INTERNATIONAL JOURNAL OF APPLIED BIOLOGY AND PHARMACEUTICAL TECHNOLOGY
www.ijabpt.com Volume-3, Issue-2, April-June-2012 Coden : IJABPT Copyrights@2012 ISSN : 0976-4550

Received: 25th Jan-2012 *Revised: 8th Feb-2012* *Accepted: 08th Mar-2012*

Research Article

IMPLICATION OF THE CYTOCHROME B NUCLEOTIDE AND PROTEIN MUTATIONS IN THE OCCURRENCE OF BREAST CANCER IN SENEGAL

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ABSTRACT: The reports provided by OMS in 2011 have showed that cancer is a major cause of death in the world, causing 7.6 million deaths in 2008. Breast cancer is in the world, the most common neoplasia of women, and it appears that low penetrance genes, but frequently mutated in the general population play an important role in the development of this cancer. The objective of this study is to evaluate the involvement of Cytochrome b mutations (mitochondrial gene) in the occurrence of breast cancer in the Senegalese women. We have analyzed by PCR-sequencing the variability of the Cytochrome b gene in thirty Senegalese patients suffering from breast cancer. The results of molecular analysis of a portion of Cytochrome B indicate the existence of nucleotide variability at intra and inter-individual with a genetic differentiation between healthy and cancerous tissue, as well as the existence of a correlation between this genetic differentiation at the age of the patients and location of tumors (right breast or left breast). 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%) the number 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.

Keywords: Mutations, Cytochrome B, Variability, 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 health problem public. Cancer is the emergence of a cell clone that proliferates, invades, metastasis, 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, he moved slowly among the poor in Senegal. Most cancer patients die due to lack of means to support this costly disease in terms of drug costs 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 et al., 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).

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Breast cancer is in the world, the most common malignancy of women causes approximately, 30% of 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 16-55% of these tumors belong to the sub-group known as the triple negative (Ly et al., 2011). One of the problems including the Curie Institute in Dakar faces is the resurgence of the disease in young women. In the literature, breast cancer in young women for either the age of 35, sometimes less than 40 years, sometimes less than 50 years (Espié et al., 2003). We will stick to the third option.

The overall objective of this study is, next to the diagnostic histopronostic to find new molecular biomarkers that can guide clinical decision making and secondly, to clarify the prognosis and better target the treatment. It will also be in the very near future, to propose to the group risk factor for minor or moderate a test needs to be performed by regular time intervals as a precaution. This general objective, it follows as a specific objective study in the short term, to study the genetic diversity and protein Cyt.B between healthy tissue and cancer, to determine the penetrance of this gene in breast cancer in the Senegalese women. And possibly try to see if differences are observed between breast cancer in young woman and of older woman.

MATERIALS AND METHODS

Study population

One of the first stages of this study is to obtain and collect the samples required for its completion. For each patient, a perfectly healthy tissue sample and a sample of cancerous tissue are removed. Samples are taken by Professor Ahmadou DEM of Institute Joliot Curie of Hospital Aristide le Dantec and his staff for their work. They are immediately sent to the Molecular Biology laboratory, of center for Biology and Population Management (CBGP) of IRD in Bal-Air, where will the various stages of the analysis. The samples are preserved in alcohol 96°. 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 availed in the laboratory. The short-term analysis of 30 patients, all blacks. Some of these biopsies were extracted nucleic acid (DNA).

DNA extraction and PCR

Total DNA was extracted from tissues using standard Qiagen method (Qiagen Dneasy Tissue Kit). Once the DNA extracted a portion of which Cyt.B of great interest was amplified and sequenced. The Cyt.B is an area of over a thousand base pairs of the mitochondrial genome, located at positions 14201 and 15341 in the human sequence (Anderson, 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. The amplification is performed in a reaction volume of 50 µL containing 28.9 µl of MilliQ water, 5 µl of buffer (10X) containing Mg^{2+} ions at an initial concentration of 15 mM, 2 µl of dNTP, 5 µl of each primer are: H15915 (TCT-CCA-TTT-CTG-GTT-TAC-AAG-AC) and L14723 (ACC-AAT-GAC-ATG-AAT-AAA-CAT-GGT-T), 0.1 µl of Taq polymerase and 4 µl of DNA extract. The amplification is performed by repeated cycles, which ensures a doubling of the target DNA at each cycle (2^{40}). PCR takes place in a thermocycler type Eppendhorf under the following conditions: denaturation at 94°C Preliminary (3 minutes), followed by a repetition of 40 cycles of initial denaturation at 92°C (45 seconds), annealing at 50°C (1 minute) and elongation of the complementary DNA strands at 72°C for (1 minute 30 seconds) and is closed by a final elongation (10 minutes). The sequencing was carried out in the city of Seoul in South Korea by a company named American Macrogen from 30µl of the PCR product.

Molecular analysis

The sequences of Cyt.B, healthy and cancerous tissue are carefully checked, adjusted and aligned with BioEdit software version 7.0.8. Each healthy tissue is aligned next to the cancerous tissue to visualize and locate the mutations.

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The nucleotide compositions of individuals are calculated with the same software BioEdit. The standard indices of genetic variation: the nature of mutations, number of sites varying 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). 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.

RESULTS

Alignment and Genetic distance of Cyt.B

A portion of Cyt.B of cancer cells 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 N°13 was eliminated because with a high genetic diversity. Analyses of genetic diversity and protein have 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. For all individuals, the nucleotide composition A+T is higher than that of C + G and this applies both within the same individual and between individuals. In 75.9% cases, transversions are higher than transitions. Among our patients, more than half (63.3%) cases were infected before age 50. Young women and older women, constituting the two groups in our study population, the transversions are respectively 72.2 and 72.7% of higher.

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 (Table 1).

Table 1: Genetic distances within and between groups.

Groups	Genetic distances	
	Intra-group	**Inter-group**
Healthy tissus	0,400	0,340
Cancerous tissue	0,281	

Young women representing 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). For cons, 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). The correlation results are shown in Table 2. 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.

Table 2: Genetic distances versus patient's age. TSFj: healthy tissue young women; TCFj: cancerous tissue of younger women. TSFa: healthy tissue older women; TCFa: cancerous tissue of older women.

Groups	Genetic distances				
	Intra-group	**Inter-group**			
		TSFj	TCFj	TSFa	TCFa
TSFj	0,461				
TCFj	0,275	0,364			
TSFa	0,310	0,378	0,296		
TCFa	0,291	0,372	0,283	0,297	

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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). The correlation results are summarized in Table 3. 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.

Table 3: Genetic distances versus location of tumors. TSSD = healthy tissue located in the right breast; TSSG = healthy tissue located in the left breast. TCSD = cancerous tissue located in the right breast; TCSG = cancerous tissue located in the left breast.

Groups	Genetic distances				
	Intra-groups	Inter-groups			
		TSSd	TSSg	TCSd	TCSg
TSSd	0,461				
TSSg	0,249	0,362			
TCSd	0,271	0,366	0,253		
TCSg	0,279	0,375	0,255	0,264	

Cyt.B protein diversity

The protein sequences were obtained after a transformation of the nucleotide sequences into amino acid sequences. After a test phase on three individuals, it was agreed that the second reading frame which is by far the most appropriate, because with 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 (0.0385) is not significant. The correlation line is embodied 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%) the number of phenylalanine in cancerous tissues, with very different proportions.

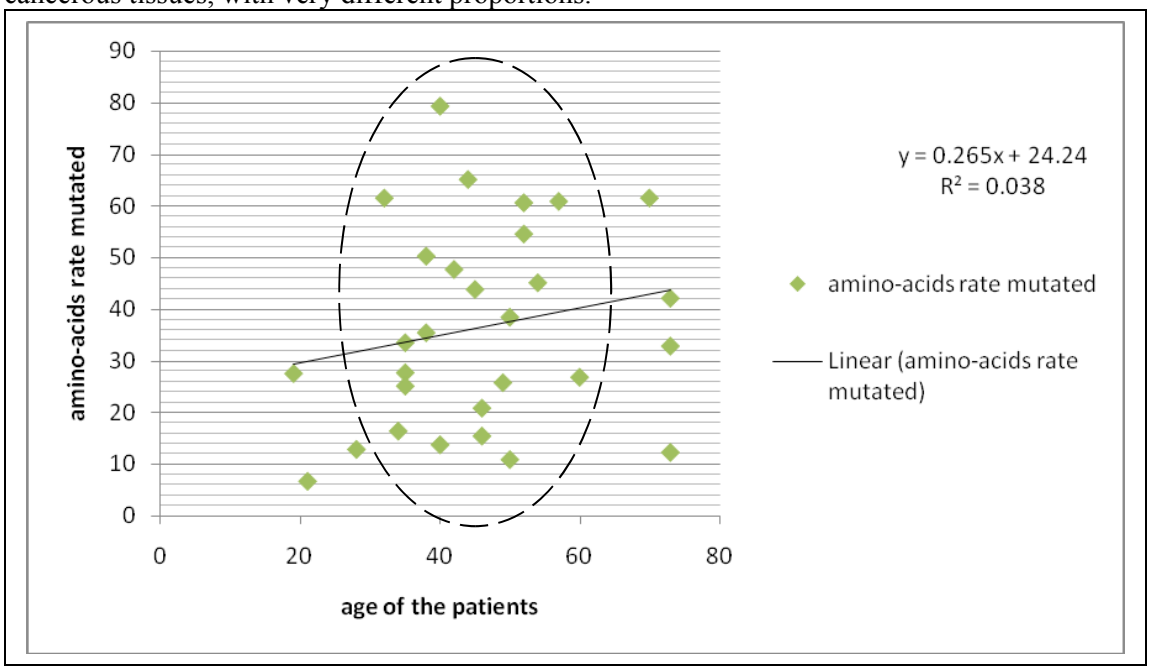

Figure 1: Curve of correlation of the rate of mutated amino acids at the age of the patients.

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DISCUSSION

The objective of this work is to study the genetic diversity and protein Cyt.B between healthy and cancer tissue, to determine the penetrance of the mitochondrial gene encoding the breast cancer in women in Senegal, especially women that are received at the institute of Joliot Curie Hospital Aristide Le Dantec. The choice of mitochondrial DNA, to study for the first fell on the Cyt.B because of the work done in laboratories; suggest that he had a relatively high variability, although it is a gene. We analyzed by PCR-sequencing variability Cyt B in 30 patients suffering from Senegalese 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 Cyt.B

In their project "Cancer Genome Atlas' Americans 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 other differences. Each type of cancer is a disease very specific, requiring a specific treatment, the researchers said. Going further, they explain that each patient is different from the other. Our results show a high variability 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 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 sex normal DNA / DNA mutated highly variable 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 et al., 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 predispose to neoplastic transformation.

Of all the sequences the rate of adenine and thymine is higher than that of guanine and cytosine. This is observed from one individual to another but also within the same individual between the two tissues. The DNA molecule of these patients is more prone to mutations. As such, the laboratory of L. Loeb has shown that the genome of cancer cells present genetic instability as a significant increase in the rate of random mutations (Loeb et al., 1974 in Lemee, 2009). Indeed, these mutations are estimated to be less than 10^{-8} per base pair mutations in normal tissues. The average frequency of mutations observed in tumors (210×10^{-8} per base pair) is at least 200 times higher compared to adjacent normal tissue (Bielas et al., 2006).

In the study population, more than half of patients (63.3%) were infected before age 50. This distribution is similar to the work of Dem et al. (2008). Only the average age of 45.7 that between 19 and 73 years is still lower. Of these women, 72.2% of cases, mutations of type's transversions are higher which is virtually identical in women who developed breast cancer after 50 years where transversions are higher in 72.7% of cases. To say that at this stage, it is difficult to show any difference between breast cancer in young women and of older women.

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 all 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 control of it.

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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 the woman. Therefore, the number of cell differentiation and growth is more important than any other organ. What makes the mammary gland more susceptible to cancer process (Antoine et al., 2010).

The genetic distance correlated with patient age, reveals that observed at the intra-healthy tissue of younger women is higher than the genetic distance 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, higher in older women, 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. Vascularization of the tumor would not it 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 both in younger women than older women, but also for tumors that are localized in the right breast. For cons for tumors localized in the left breast, the proliferation of the cancer cell is faster than the normal cell from which it derives.

Diversity of protein Cyt.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, reflect 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 are among the eight essential amino acids as cannot be synthesized by the body so it's our food that should bring them. T cells are key players of immune rejection reactions that can lead to the elimination of cancer cells and 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., Seminar). The TDO is present in the liver and IDO 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). Still on 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, observed on the one hand that the majority of human tumors expressing this enzyme and one the other hand, the 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, leads 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.

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It's 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). The mutations that are causing the change of Trp to stop codon, resulting in the appearance of a truncated protein (nonsense mutation) or different 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 by a thymine or cytosine. Phe UUU and UUC encoded by the formula UUU was found in 86.75% of cases. In other words when the mutation is the Thymine found 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 to adapt the management of patients. The results revealed the 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 at tumor localization (left breast or right breast). Any modification of tryptophan 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 Tryptophan and Phenylalanine 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.

Acknowledgments

I warmly thank all members of the CBGP, especially Tofféne Diome for his very helpful.

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