

SOCIOECONOMIC ANALYSIS OF BREAST CANCER BETWEEN COUNTRIES, 2012-2018 PERIOD

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ABSTRACT

The breast cancer among women is a critical health and social issue worldwide. The goal of this study is to investigate breast cancer mortality in association with breast cancer incidence and socioeconomic factors between countries. Data of breast cancer incidence and mortality are from IARC/WHO for 2012 and 2018 and measured in age-standardized rate per 100,000 persons per country. Data of socioeconomic factors and diagnostic equipment are from The World Bank, United Nations and WHO. Results show that a 1% higher level of breast cancer incidence, it increases the expected mortality by 0.79% in poor countries, by 0.50% in countries with average in-come and by 0.31% in rich countries. These findings suggest that the risk of breast cancer mortality is increasing worldwide. These results explain trends of breast cancer between countries that can be used to gain insights at country-level for designing social “best practices” for health improvement of countries. However, these conclusions are of course tentative. There is need for much more detailed research into the relations between socioeconomic factors and breast cancer.

KEYWORDS: Breast Cancer, Gross Domestic Product per Capita, Health Policy

JEL codes: I14, I15, I18, I39, O10, O3, O55, Q50

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1 GOAL OF THIS INVESTIGATION

The risk of mortality in breast cancer among women is a critical health issue worldwide. Scholars argue that breast cancer mortality rates have decreased in many advanced countries overall. However, about 50% of world population in 2017 was in poor and developing countries (more than 3,652 million with 50.24% female) and breast cancer mortality rates differ among nations also because of socioeconomic factors (cf., Bray et al., 2018).

About 40 years ago, Myron Moskowitz argued “How Can We Decrease Breast Cancer Mortality?”, suggesting: “The data reviewed indicate that early detection is vital in decreasing breast cancer mortality. Early biopsy of minimally suspicious findings is important. Mortality can be reduced by perhaps 50 percent through physical examination and mammography.” (Moskowitz, 1980, pp. 276-277). Although efforts in this direction of healthcare system in many countries, the risk of breast cancer mortality and incidence is still high in both rich and poor countries (Canto et al., 2001). Hence, Moskowitz’s question in 1980 is still a current problem in 2019.

The purpose of this study is to analyze the risk of mortality in breast cancer, both in rich and poor countries, though a global analysis of this disease per nation to clarify comprehensive trends between countries and support appropriate health policies.

2 LITERATURE OF RELATED STUDIES

In medicine, cancer is an organism, which lives off a host organ, growing by bio-genetic-molecular mechanism (Coccia, 2014). In the world, 9.6 million people died of cancer in 2018 – more than from HIV, malaria and tuberculosis combined. The incidence of cancer is estimated to double by 2030s, with most of these cases expected to occur in low-to-middle income countries: in particular, 60% of cancer cases and 75% of cancer deaths occur in poor countries (cf., Chagpar and Coccia, 2019; Prager et al., 2018). Table 1 shows that lung and breast cancer have the highest mortality rate worldwide (cf. also, Bray et al., 2018; Parkin et al., 2005).

Table 1. Incidence and mortality of big 8 cancers in 2018 (worldwide data for both sexes, all ages)

Cancer	Incidence ASR (W)*	Mortality ASR (W)*
Lung	22.5	18.6
Breast	46.3	13.0
Colorectum	19.7	8.9
Prostate	29.3	7.6
Stomach	11.1	8.2
Pancreas	4.8	4.4
Ovary	7.8	3.9
Liver	9.3	8.5

Note: *Age-Standardized Rate-ASR (W): A rate is the number of new cases or deaths per 100,000 persons per year. An age-standardized rate is the rate that a population would have if it had a standard age structure.

Source. World Health Organization, International Agency for Research on Cancer.

<http://apps.who.int/gho/data/view.main.CTRY2450A?lang=en> (accessed January 2019).

The R&D in oncology is supporting the convergence of different research fields, such as genetics¹, genomics², nanotechnology, nanomedicine, computer sciences, etc., that are generating new techno-logical pathways for diagnostics and therapeutics (Coccia, 2014; 2016; 2018; 2019; Coccia & Wang, 2015)³.

Breast cancer is the most frequent cancer worldwide among women (see tab. 1; cf., Chagpar & Coccia, 2019). Studies based on advanced countries show that the incidence of breast cancer is increasing (Coccia, 2013). In fact, breast cancer incidence tends to be higher in more developed countries due to delayed childbearing, a higher use of hormone replacement therapy and oral contraceptives, a higher rate of screening, and improved tumor registries (Coccia, 2013). Some studies have also argued that higher income countries may generate a higher fat diets and an increased rate of obesity, both correlated with higher breast cancer incidence rates. In general, scholars note that many Western populations have a higher incidence rate of breast cancer than poor regions in Africa and Asia (Coccia, 2013; cf., Chagpar & Coccia, 2019; Engmann et al., 2017). Finally, Bellanger et al. (2018) show that breast cancer incidence increases with higher income levels in all ages. However, women in poor countries have a relatively higher burden of breast cancer mortality, particularly women younger than age 50 years.

3 STUDY DESIGN

Sample of countries

Global data of this study are divided according to the classification by The World Bank⁴ to create homogenous groups for analysis, given by

- N1=78 low-to-middle income countries (LMICs)
- N2=50 upper-to-middle-income countries (UMICs)
- and N3=63 high income countries (HCIs)

These three groups are analyzed over a period from 2012 to 2018.

Measures

- o Breast cancer incidence and mortality are measured in age standardized rate per 100,000 population and data were obtained from IARC/WHO⁵.
- o Socioeconomic factors of nations under study here are Gross Domestic Product (GDP) per capita in 2015 year and Total Population 2017 using data obtained from The World Bank⁶.
- o Screening for detection of breast cancer is measured with density of mammographs (per million females aged between 50 and 69 years old) using data of 2014 from the World Health Organization⁷.

Methods for the analysis of data

Data, in the presence of not normal distribution, are transformed in log scale. Our samples N1, N2 and N3 were analyzed with descriptive statistics, partial correlation (using as control variables density of mammographs 2014 and GDP per capita 2015) and regression analyses. Some variables of the study here have a time lag to logically assess the effects on incidence and mortality in breast cancer. Linear regression is used to analyze the predicted value of the dependent variable of breast cancer mortality in 2018 on breast cancer incidence in 2012

¹ Genetics studies the molecular structure and function of genes in the context of a cell or organism.

² Genomics is a discipline in genetics that studies the genomes of organisms. In particular, it determines the entire DNA sequence of organisms and fine-scale genetic mapping efforts.

³ cf., Coccia 2012; 2012a; 2015a; 2017; 2018a; 2019a.

⁴ <https://data.worldbank.org/indicator/> (accessed August 2018).

⁵ <http://gco.iarc.fr/>

⁶ <https://data.worldbank.org/indicator/> (accessed August 2018).

⁷ <http://apps.who.int/gho/data/node.main-emro.510?lang=en> (accessed November 2018).

(independent variable). The study also calculates from this model a *new variable* y^* given by predicted values of breast cancer mortality in 2018 on breast cancer incidence in 2012 (the first stage). Then, in the second stage, using a linear regression model, it is estimated a relationship between them using the variable y^* on GDP per capita in 2015 to assess future trends in breast cancer between countries. The analysis also calculates the burden of population with an increasing risk and decreasing risk of breast cancer considering the population in 2017.

Finally, a paired-Samples t-Test compares two means of variables under study in 2012 and 2018 within the same group of nations LMICs, UMICs and HICs⁸. The purpose of the test is to determine whether breast cancer incidence and mortality are significantly increased or decreased from 2012 to 2018. In particular, the hypotheses are that the paired year means of breast cancer incidence and mortality are equal:

- (null hypothesis), $H_0: \mu_{2012} = \mu_{2018}$ within LMICs, MUICs and HICs versus the hypothesis that paired year means are not equal is
- (alternative hypothesis), $H_1: \mu_{2012} \neq \mu_{2018}$ within LMICs, MUICs and HICs

These results are compared with previous analyses to assess similarities and/or differences for suggesting appropriate predictions for best practices for health improvement.

4 STATISTICAL ANALYSES AND FINDINGS

Table 2. Descriptive statistics

Category			Breast Cancer Incidence 2012	Breast Cancer Incidence 2018	Breast Cancer Mortality 2012	Breast Cancer Mortality 2018
LMICs	N	Valid	73	71	73	71
		Missing	5	7	5	7
	Mean (M)		27.84	30.58	13.53	14.70
	Std. Deviation (SD)		10.67	11.84	5.16	5.81
MUICs	N	Valid	44	45	44	45
		Missing	6	5	6	5
	Mean		42.00	46.08	14.30	15.35
	Std. Deviation		16.49	15.26	5.58	5.85
HICs	N	Valid	54	53	54	53
		Missing	9	10	9	10
	Mean		68.36	71.87	15.18	14.89
	Std. Deviation		21.78	19.96	3.84	4.69

Note: LMICs, low-to-middle income countries
 UMICs, upper-to-middle income countries
 HICs, high-income countries.

Table 2 shows that breast cancer incidence is higher in HICs than LMICs and UMICs both in 2012 and in 2018. The average burden of mortality in 2012 and 2018 also shows a higher level in rich countries than poor countries. However, temporal comparison of the groups of countries under study shows that from 2012 to 2018, breast cancer mortality is increased in LMICs and UMICs, whereas in HICs it has a moderate decline. Temporal variation of breast cancer

⁸ *Abbreviations in the text:* LMICs, low-to-middle income countries; UMICs, upper-to-middle income countries; HICs, high income countries; MPI, mortality-per-incident breast cancer ratio; MMG, mammography; GDP, Gross Domestic Product per capita.

incidence over 2012-2018 shows a general increase worldwide in each group of country under study.

The partial correlation of variables between breast cancer mortality 2018 and breast cancer incidence 2012, controlling density of mammograms (year 2014) and GDP per capita (year 2015) shows a significant high association: LMICs ($r=.75$, $p\text{-value}<.001$), UMICs ($r=.53$, $p\text{-value}<.004$) and HICs (LMICs ($r=.62$, $p\text{-value}<.001$).

Table 3. Estimated relationships

		Unstandardized Coefficients		Stand. Coefficients	t	Sig.	F	Sig.	R ² adj
		B	Std. Error	Beta					
LMICs	<i>Log Breast Cancer Incidence 2012</i>	.790	.084	.753	9.450	.001	89.298	.001	.561
	(Constant)	.025	.275		.089	.929			
UMICs	<i>Log Breast Cancer Incidence 2012</i>	.497	.109	.577	4.577	.001	20.945	.001	.317
	(Constant)	.841	.400		2.104	.041			
HICs	<i>Log Breast Cancer Incidence 2012</i>	.313	.113	.362	2.770	.008	7.672	.008	.288
	(Constant)	1.348	.474		2.847	.006			

Note: The dependent variable is *Log Breast Cancer Mortality 2018*

Explanatory variable is *Log Breast Cancer incidence 2012*

LMICs, low-to-middle income countries; UMICs, upper-to-middle income countries;

HICs, high-income countries.

Table 3 shows estimated relationships of breast cancer mortality in 2018 on breast cancer incidence in 2012. In LMICs, results indicate that a 1% higher level of breast cancer incidence, increases the expected mortality by 0.79% ($p\text{-value} < .001$, $F=89.30$, $sig. =0.001$, Adjusted $R^2=0.56$). In UMICs, results indicate that a 1% higher level of breast cancer incidence increases the expected mortality by 0.50% ($p\text{-value} < .001$, $F=20.95$, $sig. =0.001$, Adjusted $R^2=0.32$). Finally, in rich countries (HICs), results indicate that a 1% higher level of breast cancer incidence increases the expected mortality by 0.31% ($p\text{-value} < .008$, $F=7.67$, $sig. =0.008$, Adjusted $R^2=0.29$). In general, statistical evidence here shows that the breast cancer mortality has an expected increase worldwide, though with a different magnitude that is lower for rich countries, whereas it is higher for poor countries (cf., trends of regression lines are in Fig. 1).

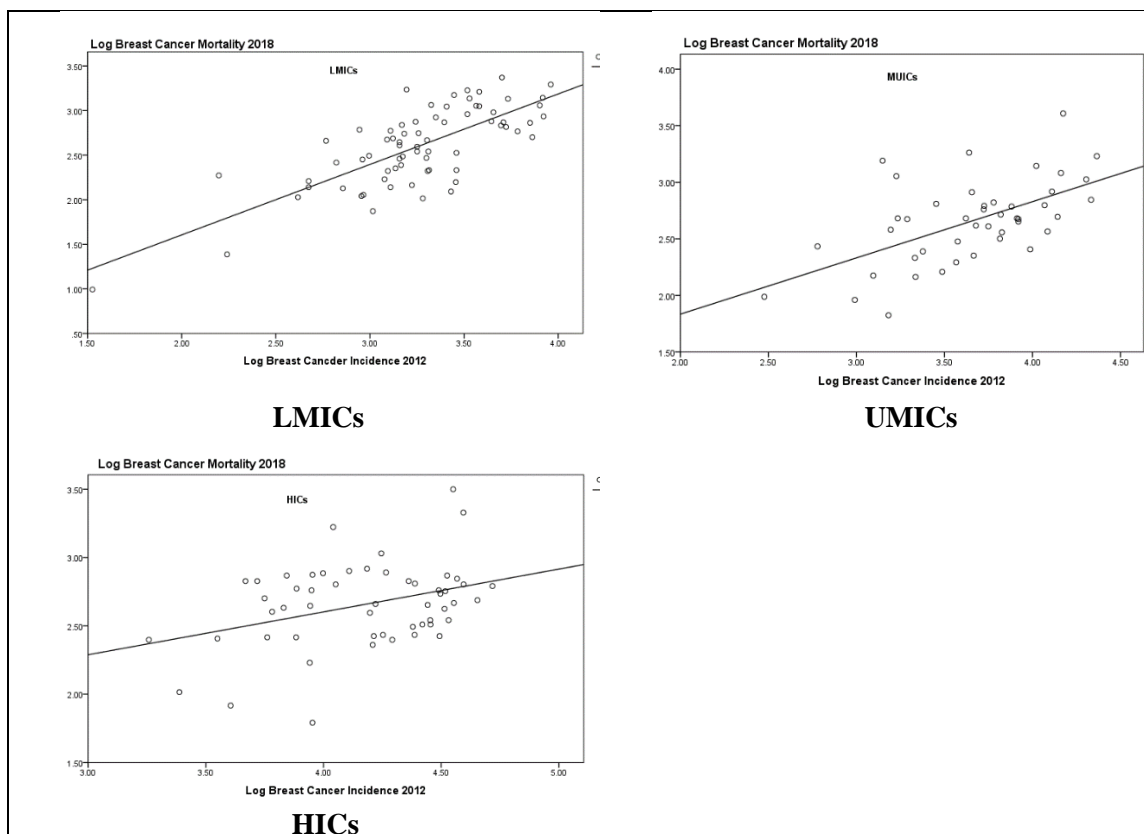


Figure 1. Increasing trends of the risk of mortality in breast cancer across homogenous group of countries.

Moreover, paired samples test shows, from 2012 to 2018, the significant increase of breast cancer mortality ($t_{69}=2.26$, $p\text{-value}<0.03$) and breast cancer incidence ($t_{69}=2.64$, $p\text{-value}<0.01$) in LMICs; in the same period, MUICs have an increase of mortality not significant, whereas the increase of breast cancer incidence is significant ($t_{43}=2.69$, $p\text{-value}<0.01$). Finally, this test shows that in rich countries (HICs), breast cancer mortality from 2012 to 2018 has a not significant decrease, whereas breast cancer incidence has a significant increase ($t_{52}=2.87$, $p\text{-value}<0.006$).

Empirical data also shows that countries reducing breast cancer mortality over 2012-2018 have 42.30% of worldwide population in 2017; whereas the countries increasing breast cancer mortality over 2012-2018 represent 57.70% of worldwide population in 2017. Breast cancer incidence shows a higher difference over 2018-2012 between countries that are reducing incidence (about 40% of worldwide population) and countries that are increasing incidence (roughly 60% of worldwide population).

Finally, the estimated relationship of predicted breast cancer mortality 2018 with breast cancer incidence 2012 (from curve fit of model linear in log scale) on GDP per capita 2015 is significant only in rich countries. In particular, HICs show that a 1% higher level of GDP per capita increases the expected breast cancer mortality (based on breast cancer incidence 2012) by 0.1% ($p\text{-value}<.001$, $F=17.80$, $\text{sig.}=0.001$, $\text{Adjusted } R^2=0.25$). These results seem to confirm that breast cancer mortality in rich countries can also continue to increase in the future (Figure 2).

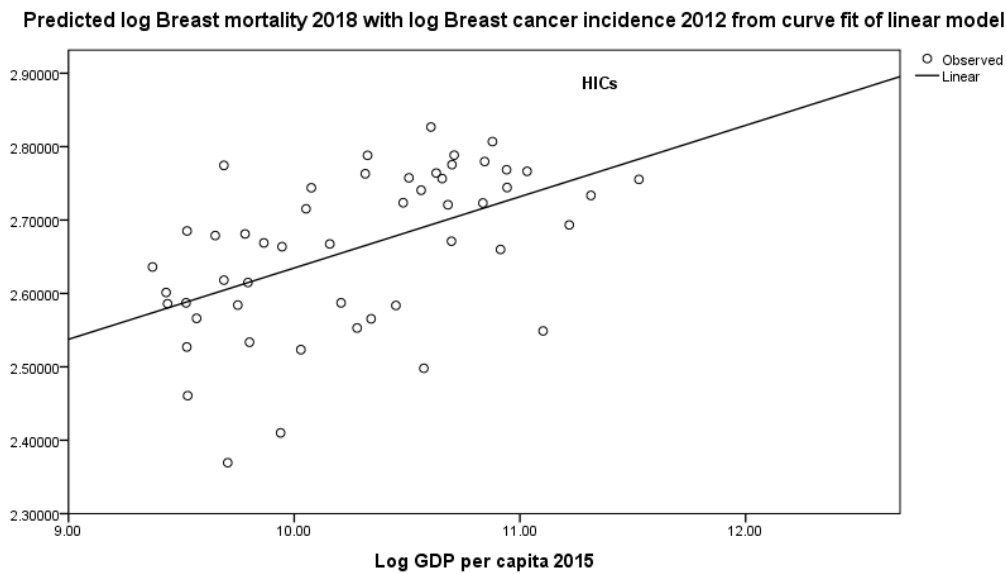


Figure 2. Estimated relationship of expected increase of the risk of mortality in breast cancer on GDP per capita

Figure 3 shows the spatial analysis of the *variation of incidence across countries*. Results reveal a general increase of breast cancer incidence from 2012 to 2018, except in USA, Ecuador, Guyana, Libya, some countries in Central Africa, Saudi Arabia, India, Pakistan, Iraq, Uzbekistan and some other.

Figure 4 shows that the increase of *breast cancer mortality* is mainly in Mexico, some countries of Central America, Venezuela, Colombia, Bolivia, Paraguay, sub-Saharan Africa, India and China.

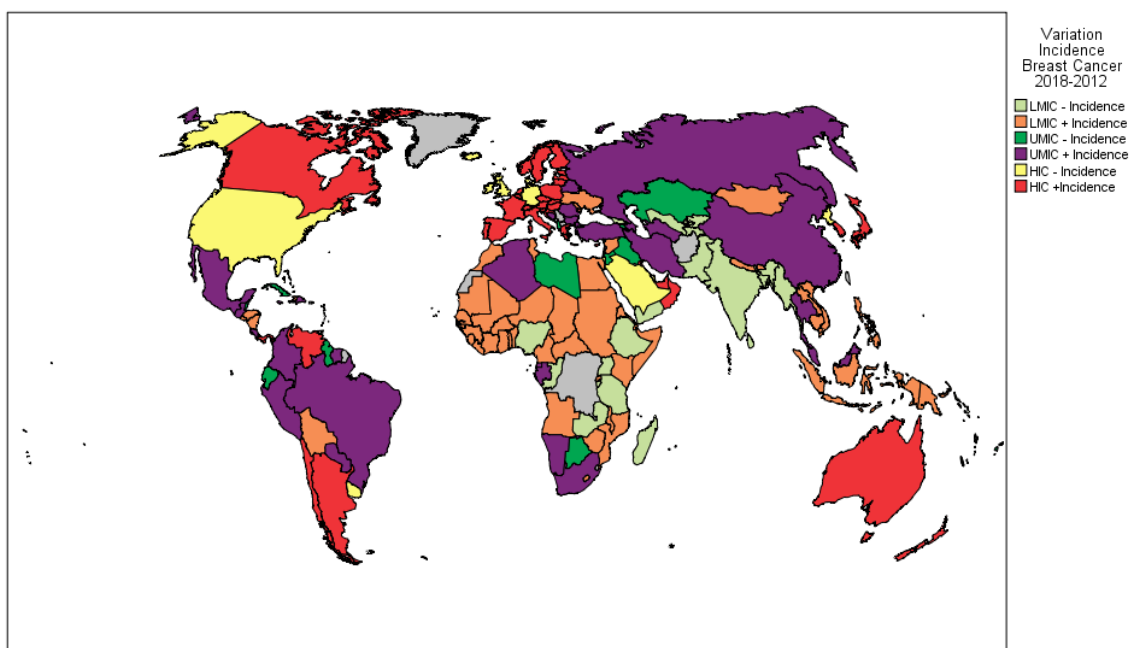


Figure 3. Global map of the variation of breast cancer incidence over 2012-2018 in countries.

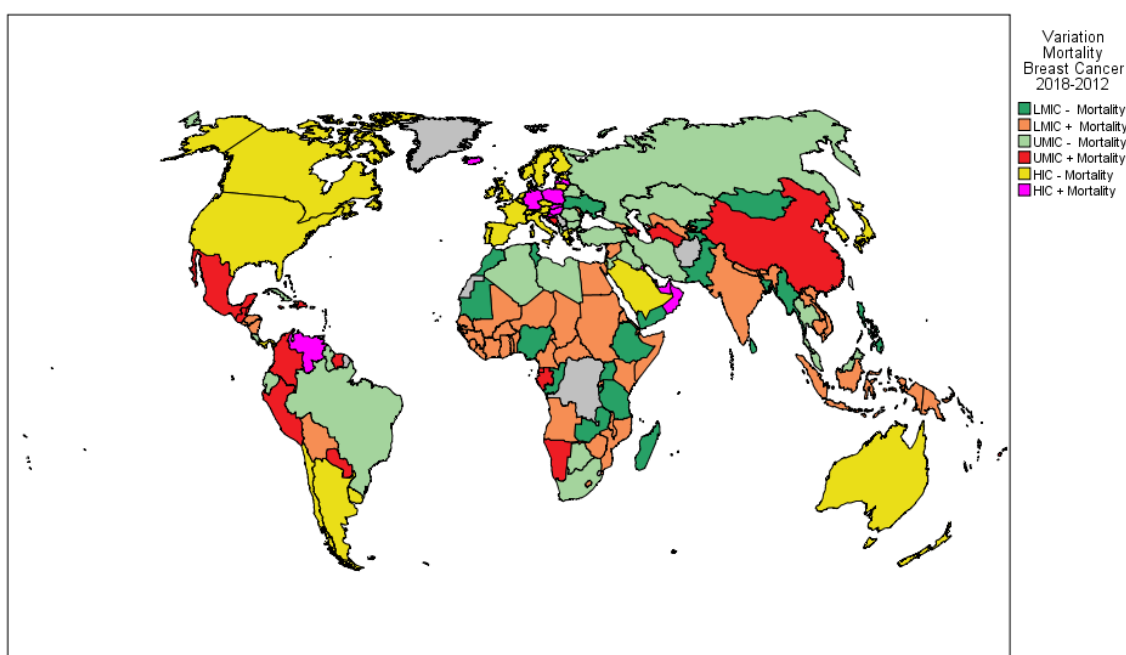


Figure 4. Global map of the variation of breast cancer mortality over 2012-2018 in countries

5 DISCUSSION AND CONCLUDING REMARKS

DeSantis et al. (2017) and Mettlin (1999) argued that breast cancer mortality is declining in the United States and Canada, as well as in other advanced nations because of increasing screening (cf., Brentnall et al., 2018) and new therapies (cf., Bray et al., 2018). The global analysis here reveals that though an improvement of world-wide wellbeing, the risk of incidence and mortality in breast cancer seems to be increased. Countries with a problematic socioeconomic system (e.g., LMICs and UMICs) are at high risk. In particular, in 2017, more than 49% of world-wide population was in LMICs (more than 3,652 million with 50.24% female) with an average rate of growth of 1.93% annually, whereas roughly 16% of population was in HICs with a mere rate of growth of about 0.86%.

Results, based on paired samples test, reveal that from 2012 to 2018:

- LMICs (poor countries) have a significant increase of breast cancer mortality and of breast cancer incidence.
- MUICs, in the same period, have an increase of mortality not significant, whereas the increase of breast cancer incidence is significant.
- HICs (rich countries) have a decrease of breast cancer mortality from 2012 to 2018 not statistically significant, whereas breast cancer incidence has a significant increase. In addition, the estimated relationship of predicted breast cancer mortality 2018 with breast cancer incidence 2012 (*variable y**) on GDP per capita 2015 is statistically significant in rich countries. In particular, results suggest that within HICs a 1% higher level of GDP per capita can increase the expected breast cancer mortality (i.e., based on breast cancer incidence 2012) by 0.1% (p -value $<.001$, $F=17.80$, $sig.=0.001$, Adjusted $R^2=0.25$). In short, these statistical analyses combined seem to confirm that breast cancer mortality in rich countries can continue to increase also in the future, supporting main sources of worries and social issues for healthcare authorities.

Bellanger et al. (2018) argue that “country-level cancer prevention policy indicators contributed little to the explanation of the overall variation in incidence and mortality after analysis accounted for age and country-level income; however, an overall resource summary

index of greater economic development and cancer prevention policies was related to lower mortality within each major income level”.

In this context, this study shows that, though higher wealth and wellbeing within and between countries (Coccia, 2010; 2014a)⁹, it seems that the risk of mortality and incidence in breast cancer is continuing to grow likely associated with the dynamics of socioeconomic evolution of nations (cf., Coccia, 2013).

Bellanger et al. (2018) also find that: “in women younger than age 50 years, country-level income explained 68% of incidence and 59% of mortality; economic development indicators additionally increased this percentage by approximately 4%”.

To conclude, findings here suggest that the risk of breast cancer mortality is increasing worldwide. These results explain trends of breast cancer between countries with different levels of income per capita that can be used to gain insights at country-level for designing social “best practices” for health improvement within countries. However, these conclusions are of course tentative. There is need for much more detailed research into the relations between socioeconomic factors and breast cancer to shed further theoretical and empirical light on patterns of incidence and mortality of breast cancer within and between countries during the process of the evolution of nations. Hence, to reiterate, this study is exploratory in nature and future efforts in this research field should provide more statistical evidence to substantiate the results here.

6 REFERENCES

- Bellanger, M., Zeinomar, N., Tehranifar, P., & Terry, M.B. (2018). Are Global Breast Cancer Incidence and Mortality Patterns Related to Country-Specific Economic Development and Prevention Strategies? *Journal of Global Oncology*, 4, pp. 1-16. Available at <https://ascopubs.org/doi/full/10.1200/JGO.17.00207>
- Bray, F., Ferlay, J., Soerjomataram, I., Siegel, R.L., Torre, L.A., & Jemal, A. (2018). Global Cancer Statistics: GLOBOCAN Estimates of Incidence and Mortality Worldwide for 36 Cancers in 185 Countries. *CA Cancer J Clin*; 68, pp. 394-424. <https://doi.org/10.3322/caac.21492>.
- Brentnall, A.R., Cuzick, J., Buist, D.S.M., & Aiello Bowles, E.J. (2018). Long-term Accuracy of Breast Cancer Risk Assessment Combining Classic Risk Factors and Breast Density. *JAMA Oncol.*, 4(9). Available at <https://www.ncbi.nlm.nih.gov/pubmed/29621362>
- Canto, M.T., Anderson, W.F., & Brawley, O. (2001). Geographic Variation in Breast Cancer Mortality for White and Black Women: 1986-1995. *CA Cancer J Clin*, 51(6), pp. 367-370.
- Chagpar, A.B., & Coccia, M. (2019). Factors associated with breast cancer mortality-per-incident case in low-to-middle income countries (LMICs). *Journal of Clinical Oncology*, 37(15), suppl. pp. 1566-1566. DOI: 10.1200/JCO.2019.37.15
- Coccia, M. (2010). Democratization is the driving force for technological and economic change. *Technological Forecasting & Social Change*, 77(2), pp. 248-264, <https://doi.org/10.1016/j.techfore.2009.06.007>.
- Coccia, M. (2012). Evolutionary growth of knowledge in path-breaking targeted therapies for lung cancer: radical innovations and structure of the new technological paradigm. *International Journal of Behavioural and Healthcare Research*, 3(3-4), pp. 273-290. <https://doi.org/10.1504/IJBHR.2012.051406>
- Coccia, M. (2012a). Driving forces of technological change in medicine: Radical innovations induced by side effects and their impact on society and healthcare. *Technology in Society*, 34(4), pp. 271-283. <https://doi.org/10.1016/j.techsoc.2012.06.002>
- Coccia, M. (2012b). Political economy of R&D to support the modern competitiveness of nations and determinants of economic optimization and inertia. *Technovation*, 32(6), pp. 370-379. DOI: 10.1016/j.technovation.2012.03.005
- Coccia, M. (2013). The effect of country wealth on incidence of breast cancer. *Breast Cancer Research and Treatment*, 141(2), pp. 225-229. <https://doi.org/10.1007/s10549-013-2683-y>
- Coccia, M. (2014). Path-breaking target therapies for lung cancer and a far-sighted health policy to support clinical and cost effectiveness. *Health Policy and Technology*, 1(3), pp. 74-82. <https://doi.org/10.1016/j.hlpt.2013.09.007>

⁹ cf. also, Coccia 2012b, 2015, 2018, 2019.

- Coccia, M. (2014a). Religious culture, democratisation and patterns of technological innovation. *International Journal of Sustainable Society*, 6(4), pp. 397-418. <http://dx.doi.org/10.1504/IJSSOC.2014.066771>.
- Coccia, M. (2015). Patterns of innovative outputs across climate zones: the geography of innovation, Prometheus. *Critical Studies in Innovation*, 33(2), pp. 165-186. <https://doi.org/10.1080/08109028.2015.1095979>
- Coccia, M. (2015a). The Nexus between technological performances of countries and incidence of cancers in society. *Technology in Society*, 42, August, pp. 61-70. <http://doi.org/10.1016/j.techsoc.2015.02.003>
- Coccia, M. (2016). Problem-driven innovations in drug discovery: co-evolution of the patterns of radical innovation with the evolution of problems. *Health Policy and Technology*, 5(2), pp. 143-155. <https://doi.org/10.1016/j.hlpt.2016.02.003>
- Coccia, M. (2017). Sources of technological innovation: Radical and incremental innovation problem-driven to support competitive advantage of firms. *Technology Analysis & Strategic Management*, 29(9), pp. 1048-1061. <https://doi.org/10.1080/09537325.2016.1268682>
- Coccia, M. (2018). Optimization in R&D intensity and tax on corporate profits for supporting labor productivity of nations. *The Journal of Technology Transfer*, 43(3), pp. 792-814, DOI: 10.1007/s10961-017-9572-1
- Coccia, M. (2018a). General properties of the evolution of research fields: a scientometric study of human microbiome, evolutionary robotics and astrobiology. *Scientometrics*, 117(2), pp. 1265-1283. <https://doi.org/10.1007/s11192-018-2902-8>
- Coccia, M. (2019). Why do nations produce science advances and new technology?. *Technology in society*. <https://doi.org/10.1016/j.techsoc.2019.03.007>
- Coccia, M. (2019a). The theory of technological parasitism for the measurement of the evolution of technology and technological forecasting. *Technological Forecasting and Social Change*, 141, pp. 289-304. <https://doi.org/10.1016/j.techfore.2018.12.012>
- Coccia, M., & Wang L. (2015). Path-breaking directions of nanotechnology-based chemotherapy and molecular cancer therapy. *Technological Forecasting & Social Change*, 94, pp. 155-169, DOI: 10.1016/j.techfore.2014.09.007
- DeSantis, C.E., Ma, J., Goding Sauer, A., Newman L.A., & Jemal, A. (2017). Breast Cancer Statistics, 2017, Racial Disparity in Mortality by State. *CA Cancer J Clin* 67, pp. 439-448. DOI: 10.3322/caac.21412.
- Engmann, N.J., Golmakani, M.K., Miglioretti, D.L., Sprague, B.L., Kerlikowsk K., et al. (2017). Population-Attributable Risk Proportion of Clinical Risk Factors for Breast Cancer. *JAMA Oncol.*, 3(9), pp. 1228-1236. DOI:10.1001/jamaoncol.2016.6326
- Mettlin, C. (1999). Global Breast Cancer Mortality Statistics. *CA Cancer J Clin*, 49, pp. 138-144.
- Moskowitz, M. (1980). How can we decrease breast cancer mortality? *CA Cancer J Clin*. Sep-Oct., 30(5), pp. 272-277.
- Parkin, D.M., Bray, F., Ferlay, J., & Pisani, P. (2005). Global cancer statistics 2002. *CA Cancer Journal of Clinic Oncology*, 55(29), pp. 74-108.
- Prager, G.W. et al. (2018). Global cancer control: responding to the growing burden, rising costs and inequalities in access. *ESMO Open*, 3(2). DOI: 10.1136/esmoopen-2017-000285.