academicJournals

Vol. 7(2), pp. 13-19, August 2015
DOI: 10.5897/JCREO2015.0122
Article Number: DF340B655106
ISSN 2141-2243 ©2015

http://www.academicjournals.org/JCREO

Journal of Cancer Research and Experimental Oncology

Full Length Research Paper

Clinicopathological and survival significance of BAT-25 and BAT-26 instability in breast cancer among Senegalese patients

Fatimata Mbaye[1,2]*, Sidy Ka[3], Ahmadou Dem[3], Mamadou Kane[2] and Mbacké Sembène[1,2]

[1]Department of Animal Biology, Faculty of Science and Technology, Cheikh Anta Diop University, Dakar, Senegal.
[2]Sudanian Sahel Animal Populations Biology (BIOPASS), Research Institute for Development, IRD / Bel-Air, Senegal.
[3]Cancer Institute, Faculty of Medicine, Pharmacy and Odontology, Cheikh Anta Diop University, Dakar, Senegal.

Received 25 July, 2015, Accepted 21 August, 2015

In some tumors, defects in mismatch repair enzymes lead to errors in the replication of simple nucleotide repeat segments. This condition is commonly known as microsatellite instability (MSI) because of the frequent mutations of microsatellite sequences. The primary aim of this study is to evaluate the clinicopathological and survival significance of *BAT-25* and *BAT-26* instability, in 60 patients with breast cancer. Polymerase chain reaction was used to amplify the following microsatellite repeat loci *BAT-25* and *BAT-26*. Medical records were studied in order to determine clinical data of *BAT-25* and *BAT-26,* analysis was carried out. 60.71% of cancer tissues analyzed were found to be unstable for both markers.*BAT-26* instability has an impact on the age (Od: 15.47; CI 1.08-974; 19, P: 0.020) and survival (P: 0.0342) of patients. *BAT-26* which has a poly A sequence, can be considered alone as a good marker for the detection of MSI tumors in breast cancer.

Key words: Cancer, breast, polymorphism, microsatellites, Senegal.

INTRODUCTION

The process of carcinogenesis is a complex process, driven by the gradual accumulation of genetic and epigenetic alterations affecting differentiation controlling factors, the division and cell death. This is a dynamic phenomenon, which, with regards to the species evolution theory according to Darwin, is based on a succession of selections phases and clonal expansions, each of which is subsequent to the acquisition by a cell of a proliferation or survival advantage (Moyret-Lalle et al., 2008). It is generally accepted that the malignant transformation of a cell requires an alteration of 5 to 10 different genes leading to the deregulation of specific signaling pathways.

Recent analyzes by human tumor sequencing confirm the "multi-gene" hypothesis of cancer, a given tumor with an average of fifteen deleterious mutations, along with dozens of mutations called transient within the coding regions (Wood et al., 2007). Taking into account the entire genome, these observations suggest that cancer cells have thousands of different mutations. Upon 1974,

*Corresponding author. E-mail: fatimata.mbaye@ucad.edu.sn

Lawrence Loeb had hypothesized that the tumor development process required the loss of genomic stability (Loeb et al., 1974).

A few years ago, the discovery of a link between the occurrence of certain cancers and the existence of anomalies of the deoxyribonucleic acid (DNA) errors repairing replication system (MMR system for Mismatch Repair) opened new horizons in the study of carcinogenesis in Humans (Aaltonen et al., 1993; Ionov et al., 1993). This deficiency leads to nucleotide instability of the DNA affecting mainly the microsatellite repeated sequences of the genome, without associated chromosomal abnormality. In some cases, these microsatellites are located in intronic regions, or 5 'or 3' untranslated regions of some human genes, and it has been described that they may play a regulatory role in the expression of said genes.

According to Suraweera et al. (2001), the instability noticed in such sequences may occur during Microsatellite instability (MSI-H) carcinogenesis (microsatellite instability-high), but this remains to be demonstrated. MSI-H cancers are common in humans. They can be inherited. However, they are in most cases of sporadic occurrence, representing about 15% of cases of colon cancer, stomach, pancreas or endometrial cancer (Borie et al., 2004). Previous MSI reports on sporadic breast cancers are probably incompatible with some studies which have noted an absence or scarcity of microsatellite instability in breast tumors (Hye-Jung et al., 1993; Peltomaki et al., 1993; Wooster et al., 1994), while others studies have reported a remarkably high frequency of MSI in breast cancer (Kim et al., 1994; Yee et al., 1994; Aldaz et al., 1995; Contegiacomo et al., 1995; Karnik et al., 1995; Shaw et al., 1996; Toyama et al., 1996; Toyama et al., 1996b; Paulson et al., 1996; Sourvinos et al., 1997). The shortening of microsatellite allele is observed systematically in MSI-H cancers, while it is very monomorphic in the genome of normal cells and non-defective tumor for the MMR system (Zhou et al., 1998).

Comparing the two proposed panels for MSI tumors determination, Yick et al. (2006) pointed out that the use of BAT-25 and BAT-26 alone was sufficient to detect MSI tumors since these two markers were unstable in relation to the corresponding normal DNA. Over the years, several authors demonstrated that the specificity of the BAT-25 and BAT-26 single-nucleotide markers is sufficient to allow them only to establish the MSI without reference to the normal DNA in the case of colorectal cancer (Zhou et al., 1998; Surawera et al., 2002). The BAT-25 locus consists of 25 (T) located within the intron 16 of the c-kit proto-oncogene. c-kit gene is located on the long arm of chromosome 4 at position 12 (4q12). Whereas, BAT-26 contains a repetition of 26 (A) and is located within the fifth intron of the MSH2 gene on chromosome 2 (2p21). MSH2 is a tumor suppressor and more particularly a transition gene which codes for a mismatch repair protein. Both loci have been shown to be markers, which manifest themselves with a size shortening of mono-nucleotide repeat. However, in the MSS tumors or normal tissue, BAT-25 and BAT-26 were described as having little size variations (Parsons et al., 1995; Zhou et al., 1997).

This study will therefore aim, at accurately establishing the incidence of MSI phenotype in breast cancers by using two BAT-25 and BAT-26 single-nucleotide markers and at assessing the correlation between the instability of microsatellite loci and clinicopathological characteristics as well as the and survival time of patients.

MATERIALS AND METHODS

This study received the approval of the ethics committee of Cheikh Anta Diop University. Tumors tissues diagnosed as breast carcinoma were obtained from a surgical pathology file of the Joliot Curie CancerologyInstitut. All tumors are ductal carcinomas infiltrates. Blood samples were also performed in control subjects. DNA extraction was described previously by Mbaye et al. (2012). DNA samples obtained from blood samples and tumor tissues were amplified using two different oligonucléotide pairs specific for the recommended microsatellite loci BAT-25 and BAT-26. All primers were obtained from Research Genetics (Buhard et al., 2006). Primers sequences were BAT-25 (forward 5'-TACCAGGTGGCAAAGGGCA-3' and reverse 5'-TCTGCATTTTAACTATGGCTC); and BAT-26 (forward 5'-CTGCGGTAATCAAGTTTT and reverse AACCATTCAACATTTTTAACCC). PCR reactions were performed in 50 µl containing 5 µl buffer 10X, 1 µl Mgcl2, 2.5 µl of each primer, 2 µl dNTP, 2 µl DNA and 0.1 µl Taq polymerase.

Amplification of BAT-25 was performed by (denaturation initial at 95°C for 10 min, followed by 30 cycles of denaturation at 94°C for 45s, annealing at 57°C for 45 s, extension at 74°C for 45 s), the reaction was terminated by extension at 74°C for 7 min and amplification of BAT-26 was performed by (95°C for 5 min ; 35 cycles (95°C for 30 s; 47°C for 1 min; 70°C for 1 min); 70°C for 10 min. The obtained amplicons were shipped to Macrogen, South Korea for purification and sequencing with 30 µl PCR products and 15 µl primers (10µM) for each sample. Sequences resulting to mononucleotide repeat BAT-25 and BAT-26 were aligned by BioEditsoftware (Hall, 1999). MSI-H were defined as having instability in two markers, where as microsatellite instability-Low (MSI-L) tumors were defined as having instability in one makers. Lack of instability in any markers described the microsatellite stable (MSS).

Associations between clinical parameters and presence of microsatellite instability status were analyzed by Fisher's exact tests using the Statview software. A probability value of < 0.05 was considered. Survival data was obtained using the Kaplan-Meir method, and comparison of survival was made using the log-rank test, with $p<0.05$ as the significant limit.

RESULTS

A difference of size and patterns were noted on both markers studied in patients with breast cancer (Table 1). Among the 38 tumors analyzed, 34 (89.47%) proved unstable for the c-kit oncogene *BAT-25* marker while 24

Table 1. Different patterns of *BAT-25* and *BAT-26* markers.

BAT-25	Patterns	Haplotypes	CT	CS
	TTTTTTTTTTTTTTTTTTTTTTTT	25 T	4	10
	- - - - - - TTTTTTTTTTTTTTTTTT	Del $T_{1\text{-}6}$	9	
	- - - - - TTTTTTTTTTTTTTTTTTT	Del $T_{1\text{-}5}$	1	
	- - - - TTTTTTTTTTTTTTTTTTTT	Del $T_{1\text{-}4}$	21	
	- - - - TTTTTTTTTTTTTTT- TTTTT	Del T_{1_4} Del T_{20}	1	
	- - - - TTTTTTTTTTTTTT- TTTTTT	Del T_{1_4} Del T_{19}	1	
	- - - - TTTTTTTTTTTTT - -TTTTTT	Del T_{1_4} Del T_{18_19}	1	
BAT-26	**Patterns**	**Haplotypes**	**CT**	**CS**
	AAAAAAAAAAAAAAAAAAAAAAAAAA	26A	1	
	AAAAAAAAAAAAAAAAAAAAAAAAA	25A	10	10
	AAAAAAAAAAAAAAAAAAAAAAAA -	24A +Del A_{25}	16	
	- AAAAAAAAAAAAAAAAAAAAAAA -	DelA_1+23A+DelA_{25}	2	
	AAAAAAAAAAAAAAAAAAAAAAAAG -	23A Sub A_{24} →G+DelA_{25}	4	
	AAAAAAAAAAAAAAAAAAAAAAAGG -	SubA_{23_24}→G+DelA_{25}	1	

CT: Cancerous Tissue; CS: Control Sample.

Table 2. (MSI) Status in breast cancer. (+): unstable for a marker; (-): Constant for a marker; NA: Not Amplified; (?): Not determined status.

Patients	Locus		MSI status
	BAT-25	BAT-26	
1	-	-	MSS
2	+	-	MSI-L
3	+	-	MSI-L
4	+	-	MSI-L
5	+	-	MSI-L
6	+	+	MSI-H
7	+	+	MSI-H
8	+	NA	?
9	+	-	MSI-L
10	+	-	MSI-L
11	+	+	MSI-H
12	-	+	MSI-L
13	+	+	MSI-H
14	NA	+	?
15	-	+	MSI-L
16	+	+	MSI-H
17	+	+	MSI-H
18	+	+	MSI-H
19	+	+	MSI-H
20	+	+	MSI-H
21	+	+	MSI-H
22	+	+	MSI-H
23	+	+	MSI-H
24	+	+	MSI-H
25	+	+	MSI-H
26	+	-	MSI-L
27	+	+	MSI-H
28	+	-	MSI-L
29	+	+	MSI-H
30	+	+	MSI-H
31	NA	-	?
32	NA	+	?
33	NA	+	?
34	NA	-	?
35	+	NA	?
36	+	NA	?
37	+	NA	?
38	+	NA	?

(70.58%) were unstable for BAT-26 marker out of 34 tumors analyzed. In most cases, it was noted for the BAT-25 marker, large deletions ranging from four to six (T) respectively out of 21 (61.76%) and 9 (26.47%) analyzed tumors. The *BAT-26* instability is characterized by 5 reasons related to one up to two base pairs (Table 1). Control samples consist of 25T and 25A respectively for the BAT-25 and BAT-26.

Among the twenty eight (28) patients for which both markers were amplified, one (1) has a stability for both markers (MSS), 8 (28.57%) have a volatility for the BAT-25 marker, 2 (7.14 %) have an unstable BAT-26 only. In other words, (1/28) tumors is microsatellite stable (MSS); 10/28 (35.71%) were MSI-low and 17 (60.71%) were MSI-High. The results are reported in Table 2.

None of the tested parameters is significantly correlated to the instability of BAT-25. The results are shown in Table 3. Contrarily to the BAT-25 marker, the instability of BAT-26 is significantly associated with the patient age (P = 0.02;Od = 15.47, CI = 1.08-974.19). The results are shown in Table 4. Survival curve according to BAT-25 stability and instability is shown in (Figure 1a).

Table 3. BAT-25 Stability and instability vs prognostic factors and response to chemotherapy.

Variable		BAT-25 (+)	BAT-25 (-)	P-value
Age	<50	17	0	0.076
	≥50	5	2	
Stage	IV	3	1	0.490
	III	12	1	
	II	1	0	
Grade	SBRIII	3	0	1
	SBRII	9	2	
	SBRI	1	0	
Response to chemotherapy (%)	<25	7	1	0.423
	25-75	1	1	
	>75	5	2	

P-value: Fischer exact test; Are shown in bold P values that are significant.

Table 4. BAT-26 Stability and instability vs prognostic factors and response to chemotherapy.

Variable		*BAT-26* (+)	*BAT-26* (-)	P-value
Age	<50	14	3	0.020
	≥50	1	4	Od : 15,47 ; IC : 1.08-974,19
Stage	IV	2	2	
	III	8	4	0.402
	II	-	1	
Grade	SBRIII	2	-	
	SBRII	7	4	0.439
	SBRI	-	1	
Response to chemotherapy (%)	<25	4	4	
	25-75	1	1	0.563
	>75	5	2	

P-value: P-value: Fischer exact test; Are shown in bold the P values that are significant.

The survival time of patients who have a stable BAT-25 falls drastically, but without any statistical significance (P = 0.473). Kaplan Meir test shows that the BAT-26 instability was significantly (P = 0.0342) associated with a much longer postoperative survival time (Figure 1b).

DISCUSSION

The two most predictive MSI markers included in the group of markers from the National Cancer Institute and the multiplex assay of Bacher and Suraweera, being the loci BAT-25 and BAT-26 were amplified (Suraweera et al., 2002; Bacher et al., 2004). Using BAT-25 and BAT-26, microsatellites for the characterization of MSI has been revealed to be advantageous with regards to many di, tri or tetra microsatellites because of their quasi-monomorphic nature and sensitivity to MSI.

With control patients, BAT-25 and BAT-26 are monomorphic with 25 (T) and 25 (A). Contrary to what has been described in theory, the BAT-26 loci consists of a repetition of 25 (A) in controlpatients instead of 26 (A). Pyatt et al. (1999) have found variations in the size of single nucleotide sequence of BAT-26 in 12.6% among African American women in good health, and that 2.9% had changes in both BAT-25 and BAT-26. According Pyatt et al. (1999) and Samowitz et al. (1999), there exists particularly in African, natural polymorphisms of these two markers, which stresses the necessity to use them carefully with regards to ethnic groups to which patients belong. The study results support the need for comprehensive studies taking into account ethnicity to

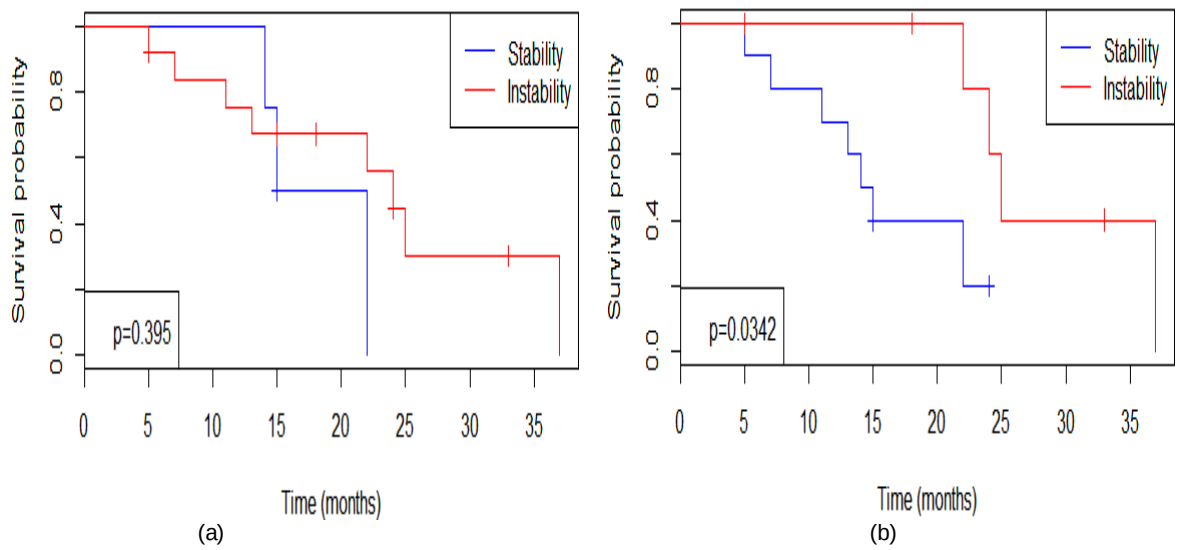

Figure 1. Survival curve according to the stability and instability of *BAT-25* (a) and *BAT-26* (b).

define different profiles, and BAT-25 and BAT-26 microsatellites allele frequencies within the Senegalese population.

Both loci show the MSI sensitivity which manifest itself by loss of a variable number of repeated mononucleotide causing a shortened size in the majority of analyzed cancer tissues. Among Senegalese women with breast cancer, c-kit oncogene BAT-25 marker is much more volatile 89.47% (34/38) with large deletions ranging from 4 to 6 (T) in respectively 21 (61.76%) and 9 (26.47%) cancer tissues analyzed and which are compared to the MSH2 gene BAT-26 marker, the volatility 70.58% (24/34) of which results in the majority of cases in a deletion / substitution of one or two base pairs. The literature contains suggestive evidence of a greater allelic variation at the BAT-26 loci. Demokan et al. (2006), observed in cancer at the head level and the neck level, BAT-25 instability in 15% and BAT-26 in 19% of cases. Zhou et al. (1997), showed in a series of studies that the BAT-26 loci showed a reduction in the number of adenines in the 18 out of the 19 tumors analyzed in 100% of the 27 cell lines (Parsons et al., 1995), and in the 41 out of 42 colorectal tumors and cell lines (Hoang et al., 1997).

60.71% (17/28) of the cancer tissue the study has analyzed proved to be unstable for BAT-25 and BAT-26 markers, which confirms their MSI-H status. If one refers to Zhou et al. (1998), the shortening of allele microsatellite is observed systematically in MSI-H cancers. The frequency of tumors with the two markers instability is high. This is in line with some studies which reported a remarkably high frequency of MSI in breast cancer (Kim et al., 1994; Yee et al., 1994; Aldaz et al., 1995; Contegiacomo et al., 1995; Karnik et al., 1995; Shaw et al., 1996; Toyama et al., 1996a; Toyama et al., 1996b; Paulson et al., 1996; Sourvinos et al., 1997; Fujii et al., 1998; Siah et al., 2000). According to Siah et al. (2000), such variability suggests that the mismatch repair defects, resulting in an increase of MSI, can play a role in the pathogenesis of particular breast cancer. However, the high frequency MSI found in this study is at odds with what has been reported in the literature for breast cancer in general where the MSI was observed in 0 to 50% of cases (Hye-Jung et al., 1993; Peltomaki et al., 1993; Wooster et al., 1994; Demarchis et al., 1997; Van Der Looij et al., 2001). Anbazhagan et al. (1999), have concluded that characteristics mismatch repair errors of MSI phenotype are rare in human breast cancer.

According to Lacave and Larsen (2005), in breast cancer, due to low levels of microsatellite instability observed in tumor cells, a minor role of the genes of mismatch repair systems in the oncogenesis is allowed. No significant association related to the BAT-25 and BAT-26 instability was noted for prognostic factors (stage and histological grade) and the response to chemotherapy. However, a correlation study of the frequency of BAT-25 or BAT-26 marker instability with clinicopathological factors helped to determine that only age is associated with the BAT-26 instability (P = 0.020; Od: 15.47, CI 1.08-974.19). Siah et al. (2000), found no instability of the two (BAT-25 and BAT-26) markers out of the 66 patients with breast cancer under the age of 45 at the time of diagnosis. The importance of determining the status of instability comes from the clinicopathological properties of MSI tumors that differentiate them from non-MSI tumors: their prognosis and response to treatment. Recently, a meta-analysis by Popatet al. (2005), combining data from 32 different studies (being a total of 7642 patients, including 1277 colorectal cancer MSI), have significantly confirmed the prognostic advantage of MSI.

In this study, the instability of BAT-26 is significantly associated with a longer duration of postoperative survival (P = 0.0342). Many studies have shown that MSI tumors (panel of 5 markers) in the colorectal cancer have better survival rates (Jass, 1999; Gryfe and Gallinger, 2001). Carvalho et al. (2005) found in the colorectal cancer that 5-year survival was 85% in patients with unstable BAT-26 compared to patients who are BAT-26 stable. The reasons for the survival benefit is not known, but it may be due to a self-destructive effect of many mutations accumulated in the genome of the cell, maybe these mutations are those of the genes necessary for the variability of the malignant clone (Hemminki et al., 2000). According to Chiaravalli et al. (2001), the BAT-26 locus is the most effective single nucleotide marker for the determination of the MSI-H tumors in various cancers, without the need for a normal DNA correspondence.

Conclusion

The analysis of the BAT-25 and BAT-26 polymorphism confirmed the hypothesis that, among Senegalese women, mammary carcinogenesis is associated with unstable microsatellite loci with 60.71% of tumors that have a MSI-H phenotype. The study may think that the MMR repair system is defective in breast tumors in these patients. Despite the high volatility (60.71%) found in breast cancer tissue, it would be interesting to complete the analysis with three other markers of pentaplex assay, being NR-21, NR-24 and NR-27 proposed at the consensus meeting on "Diagnosis Guidelines for Hereditary Non-Polyposis Colorectal Cancer and Microsatellite Instability" of Bethesda in 2002 (Umar et al., 2004). BAT-26 Polymorphism has an impact on patient survival. BAT-26 which has a poly A sequence can be considered alone as a good marker for the detection of MSI tumors in breast cancer among Senegalese women.

Conflict of Interest

The authors have not declared any conflict of interest.

ACKNOWLEDGMENTS

The authors acknowledge the higher education ministry (Project PAPES) for their support.

Conflicts of interest

The authors declare that they have no conflicts of interest

REFERENCES

Aaltonen LA, Peltomaki P, Leach FS, Sistonen P, Pylkkänen L, Mecklin JP, Järvinen H, Powell SM, Jen J, Hamilton SR, Petersen G, Kinzler K, Vogelstein B, de la Chapelle A (1993). Clues to the pathogenesis of familial colorectal cancer. Science 260(5109):812-816.

Aldaz CM, Chen T, Sahin A, Cunningham J, Bondy M (1995). Comparative allelotype of *in situ* and invasive human breast cancer: high frequency of microsatellite instability in lobular breast carcinomas. Cancer Res. 55(18):3976-3981.

Anbazhagan R, Fujii H, Gabrielson E (1999). Microsatellite Instability Is Uncommon in Breast Cancer. Clin. Cancer Res. 5(4):839-844.

Bacher JW, Flanagan LA, Smalley RL, Nassif NA, Burgart LJ, Halberg RB, Megid WM, Thibodeau SN (2004). Development of a fluorescent multiplex assay for detection of MSI-High tumors. Dis. Markers. 20:237-250.

Borie C, Raphael M, Hamelin R, Duval A (2004). Instabilité des microsatellites : un nouveau mécanisme de carcinogenèse associé à l'immunodépression dans les lymphomes non hodgkiniens chez l'homme. Méd. Sci. 20(6-7):641-642.

Buhard O, Cattaneo F, Wong YF, Yim SF, Friedman E, Flejou JFO, Duval A, Hamelin R (2006). Multipopulation Analysis of Polymorphisms in Five Mononucleotide Repeats Used to Determine the Microsatellite Instability Status of Human Tumors. J. Clin. Oncol. 24(2):241-251.

Carvalho F, Santos MM, Pena SD, Vettore A, Lopes A, Ferreira FO, Junior SA, Nakagawa WT, Rossi BM (2005). Clinicopathological significance of BAT-26 instability in 184 patients with colorectal cancer. Appl. Cancer Res. 25(1):36-40.

Chiaravalli AM, Furlan D, Facco C, Tibiletti Mg, Dionigi A, Casati B, Albarello L, Riva C, Capella C (2001). Immunohistochemical pattern of hMSH2/hMLH1 in familial and sporadic colorectal, gastric, endometrial and ovarian carcinomas with instability in microsatellite sequences. Vichows Achiv. 438(1):39-48.

Contegiacomo A, Palmirotta R, De Marchis L, Pizzi C, Mastranzo P, Delrio P, Petrella G, Figliolini M, Bianco AR, Frati L, Cama A, Mariani-Costantini R (1995). Microsatellite instability and pathological aspects of breast cancer. Int. J. Cancer 64(4):264-268.

De Marchis L, Contegiacomo A, D'amico C, Palmirotta R, Pizzi C, Ottini L, Mastranzo P, Figliolini M, Petrella G, Amanti C, Battista P, Bianco AR, Frati L, Cama A, Mariani-Costantini R (1997). Microsatellite instability is correlated with lymph-nodepositive breast cancer. Clin. Cancer Res. 3(2):241-248.

Demokan S, Suoglu Y, Demir D, Gozela M, Daloy N (2006). Microsatellite instability and methylation of the DNA mismatch repair genes in head and neck cancer. Ann. Oncol. 17:995-999.

Fujii S, Takeshima Y, Arihiro K, Kaneko M, Inai K (1998). Microsatellite instability in breast cancers with special reference to patient's age and bilaterality. Hiroshima. J. Med. Sci. 47(3):89-97.

Gryfe R, Gallinger S (2001). Microsatellite instability, mismatch repair deficiency, and colorectal cancer. Surgery 130(11):17-21.

Hall TA (1999). BioEdit: a user-friendly biological sequence alignment editor and analysis program for Windows 95/98/NT. Nucl. Acid. Res. 44:211-232.

Hemminki A, Mecklin JP, Ja"Rvinen H, Aaltonen LA, Joensuu H (2000). Microsatellite Instability is a favorable prognostic indicator in patients with colorectal cancer receiving chemotherapy. Gastroenterol. 119(4):921-928.

Hoang JM, Cottu PH, Benedicte T, Salmon RJ, Thomas G, Hamelin R (1997). Bat26, an indicator of the replication error phenotype in colorectal cancers and cell lines. Cancer Res. 57(2):300-303.

Hye-Jung H, Yanagisawa A, Kato Y, Park J, Nakamura Y (1993). Genetic instability in pancreatic cancer and poorly differentiated type of gastric cancer. Cancer Res. 53(11):5087-5089.

Ionov Y, Peinado MA, Malkhosyan S, Shibata D, Perucho M (1993). Ubiquitous somatic mutations in simple repeated sequences reveal a new mechanism for colonic carcinogenesis. Nat. 363(6429):558-561.

Jass JR (1999). Towards a molecular classification of colorectal cancer. Int. J. Col. Dis. 14(4-5):194-200.

Karnik P, Plummer S, Casey G, Myles J, Tubbs R, Crowe J, Williams BR (1995). Microsatellite instability at a single locus (*D11S988*) on chromosome 11p15.5 as a late event in mammary tumorigenesis. Hum. Mol. Genet. 4(10):1889-1894.

Kim H, Jen J, Vogelstein B, Hamilton SR (1994). Clinical and pathological characteristics of sporadic colorectal carcinomas with DNA replication errors in microsatellite sequences. Am. J. Pathol.

145(1):148-156.
Lacave R, Larsen CJ (2005). Robert J. Cancérologie fondamentale. Collection Société française. Editeur: John LibbeyEurotext.
Loeb LA, Springgate CF, Battula N (1974). Errors in DNA replication as a basis of malignant changes. Cancer Res. 34: 2311-2321.
Mbaye F, Fall M, Dem A, Sembène M (2012). Biological evolution of Tryptophan and Phenylalanine in the occurrence of breast cancer in Senegalese women. Int. J. Med. Med. Sci. 4(4):103-109.
Moyret-Lalle C, Falette N, Grelier Gaël, Puisieux A (2008). Tumor genomics: an unstable landscape. Bull. Cancer 95(10):923-930.
Paulson TG, Wright FA, Parker BA, Russack V, Wahl GM (1996). Microsatellite instability correlates with reduced survival and poor disease prognosis in breast cancer. Cancer Res. 56(17):4021-4026.
Parsons R, Myeroff LL, Liu B, Willson JKV, Markowitz SD, Kinzler KW, Volgelstein B (1995). Microsatellite instability and mutations of the transforming growth factor B type II receptor gene in colorectal cancer. Cancer. Res. 55(23):5548-5550.
Peltomaki P, Lothe RA, Aaltonen LA, Pylkkanen L, Nystrom-Lahti M, Seruca R, David L, Holm R, Ryberg D, Haugen A, Brugger A, Borrensen A, Chapelle A (1993). Microsatellite instability is associated with tumors that characterize the hereditary non-polyposis colorectal carcinoma syndrome. Cancer Res. 53(24):5853-5855.
Popat S, Hubner R, Houlston RS (2005). Systematic review of microsatellite instability and colorectal cancer prognosis. J. Clin. Oncol. 23(3):609-618.
Pyatt R, Robert B, Chadwick, Johnson CK, de la Chapelle CAA, Prior TW (1999). Polymorphic variation at the Bat-25 and Bat-26 loci in individuals of African origin. Am. J. Pathol. 155(2):349-353.
Samowitz WS, Slattery ML, Potter JD, Leppert MF (1999). BAT-26 and BAT-40 instability in colorectal adenomas and carcinomas and germline polymorphisms. Am. J. Pathol. 154(6):1637-1641.
Shaw JA, Walsh T, Chappell SA, Carey N, Johnson K, Walker RA (1996). Microsatellite instability in early sporadic breast cancer. Brit. J. Cancer 73(11):1393-1397.
Siah SP, Quinn DM, Brennett GD, Casey G, Flower RL, Suthers G, Rudzkiz (2000). Microsatellite instability markers in breast cancer: a review and study showing MSI was not detected at 'BAT 25' and 'BAT 26' microsatellite markers in early-onset breast cancer. Br. Cancer. Res. Treat. 60(2):135-142.
Sourvinos G, Kiaris H, Tsikkinis A, Vassilaros S, Spandidos DA (1997). Microsatellite instability and loss of heterozygosity in primary breast tumours. Tumor. Biol. 18(3):157-166.
Suraweera N, Iacopetta B, Duval A, Compoint A, Tubacher E, Hamelin R (2001).Conservation of mononucleotide repeats within 3' and 5' untranslated regions and their instability in MSI-H colorectal cancer. Oncog. 20(51):7472-7477.
Suraweera N, Duval A, Reperant M, Vaury C, Furlan D, Leroy K, Seruca R, Lacopette B, Hamelin R (2002). Evaluaton of tumor microsatellite instability using five quasimonomorphic mononucleotide repeats and pentaplex PCR. Gastroenterol. 123(6):1804-1811.
Umar A, Boland CR, Terdiman JP, Syngal S, de la Chapelle A, Rüschoff J,Fishel R, Lindor NM, Burgart LJ, Hamelin R, Hamilton SR, Hiatt RA, Jass J, Lindblom A, Lynch HT, Peltomaki P, Ramsey SD, Rodriguez-Bigas MA, Vasen HF, Hawk ET, Barrett JC, Freedman AN, Srivastava S (2004). Revised Bethesda guidelines for hereditary nonpolyposis colorectal cancer and microsatellite instability. J. Nat. Cancer. Inst. 96(4):261-268.
Toyama T, Iwase H, Iwata H, Hara Y, Omoto Y, Suchi M, Kato T, Nakamura T, Kobayashi, S (1996b). Microsatellite instability in *in situ* and invasive sporadic breast cancers of Japanese women. Cancer Lett. 108(2):205-209.
Toyama T, Iwase H, Yamashita H, Iwata H, Yamashita T, Ito K, Hara Y, Suchi M, Kato T, Nakamura T, Kobayashi S (1996a). Microsatellite instability in sporadic human breast cancers. Int. J. Cancer. 68(4):447-451.
Van Der Looij M, Papp J, Sztan M, Pulay T, Elfadil I, Besznyak I, Toth J, Devilee P, Olah E (2001). Allelic imbalance and microsatellite instability in BRCA1 associated breast and ovarian tumors. Int. J. Oncol. 18(8):775-780.
Wood LD, Parsons DW, Jones S, Lin J, Sjöblom T, Leary RJ, Shen D, Boca SM, Barber T, Ptak J, Silliman N, Szabo S, Dezso Z, Ustyanksky, Nikolskaya T, Nikolsky Y, Karchin R, Wilson PA, Kaminker JS, Zhang Z, Croshaw R, Willis J, Dawson D, Shipitsin M, Willson JK, Sukumar S, Polyak K, Park BH, Pethiyagoda CL, Pant PV, Ballinger DG, Sparks AB, Hartigan J, Smith DR, Suh E, Papadopoulas N, Buckhaults P, Markowitz SD, Parmigiani G, Kinzler KW, Velculescu VE, Vogelstein B (2007). The genomic landscapes of human breast and colorectal cancer. Science 318:1108-1113.
Wooster R, Cleton-Jansen AM, Collins N, Mangion J, Cornelis RS, Cooper CS, Gusterson BA, Ponder BA, von Deimling A, Wiestler OD, Cornelisse CJ, Devilee P, Stratton MR (1994). Instability of short tandem repeats (microsatellites) in human cancers. Nat. Genet. 6(2):152-156.
Zhou XP, Hoang JM, Cottu P, Thomas G, Hamelin R (1997). Allelic profiles of mononucleotide repeat microsatellites in control individuals and colorectal tumors with and without replication errors. Oncog. 20(15):1713-1718.
Zhou XP, Hoang JM, Li YJ, Seruca R, Carneiro F, Sobrinho-Simoes M, Lothe RA, Gleeson CM, Russell SEH, Muzeau F, Flejou JF, Hoang-Xuan K, Lidereau R, Thomas G, Hamelin R (1998). Determination of the replication error phenotype in human tumors without the requirement for matching normal DNA by analysis of mononucleotide repeat microsatellites. Genes. Chrom. Cancers 21(2):101-107.
Yee CJ, Roodi N, Verrier CS, Parl FF (1994). Microsatellite instability and loss of heterozygosity in breast cancer. Cancer Res. 54(7):1641-1644.
Yick KY, Stocker R, Peacock T (2006). Microscale Synthetic schlieren. Exp. Fluids. 42(1):41-48.