. Would vascularization of the tumor not be more developed among young people? Taking into account the location of the tumor, the results show that the genetic distance intra-healthy tissue, localized in the right breast is higher than that observed in healthy

tissue located in the left breast. The proliferation of normal cells would be much faster in the right breast. The opposite effect is observed at the intra-cancerous tissue. The proliferation of the cancer cell is faster in the left breast, suggesting that the location of the tumor in it would be in favor of a faster evolution of the different process of carcinogenesis. In general, the proliferation of normal cells is faster than the cancer cell. This is valid not only in younger women than older women, but also for tumors that are localized in the right breast. For tumors localized in the left breast, the proliferation of the cancer cell is faster than the normal cell from which it is derived.

Protein diversity of cytochrome B

The total percentage of mutated protein levels on all patients is not significant enough. However, the Cyt.B being a gene, these substitutions may change the nature of the amino acid encoded, depending mainly on the position of substitution in codon but also according to the nature of the substitution. Through the right correlation between the rate of mutated amino acid and age of patients, our results confirm the work of Dem et al. (2008) namely that in Senegal, breast cancer occurs from 20 years, increase in frequency from 30 years to reach a peak between 44 and 50. As such, it is important to identify specific alterations, reflecting the occurrence of these tumors to less than 50 years without any hereditary background.

Mutations leading to a deficit of tryptophan (Trp) in normal tissues, as well as increased levels of Trp and phenylalanine (Phe) in cancerous tissues were identified. The Trp plays an important role in T cell proliferation, and Phe is among the eight essential amino acids that cannot be synthesized by the body so it is our food that should bring them. T cells are key players of immune rejection reactions that can lead to the elimination of cancer cells, which are based on various approaches to immunotherapy currently tested. Indeed, the methods used are designed to stimulate the immune system to recognize and destroy tumor cells. However, *in vivo*, cancer cells are able to develop mechanisms that allow tumors to resist and evade the immune system. Among these mechanisms, two enzymes are the key players: tryptophan 2, 3-dioxygenase (TDO) and indoleamine 2, 3-dioxygenase (IDO) (Moineaux et al., 2010). TDO is present in the liver, and IDO is expressed by the vast majority of tissues. By inhibiting the proliferation of T cells via the reduction of local rates of Trp, IDO is involved in the survival of tumor cells (Andre, 2008). Always in the same vein, Eyndeb et al. (2003), studying a new mechanism of tumor resistance to the immune system, based on the degradation of Trp by indoleamine, firstly, observed that the majority of human tumors expres this enzyme, and secondly, that expression of this enzyme by tumor cells of mice enabled them to escape immune rejection. Consistent with these results, such a change could be a risk factor for the occurrence of breast cancer. Immunotherapy could be suggested as a treatment by administration of an inhibitor of IDO obviously with other additional studies. These changes were observed in 21 individuals, or 72.41% of the study population.

The opposite effect occurs, always healthy tissue to cancerous tissue, leading to the appearance of a greater number of tryptophan in cancerous tissues. The amino acids that change in Trp healthy tissue to cancerous tissue are most often: Phe, Gly, Arg, Cys, the Pro, His, Leu, Glu sometimes in the same position, sometimes very different positions. It is as if there were repair systems that are mobilized to eliminate damage in the cancerous tissue. This is undoubtedly responsible for the transformation of the stop codon or other amino acids Trp, to allow T cells to proliferate and to play their advocacy role, recognizing cancer cells. Indeed, in normal cells, there are mechanisms of DNA repair involved to correct mutations that could for example be the cause of the cancer process. There are many eukaryotic repair systems, each suited to one or more types of lesions: MMR (mismatch repair): mismatch repair; NER (Nucleotide Excision Repair): nucleotide excision repair; BER (Base Excision Repair): base excision repair; the TS (Translesion Synthesis): direct repair; repair of DNA carrying agent and DSBR (Double Strand Break Repair): double-strand break repair; which includes the HR (Homologous Repair) and NHEJ (Non Homologous End Joining) (de Feraudy, 2007). The balance between the occurrence of DNA damage and repair is critical to the risk of developing cancer (Moisan, 2009). Mutations that are causing the change in Trp to stop codon, resulting in the appearance of a truncated protein (nonsense mutation) or other amino acids (missense mutations) are inactivating. Therefore, the gene Cyt.B could be considered a new susceptibility gene for breast cancer.

Similarly, an increase of Phe was observed on almost all (79.3%) cancerous tissues of individuals sampled, with very different proportions. This could be explained by the progress of the disease. Recall that we used biological samples representing different stages of tumor progression. Sometimes it is a transition, a transversion sometimes but in most cases it is a transversion. Adenine, guanine or cytosine is replaced with a thymine or cytosine. Phe UUU and UUC encoded by the formula UUU was found in 86.75% of cases. In other words, situations where the mutation is the thymine was found to be much more. Penetrance is high, the quantification of the rate of Phe in the body could be considered as a screening.

Conclusion

Faced with this real public health problem posed by

breast cancer in women, the establishment of a genetic test will allow sensitive and rapid management of patients. The results revealed one hand, nucleotide variability at intra-and inter-individual as well as genetic differentiation between healthy tissue and cancerous tissue; and secondly, that this genetic differentiation is linked both to the patient age and tumor localization (left breast or right breast). Any modification of Trp leading to a deficiency of this amino acid in normal tissues, as well as increased levels of Trp and Phe in cancerous tissues, could be correlated with an increased risk of developing breast cancer. The search rate of tryptophan and phenylalanine in the blood could be proposed as a screening test, and immunotherapy as a treatment. But these assumptions need to be confirmed by genetic analysis of a larger number of samples and by sequencing a larger number of coding genes.

ACKNOWLEDGEMENT

The authors warmly thank all members of the CBGP, especially Tofféne Diome for being very helpful.

REFERENCES

Anderson S, Bankier AT, Barrel BG, de Bruijn MHL, Coulson AR, Drouin J, Eperon IC, Nierlich DP, Roe BA, Sanger F, Schreier, Smith AJ, Staden R, Young IG (1981). Sequence and organization of the human mitochondrial genome. Nature, 290(5806): 457-465.

Andre C (2008). Study of the role of cytokines in the activation of indoleamine 2,3-dioxygenase brain involved in behavioral alterations associated with inflammation. Thesis University of Toulouse. 285 pages.

Dem A, Traoré B, Dieng MM, Ouajdi T, Lalani MT, Diop M, Dangou JM and Touré P (2008). Gynaecological and breast cancers at the Dakar Cancer Institute. Cah. Sant. 18(1): 25-29.

De Feraudy (2007). Molecular mechanisms to repair of DNA damage and human tumor pathology. Role of the translesional polymerase Ƞ in DNA replication. Thesis University Paris Descartes. 75 pages.

D'hondt V, Picart M, Sotiriou C (2008). Introduce profiles genomic expression in clinical: when the molecular signatures at the bedside? Bull. Can. 95(3): 336-343.

DiMauro S, Schon EA (2001). Mitochondrial DNA mutations in human disease. Am. J. Hum. Genet. 106(1): 18-26.

Espié M, Cottu PH (2003). Breast cancer in young women: problems and questions. Path. Biol., 51: 391-392.

Eyndeb VD, Goldmanm BJ, Magdi Y, Auf H (2003). A new mechanism of tumor resistance to the immune system, based on tryptophan degradation by indoleamine. Bulletin and memories of the Royal Academy of Medicine of Belgium: 58(7-9): 356-365.

Futreal PA, Coin L, Marshall M, Down T, Hubbard T, Wooster R, Rahman N, Stratton MR (2004). A census of human cancer genes. Nat. Rev. Cancer, 4(3): 177-183.

Ly M, Antoine M, André F, Callard P, Bernaudin JF, Diallo DA (2011). Breast cancer in Sub-Saharan African women: review. Bull. Can. 98 (7): 797-806.

Moineaux L, Charlier C, Dolusic E, Larrieu P, Pilotte L, Colau D, Stroobant V, Galleni M, Masereel B, Eyndeb BVD, Wouters J, Fredericka R (2010). Design, synthesis and study of inhibitors of tryptophan 2,3-dioxygenase (TDO), a promising target for cancer therapy. Seminar. page. 1.

Moisan F (2009). Study of the influence polymorphism genes repair of DNA by nucleotide excision on the activity of anticancer agents. Thesis University of Angers. Pages 119.

Montgelard C, Bentz S, Tirard C, Verneau O, Catzeflis FM (2002). Molecular Systematics of Sciurognathi (Rodentia): The Mitochondrial Cytochrome *b* and 12S rRNA Genes Support the Anomaluroidea (Pedetidae and Anomaluridae). Mol. Phylogenet. Evol., 22(2): 220-233.

OMS / Cancer, 2011. Aide mémoire (297).

Palacios J, Robles-Fria MJ, Castilla MA, Lopez-Garcia MA, Benitez J (2008). The molecular pathology of heredity breast cancer. Path biol., 75: 85-9

Sobol H, Eisinger F (2004). Genetic predisposition to cancer. 197-211. in Ben Soussan P (2004). Cancer: psychodynamic approaches in the adults. Publisher: eras. Pages 352

Stoppa-Lyonnet D, Stern MH, Soufir N, Lenoir G (2010). Genetic predisposition to cancer: present and future in 2010.Path Biol., 58:324-330.

Tamura K, Dudley J, Nei M, Kumar S (2007). MEGA4: Molecular Evolutionary Genetics Analysis (MEGA) Software version 4.0. Mol. Phylogenet. Evol., 24: 1596-1599.

Theillet C (2010). Towards an inventory of oncogenic mutations in human cancers. Bull Can: 97(11) 1223-1229.