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Original Article

Influence of the codon 72 polymorphism of the *TP53* gene in the susceptibility of female cancers in Widou Thiengoly

Fatimata Mbaye, Joseph Dominique Sendar Seck, Mbacké Sembene

Laboratory of Genomics, Department of Animal Biology, Faculty of Science and Technology, Cheikh Anta Diop University, Dakar, Senegal

Correspondence

Fatimata Mbaye

Laboratory of Genomics, Department of Animal Biology, Faculty of Science and Technology, Cheikh Anta Diop University, Dakar, Senegal, BP 5005

Tel.: 221773665998

E-mail: fatimata2.mbaye@ucad.edu.sn

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Abstract

Genetic factors have been implicated in the predisposition to cancer in Senegalese women. The arginine allele at codon 72 of exon 4 of the *TP53* gene has been associated with a predisposition to several cancers in different populations. The objective of this study was to determine the effect of this polymorphism in a Senegalese population located in the locality of Widou Thiengoly. Two hundred and six (206) women living in Widou were recruited as well as thirty-two (32) control women, all assumed to be healthy. Genotyping of codon 72 of exon 4 of the *TP53* gene was performed by Polymerase Chain Reaction and Restriction Fragment Length Polymorphism (PCR-RFLP) in 122 women. A significant association was found in the distribution of allelic and genotypic frequencies depending on the locality (*p value*: 5.6 x 10^{-09}; OR: 0.015; IC_{95}: $3.5e^{-04}$-$11e^{-02}$). However, no correlation was found between the risk factors (age, menopause, oral contraception, parity, gestational age, date of onset of first menstrual period, marital status) and the distribution of the allele frequency in the Widou locality. Due to the strong presence of the Arg allele in the Widou locality, a vast screening campaign for female cancers would be recommended.

Introduction

The profile of Senegal is still that of a country where much remains to be done for the proper management of the health of the population. According to the United Nations Development Program [1], the country is ranked 162 out of 191 in the world and 32 out of 53 in Africa in terms of its human development index (HDI). While overall, the level of mortality is decreasing and inequalities persist according to place of residence. The comparison of crude mortality rates (after standardization) between urban and rural areas shows that the risk of death remains relatively higher in rural areas (8.9 ‰) than in urban areas (6.3 ‰) [2]. Most people with diseases such as cancer do not have access to screening, early diagnosis, treatment, or palliative care [3]. According to Tine et al. [4], women living in urban areas would be more likely to use screening than rural women. The study by Faye et al. [5] has shown that cervical cancer screening is low in rural Senegalese areas and that cervical cancer control strategies will need to focus on information and access to quality healthcare for these women. This situation is the result of a poor distribution of hospital structures and health personnel as well as high-tech equipment, which therefore creates an imbalance in the health map with an excessive concentration in Dakar [3].

Cancer is a genetic disease of the cell. This is a dogma that the last 30 years of research has consistently verified [6]. The cells will suffer from various genetic damages mainly in two categories of genes. On the one hand, the proto-oncogenes, which will become "activated" oncogenes when mutated, and on the other hand, the tumor suppressor genes. Among the latter, the *TP53* gene is frequently mutated. Indeed, studies have shown the alteration of this gene in more than half of cancers, including female cancers [7-9]. Numerous polymorphisms have been described for the *TP53* gene and, among them, the polymorphism of codon 72 of exon 4 resulting in a substitution of proline (PRO) by an arginine (ARG), which would be responsible for the decrease in the activity of the protein. This polymorphism is located in the proline-rich domain of the *TP53* gene involved in apoptosis. All these inter-regional health inequalities, associated with *TP53* gene polymorphisms and cancer risk factors, may make rural women more likely to develop cancer than women living in urban areas. Thus, the objective of this study is to evaluate the influence of the ARG72PRO polymorphism of the *TP53* gene in the susceptibility of female cancers at Widou Thiengoly.

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Methodology

Study population

This study compares the distribution of genotypic and allelic frequencies of the polymorphism of codon 72 of the *TP53* gene between the population of Widou Thiengoly (rural area) and another population of the same ethnic group residing in Dakar (urban area). Both of these populations are made up of supposedly healthy Fulani women. The village of Widou Thiengoly is located in the rural community of Téssékéré in the Ferlo. The present study has obtained the approval of the Research Ethics Committee (CER) of UCAD under the Protocol number 0270/2018/CER/UCAD. An epidemiological survey was conducted among 206 women from Widou and 32 from Dakar, after which blood samples were taken in EDTA tubes. In Dakar, all the women were sampled, unlike in Widou where only 90 individuals were sampled.

DNA extraction and PCR-RFLP

DNA extraction was performed from the whole blood of the 122 individuals sampled. The Zymo research Kit was used according to the manufacturer's instructions. Exon 4 of the *TP53* gene was amplified using primers p53F (5'-TCCCCCTTGCCGTCCCAA-3') and p53R (5'-CGTGCAAGTCACAGACTT-3'), thereby flanking the codon 72 polymorphism region. PCR was carried out with a reaction volume of 25 µl containing: 1 µl of $MgCl_2$, 2.5 µl of 10X buffer, 0.1 µl of Taq polymerase, 1.25 µl of each primer, 0.5 µl of dNTP, 16.4 µl of MilliQ water, and 2 µl of DNA. Exon 4 of the *TP53* gene was amplified under the following conditions: initial denaturation at 94°C for 5 min, 35 cycles (94°C for 30 s, 58°C for 45 s, 72°C for 40 s), final elongation at 72°C for 5 min. The digestion of PCR products was performed in a reaction volume of 20 µl (0.5 µl of BstUI enzyme, 2 µl of buffer, 2.5 µl of milliQ water and 15 µl of PCR product) at 60°C. The resulting restriction fragments were separated by electrophoretic migration on a 2% agarose gel for one hour.

Statistical analysis

The epidemiological and genetic data obtained in this study were entered on the Excel 2013 program and analyzed with R software version 3.5. Quantitative variables (age, parity, gestational age, date of onset of first menstrual period (DMP), age of first pregnancy) were described in terms of mean and standard deviation. Qualitative variables (menopausal status, oral contraception, marital status, genotypes and alleles) were presented in terms of numbers and percentages. Contingency tables were analyzed using Pearson's Chi-squared or Fisher's test depending on the application conditions. The odds ratio (OR) was also calculated to assess the degree of dependence between qualitative variables with a 95% confidence interval. A significance level of 5% was retained.

Logistic regression was used to measure the association between certain variables to be explained (genotypic and allelic frequencies) and the explanatory variables (locality, age, DMP, parity, gestational age and age of first pregnancy). The age groups [15-35[, [35-55[and [55 and over] were selected according to the study by Gbessemehlan [10]. Based on the number of pares, women were classified into: nulliparous (0), primiparous (1), pauciparous (2), multiparous (3-4) and large multiparous (more than 5). The association between genetic factor and susceptibility to develop female cancer by comparing the allelic and genotypic frequencies of the *TP53* gene codon 72 polymorphism between the Widou and Dakar populations was tested in this study. In addition, the relative risk of developing cancer related to the *TP53* gene codon 72 polymorphism was tested. The association between the distribution of alleles and menopausal status, but also with the use of contraception and marital status was investigated in the Widou population. For logistic regression, the Akaike information criterion, which is a measure of the quality of a statistical model proposed by Hirotugu Akaike in 1973, was used to evaluate our model.

Results

Sociodemographic characteristics

We have a very high representation of young people in our study: 47% of the population of Widou and 62% of the population of Dakar are under 35 years old. The age of our populations varied from 15 to 80 years old with an average of 37.66 ± 15.09 years in Widou and from 19 to 61 years with an average of 34.09 ± 12.61 years in Dakar (Figure 1).

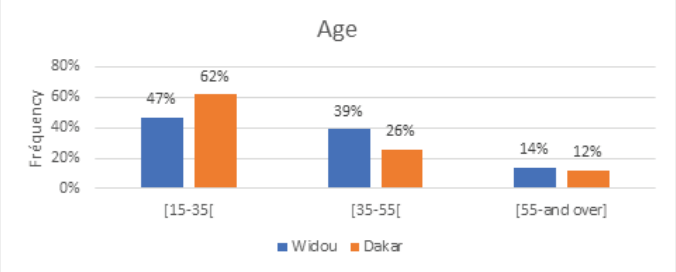

Figure 1. Distribution of populations by age categories.

The majority of our populations were married women, with 81% and 85% for Widou and Dakar, respectively (Figure 2).

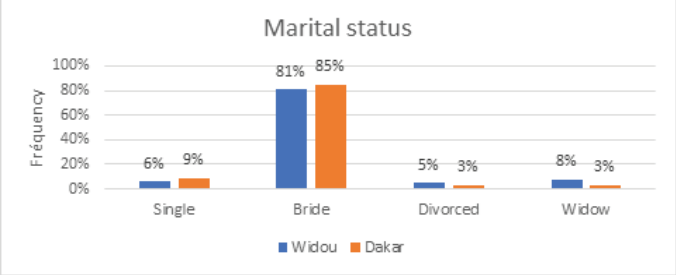

Figure 2. *Distribution of populations according to marital status.*

38% of our urban population have never heard of this pathological condition, with only 9% having heard of it at school and 3% from health services. This same observation was made in the Widou population (1% at school and 2% with health services) (Figure 3).

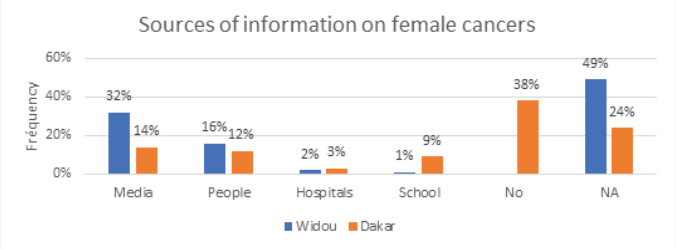

Figure 3. *Representation of the different sources of information on female cancers for our populations.*

Table 1. *Hormonal and reproductive activities in women.*

Localities \ Risk Factors		DMP (years)	Age 1st pregnancy (years)	Gestation age (number of pregnancies)	Interval between pregnancies (years)
Widou	Minimum	09	10.00	0.00	1
	Average	14.37 ± 2.19	18.64 ± 3.10	3.77 ± 2.44	3.36 ± 1.83
	Maximum	20	32.00	11.00	10
Dakar	Minimum	10.00	16	0.00	1.00
	Average	14.56 ± 3.94	21.35 ± 3.53	2.5 ± 2.5	3.39 ± 1.48
	Maximum	34.00	28	09	6.3

DMP: date of onset of first menstrual period

Reproductive characteristics

The average ages of onset of the first menstrual period were almost the same in Widou and Dakar (14.37 ± 2.19 with a minimum of 9 years and a maximum of 20 years in Widou and 14.56 ± 3.94 with a minimum of 10 years and a maximum of 34 years in Dakar). The minimum age of first pregnancy was lower in Widou (10 years) with an average of 18.64 ± 3.10 and a maximum of 32 years. On the other hand, it was higher in Dakar (16 years) with an average of 21.35 ± 3.53 and a maximum of 28 years. The average number of pregnancies among women in Widou was 3.77 ± 2.44 and 2.5 ± 2.5 in Dakar. The highest number of pregnancies was observed in Widou (11 pregnancies). The time intervals between pregnancies were identical in both populations (Table 1).

Among the women of Widou, 83% of them have at least one child. Whereas among urban women, 68% were mothers. In Widou, 30% of women had 3 to 4 children and 24% had at least 5 children. This is in contrast to women in the city who are more nulliparous (32% as against 13% in Widou). In the nulliparous group, the average age was 26.29±13.62 years and 26.82±9.11 years for Widou and Dakar, respectively. For the multiparous group, the average age was 46.14±11.40 years and 54.2±7.39 years in Widou and Dakar, respectively. The average number of children was 3.47±2.37 and 2.11±2.16 in Widou and Dakar, respectively (Figure 4).

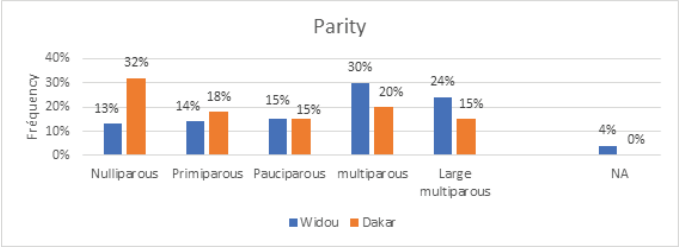

Figure 4. *Distribution of our populations according to the number of children..*

Urban women use oral contraception more than rural women, with 41% and 37% in Dakar and Widou, respectively (Figure 5).

In our study, we have more women in childbearing status than menopausal women, with 79% and 68% in Dakar and Widou, respectively. Among menopausal women, the average age was 56 ± 9.26 in Widou with a minimum of 44 years and 55.14 ± 4.77 in Dakar with a minimum of 50 years (Figure 6).

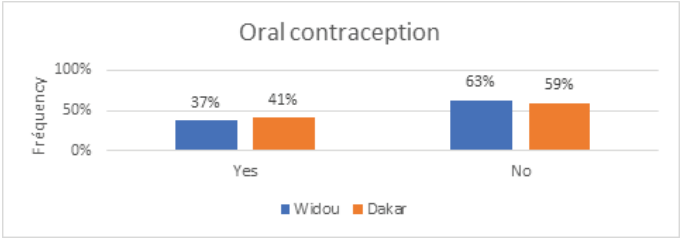

Figure 5. *Distribution of our populations according to the use of oral contraception.*

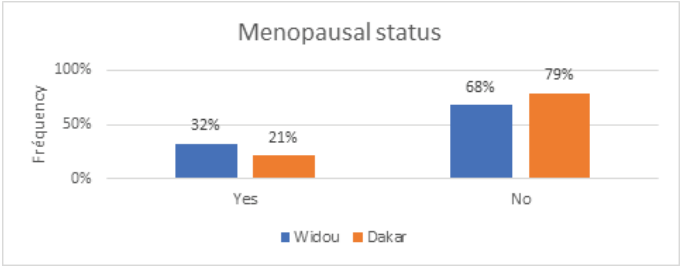

Figure 6. *Distribution of our populations according to menopausal status*

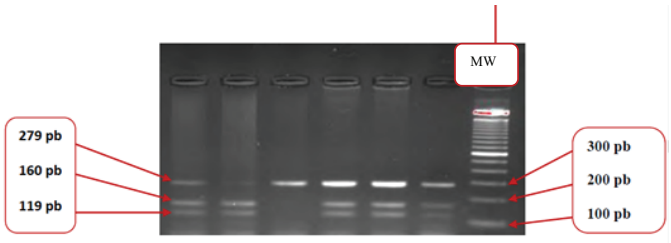

Figure 7. *Electrophoretic migration profile of BstUI-digested PCR products from 6 individuals in Widou.*

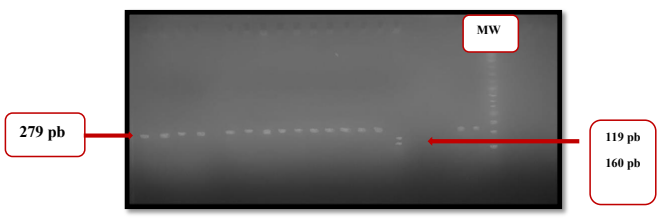

Figure 8. *Electrophoretic migration profile of BstUI-digested PCR products from 17 individuals in Dakar.*

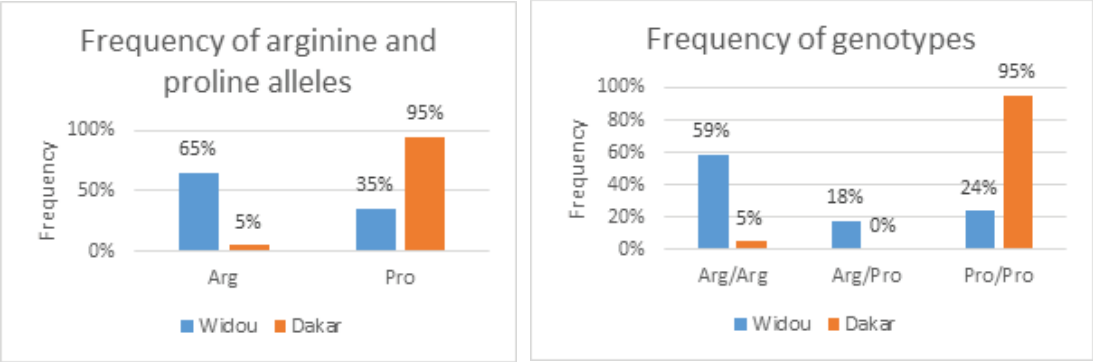

Figure 9. *Allelic and genotypic frequencies of our two populations.*

Table 2. *Hardy Weinberg test on our populations.*

Localities	Frequencies (%)	Genotypes			P. value
		Arg/Arg	Arg/Pro	Pro/Pro	
Widou	Theoretical	42.25	45.50	12.25	0.199
	Observed	58.82	17.64	23.52	
Dakar	Theoretical	0.25	9.5	90.25	1
	Observed	4.76	0	95.23	

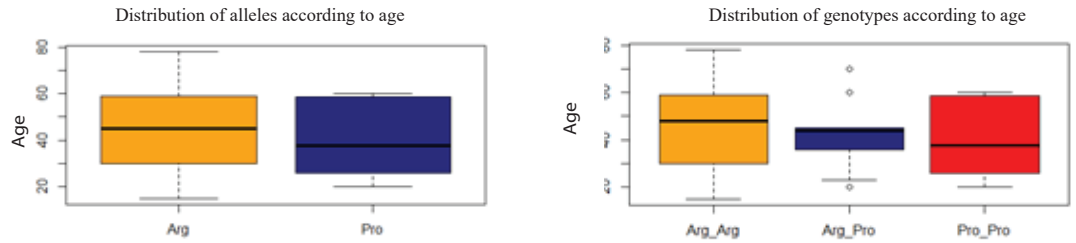

Figure 10*. Distribution of allelic and genotypic frequencies according to age in the Widou population.*

Genetic characteristics

Genotyping of codon 72 of the TP53 gene

PCR amplification of exon 4 of the *TP53* gene yielded a 279 bp fragment corresponding to the expected size. We performed RFLP on a total of 72 individuals, consisting of 51 in the Widou population and 21 in the Dakar population. Enzymatic digestion of the PCR products showed three different genotypes at Widou (Figure 7):

- the homozygous Pro/Pro genotype corresponding to the observed band 279 bp;
- the homozygous Arg/Arg genotype corresponding to the two bands observed at 119 and 160 bp;
- the heterozygous Arg/Pro genotype corresponding to the three bands observed at 119, 160 and 279 bp.

Unlike the Widou population, the Dakar population has only two genotypes: the homozygous Pro/Pro genotype and the homozygous Arg/Arg genotype (Figure 8).

Allelic and genotypic frequencies

In Widou Thiengoly, Fulani women expressed the Argine allele more often than the Proline allele (65.00% Arg *vs.* 35.00% Pro) unlike Fulani women in urban areas (Dakar) where the Proline allele is much more frequent (95.23% Pro *vs.* 4.76% Arg). The Arg/Arg, Arg/Pro and Pro/Pro genotypes were all observed in the Fulani women of Widou with proportions of 58.82%, 17.64% and 23.52%, respectively. In contrast, among the Fulani women of Dakar, only the Arg/Arg and Pro/Pro genotypes were identified in proportions of 4.76% and 95.23%, respectively (Figure 9).

In our study populations, the Hardy Weinberg equilibrium was not observed (Table 2).

On these graphs, we see that the age range is greater in

Table 3. *Association test between the frequency of the alleles and the locality.*

	Genotypes						Alleles		OR	P*	IC 95%
	Arg/Arg		Arg/Pro		Pro/Pro		Arg				
	n	%	n	%	n	%	n	%			
Dakar	1	4.76	0	-	20	95.23	1	4.76	-		
Widou	30	58.82	9	17.64	12	23.52	39	53.42	0.015	5.6e^{-09}	3.5e^{-04} – 11e^{-02}

OR: Odds Ratio; P*: significant P-value <5%; 95% CI: 95% confidence interval

Table 4. *Association test between the frequency of alleles and certain risk factors in Widou.*

		Genotypes						Alleles		OR	P*	IC 95%
		Arg/Arg		Arg/Pro		Pro/Pro		Arg				
		n	%	n	%	n	%	n	%			
A	Yes	27	52.94	8	15.68	10	19.6	35	68.62	0.57	0.61	0.07 – 7.27
	No	3	5.88	1	1.96	2	3.92	4	7.84			
B	Yes	11	22.44	3	6.12	6	12.24	14	28.57	2.62	0.27	0.51 – 14.94
	No	19	38.77	6	12.24	4	8.16	25	51.02			
C	Yes	16	31.37	4	7.84	5	9.8	20	39.21	0.68	0.74	0.14 – 3.01
	No	14	27.45	5	9.8	7	13.72	19	37.25			

A: Marital status; B: oral contraception; C: Menopause

Table 5. *Logistic model explaining the distribution of TP53 gene codon 72 polymorphism alleles as a function of different explanatory variables.*

	Variables to be explained					
	Allelic frequency					
Explanatory variables	P*	AIC	OR	P* of OR	Deviance (variance)	P * of Deviance
Age	0.774		1.01	0.773	32	0.773
DMP	0.612		1.13	0.612	32	0.603
Gestational age	0.589	42	0.7	0.588	32	0.578
Parity	0.985		1.01	0.984	32	0.984
Age.1st. pregnancy	0.992		1	0.992	32	0.992

AIC = Akaike information criterion; DMP: date of onset of first menstrual period

the group of individuals carrying the Arginine allele than the Proline allele alone, and the same is true for the median age, 45 years *vs.* 38 years. 75% of those who carry the Arginine allele are under 60 years of age. The median age is higher in the groups of women who have a genotype where the Arginine allele is present (Figure 10).

We found a statistically significant difference in the distribution of genotypic (Arg/Arg, Arg/Pro, and Pro/Pro) and allelic (Arginine and Proline) frequencies of the *TP53* gene codon 72 polymorphism according to locality (p-value: 5.6e-^{09}) (Table 3).

No association was found between the distribution of genotypic and allelic frequencies and risk factors, such as the use of oral contraception, menopausal status, and marital status in Widou (Table 4).

In this model, we found no association between the explanatory variables studied and the distribution of allelic frequencies in the Widou population (Table 5).

Discussion

Cancer nowadays constitutes one of the main causes of death in the world [11]. In Africa, women are more affected with 57.10% of new cases and 54.47% of deaths [12]. 5 to 10% of cancer cases are due to a hereditary predisposition [13]. Thus, the identification of predisposition genes for these types of cancers has made significant progress in recent years. This is the case for the tumor suppressor gene, *TP53*.

In this study, we have a strong representation of young people. 62% in Dakar and 47% in Widou are under 35 years old. The average ages were 37.66 years and 34.09 years in Widou and Dakar, respectively. The average age at diagnosis of cancer differs according to the population. Dem et al. [14] found an average of 47.6 years in women with breast cancer and 50.1 years in women with cervical cancer. The average age at cancer diagnosis in Cameroon was 46.08 years for breast cancer and 52.43 years for cervical cancer [15]. The majority of breast cancers occur in the age group of 41-60 years [16]. Screening

strategies in Africa must be adapted to this reality; the latter, classically recommended from the age of 50, should be as early as 40 years [16]. The majority of our populations are married women, with 81% and 85% in Widou and Dakar, respectively. Female cancers remain little or poorly known among women in Widou and Dakar. In our results, 38% of urban women are not aware of this tumor pathology. The main source of information on female cancers in Senegal remains the media. The rate of involvement of health personnel in raising awareness of this disease remains low (2 to 3%), which is consistent with the results of Gueye et al. [16] where 74.2% of women had learned about this pathological condition through the media and only 21.4% knew about it through a health personnel.

The average age of onset of the first menstrual period was 14.37 years in Widou and 14.56 years in Dakar. This average age has remained constant over the years. A study by Ferry [17] on fertility in Senegal reported a similar value (14.3 years). The average age of first pregnancy is significantly lower in rural areas than in urban areas (18.64 years compared to 21.35 years). Ferry's [17] study found that rural women had their first sexual intercourse at an average age of 18.5 years. This corresponds to the average age of the first pregnancy found in the Widou locality. This average has changed more for urban women than for rural women. These results are in agreement with those found by the ANSD (21.4 years in urban areas *vs.* 18.4 in rural areas) [18]. In Dakar, 32% of women are nulliparous, unlike in Widou where the majority of women have at least 3 children (54%). Women in rural areas have a much higher fertility than urban women (3.47 *vs.* 2.11). This is consistent with the results of the ANSD [19] report on key indicators. Oral contraceptives are used more by urban women than rural women, with respective values of 41% and 37%. But in general, the use of oral contraception still remains low, which is corroborated by the results of Sougou et al. [20] who found a rate of 26.6% of women using modern contraceptive methods. The average age of menopause is practically identical in our two populations; that is, 56 years in Widou and 55.14 years in Dakar, contrary to the results of Diouf et al. [21] who obtained an average of 48 years. In this study, 7% of women in Widou and 6% of women in Dakar had at least one family member who had previously suffered from cancer.

The Hardy-Weinberg equilibrium was not observed in our populations. This could be due to several factors such as inbreeding and the small size of our sample. In Widou Thiengoly, Fulani women preferentially expressed the Argine allele rather than the Proline allele, unlike Fulani women in urban areas (Dakar) where the Proline allele is much more frequent. Our results revealed a statistically significant difference in the distribution of the *TP53* gene codon 72 polymorphism (OR: 0.015; CI95: $3.5e^{-04}$-$11e^{-2}$). This result is in agreement with those found in studies carried out in populations of different geographical origins. Furthermore, in 1994, Beckman et al. [22] reported a difference in the genotypic distribution of the *TP53* gene codon 72 polymorphism in India, depending on the geographical area. Siddique et al. [23] verified that healthy heterozygous Asians preferentially express the Pro allele, whereas Caucasians preferentially express the Arg allele; however, approximately 75% of heterozygous Chinese breast cancer patients preferentially express the Arg allele. The study by Buyru et al. [24] revealed a significant increase in the presence of the Arg allele in cancer patients compared to controls, as well as studies conducted in Greece [25,26]. In South Africa, Pegoraro et al. [27] found a significant increase in the frequency of the Arg allele in women with cervical cancer infected with low or intermediate-risk HPV viruses. The association of the Arg allele with an increased risk of various cancers is consistent with several studies including those on cervical cancer [28,29], lung [30] and skin [31]. Although the Arginine form may be able to induce apoptosis better than the Proline form, it may not be effective in preventing cancer formation [25,32,33]. However, the association between the Arg/Arg genotype and certain cancers still remains controversial. Some reports have found no difference in the frequency of the Arg allele between breast cancer patients and controls [34,35]. This same trend has been found in studies where the Pro allele was observed more frequently in breast cancer patients compared to the control group [32,33]. It is possible that differences between studies reflect the populations analyzed, as inherent differences occur in the relative prevalence of polymorphic alleles in various populations. The study of the association between the *TP53* gene codon 72 polymorphism and the risk factors revealed that there was no link between the latter and the genotypes observed in Fulani women in Widou. In other words, age, DMP, menopause, marital status, gestational age and parity have no influence on the distribution of alleles in Widou. Contrary to our results, studies have shown the interference of these factors in the occurrence of cancer in African women [36,27]. The conflicting results on the correlation between the genotype of codon 72 of the *TP53* gene and the risk of breast cancer could be due to inter-ethnic and geographical variations.

Conclusion

In this work, we investigated the potential effect of the Arg72Pro polymorphism of the *TP53* gene on the occurrence of cancer among women from Widou Thiengoly (Senegal).

We found a significant difference in the distribution of genotypic and allelic frequencies between the Fulani women of Dakar and those of Widou, all of whom were assumed to be healthy. The Arginine allele associated with an increased risk of various cancers is significantly present in Widou Thiengoly. No relationship between risk factors documented in the literature and allelic and genotypic frequency distribution was found in this study.

Acknowledgement

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References

1. United Nations Development Program. Human Development Report 2019; 410 p.
2. National Agency of Statistics and Demography. Senegal: General Census of Population and Housing, Agriculture and Livestock (RGPHAE 2013) 2014; 418 p.
3. Ministry of Health and Social Action and the Division of Non-Communicable Diseases. 2015-2019. Strategic Plan for Cancer Control. 72 p.
4. Tine JAD, Niang K, Samiratou A, Faye A, Tal AD. Study of the

determinants of the use of breast cancer screening in women 35 to 65 years in the region of Thiès (Senegal). Open J Epidemiol. 2018; 8(4):201-212.

5. Faye A, Mbengue TE, Tal-Tal A. Factors associated with screening for cervical cancer in rural Senegal. Rev Epidemiol Health 2017; 65:S77.
6. Stoppa-Lyonnet D, Stern MH, Soufir N, Lenoir G. Cancer genetic predisposition: Current events and perspectives 2005. Med Sci. 2010; 21(11):962–968.
7. Beaucourt S. Study of 2 genes targeted by the P53 protein: siah (seven in absentia human homologue) and tsap6 (tumor suppressor-activated pathway 6). Cellular Biology. Thesis for obtaining a doctorate in cancerology. University of Paris Sud - Paris XI. 2005; 139 p.
8. Dridi W, Krabchi K, Gadji M, et al. Dominant negative activity of mutated p53 proteins. Med Sci (Paris). 2006; 22(3):301–307.
9. Jaber S, Simeonova I, Toledo F. Moderation in all things: p53 deregulation, cancer and telomere syndromes. Med Sci (Paris). 2013; 29(12):1071–1073.
10. Gbessemehlan AN. Evaluation of women's knowledge and attitudes towards antenatal care in Commune II of the Bamako District: Case of the Medina Coura District. Thesis for obtaining a doctorate in medicine. University of Bamako. 2011; 75 p.
11. World Health Organization. 2021. Cancer Report 2020.
12. International Agency for Research on Cancer. 2020. Latest global cancer data.
13. Cohen-Haguenauer O. Hereditary predisposition to breast cancer: Genetics. Med Sci (Paris). 2019; 35(2):138–151.
14. Dem A, Traoré B, Dieng MM, et al. Gynecological and breast cancers at the Dakar Cancer Institute. Sante. 2008; 18(1):25-29.
15. Sando Z, Fouogue JT, Fouelifack FY, Fouedjio JH, Mboudou ET, Essame JLO. Profile of breast and gynecological cancers in Yaoundé - Cameroon. Pan Afr Med J. 2014; 17:28.
16. Gueye SMK, Gueye M, Coulbary SA, Diouf A, Moreau JC. Issues involving breast cancer management in Senegal: a cross-sectional study. Pan Afr Med J. 2016; 25:3.
17. Ferry B. Recent data on fertility in Dakar (Senegal). In: population, 31st year, 1976; 3:717-722.
18. National Agency of Statistics and Demography. Continuous Demographic and Health Survey (EDS-Continuous) 2017; 646 p.
19. National Agency of Statistics and Demography. 2016 Economic and Social Situation of Senegal 2019; 30 p.
20. Sougou NM, Niokhor Diouf JB, Ka D, et al. Factors associated with the use of modern contraception in 5 cities of Senegal. Black Afr Med. 2019; 6605:235-244.
21. Diouf AA, Diallo D, Niang PY, et al. Sexuality in postmenopausal women in sub-Saharan Africa: example from Senegal. Pan Afr Med J. 2019; 32:1.
22. Beckman G, Birgander R, Sjalander A, et al. Is p53 polymorphism maintained by natural selection? Hum Hered. 1994; 44(5):266-270.
23. Siddique MM, Balram C, Fiszer-Maliszewska L, et al. Evidence for selective expression of the p53 codon 72 polymorphs: implications in cancer development. Cancer Epidemiol Biomarkers Prev. 2005; 14(9):2245-2252.
24. Buyru N, Altinisik J, Demokan S, Dalay N. p53 genotypes and haplotypes associated with risk of breast cancer. Cancer Detect Prev. 2007; 31:207–213.
25. Papadakis EN, Dokianakis DN, Spandidos DA. p53 codon 72 polymorphism as a risk factor in the development of breast cancer. Mol Cell Biol Res Commun. 2000; 3(6):389-392.
26. Li T, Zu ZM, Guo M, et al. p53 codon 72 polymorphism (C/G) and the risk of human papillomavirus-associated carcinomas in China. Cancer. 2002; 95(12):2571-2576.
27. Pegoraro RJ, Rom L, Lanning PA, Moodley M, Naiker S. p53 codon 72 polymorphism and human papillomavirus type in relation to cervical cancer in South African women. Int J Gynecol Cancer. 2002; 12(4):383-388.
28. Zehbe I, Voglino G, Wilander E, Genta F, Tommasino M. Codon 72 polymorphism of p53 and its association with cervical cancer. Lancet. 1999; 354(9174):218-219.
29. Makni H, Franco EL, Kaiano J, et al. P53 polymorphism in codon 72 and risk of human papillomavirus-induced cervical cancer: effect of inter-laboratory variation. Int J Cancer. 2000; 87(4):528-533.
30. Murata M, Tagawa M, Kimura M, Kimura H, Watanabe S, Saisho H. Analysis of a germ line polymorphism of the p53 gene in lung cancer patients; discrete results with smoking history. Carcinogenesis. 1996; 17(2):261-264.
31. Dokianakis DN, Koumantaki E, Billiri K, Spandidos DA. P53 codon 72 polymorphism as a risk factor in the development of HPV-associated non-melanoma skin cancers in immunocompetent hosts. Int J Mol Med. 2000; 5(4):405-414.
32. Sjalander A, Birgander R, Hallmans G, et al. p53 polymorphisms and haplotypes in breast cancer. Carcinogenesis. 1996; 17(6):1313-1316.
33. Weston A, Pan C, Ksieski HB, et al. p53 haplotype determination in breast cancer. Cancer Epidemiol Biomarkers Prev. 1997; 6(2):105-112.
34. Wang-Ghorke S, Relobeck TR, Besenfelder W, Kreinberg R, Runnebaum IB. p53 germline polymorphisms are associated with an increased risk for breast cancer in German women. Anticancer Res. 1998; 18(3B):2095-2099.
35. Suspitsin EN, Buslov KG, Grigoriev MY, et al. Evidence against involvement of p53 polymorphism in breast cancer predisposition. Int J Cancer. 2003; 103(3):431-433.
36. Sun YS, Zhao Z, Yang ZN, et al. Risk factors and preventions of breast cancer. Int J Biol Sci. 2017; 13(11):1387–1397.
37. Khalis M. Risk factors for breast cancer among Moroccan women in the Fez region, Morocco. Public health and epidemiology. Thesis for obtaining a doctorate in epidemiology, University of Lyon. 2019; 185 p.