



## EFFECTS OF FETAL MICROCHIMERISM ON FEMALE BREAST CANCER: STATE OF THE ART AND EVOLUTIONARY POINT OF VIEW

Diop Ndiaga<sup>1,2</sup>, Gueye Mame Vénus<sup>1,2</sup>, Sy Mama<sup>1,2</sup>, Diallo Abdoulaye Séga<sup>1,2</sup>,  
Dial Chérif<sup>5</sup>, Ndiade Amadou<sup>3</sup>, Ngom Aminata Issa<sup>3</sup>,  
Diatta Ange Lucien<sup>4</sup> and Faye Oumar<sup>1,2</sup>

<sup>1</sup>Histology-Embryology Laboratory, Department of Biology and Functional Explorations, Faculty of Medicine, Pharmacy and Odontology, Cheikh Anta Diop University, Dakar, Senegal

<sup>2</sup>Laboratory of clinical cytology, cytogenetics, the biology of reproduction and human development, Aristide Le Dantec Hospital, Dakar Senegal

<sup>3</sup>Laboratory of histology-embryology-cytology-cytogenetics and reproductive biology of Alioune Diop University, Bambey, Senegal.

<sup>4</sup>Laboratory of histology-embryology-cytology-cytogenetics and reproductive biology of the Assane SECK University, Ziguinchor, Senegal

<sup>5</sup>Laboratory of Anatomy and Pathology, Faculty of Medicine, Pharmacy and Odontology, Cheikh Anta Diop University, Dakar, Senegal

Corresponding author email: [ndiaga6.diop@ucad.edu.sn](mailto:ndiaga6.diop@ucad.edu.sn), [diopndiagaleu@gmail.com](mailto:diopndiagaleu@gmail.com)

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**ABSTRACT: Introduction:** Fetal microchimerism is a frequent phenomenon occurring in all human pregnancies, which allows the transfer of fetal cells of various phenotypes to the mother. Recent data suggest an association between pregnancy, microchimerism, and cancer. A pregnancy history has been identified as a consistent protective factor against breast cancer. Thus, it is conceivable that undefined characteristics of previous pregnancies could explain why some women with positive parity have a reduced risk of breast cancer while others do not. In this context, we undertook this study to evaluate the relationship between fetal microchimerism and female breast cancers through a literature review. **Materials and Methods:** To meet this objective, namely, to evaluate the relationship between fetal microchimerism and female breast cancer, a literature review was performed using mainly a bibliographic data search engine (Pubmed). **Results and Discussion:** This study found microchimerism more in healthy women than women with breast cancer, with a statistically significant difference. These results suggest that microchimeric cells may reduce the risk of breast cancer in women. This protective effect may be explained by the differentiation and tissue regeneration properties associated with the immunoregulatory properties of fetal microchimeric stem cells. However, the correlation is not linear. **Conclusion:** In this study, our results indicate that microchemical cells may help reduce the risk of breast cancer in women. Good knowledge of the mechanisms of these microchemical stem cells could potentially serve as an innovative therapeutic approach for breast cancer patients.

**KEYWORDS:** Fetal, Microchimerism, Breast, Cancer



## INTRODUCTION

In Greek mythology, the chimera is a fantastic creature with the tail of a snake, the body of a goat, and the head of a lion that breathes fire and devours humans.

The interpretations of this myth are multiple but seem to represent the association of time-nature (three ages of a woman's life associated with three seasons of nature) in society with matriarchal filiation of the Achaeans.

In genetics, a *chimera* is an organism derived from two or more genetically distinct cell populations, as opposed to mosaicism, in which the different cell populations are derived from a single individual and constitute an epigenetic variation of that individual. *Microchimerism* is the reciprocal and, therefore, bidirectional transplacental exchange [1] of semi-allogeneic genetic material, between mother and fetus. It is a different form of heredity from genetic heredity.

In women carrying a male fetus, this microchimerism is easier to identify because the foreign genetic material is male and therefore carries all the genes of the Y chromosome, a chromosome absent in the host.

The discovery of microchimerism is attributed to Christian Georg Schmorl [2], a German pathologist who, in 1893, first assumed that eclampsia was a systemic disease that affected multiple organs. He also highlighted the role of the placenta in the pathogenesis of the disease. In addition, he was the first to identify the presence of multinucleated syncytial giant cells in the maternal body. Schmorl also hypothesized that fetomaternal trafficking could occur in normal gestations and eclampsia.

This hypothesis was confirmed decades later by Herzenberg 1979 [3], who demonstrated the presence of fetal cells in the maternal blood.

This finding was initially attributed to a pathological context. Thus, only immunocompromised patients did not have the physiological means to eliminate these foreign cells naturally presented maternal DNA [4]. However, Nelson et al, 1999 [5] demonstrated the presence of DNA of maternal origin in subjects of different ages with a functional immune system.

- Sources of microchimerism:
  - During pregnancy: transplacental cell transit is a constant, bidirectional phenomenon, starting around the fourth week [6]. Because cell transfer occurs in both directions, two types of microchimerism during pregnancy are encountered [3]:
    - Fetal microchimerism (MCF) (feto-maternal transfer);
    - maternal microchimerism (maternal-fetal transfer).

Microchimerism is not limited to an exclusive bidirectional exchange between maternal and fetal cells. Cells from older siblings and even maternal grandmother cells can also be transferred to the fetus [7]



- Apart from pregnancy, other unnatural sources of microchimerism can be observed in organ transplants [8], where donor cells are genetically different from the host persist in the host. The same applies to blood transfusions.
- Effects on the maternal body:

There would be good and bad microchimerism. Good microchimerism would allow tissue repair, regeneration, and defence against cancers and infections. Bad microchimerism is associated with pathologies of pregnancy, autoimmune diseases, and modifies the results of allogeneic stem cell transplants [9].

Recent data suggest an association between pregnancy, microchimerism, and cancer [10]. Multiparous women with microchimerism are less likely to develop cancer than those without microchimerism [11]. MCF would be less frequent in the peripheral blood of women with certain types of cancer [12,13]. Survival time and response to treatment are better in women with microchimerism [14]. These findings are mainly related to typical female cancers such as cervical [15], breast [16], and thyroid [17]. Recent studies have implicated MCF in lung tumours [18], melanoma, and haematological diseases [14].

The modifiers of risk for cancer development are both genetic and environmental in breast cancer. The known genetic risk modifiers to date are few (e.g., BRCA1 and BRCA2) and overall account for only 2-10% of all cases [19-20]. Environmental risk modifiers, including but not limited to reproductive factors, endogenous and exogenous hormones, anthropometric characteristics, and some lifestyle factors, are known to impact the risk of breast cancer development in women. A pregnancy history has been identified as a consistent protective factor against breast cancer, but the magnitude of this risk reduction is relatively modest [21,22]. Thus, it is conceivable that undefined characteristics of previous pregnancies could explain why some women with positive parity have a reduced risk of breast cancer while others do not [23]. In this context, we undertook this study to evaluate the relationship between fetal microchimerism and female breast cancers through a literature review.

## MATERIALS AND METHODS

To meet this objective, namely, to evaluate the relationship between fetal microchimerism and female breast cancer, a literature review was performed using mainly a bibliographic data search engine (Pubmed).

We opened Pubmed via the list of databases on the libraries and archives site (usherbrooke.ca). We used the Boolean operators "AND" and "OR" in our search equation to combine keywords. The "OR" operator was used between synonyms and the "AND" between concepts of particular interest.

Different sets of keywords were required for the most comprehensive result possible:

- **"fetal" AND "chimerism OR microchimerism" fetal " AND " chimerism OR microchimerism " AND "cancer OR neoplasms**
- **" fetal " AND " chimerism OR microchimerism " AND "cancer OR neoplasms " AND "breast "**



For the sake of precision, inclusion and non-inclusion criteria were defined.

**The inclusion criteria were:**

Articles about fetal microchimerism and breast cancer. Prospective, retrospective, or clinical trials. Regardless of the year of publication: a publication date limit was not set to be more inclusive.

Meta-analyses and literature reviews were not included in this study

All articles found in the databases were subjected to a rapid selection procedure described in *the 2000 literature review and recommendation grading guide (Appendix I)*

For each article was retained:

- The publication reference includes the name of the principal author, the name of the journal, and the year of publication
- The objectives of the study
- The type of study in question, the characteristics of the study population, and the type of male fetal DNA analysis method
- The main results of the study
- Biases found

The level of scientific evidence for each article was also assessed using the grade of recommendations submitted by ANAES from the Guide to the literature analysis and gradation of recommendations, ANAES 2000 (**Appendix II**).

## RESULTS

After searching the following keyword databases:

- **"fetal" AND "chimerism OR microchimerism**
- **" fetal " AND " chimerism OR microchimerism " AND "cancer OR neoplasms**
- **" fetal " AND " chimerism OR microchimerism " AND "cancer OR neoplasms " AND "breast "**

A total of 23 results were found.

- The keywords [**"fetal" AND "chimerism OR microchimerism"**] were found in all 23 articles
- The keywords [**"fetal" AND "chimerism OR microchimerism" AND "cancer OR neoplasms"**] were found in 17 articles
- The keywords [**"fetal" AND "chimerism OR microchimerism" AND "cancer OR neoplasms" AND "breast"**] were found in 10 articles. After reading



these ten articles, we found that two were not scientific articles and were excluded? In total, eight articles were selected for the study.

All selected articles have a level of scientific evidence between 2 and 3

The classification is done by year.

- **2007, Vijayakrishna K et al [24]** hypothesized that fetal microchimerism confers a protective effect against breast cancer based on two observations.

- First, allogeneic stem cells reduce the risk of recurrent malignancy in hematopoietic cell transplantation.
- Second, the reduced risk of breast cancer is recognized in women with positive parity compared to nulliparous women.

To test this hypothesis, a case-control study of a cohort of 82 women, 35 with breast cancer and 47 healthy, was performed to look for male DNA in peripheral blood. Male DNA levels were determined by real-time quantitative PCR for the Y-chromosome-specific gene *DYS14*. The epidemiological and clinical characteristics of the study population are detailed in **Table 1**. Among women with breast cancer, 5 (14%) had male DNA compared with 20 (43%) healthy women. When the absence of fetal microchimerism was treated as a risk factor for breast cancer, the odds ratio was 4.4 (95% CI, 1.34-16.99;  $p = 0.006$ ). When the analysis was restricted to women who had a son, the prevalence of fetal microchimerism was 14% (3 of 22), compared with 48% (14 of 29) in controls (odds ratio, 5.9; 95% CI, 1.29-36.69;  $p = 0.01$ ) (**Table 2**).

**Table 1: Epidemio-clinical characteristics of breast cancer patients and healthy controls [24].**

Characteristic	Breast cancer ( <i>n</i> = 35)	Healthy ( <i>n</i> = 47)
	<i>n</i> (%)	<i>n</i> (%)
<b>Obstetrics history</b>		
Parous	26 (74)	34 (72)
Nulliparous and nulligravid	6 (17)	5 (11)
Nulliparous and gravid	3 (9)	8 (17)
<b>Male children</b>		
Yes	22 (63)	29 (62)
Median age at first live birth (range)	28 (19-38)	28 (16-34)
<b>Stage (0-IV)</b>		N.A.
<i>In situ</i> (0)	8 (23)	
Invasive (I-IV)	27 (77)	
Median days from diagnosis to phlebotomy (range)	51 (7-2646)	N.A.
<b>Chemotherapy</b>		N.A.
Yes	8 (23)	
No	27 (77)	

Abbreviation: N.A., not applicable.

**Table 2: Prevalence of fetal microchimerism in women with breast cancer and control women [24]**

	<i>n</i> (%)	Odds ratio (95% CI)	<i>P</i>
<b>Total cohort</b>			
Breast cancer	5/35 (14)	4.4 (1.34–16.99)	0.006
Healthy controls	20/47 (43)		
<b>Prior male birth</b>			
Breast cancer	3/22 (14)	5.9 (1.26–36.69)	0.01
Healthy controls	14/29 (48)		

- **2008, Vijayakrishna K [23]** conducted a case-control study of 100 female participants (with at least one male child) to determine whether the presence of fetal microchimerism, commonly acquired during pregnancy, is a protective factor against breast cancer. These women were tested for fetal microchimerism by quantitative PCR. A total of 54 women with primary invasive breast cancer and 45 controls from the general population were evaluable for fetal microchimerism, and one woman was excluded from the final analysis due to a lack of clinical data

The prevalence of fetal microchimerism was 56% (25/45) and 26% (14/54) in controls and cases, respectively (**Table 3**). Women with fetal microchimerism were less likely to have breast cancer (OR = 0.29, 95% CI 0.11-0.83;  $p = 0.02$ , after adjustment for age, number of children, the birth of a son, history of miscarriage, and total DNA tested). In addition, microchemical cell concentrations were higher in controls than in cases ( $p = 0.01$ ).

**Table 3: Breast cancer risk and fetal microchimerism [23]**

Presence of FMc	Proportions by Disease Status		OR (95% CI)	<i>p</i>
	No. Cases (%)	No. Controls (%)		
No	40 (74)	20 (54)	1.0	–
Yes	14 (26)	25 (56)	0.20(0.08–0.53)	0.001*
			0.29 (0.11–0.83)	0.02**

\* Adjusted for age, number of children, birth of a son, history of miscarriage;

\*\* adjusted for above and total number of cell equivalents tested.

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- **2009, Dubernard G et al [25]** sought to show the presence of fetus-derived stem cells in mammary carcinomas using a mouse model. To induce mammary tumours, 24 MMTV-H-Ras virgin transgenic female mice were mated at 6 to 10 weeks of age with wild-type FVB males or V-Luc males transgenic for luciferase under the control of the vascular endothelial growth factor (VEGFR2) promoter. All of these female mice gave birth to at least one male pup. Tumours that developed during or after gestation were analyzed and graded for a nuclear grade. Y-chromosome FISH detected fetal cells. Of the 24 mice that became pregnant, ten developed tumours within ten weeks of mating. Of these ten tumours, one appeared before the first gestation (14 days before), three appeared during gestation, and six within weeks of gestation. Of these ten tumours, 9 were mammary carcinomas, and one was a salivary tumour. Ten tumours samples were analyzed by FISH, combined with liver samples obtained from the same mice (used as matched controls). Fetal cells were detected in 9/10 female MMTV-H-Ras mice with pregnancy-associated mammary carcinoma. These cells were located exclusively in dense tumour areas. In contrast, fetal cells were found in only 2/8 control liver samples ( $p=0.013$ ). Salivary gland carcinoma was the only tumour with no fetal cells (**Table 4**). The authors also assessed the frequency of fetal cells in maternal tissues. In breast tumours, 20 fetal cells per million maternal cells were identified, whereas, in the liver, only 4.9 fetal cells per million maternal cells were found ( $p=0.011$ ). Importantly, fetal cells were more frequent in high-grade tumours than in low-grade tumours (29 versus 13.8 fetal cells per million maternal cells,  $p=0.032$ ).

**Table 4: Clinical, histological, and microchimerism assessment features in tumour and control samples [25].**

Mice	Chronology		Tumour				Liver		
	Time of tumour according to pregnancy	Histological Type	Presence of MC cells	Number of MC cells	Total number of cells scored	Number of MC cells / 10 <sup>6</sup> maternal cells	Presence of MC cells	Number of MC cells	Number of MC cells / 10 <sup>6</sup> maternal cells
1	P > T	Breast Carcinoma	Positive	18	664,259	27	Negative	0/73953	0
2	P > T	Breast Carcinoma	Positive	7	435,896	16	Negative	0/103125	0
3	P > T	Breast Carcinoma	Positive	14	615,400	23	-	-	-
4	T > P	Breast Carcinoma	Positive	11	299,404	38	Positive	2/81360	25
5	T = P	Breast Carcinoma	Positive	12	565,600	21	Negative	0/10000	0
6	P > T	Breast Carcinoma	Positive	18	477,664	38	Negative	0/55188	0
7	T = P	Breast Carcinoma	Positive	7	416,960	19	Negative	0/36720	0
8	P > T	Breast Carcinoma	Positive	1	112,000	9	Negative	0/31273	0
9	P > T	Breast Carcinoma	Positive	22	2,486,000	9	Positive	1/71656	14
10	P = T	Salivary Carcinoma	Negative	0	116,688	0	-	-	-

P > T pregnancy before the tumour, P = T tumour developed during pregnancy, T > P tumour presents before pregnancy, MC microchimeric.

- **2010, Gadi VK et al [26]** conducted a case-control study on 38 non-tumour breast tissues from 19 subjects with a history of breast cancer and 19 subjects without a history of breast cancer. Testing for fetal microchimerism was done by quantitative PCR. The objective of this study was to determine whether the presence of fetal microchimerism in breast tissue would be associated with protection against breast cancer. Fetal microchimerism was more frequently found in breast tissue from women without a history of cancer (63%) than in normal breast tissue from women with breast cancer (26%). The odds ratio for the association between fetal microchimerism and no breast cancer was 0.21 (0.05-0.83 95% confidence interval;  $p=0.03$ ).



The odds ratio corrected for the total amount of DNA tested was 0.17 (95% confidence interval, 0.04-0.76  $p=0.02$ ).

- **2012, Kamper-Jorgensen M et al [27]** set out to determine whether there is a possible beneficial effect of fetal microchimerism and whether this effect was specific to breast cancer. Secondly, to see if the low levels of fetal microchimerism were seen before the diagnosis of cancer or appeared with breast cancer. They conducted a case-control study in a cohort of Danish women aged 50 to 64 years enrolled in the DCH "Diet, Cancer and Health" cohort. Blood samples and questionnaire data were obtained between 1993 and 1997 when all women were healthy. In 2006, a follow-up of breast and colon cancer incidence of all women in the cohort was performed in the national registries. A QPCR analysis to identify the Y-chromosome-specific gene *DYS14* (a marker of fetal microchimerism) was performed in 100 women who developed breast cancer (15% of those available in the DCH cohort), 77 women who developed colon cancer (57% of those available in the DCH cohort), and 300 cancer-free controls. They then excluded 11 breast cancer cases (11%), ten colon cancer cases (13%), and 28 (9%) cancer-free controls because blood samples were missing or the Q-PCR failed. The median age at enrollment was 57 (53-61) years in breast cancer cases, 59 (56-63) years in colon cancer cases, and 57 (53-60) years in cancer-free controls.

In cancer-free controls, 70% of tests were positive for microchimerism, whereas microcells were found in 40% of women who developed breast cancer and 90% of those with colon cancer (**Table 5**).

**Table 5 [27]: Association between microchimerism and breast and colon cancer**

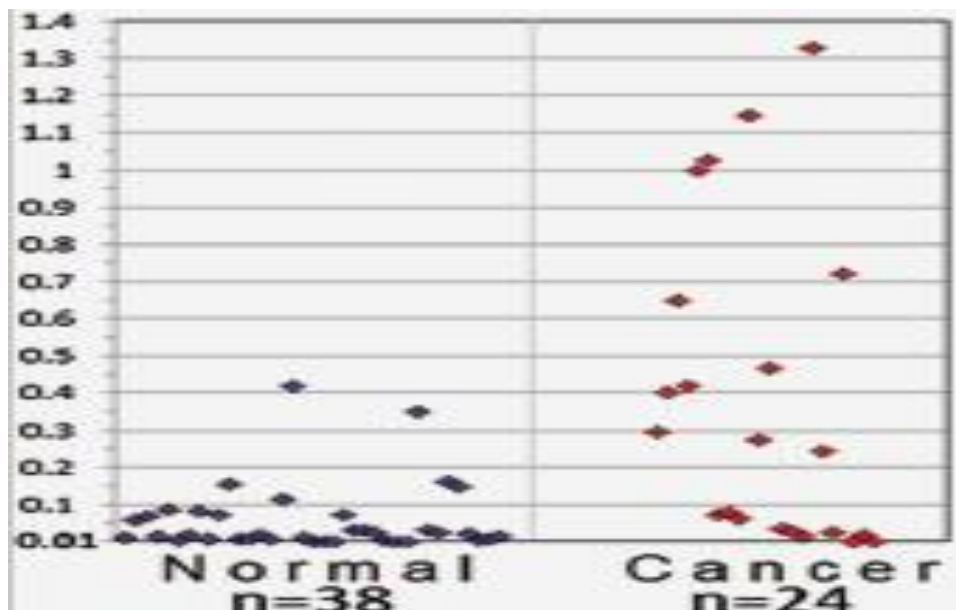
	Breast cancer ( <i>n</i> = 89)	Colon cancer ( <i>n</i> = 67)	Cancer-free ( <i>n</i> = 272)
Detection of microchimerism ( <i>n</i> , column %)			
No	53 (59.6)	7 (10.4)	82 (30.1)
Yes	36 (40.4)	60 (89.6)	190 (69.9)
Odds ratio (95% confidence interval (CI))			
Adjusted	0.30 (0.17-0.52)	3.93 (1.63-9.52)	1 (Ref.)

- **2013, Dhimolea E et al [28]** investigated whether microchemical embryonic/fetal stem cells play a role in female breast cancer. A case-control study of 206 patient samples was done. In this sample, 182 results were exploitable. A highly sensitive Y-chromosome test was developed to trace and quantify male allogeneic cells (from male fetuses) in women. Results showed that of the 68 healthy women in the sample, more than half (56%  $n=38$ ) carried male cells in their breast tissue for decades, while only one in five (21%  $n=24$ ) in the sample pool of 114 women with cancer (odds ratio = 4.75;  $p=0.0001$ )

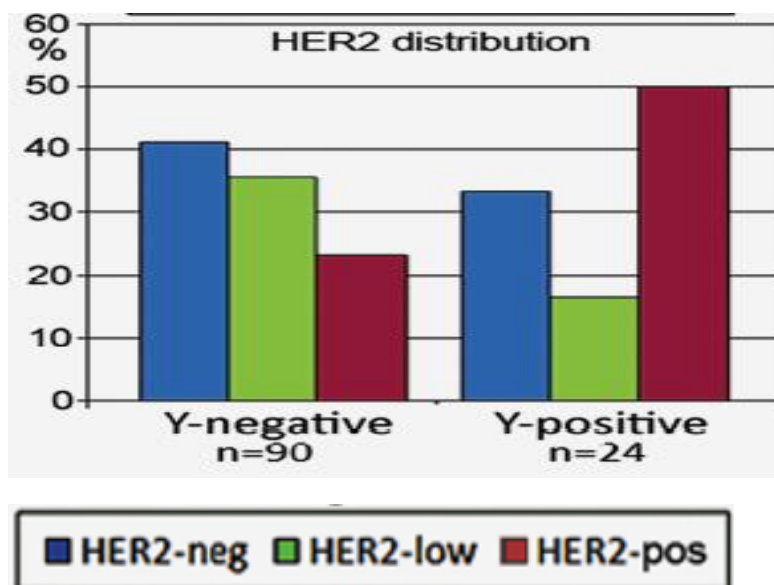
In the cancer cohort, the mean normalized Y signal was 16 times higher than in control ( $n=62$ ;  $p=0.0001$ ) (**Figure 1**).

In the 90 Y-negative cases, only 21 cases of HER2-positive cancers (23%) were found, whereas HER2 status was positive in half of the Y-positive malignancies (**Figure 2**)





**Figure 1: Dot-plot representation of Y-signal levels in normal (blue) and cancer samples (red) [28]**



**Figure 2: HER2 incidence distribution in Y-negative versus Y-positive in women with cancers [28]**

- 2013, Eun JK et al. [29] sought to determine whether there is a fundamental failure in acquiring or maintaining chimeric fetal cells in these women with breast cancers. They performed a case-control study on a cohort of 100 women with a history of breast carcinoma in situ (BIS) and 100 healthy control women. The presence and amount of fetal microchimerism were determined by targeting the DYS14 sequence of the Y chromosome by



quantitative PCR over seven months. 11 case samples and 12 control samples were excluded from analysis because the quality or quantity of DNA was insufficient for PCR. Fetal microchimerism was detected in 75 of 88 controls (85%) and 57 of 89 CIS patients (64%). The odds ratio for protection against noninvasive breast disease was 0.26 (95% confidence interval: 0.12-0.56)  $p=0.001$

- **2016, Dragos N et al [30]** investigated the frequency and concentration of fetal microchimerism in the local breast cancer setting. The study population consisted of 19 patients with confirmed breast neoplasia without chemotherapy, radiotherapy, or preoperative endocrine therapy specifically administered to treat breast cancer. They underwent a mastectomy, during which three fresh samples were taken. These samples, consisting of tumour breast tissue, breast tissue at the periphery of the tumour, and adjacent normal breast tissue was analyzed by quantitative PCR for the sex-determining region (SRY) gene of the Y chromosome.

Based on their obstetric history, the 19 patients were classified into three groups:

- without any pregnancy (two cases);
- no male deliveries, but abortions (three cases)
- with at least one male child (14 cases).

There was no amplification of the SRY gene, for all samples, in the two nulliparous women, thus confirming the negative controls.

In the women who gave birth to at least one son, they detected fetal microchimerism in 100% of the samples from tumours and their peripheries and in 64% (9 of 14) of those from normal breast tissue (**Table 6**). The tumour tissue and its periphery carried significantly more SRY copies than the surrounding normal breast tissue ( $p = 0.005$ ).

The median normalized SRY signal was higher in the tumour (approximately 77-fold) and periphery (14-fold) than in normal breast tissue.

**Table 6: Characteristics of fetal microchimerism in women who gave birth to a son [30]**

	Tumor	Periphery	Normal breast
SRY-positive	14 (100%)	14 (100%)	9 (64%)
SRY copies	171.5 (32-2454)	86 (8-1113)	7 (0-7) <sup>a</sup>
RelExpRatio (vs. normal)	76.7 (3.2-21467)	14.3 (1.3-2690)	1
RelExpRatio (vs. periphery)	5.5 (1.1-389.4)	1	-
Total human, $\times 10^5$ gEq/ml	79 (5.4-1032)	153.5 (30.2-522)	28.9 (3.9-438)

Data are presented as count (%) or median (range). RelExpRatio: relative expression ratio. gEq: genome equivalents.

<sup>a</sup>All, with except one samples from the normal breast tissue, had the concentration of male DNA below the limit of quantification (23 pg/ $\mu$ l).



## **DISCUSSION**

### **I. Internal validity of our study**

The main difficulty encountered during the realization of this research work was related to the weakness of the number of references on the subject: despite its discovery nearly 150 years ago by Georg Schmorl and the polymorphism of the studies of the effects of microchimerism on maternal health and diseases, the studies of the relationship between fetal microchimerism and cancer, in particular breast cancer, are relatively recent.

However, a selection bias can be noted because we consulted only one database (PubMed).

### **II. Internal validity of articles**

The selected articles had a level of scientific evidence between 2 and 3. The main objective of all articles was to determine the effects of fetal microchimerism in breast cancer through the search for male DNA in maternal blood, normal breast tissue, and/or cancerous breast tissue.

However, some biases can be noted:

- The inclusion of women who had previously undergone chemotherapy or radiation therapy could potentially bias our hypothesis. Chemotherapy and cytotoxic radiation therapy alter tumour cell populations for some time after treatment
- Information bias: blood transfusion history was not always available for the subjects in the selected studies (blood transfusion is one source of microchimerism occurring outside of pregnancy)
- Another possibility is acquiring microchimeric cells from an older brother transmitted to the subjects via the maternal circulation.
- The presence of potential contamination of samples during analysis would also be a bias.
- Only male microchimeric cells were identified. The potential female fetuses contribution to microchimerism was not considered, which could have modified the result.

### **III. Analysis of the results**

Fetal microchimerism was more frequently found in the breast tissue of healthy women without a history of cancer than in breast tissue of women with breast cancer [23, 24, 26, 27, 28, 29, 30], with a statistically significant difference. These data confirm that microchimerism is common in normal breast tissue. This fact may have an evolutionary explanation. Indeed, microchimerism is found in placental mammals. The placenta appeared 100 million years ago in eutherian reproduction, so mammals, e.g., mice, also had microchimerism during pregnancy [31]. During evolution, the placenta underwent morphological and functional changes. The growing fetal brain in primates increased oxygen consumption, while vertical bipedalism limited uterine circulation. To respond to the high demand for resources, the primate placenta became a deeply invasive hemochorionic structure (6-8 million years ago) [32]. This placental invasion also allows for greater exchange of maternal and fetal cells by improving the transfer of nutrients from mother to fetus.



Microchimerism in breast tissue is more common in healthy women than in breast cancer patients [23, 24, 26, 27, 28, 29, 30]. These data show a protective effect of microchimeric cells on breast tissue. The protective effect is even stronger in women who have given birth to boys [24]. This protective effect can be explained by fetal microchimeric stem cells' differentiation and tissue regeneration properties [5].

In addition, microchimeric cells have immunoregulatory properties. They do not induce adult T-cell proliferation and can block lymphocyte proliferation induced by mitogenic agents [31, 33].

However, the correlation is not linear as excess male microchimerism (hyperchimerism) is also implicated in cancer. Data suggest a link between "hyperchimerism" and HER2+ cancers, while decreased chimerism (hypochimerism) is associated with ER/PR positive (luminal type) breast cancers. [28].

*Pregnancy-associated breast cancer (PABC)* is an aggressive tumour [25]. Within these cancerous fetal cells are identified in 90% of cases, they are absent from the breast of pregnant women without cancer or with a benign tumour [34]. The more aggressive the tumour, the more it would attract fetal cells [35].

The fetal stem cells would be captured by specific signals in the tumour tissue to repair the damaged tissue. This effect would explain the low levels of fetal microchimerism circulating in the blood of these sick women. Alternatively, stem cells acquired during gestation, nested in the breast tissue, would allow invasion of the glandular tissue by differentiating into endothelial cells, forming new vessels [36]. Markers of fetal cells in the vicinity of tumours show that they are cells of epithelial or mesenchymal origin expressing cytokeratin or vimentin and, to a lesser degree, endothelial cells and never leukocytes [25, 34]. These cells would not be part of the neoplastic clone, as they are isolated and not clustered in focus [25, 34]. The fetal cells are disseminated in the tumour stroma, which influences tumour behaviour. Through the stroma, these cells could alter the prognosis. Fetal stromal cells are thought to differ from their adult counterparts by expressing a greater degree of plasticity, proliferating more rapidly, possessing a longer telomere, and expressing the HLA-G antigen. During normal pregnancies, HLA-G antigens expressed by fetal tissues participate in maternal tolerance to antigens of paternal origin. HLA-G expressing fetal cells attracted to the stroma, by modulating the maternal immune response, could be involved in the behaviour of cancers [37]. The decrease in circulating microchimerism in breast tumours could be explained by aspiration of fetal cells by the tumour. The more aggressive the tumour, the more it would attract fetal cells.

## CONCLUSION

*Fetal microchimerism* is a frequent phenomenon that probably occurs in all human pregnancies and allows the transfer of fetal cells of various phenotypes to the mother. These cells may persist for decades in the mother. Some fetal cells have the properties of stem cells, with a power of proliferation and a capacity of differentiation that can be of benefit to the mother.

In this study, our results indicate that microchemical cells may help reduce the risk of breast cancer in women.



Good knowledge of the mechanisms of action of these microchemical stem cells could potentially serve as an innovative therapeutic approach for breast cancer patients.

## DECLARATIONS SECTION

**Ethical approval and consent to participate:** All authors of this manuscript participated freely and ethically

- **Consent to Publication:** For all selected articles, informed consent from study participants was documented.

- **Availability of Data and Materials:** All data used to complete this work are available and accessible.

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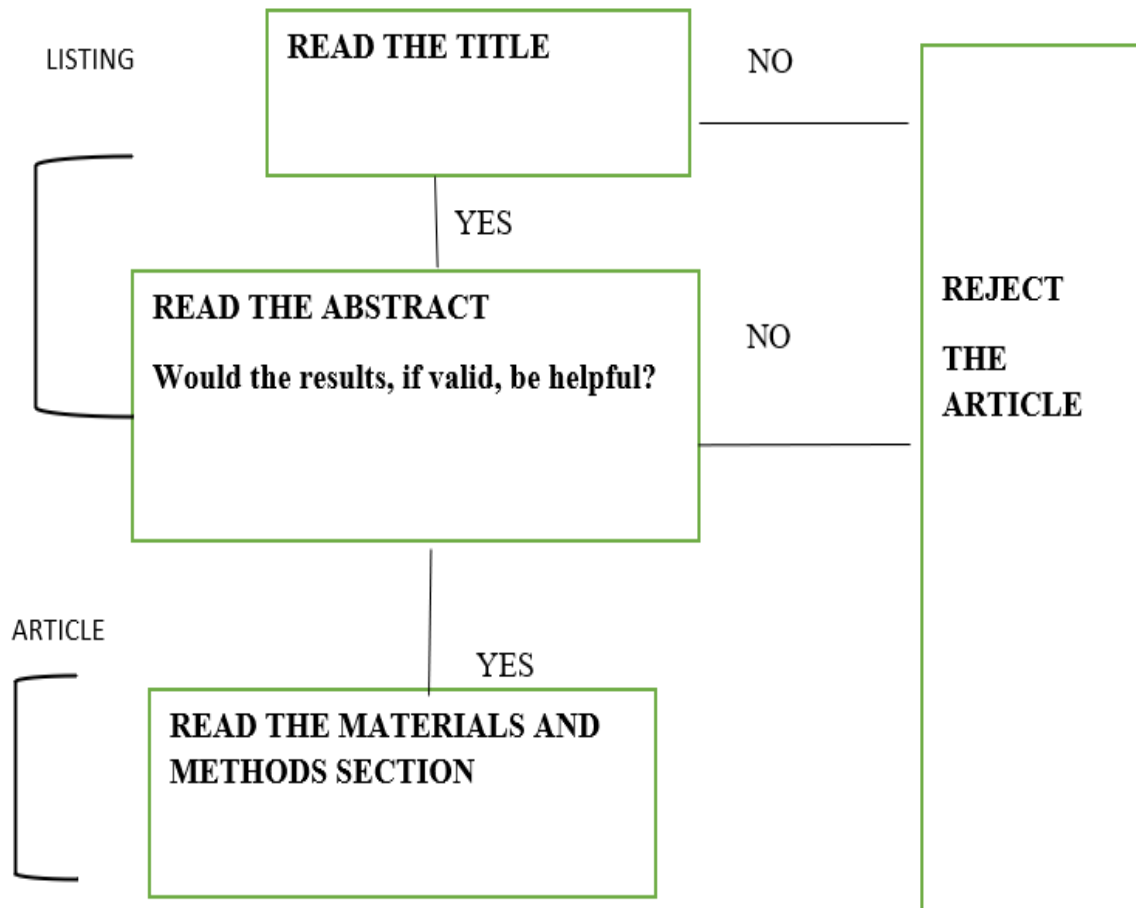


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**APPENDIX**

**Appendix I: First Steps in Selecting a Medical Article According to the 2000 Literature Review Guide and Grading of Recommendations**





**Appendix II Level of scientific evidence and grade of recommendations from *Guide to the analysis of the literature and gradation of recommendations, ANAES 2000***

<b>LEVEL OF SCIENTIFIC EVIDENCE PROVIDED BY THE LITERATURE</b>	<b>GRADE OF RECOMMENDATIONS</b>
<b>Level 1</b> - High power randomized controlled trials - Meta-analysis of randomized controlled trials - Decision analysis based on well-conducted studies	<b>A</b> <b>scientific evidence</b>
<b>Level 2</b> - Low power randomized controlled trials - Well-conducted non-randomized controlled studies - Cohort studies	<b>B</b> <b>Scientific Presumption</b>
<b>Level 3</b> - Case-control studies	<b>C</b> <b>Low level of scientific evidence</b>
<b>Level 4</b> - Comparative studies with significant bias - Retrospective studies - Case series - Descriptive epidemiological studies (cross-sectional, longitudinal)	