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Breast Cancer Analysis in 49 Countries in Relation to Iron Deficiency Anemia (IDA), Chlamydia and HIV Infections

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ABSTRACT

Background: *Iron deficiency anemia (IDA), chlamydia and HIV infections were found to be directly correlated with prostate cancer (PCa).*

Objective: *To determine if the same diseases were correlated also with breast cancer (BCa).*

Material and Methods: *Among the 191 countries listed by WHO, the analysis was conducted in 49 countries with an approved cancers and diseases registry. BCa values in terms of Age Standardized Death Rate x 100000 people (ASDR) in the years 2000, 2010, and 2016 were compared in relation to IDA, HIV, and chlamydia infections.*

The ecological, demographical/social, economical and environmental variables (in total 17) were also used to determine a possible correlation with BCa. The Stepwise analysis and the Prevision profiler method were used to determine the correlations between all the variables and BCa.

Results: *A significant reduction of ASDRs for BCa was shown (-15.8 %) despite the increase in female population (+17.8). The correlation of BCa in 2016 was significantly positive for HIV and chlamydia in 2000, whereas IDA seems to have no impact on the cancer. In terms of ecological variables, the % of forest in the country, the forests as Km^2/1000 inhabitants, and surprisingly the particular matter (PM2.5 and PM10 in mcg/m^3) were found also to have some protective effect.*

Conclusion: *The ASDR of BCa in 2016 was shown to be directly correlated with ASDRs of HIV and Chlamydia in 2000 but not in the following years indicating a causative role.*

Keywords

Breast cancer, HIV, Chlamydia, Prostate cancer.

Introduction

In a recent paper [1], the ASDRs (Age Standard Death Rates x 100000 people) for prostate cancer (PCa) in 2016 were found to be significantly correlated with Iron deficiency anemia (IDA), with HIV in males, and also with Chlamydia in females in 2000.

The hypothesis was that a sort of road map can be tracked, starting with IDA which causes immune depression followed by HIV and/or Chlamydia infections ending up 16 years later with a death for PCa [1].

Similarities of PCa and breast cancer (BCa) in terms of common genetic, biochemical and epidemiological features have been described [2-4] showing a very high similarity in the pathogenesis of the two diseases [4,5]. The aim of our study was to analyze whether IDA, HIV and chlamydia infections can determine the risk of BCa. Some of the most common ecological and environmental variables were also considered based on a previous study on life expectancy (LE) [6].

Material and Methods

Criteria of choice for the variables and time frame

The Age-Standardized Death Rate x 100000 population (ASDRs) for BCa and PCa were considered. In particular, ASDRs values were chosen because they are free of the bias related to the age distribution unlike crude data or prevalence/incidence measures. The ASDRs data listed as Global Health Estimates 2016 published in 2018 were used, limited to females [7], and: to the time frame from 2000 to 2016. Values of IDA, HIV/AIDS, and Chlamydia were considered in the period of 2000, 2010, and 2016, together with ecological, environmental and demographic variables limited to 2106 [8,9].

The list of the 49 SC countries

Armenia, Australia, Austria, Bahamas, Belgium, Brazil, Brunei, Canada, Chile, Croatia, Cuba, Czechia, Denmark, Estonia, Finland, France, Germany, Grenada, Guatemala, Hungary, Iceland, Ireland, Israel, Italy, Japan, Kyrgyzstan, Latvia, Lithuania, Luxembourg, Malta, Macedonia, Mauritius, Mexico, Moldova, Netherlands, New Zealand, Norway, Romania, Saint Vincent & Grenadinas, South Corea, Trinidad & Tobago, United Kingdom, USA, Uzbekistan.

Data collection

The values up to the fourth decimal place were taken from the WHO records. For the ecological, environmental, and demographic variables were considered only the values of 2016 because of very high correlation ($r^2 > 0.9$) with the previous years.

Criteria of choice of the countries

The data used for correlations were relative to the 49 countries (selected countries or SC) considered by the WHO "*with high completeness and quality of cause-of-death assignment*" that "*may be compared and time series may be used for priority setting and policy evaluation"* [7].

For the same 49 countries the following 17 variables (ecological, environmental, and demographic) were considered, taken by CIA World Factbook 2016 [8] and from the Atlante Geografico DE Agostini 2016 Ed De Agostini Novara Italy [9].

Within 191 countries with all the available data the following variables were chosen:
Life expectancy (LE): years
Population density: as number of subjects/km^2.
Urban population: as % in comparison to the total population.
GDP/inhabitant (Gross Domestic Product/inhabitant) as total values/inhabitants (USD) of goods and final services related to economical activities, capital investments.
Unemployment: as % of people looking for a job in relation to the labor force.
GDP 1: GDP rate as % in relation to primary industry bound to agriculture, forests, livestock, fishing.
GDP 2: GDP rate as % in relation to industry, mining and construction industry.
GDP 3: GDP rate as % in relation to commerce, transportation, communication, tourism, insurance.
GDP 2+3: sum of the rates as % related to GDP 2 + GDP 3.
Education: as % of the investments in public and private instruction in relation to GDP.
Hospital beds: number of hospital beds/1000 inhabitants.
PM: particulate matter (PM2.5 and PM10) in mcg/m^3 measured in cities with > 100,000 inhabitants.
Forests: rate as % of country surface covered by forests.
Forests Km^2: square kilometers of forest/1000 inhabitants.
Cars: number of cars/1000 inhabitants.
Cell: number of mobiles/1000 inhabitants.
Internet: number of people connected to internet/1000 inhabitants.

Statistical evaluation

For all the variables the mean values and dispersion indexes were calculated. Correlations between BCa and PCa in terms of r^2 were determined. The Mann-Whitney U test was used to calculate the difference in ASDRs among the periods (2000-2016).

The Stepwise analysis followed by the Prediction profiler fitting were used [10,11] to assess the relation of all the variables with BCa. The JMP14 Pro of SAS Institute were used for the analysis.

Results

Correlation between BCa and PCa

The ASDRs of the two cancers are reported in Table 1.

Type of Cancer	Years			%
	2000	2010	2016	2016 Vs 2000
BCa (females)	21.37 ± 7.060	18.55 ± 5.165 [a]	18.01 ± 5.3970 [a]	-15.8
PCa (males)	23.79 ± 16.114	22.53 ± 18.254 [a]	20.26 ± 15.547 [a b]	-14,8
r^2	0.4862[c]	0.4464[c]	0.6570[c]	

Table 1: ASDRs of Breast cancer (BCa) and prostate cancer (PCa) between 2000 and 2016: mean values ± SD and relative correlations (r^2). a: Mann-Whitney U test vs 2000 $p<0.05$; b: Mann-Whitney U test 2010 vs 2016; c: $p < 0.001$.

A significant reduction of ASDRs was shown during the time between 2000 and 2016; for BCa no significant decline was found when comparing the years 2010 and 2016. The two types of cancer were significantly correlated in all the periods considered. In the same period the ASDRs for IDA, chlamydia and HIV were calculated in females and reported in Table 2.

Disease	Years			% 2016 Vs 2000
	2000	2010	2016	
IDA	0.686 ± 1.0303	0.671 ± 0.9845	0.570 ± 0.8357[a b]	-16.9
Chlamydia	0.024 ± 0.0253	0.015 ± 0.0143[a]	0.010 ± 0.0103[a b]	-58.3
HIV/AIDS	2.88± 9.004	2.09 ± 4.463[a]	2.11 ± 5.522[a]	-26.7
Female population x 10^6	662.603	709.510	737.676	+17.8

Table 2: ASDRs for IDA, chlamydia, and HIV: mean values ± SD in the

years between 2000 and 2016 and total female population in the 49 SC. a= Mann-Whitney U test Vs 2000 $p<0.05$; b = Mann-Whitney U test 2010 Vs 2016 $p<0.05$.

Comparing the years 2000 and 2016, the female population was increased whereas the ASDRs of the 3 diseases decreased at different rates. Chlamydia was the only disease showing a significant progressive reduction among the years, whereas for IDA no significant difference was found between years 2000 and 2010; for HIV there was no difference between years 2010 and 2016.

The values of the total female population, ecological, environmental, and demographic variables - limited to 2016 - were listed in Table 3 comparing the 49 SC with the rest of 142 countries.

Variable [a]	Measure	49 SC	Other 142 countries
		Mean ± SD	Mean ± SD
Life expectancy (LE)	Years	80.9 ± 3.67[b]	69.85 b c ± 4.59
Population density	Subjects/Km^2	165.7 ± 222.35	153.3 ± 482.45
Urban population	% of the total	70.7 ± 19.22	50.1 ± 21.75[c]
GDP/inhabitants	USD	32253 ± 25339.2	6845 ± 11308.6[c]
Unemployment	% people	8.8 ± 6.18	10.2 ± 8.31[c]
GDP 1	% of total GDP	8.4 ± 9.34	33.1 ± 25.01[c]
GDP 2	% of total GDP	23.3 ± 6.88	20.0 ± 9.69
GDP 3	% of total GDP	68.3 ± 11.53	48.9 ± 21.12[c]
GDP 2+3	% of total GDP	91.7 ± 9.03	66.9 ± 25.11[c]
Education	% of total GDP	5.3 ± 1.71	4.4 ± 2.40[c]
Hospital beds	Number/1000 inhabitants	4.7 ± 2.28	2.3 ± 2.13[c]
Forests	% of country surface	33.0 ± 20.38	29.8 ± 23.40
Forests Km^2	Square kilometers/1000 inhabitants	10 ± 16.70	13.06 ± 35.00
Particulate matter	mcg/m^3	29.1 ± 16.2	50.6 ± 39.83[c]
Cars	Number/1000 inhabitants	361.7± 187.98	86.5 ± 124.74[c]
Mobile phones (Cell)	Number/1000	1173.2 ± 239.51	993 ± 436.96
Internet	Number of connection/1000 inhabitants	722.2 ± 198.77	319.4 ± 241.54[c]
Total population	Number of females x 10^6 in 2016	743.109	3517.989
% of total population in the 191	21.1	79.1	100.1

Table 3: Ecological, demographic/social, economical, and environmental variables in the year 2016; comparison between the 49 SC and all the other 142 countries listed in the WHO report of 2016: mean values ± SD.

a= see material and methods for details; b = females LE- all the other values are related to the total population (males and females); c = Mann-Whitney U test 49 SC vs other 142 countries $p < 0.05$.

For most of the variables the differencs between the two sets of countries were statistically significant apart from population density, GDP 2, % of forest, forest Km^2, and mobile phones.

Regression analysis

In the Stepwise regression all the variables (diseases, ecological, demographic/social, and environmental variables) were considered together. The relative value of the interconnection with BCa are summarized in Table 4.

Variable	Estimate	nDF	SS	"F" ratio	Prob > F
Life expectancy (LE)	0	1	3.7405	0.921	0.34983
Population density	0	1	0.1351	0.032	0.86064
Urban population	0	1	0.5337	0.126	0.72681
GDP/inhabitant	0	1	0.3092	0.073	0.79044
Unemployment	0	1	1.4989	0.358	0.55694
GDP 1	0	1	0.8917	0.211	0.65118
GDP 2	0.1780	1	19.1563	4.738	0.04231
GDP 3	0	1	0.7856	0.186	0.67140
GDP 2+3	0	1	0.9068	0.215	0.60840
Education	0	1	1.2046	0.287	0.59885
Hospital beds	0	1	0.04243	0.010	0.92165
Forests	-0.1283	1	121.1908	29.997	2.78e-5
Forests Km^2	-0.0617	1	25.1051	6.210	0.02211
PM	-0.2548	1	183.8553	45.477	1.92e-6
Cars	0.0141	1	56.9223	14.080	0.00135
Cell	0.0012	1	1.3996	0.346	0.56320
Internet	0	1	2.3774	0.575	0.45813
IDA 2000	0	1	0.3349	0.079	0.78209
IDA 2010	0	1	0.0341	0.009	0.92448
IDA 2016	0	1	0.4160	0.098	0.75783
Chlamydia 2000	113.5492	1	61.2252	15.152	0.00098
Chlamydia 2010	-66.6701	1	13.9061	3.455	0.07864
Chlamydia 2016	89.0407	1	14.9070	3.687	0.06997
HIV/AIDS 2000	-0.6641	1	17.3431	4.290	0.05220
HIV/AIDS 2010	1.8899	1	22.4475	5.552	0.02934
HIV/AIDS 2016	0.3360	1	1.4995	0.371	0.54972

Table 4: Stepwise regression considering all the variables (diseases, ecological, demographic/social, and environmental variables of the 49 SC.

Estimate: The current variable estimate, which is zero when the case effect is not currently in the model; SSE: Sum of squared errors for the current model; nDE: Error degrees of freedom for the current mode.

Among all the variables, those which significantly describe the correlation were respectively HIV/AIDS 2000/2010 ($p=0.05220$, $p=0.02934$), Chlamydia 2000 ($p=0.00098$), % GDP 2 ($p=0.04231$), Forests ($p =0.00003$), PM ($p<0.00000$), Cars ($p=0.00135$) and Forest Km^2 ($p=0.02211$).

For these variables the fitting RS square was very high (0.902; $p <$

0.001) as represented in Table 5.

2010	LogWorth[a]	P value
PM	5.717	0.00000
Forests	4.556	0.00003
Chlamydia 2000	3.009	0.00098
Cars	2.870	0.00135
Forests Km^2	1.665	0.02211
HIV/AIDS 2010	1.532	0.02934
GDP 2	1.374	0.04231
HIV/AIDS 2000	1.282	0.05220
Chlamydia 2016	1.155	0.06997
Chlamydia 2010	1.104	0.07864
HIV/AIDS 2016	0.260	0.5472
Cell	0.249	0.56320
Analysis of variance p < 0.001		

Table 5: Summary of fits for the significant variables describing the correlation with BCa.
a: LogWorth adjusts p-values to provide an appropriate scale of importance.

The variables describing the fit were confirmed to be PM, Forests, Chlamydia 2000, cars, Forests Km^2, HIV, GDP 2, and HIV 2000, whereas all the others do not significantly explain the BCa events.

The Prediction Profiler that describes the correlations of each of the variables is reported in Figure 1 and 2.

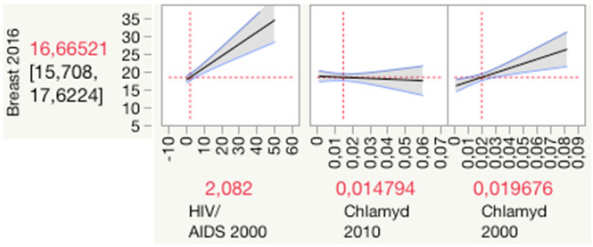

Figure 1: Prediction Profiler of diseases in comparison to BCa.

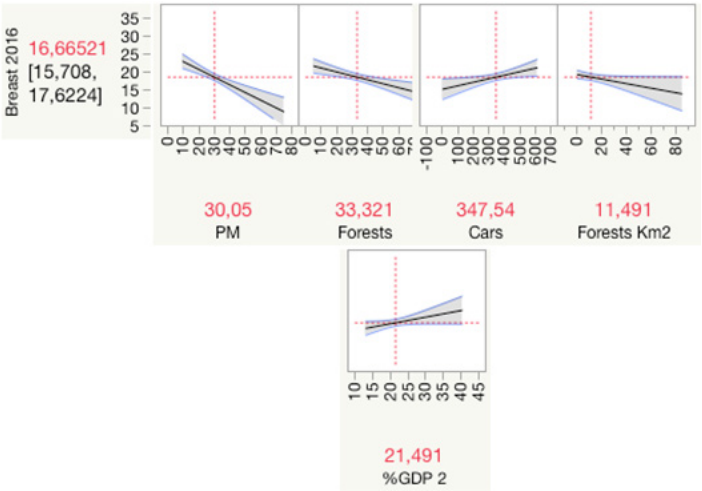

Figure 2: Predicition profilers of echological/economic variables in comparison to BCa.

The average values are reported in red; BCa is reported with the relative intervals.

Among the variables concerning the diseases, the most consistent to describe the correlation with the ASDRs of BCa 2016 were chlamydia and HIV/AIDS in 2000, which increase the proportion of death for BCa. HIV/AIDS in 2000 were much more prominent compared to Chlamydia in 2000, whereas Chlamydia in 2010 loses its importance.

In the case of the other variables, the increase of % GDP 2 seems to favor the BCa despite with a minor impact. At the opposite, the increase of PM was consistent with the decrease of BCa, as was for the increases of the territory covered by forest (%) and forests Km^2/1000 inhabitants.

Among these last variables, the PM was the more important, whereas forests and forests Km^2 and GDP 2 seemed to have a much lower impact even if significant.

Discussion

The results of the present investigation have the limitation -which is clearly described in Tables 2 - 3 due to the differences between the 49 SC and the rest of the 142 countries, particularly for life expectancy, GDP, PM, and for those variables characteristic of developed countries (cars, mobile phones, internet connections).

This means that the results cannot be taken as a worldwide picture but have to be considered within the limit of the 49 SC which represent about 21% of the total female population. Another limitation can be due to the data retrieved from the WHO records, which may have some intrinsic bias in the definition of the ASDRs for a given disease, since the death attributed to any specific illness may be due also to other concomitant pathologies.

Furthermore, for chlamydia was not possible to differentiate between *Chlamydia trachomatis* or *Chlamydia pneumoniae* since no data were available.

Despite these limitations, some interesting observations can be drawn from this analysis. Between 2000 and 2016 in the 49 SC the ASDRs of the 3 diseases tested (IDA, Chlamydia, HIV/AIDS) were significantly reduced whereas the female's population increased (+17.8 %). This indicates a general improvement of LE which can be interpreted also as an increase of the survival due to therapy.

These improvements seem related also to some of the variables mirroring -at least in part- the "wellbeing status" as represented by hospital beds number, cars, Internet connection, and education.

Time frame for BCa

The period of 16 years can be considered a sufficient period of time from the diagnosis of BCa up to the death [1]. The death for BCa is known to be determined by the cancer type, stage, race, age, and therapy but reports focusing on all these variables

were available only for a few countries. The data concerning the survival rate (approximately between 80 to 90 % at 10 years after the diagnosis) could give some more precise indication. Unfortunately, the survival rate were available only for some of the 49 SC and the period of 16 years can be considered merely as an hypothesis because longer period may be needed. However, the use of ASDRs minimize this possible bias.

One common aspect for many countries is the population screening for BCa, which allows the detection of more cancers at early stage, with the consequence that the period between diagnosis and death is increasing. This aspect was emerging in the present study (Table 1).

In relation to the 3 diseases under analysis, the first observation concerns IDA which seems to have no correlation with BCa, whereas HIV and chlamydia infections were emerging as important risk factors, and showed a significant correlation when the infections were contracted in 2000, namely 16 years before the death caused by BCa.

HIV/AIDS responsibility

In WHO records HIV and AIDS were considered together. However, a distinction should be made between HIV and AIDS because the first can be asymptomatic, and practically no pharmacological treatment is used, whereas the latter is usually treated with drugs. In any case, both represent an HIV contamination which can be the ground for many other diseases.

The relationship between HIV/AIDS and cancers has been already established for Kaposi's sarcoma and non-Hodgkin's lymphoma, and some other cancers but BCa was never mentioned [12].

Recently, some author defined that BCa is not a HIV-associated malignancy, and no difference occurs among women with or without HIV [13] and the relationship with HIV seems controversial.

However, some authors found that BCa cells were labeled with an anti-HIV-1 identifiable though Rakowicz markers (RAK markers) which have in common epitopes with the envelope protein gp120 of HIV-1 [14]. Recently, the incidence of BCa in women with HIV was growing (especially in sub-Saharan Africa) and patients experience a worse chemotherapy toxicity also [15]. Conversely, some authors found the infection did not facilitate and increase in breast cancer (Western countries of Africa) and the incidence was the same or even less compared to the general population [16,17].

In the present analysis, the disease detected in 2000 was significantly correlated with BCa, showing in the Profiler analysis the highest correlation despite seems to lose some importance in 2010, and almost with no influence in 2016 (Table 5).

The interpretation may be that HIV is a "marker infection" that needs more than 6 years before compromising the survival following the a diagnosis of BCa. On the other side, it may behave as a cause for BCa that needs time to become evident. In other terms, the HIV in 2010 could become correlated when data on BCa will be recorded in the future. The conclusion is that HIV infection seems to be causative for BCa or at least facilitative.

Within the 49 SC countries there were 25 countries showing -in the period 2000 and 2016- a reduction of BCa (from 23.7 ± 5.95 to 17,9 ± 3.68 respectively) and 14 countries where BCa was increased (from 16.5 ± 7.83 to 18.0 ± 8.20 respectively). These ASDRs in 2000 were statistically significant (Mann-Whitney U test $p<0.05$) whereas in 2010 and 2016 were comparable.

In these two sets of countries, those showing an increase of BCa were characterized by significantly higher values of HIV and lower values (Mann-Whitney U test $p <0.05$) for LE, GPD, cars, and internet connections, which can be considered variables connected to the "well-being" status. Chlamydia ASDRs were almost identical.

Chlamydia responsibility

Chlamydia was considered by WHO the most important sexual transmitted disease (STD) affecting > 130 million and recognized to have a direct impact on infertility, pregnancy, cancer, and to facilitate the sexual transmission of HIV [18]. It was supposed that *C. trachomatis* was associated with the risk of cervical cancer based on meta-analysis studies [19] and also with ovarian cancer [20], while *C. pneumoniae* may be associated to a moderate increased risk of lung cancer, based upon the increase of IgA antibody titer and setting the risk values at ≥ 16 [21].

For these reasons WHO planned a program consisting of 4 phases, where in phase 2 indicates that among the usual measures (e.g. condoms, antibiotics) the intervention against chlamydia with vaccines should be appropriate.

In the present study, considering the Profiler analysis Chlamydia in 2000 was found to be correlated with BCa. Compared to HIV, it seems that this infection is more causative than falicitative since according to the Profiler analysis it loses any correlation in 2010 and 2016 (Table 5 and Figure 1).

Ecological variables

Both in the Profiler and Stepwise analysis an inverse correlation was shown between BCa and forest (both as % of territory covered or by Km^2 forest/inhabitants). The forest presence is known to increase the O_2 and reduce the CO_2 concentration making the environment more healthy. This could be the simplest explanation of the negative correlation with BCa. However, the impact of CO_2 is controverial since an increased level of intrapulmonary CO_2 was documented as a risk factor for the development of lung cancer [22], and high CO_2 levels seems to protect *in vitro* lung cancer cells from anticancer agents [23]. No mention was found in the literature on the relationship of CO_2 or O_2 with BCa.

Surprisingly, the particulate matter (PM) showed to slightly reduce the risk of BCa. This finding has to be taken with prudence since some peculiar aspects need to be clarified.

The first is that these values were in relation to cities with > 100000 inhabitants which represent only a part of the total population, so the variable may lose some of its relevance.

Furthermore, PM is a complex mixture of chemical components to be considered together with many gas such as methane (CH_4), ozone (O_3), carbon monoxide (CO), sulfate (SO_3), nitrogen dioxide (NO_2) aerosols and all the possible widespread air pollutants present wherever people live.

These particles are able to penetrate deeply into the respiratory tract and therefore constitute a risk for health by increasing mortality from respiratory infections and diseases, lung cancer, and selected cardiovascular diseases. The WHO estimated in 2000 that the exposure to PM caused 800,000 deaths and 6.4 million years lived with disability (YLDs) and also that the developing countries accounted for two thirds of this burden [24].

In general, the WHO stated that there is no evidence of a safe level of exposure to PM or a threshold below which no adverse health effects occur, and globally > 30 % of the population lived in areas exceeding the WHO level target of 35 mcg/m^3. This safe limit is reached only in some of the 49 SC countries and the condition is even worse in the remaining countries (Table 2).

Furthermore, the data recorded in this study represents an average of the cities where the monitoring stations were available. In order to present air quality largely representative for human exposure, measurements of residential areas, commercial and mixed areas were used. Stations characterized as particular "hot spots" or exclusively industrial areas were not included and in some of the country's particles < PM10 were largely based on estimates [25].

There are several studies conducted in different parts of the world showing the negative effect of PM on health [26-28] but still there is the need for further research to define the long-term toxicity [29] and whether some components and sources of PM may be more toxic than others [30]. The indoor air pollution is also something that should be considered since it is causing apparently 3.7 million deaths [31].

In the WHO Update report of 2016 [32] a comparison was done to determine the trend of PM in the world between 2008 and 2013, showing an estimation of 5 % increase, despite some fluctuation within the macro-regions that were analyzed. In the same period the LE was increased also, in practically every of the 191 countries considered in the study, whether the PM was increasing or not.

This indicates that more precise measures should be taken in the management of PM, as in the present scenario it seems to show that it has a positive effect on the LE.

Relationship between BCA and PCa

The similarity between BCa and PCa was evident in terms of ASDRs decrease in both diseases comparing years 2000 Vs 2016 (respectively -15.8 % and -14.8 %). A part from some hypotheses, there are no clear explanations for this similarity.

Particularly, the hypothesis that oxidative stress may have an important role addresses the attention to the diet focusing the role of fats, phytoestrogens and DNA oxidative damage [4,5,33]. Women in the fertile period are under oxidative stress for at least half of the menstrual cycle, mainly in the estrogenic phase [34], and practically for all the phases in case of oral contraceptive treatment [35].

It is also important to realize that during the menopause, the condition of oxidative stress is quite a common event in at least 50 % of women [36]. This means that females are at risk of generating the groundwork for HIV and chlamydia infections.

In general, it seems that females are more affected by the oxidative stress than males. However, in the periods from 2000 to 2016, the ASDRs for PCa were found constantly higher than those for BCa (from 11% to 20 %; Table 1) meaning that events other than oxidative stress may be determinant for the death.

Conclusion

In the 49 SC, the values of ASDRs of HIV/AIDS and Chlamydia infections occurring in 2000 were found to be correlated with ASDRs of BCa in 2016. Among the variables related to the environment and ecology, the PM concentration and the presence of forests seem negatively correlated and emerging as protective.

Because of these events, it is becoming important to protect women from HIV/AIDS and chlamydia: the simplest method consists of the use of condoms (and avoiding saliva transfer) while waiting for the preparation of safe vaccinations.

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