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Title: Breast cancer and socio-economic factors

Authors: Anees B. Chagpar;[1] Mario Coccia;[2]*

Type: Original Article

JEL classification: O33; O50; H51;

Keywords: Breast Cancer, Oral Contraceptive Pill, GDP per capita, Computed Tomography, Wealth.

Abstract

Purpose: The aim of this study is twofold – on the one hand, to analyze the relationship between incidence of breast cancer, income per capita and medical equipment across countries; after that, the study here discusses the drivers of the incidence of breast cancer across countries in order to pinpoint differences and similarities.

Methods: The indicators used are incidence of breast cancer based on Age-standardized rate (ASW); Gross domestic product (GDP) per capita by purchasing power parity (current international $); computed tomography (CT) for cancer diagnosis. Data

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include 52 countries. The statistical analysis is carried out by correlation, ANOVA and an econometric modeling based on a multiple regression model of the breast cancer incidence on two explanatory variables.

Results: Partial correlation is higher: $r_{\text{breast cancer, GDP | CT}}$=60.3% (sign.0.00). The estimated relationship shows an expected incidence of breast cancer increase of approximately 0.05% for a GDP increase of 1% and an expected incidence of breast cancer increase of approximately 3.23% for a CT increase of 1%. ANOVA confirms that incidence of breast cancer is higher across richer countries, *ceteris paribus*.

Conclusions: Empirical evidence shows that the breast cancer tends to be higher across richer countries, measured by GDP per capita and number of Computed Tomography. The main determinants of these findings can be due to several socio-economic factors, mainly localized in richer countries. In addition, this research may provide an alternative interpretation to the theory of Oh *et al.* (2010) on the influence of latitude on breast cancer, focusing on socio-economic factors rather than biologic root causes.

1. Introduction

The aim of this paper is to answer to the following questions:

- How does wealth of nations affect the incidence of breast cancer in modern societies?
- What are the drivers of higher incidence of breast cancer across countries in order to pinpoint differences and similarities?

Breast cancer forms in tissues of the breast, usually the ducts (tubes that carry milk to the nipple) and lobules (glands that make milk)[3]. Breast cancer is the most frequent form of cancer affecting women in the world (GLOBOCAN, 2008). Table 1 shows the incidence and mortality of the most frequent cancer for women and in particular the highest rate of incidence and mortality of the breast cancer.

From 1975 through 1977, among women diagnosed with breast cancer in the United States, about 75% survived to the disease at least 5 years. Since 2007, although the incidence rate is higher than 1975, the breast cancer death rate has been declining steadily (Howlader *et al.*, 2010, *cf.* Evans and Howell, 2007). According to National Cancer Institute (2012) estimates, new cases of breast cancer in the United States are 230,480 (female) and 2,140 (male)

National Research Council of Italy for visiting at Yale University where this research has been originated. We thank Diego Margon for valuable research assistance. The usual disclaimer applies.

[3] Definition by National Cancer Institute (2012)

whereas deaths are 39,520 (female) and 450 (male). The presence of a significant family history is a highly important risk factor for the development of breast cancer but this operates in association with other main socio-economic determinants. This study analyzes the relationship between the incidence of breast cancer and the wealth of nations measured by both Gross Domestic Product (GDP) of countries and medical equipment (Computed Tomography) and other elements. Several works have provided many valuable insights into the breast cancer research, though, how overall wealth of countries, associated to geo-economic location, can affect the incidence of breast cancer of countries has not been accurately explored. This analysis can provide main findings for the main scientific debate to understand vital interactions and to design efficient and efficacious health policy as prevention platforms against breast cancer across countries.

Table 1. Most frequent cancers for women (World data)

	Incidence		Mortality	
CANCER	Number	ASR (W)	Number	ASR (W)
Breast	1384155	39.0	458503	12.5
Cervix uteri	530232	15.3	275008	7.8
Colorectum	571204	14.7	288654	7.0
Lung	515999	13.6	427586	11.0
Stomach	348571	9.1	273489	6.9
Corpus uteri	288387	8.2	73854	2.0
Ovary	224747	6.3	140163	3.8

Note: Age-standardized rate (W). *Source*: GLOBOCAN 2008 (IARC)-Section of Cancer Information (4 Nov. 2011).

2. Theoretical framework and related works

Breast cancer is the fifth cause of death from cancer overall and it is the leading cause of cancer in developed countries (about 189 000 deaths according to the estimate of Surveillance, Epidemiology, and End Results - SEER). In recent years breast cancer is increasing also in developing countries with 12.7% of total deaths (cf. Agarwal *et al.*, 2007). It is the most diagnosed cancer among females from 30s to 50s (Kuroki-Suzuki *et al.*, 2010). Surveillance, Epidemiology, and End Results (SEER) Program of the U.S. National Cancer Institute shows that over 2004-2008 the median age of the breast cancer incidence is 61 years: 0.0% is diagnosed under age 20; 1.9% in the range 20 – 34 years of age; 10.2% between 35 and 44; 22.6% in 45 - 54; 24.4% in the range 55 and 64; 19.7% between 65 and 74; 15.5% between 75 and 84; and 5.6% for women greater than 85 years of age (SEER,

2012). During the same period the median age of US mortality for breast cancer is 68 years, with an age-adjusted death rate equal to 23.5 per 100,000 women per year.

Table 2 shows the incidence and mortality rates by race: the higher incidence is for white women, whereas the mortality is higher for black ethnicity.

Table 2. Incidence and death rates by race (*Source*: SEER, 2012)

	Female	
Race/Ethnicity	**Incidence** per 100,000 women	**Death** per 100,000 women
All Races	124.0	23.5
White	127.3	22.8
Black	119.9	32.0
Asian/Pacific Islander	93.7	12.2
American Indian/Alaska Native	77.9	17.2
Hispanic	92.1	15.1

Table 3 shows the Annual Percentage Change (APC %) of the incidence of breast cancer that has positive and negative cyclical fluctuations over time, whereas the rate of mortality of women is reduced in 1990-2008 in comparison with 1975-1990 period.

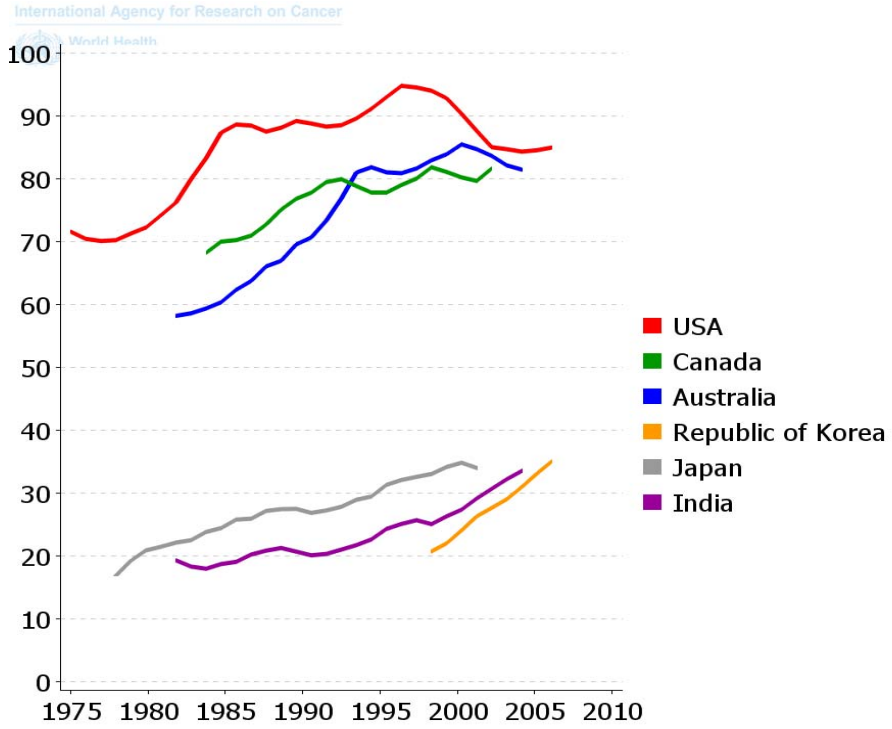
Table 3. The join point trend with associated APC % for cancer of the breast over 1975-2008. All Races Incidence and death (*Source*: SEER, 2012)

	Trend	
Period	**Incidence**	**Mortality**
1975-1980	–0.5	0.4 (1975-1990)
1980-1987	4.0	
1987-1994	–0.2	
1994-1999	1.7	–2.2 (1990-2008)
1999-2005	–2.1	
2005-2008	0.7	

The overall 5-year relative survival over 2001-2007 period is 89.1% (SEER, 2012): about 90% for white women and 77% for black women. The relative survival also depends on the stage at diagnosis: if it is localized the 5-year relative survival is higher than 98%, in case of metastases the survival is about 23.3%.

Figure 1 shows the rate of incidence of the breast cancer in age-standardized rate across some countries: higher values are in USA, Canada and Australia, instead lower ones in Republic of Korea, Japan and India. Developed countries show an increasing trend, except US and Australia where, since 1990, there is decreasing trend.

Figure 1. Trends of the incidence of breast cancer in selected countries: age-standardized rate (W) per 100,000.



Note: Australia: www.aihw.gov.au; Canada: www.statcan.gc.ca; India: Chennai cancer registry; Japan: Miyagi, Osaka and Yamagata cancer registries; Republic of Korea: www.ncc.re.kr; USA: SEER program: seer.cancer.gov
Source: WHO (www.who.int/gho) from GLOBOCAN 2008 (IARC), Section of Cancer Information (16/12/2011)

Incidence and mortality from breast cancer depend on several determinants such as food, environment, pollution, screening programs and so on. Botha *et al.* (2003) analyze 16 European countries and confirm that the incidence of breast cancer has been increasing. Instead, the reduction in mortality trend of breast cancer is noted in several countries such as Denmark, Finland, Ireland, Norway, UK, Austria, France, Germany, Italy; the decreasing rate begins in US.

Agarwal *et al.* (2007) argue that the incidence of breast cancer is lower in Asian countries, though the mortality rate is higher than western countries. As far as developing countries are concerned, Mittra (2011, p. 121) shows that the incidence of breast cancer is increasing and that when it is diagnosed, the stage is often advanced with metastases and/or implications for regional lymph nodes. Instead, Agarwal *et al.* (2007, p. 1032) display that in developing Asian countries the higher rate of breast cancer is within younger women in comparison with developed Asian and western geo-economic areas. This result is due to low information about

breast cancer, dietary habits, increasing life expectancy, lack of screening plan, low health care facilities, socio-cultural barriers, as well as traditional alternative medicine that generates a higher mortality rate (cf. also Agarwal *et al.*, 2011; El Saghir *et al.*, 2011). Lakkis *et al.* (2010, pp. 223-224), analyzing Lebanon, find that the proportion of breast cancer is 38.2% of total cancers in women and show an interesting comparison of this country with other geo-economic areas. In particular, in Lebanon the breast cancer is lower than US, West Europe and Israel, though is higher than Arab regional area, Iran and Malaysia. According to these authors the causes can be the awareness of this cancer among Lebanon women, the implementation of screening programs and the modernization in the reproductive patters of women. Some researches claim that mammographic screening is an apt and cheap strategy to detect the breast cancer in the early stages and improves a management of this disease, though some barriers can be due to socio-economic and cultural features within developing countries (Yip *et al.*, 2011). Mittra (2011) argues that the most important aspect for developing countries is to assure the minimum level of cancer care to these populations in order to sharply reduce the incidence and mortality of breast cancer. In addition, other main issues of developing countries are the higher rate of illiteracy and cultural barriers, associated to lack of funding, health infrastructures, public health schemes of prevention, etc.

Breast cancer research has also investigating the main causes across populations, considering cultural, social and economic profiles. Botha *et al.* (2003) show that the incidence of breast cancer tends to be higher in advanced socio-economic countries in North and West Europe due to some factor risks such as "avoidance of childbearing" (p. 1727). Cogliano *et al.* (2005) argue that combined oral contraceptives (OCs) have been associated to an increased risk of breast cancers among users. Ursin *et al.* (1998) show: "breast cancer risk is elevated among women with long duration of use which began at an early age. . . . before age 20" (p. 182). Oh *et al.* (2010), investigating the causes of breast cancer, have carried out an interesting research about the breast cancer seasonality. They argue that breast cancer is more diagnosed in spring and fall, this seasonality is higher across population distant from equator and this result is pronounced among women living in rural areas. Moreover, the overall incidence of breast cancer, over 2005-2006, increases as the latitude of population residence increases (p. 233, *passim).* The relationship latitude and breast cancer, according to these authors may be due to the complex season sunlight mediation of Vitamin D and of nocturnal peak level and duration. This finding could be the basis to analyze the biological rather than social determinants of breast cancer patterns. Klassen and Smith (2011), instead, review with

accuracy the scientific literature about the main relationship between social class and breast cancer, since the "breast cancer in women has historically been seen as a 'cancer of affluence' " (p. 217). They confirm the high association between breast cancer incidence and higher social class groups, though some variation of risk is due to modernization based on physical activity and changes of reproductive habits. Klassen and Smith (2011, p. 219ff) also list some breast cancer risks factor that are difficult to isolate in individual effects, such as: greater weight by women is associated with an higher risk for post-menopausal; estrogen in oral contraceptive and hormone therapy, alcohol and smoking, etc. In addition, they note that affluent western populations have rate of breast cancer higher than Africa and Asia. Social class is not a direct determinant of breast cancer, but some social classes in several counties are an indicator of behavior and style of life that contribute to increase the breast cancer risk of woman. This result is important because breast cancer of younger women can be due to genetic risk factors, whereas in post-menopausal woman is associated to lifestyle of social class (Klassen and Smith, 2011, p. 230). In addition, higher incidence of breast cancer in higher social class is associated to higher mortality of women of lower social class (and countries dominated by these social structure) that, *vice versa*, do not have access to advanced treatments and effective anticancer drugs.

This theoretical background shows that breast cancer has a heterogeneous diffusion between and within countries. It is important to analyze the relationship between diffusion of the breast cancer and wealth of nations in order to pinpoint systemic drivers and provide vital best practices to design fruitful health policy across countries for a better prevention, vast and accurate screening programs among women, diagnosis at early stages, and more effective anticancer treatments. Before discussing the results, we describe the methodology of research.

3. Method

The critical hypothesis (Hp) of this study is:

*Hp 1***:** *The breast cancer tends to be higher across richer countries.*

In fact, richness and modernization may spur behavior and style of life that contribute to increase the breast cancer risk of woman.

The purpose of the present study is to see whether statistical evidence supports this hypothesis, in order to analyze the main determinants and support an accurate prevention and health information plan across populations. The structural indicators used are:

- Incidence of breast cancer based on Age-standardized rate (ASW), that is the number of new cases 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. Standardization is necessary when comparing several populations that differ with respect to age because age has a powerful influence on the risk of cancer. Data of worldwide breast cancer are based on 2008 year from the source GLOBOCAN (2008).
- Gross domestic product (GDP) per capita by purchasing power parity - PPP (current international $) 1994-2000 period (arithmetic mean). Gross domestic product (GDP) is a measure of the economic activity. It is defined as the value of all goods and services produced minus the value of any goods or services used in their creation. Data are from World Development Indicators by World Bank 2008.
- Medical equipment for cancer diagnosis is measured by Computed Tomography (CT) - Total density per 1 000 000 population. As worldwide data on screening mammography examinations are not available, the presence of this medical equipment is a main proxy to assess the general capacity of screening among countries. In addition, this indicator also shows the quality of health service in diagnostics and also therapeutics, associated to the level of development of countries. Several research reports the effectiveness of magnetic resonance imaging (MRI) in making diagnosis, however MRI scanner can provide difference in diagnostic accuracy. The CT scanner does not generate a difference in performance for daily clinical use and provides; "images in the surgical position, and it has been reported as a useful diagnosing in the extent of breast cancer" (Kuroki-Suzuki, 2010, p. 15). For this reasons, we use CT as main marker of screening capacity of breast cancer across countries. Data consider 2008 period and are by World Health Organization (2012).

Data are based on 109 countries that have been subjected to a process of horizontal and vertical cleaning, eliminating outliers. Final dataset, with all variables, includes 52 countries. The normal distribution of variables is checked by Curtosi and Skewness coefficients, as well as by the normal Q-Q plot (tab.4), using the statistics software SPSS (Statistical Package for the Social Sciences). Data are analyzed through descriptive statistics, correlation and regression analysis, and ANOVA to measure the interaction between breast cancer and wealth across countries. In particular, correlation analyzes the association by bivariate

correlation and partial correlation, with control variables latitude, computed tomography (CT) and magnetic resonance imaging (MRI); coefficient of correlation r has a range $-1 \leq r \leq +1$.

Regression analysis is based on the functional relationship:

Incidence of Breast Cancer $_{i,\,t} = f$ (GDP $_{i,\,t-n}$, Medical Equipment -CT $_{i,\,t}$)

Assumption 1: The level of wealth of countries at time *t-n* affects the breast cancer trends of the country *i,* at time *t*.

Assumption 2: Medical equipment at time *t* plays a vital role for screening the breast cancer at time *t* of the country *i*.

The specification is based on a multiple regression *Log Linear model* with two explanatory variables:

$$LN\ BREAST\ Cancer(ASR)_{\,i,2008} = \lambda_0 + \lambda_1 LN\ GDP - PPP_{i,(1994-2000)} + \lambda_2 LN\ Medical\quad Equipment(CT)_{i,2008} + u_{i,t}$$

Remark: the *i* subscript indicates the country and *t* the time; GDP-PPP is the arithmetic mean over 1994-2000.

In addition, the study here considers two sets (1 and 2), each of size *n*, represented by: 1) countries within the temperate zone North and South (from 23.5 degrees North latitude to the approximately 66.5 degrees north latitude and from approximately 23.5 degrees south latitude to the Antarctic Circle: at approximately 66.5 degrees south latitude) and 2) complementary set of countries not in the temperate zone.

Assumption: countries of temperate zone have better socio-economic-environmental locations that spur fruitful patterns of economic growth.

Remarks: The favorable geo-economic location of countries in temperate zone, due to higher latitude, support economic growth, consumptions, needs, habits and style of life typical of advanced countries.

Statistical hypotheses, to test Hp 1 by the average GDP per capita within these sets 1 and 2, are:

$H_0 = \mu_1$ (average incidence of breast cancer ASW) $= \mu_2$ (average incidence of breast cancer ASW)

$H_1 : \mu_1$ (average incidence of breast cancer ASW) $\neq \mu_2$ (average incidence of breast cancer ASW)

It will be assumed that the sample variances are all equal. From the analysis of variance (ANOVA), considering the null hypothesis and *F*-distribution, we would expect a large value for the *F*-test in order to reject H_0 in favor of H_1. These statistical analyses are carried out by SPSS software.

4. Result

Table 4 shows the arithmetic mean, std. deviation and confirms the normality of the distribution of variables. Other main results are in table 5-7.

Table 4. Descriptive Statistics

	Mean	Std. Deviation	Skewness	Kurtosis
LN BREAST C. (ASR)	3.69	0.61	-0.35	-0.28
LN GDP PPP	8.88	1.11	-0.44	-0.65
LN CT	1.29	0.18	-0.84	0.95

Note: ASR is the incidence of breast cancer based on Age-standardized rate (ASW); GDP (Gross Domestic Product), CT (Computed Tomography)

Table 5. Correlations

		LN GDP PPP	*LN* BREAST C. (ASR)	*LN* CT
LN GDP PPP	Pearson Correlation	1	.695**	.645**
	Sig. (2-tailed)		.000	.000
LN BREAST C. (ASR)	Pearson Correlation		1	.993**
	Sig. (2-tailed)			.000
LN CT	Pearson Correlation			1
	Sig. (2-tailed)			

Note: ASR is the incidence of breast cancer based on Age-standardized rate (ASW); GDP (Gross Domestic Product), CT (Computed Tomography) ** Correlation is significant at the 0.01 level (2-tailed).

Table 6. Partial Correlation

Control Variables			
LN CT		*LN* GDP PPP	*LN* BREAST C. (ASR)
	LN GDP PPP	1.000	.603
	Significance (2-tailed)	.	.000

Note: ASR is the incidence of breast cancer based on Age-standardized rate (ASW); GDP (Gross Domestic Product), CT (Computed Tomography).

Table 7. Parametric estimates, OLS results:
incidence of breast cancer on GDP per capita and CT –*Log-linear* model

	Estimated relationship [A]			R^2Adj	*F*	*Sig.*
LN BREAST C. $(ASR)_i$=	–0.94***	+0.05*LN*GDP_i***	*+3.23LN*CT_i***	*0.99*	*2714.48*	*0.00*
	(0.07)	*(0.01)*	*(0.06)*	*S=0.06*		
	Predictors: (Constant), LN GDP-PPP, LN CT					

[A] *Definitions*: The dependent variable is the Incidence of breast cancer based on Age-standardized rate (ASW)-2008. The explanatory variables are Gross domestic product (GDP) per capita by purchasing power parity - PPP (current international $) 1994-2000 period (arithmetic mean); Medical equipment is Computed Tomography - Total density per 1 000 000 population-2008. The standard errors of the constant and regression coefficients are given in parentheses. R^2Adj is the coefficient of determination adjusted, below it there is *S* the standard error of

the estimate; to the right, *F* is the ratio of the variance explained by the model to the unexplained variance, and its *Sig.* =significance. *** The parameter is significant at 1 percent.

The first thing to be said about these results is that there is a high correlation among variables (higher than 64%), significant at the 0.01 level (tab. 5). In addition, if the relationship between incidence of breast cancer and GDP per capita is analyzed by partial correlation (tab. 6), controlling -*ceteris paribus*- the number of computed tomography across countries, $r_{breast\ cancer,\ GDP\ |\ CT}$=60.3% (sign.0.00). Table 7 shows the estimated *Log*-linear model that explains more than 90% variance in the data. The parametric estimates of the model are unbiased and the significance of coefficients and the explanatory power of the equation are excellent. In particular, the estimated relationship of multiple regression shows an expected incidence of breast cancer increase of approximately 0.05% for a GDP increase of 1% (*ceteris paribus* CT) and an expected incidence of breast cancer increase of approximately 3.23% for a CT increase of 1% (*ceteris paribus* GDP). Appendix shows the standardized residual plots (Histogram in Figure 1A, Normal probability plot in Figure 2A).

In order to apply the ANOVA, we calculate the descriptive statistics for the two sets. Table 8 shows as average incidence of breast cancer based on Age-standardized rate (ASW) clearly increases across richer countries of temperate zone that have also higher latitude and better socio-economic-environmental locations that spur fruitful patterns of economic growth.

Table 8. Descriptive statistics of variables across countries of non temperate and temperate zone.

Zone		Mean		Std. Deviation	Skewness	Kurtosis
		Statistic	Std. Error			
NON Temperate Zone	GDP 1994 2000 Per capita	4030.77	774.47	3285.81	0.67	-1.28
	Population	28266166.67	6802120.10	28858951.50	1.32	0.89
	ASR W 2008	24.19	1.64	6.94	-0.44	0.49
	Cumulative risk breast cancer 2008	2.58	0.18	0.74	-0.54	0.48
	MRI per million people	0.99	0.31	1.33	1.69	2.37
	CT per million people	2.28	0.61	2.60	1.04	-0.53
	Latitude (modulus)	12.01	1.59	6.75	-0.25	-0.91
	LN MRI (Magnetic Resonance Im.)	-0.76	0.39	1.54	-0.27	-0.83
	LN CT (Computed Tomography)	0.04	0.32	1.38	0.15	-1.58
	Valid N (listwise) 18					
Temperate Zone	GDP 1994 2000 Per capita	15833.63	1957.24	11412.55	1.34	3.08
	Population	17880852.94	4457212.71	25989792.88	2.71	8.90
	ASR W 2008	59.38	4.32	25.16	0.19	-0.73
	Cumulative risk breast cancer 2008	6.36	0.47	2.71	0.15	-0.74
	MRI per million people	7.57	1.55	9.06	2.60	8.93
	CT per million people	15.14	3.17	18.51	3.23	13.91
	Latitude(Modulus)	44.39	1.66	9.65	0.09	-0.71
	LN MRI (Magnetic Resonance Im.)	1.54	0.20	1.13	-0.25	-0.30
	LN CT (Computed Tomography)	2.39	0.19	1.03	-0.50	0.48
	Valid N (listwise) 28					

Note: ASR is the incidence of breast cancer based on Age-standardized rate (ASW); GDP (Gross Domestic Product), CT (Computed Tomography)

Correlation with control variable Latitude, Magnetic Resonance Imaging (MRI) and Computed Tomography (CT) shows a high coefficient 62.8% between incidence of breast cancer based on Age-standardized rate (ASR W) and Gross domestic product (GDP) per capita by purchasing power parity - PPP (current international $) 1994-2000 period (table 9).

Table 9. Correlation controlling Latitude, MRI and CT

Control Variables			ASR W 2008	GDP 1994-2000 PC
Latitude LN MRI LN CT	ASR W 2008	Correlation	1.000	.628
		Significance (2-tailed)	.	.000
		df	0	39
	GDP 1994-2000 PC	Correlation		1.000
		Significance (2-tailed)		.
		df		0

Note: ASR is the incidence of breast cancer based on Age-standardized rate (ASW); GDP (Gross Domestic Product), CT (Computed Tomography); MRI (Magnetic resonance Imaging)

In addition, if:

- set 1 is represented by countries of temperate zone with average incidence of breast cancer based on Age-standardized rate (ASR W) equal to 59.38 (St. error 4.32). This group has also a higher GDP per capita.
- set 2 includes countries not in the temperate zone. Group 2 has an average incidence of breast cancer based on Age-standardized rate (ASR W) equal to 24.19 (St. Error 1.64).

In short,

$\mu_{temperate\ zone}$ *set 1 = 59.38 ASR W*

$\mu_{temperate\ zone}$ *set 2 = 24.19 ASR W*

These averages ASR W between these two sets are analyzed by ANOVA that assumes equality of variance across groups.

Table 10. ANOVA of countries of temperate zone *vs*. Non temperate zone based on ASR W 2008

	Sum of Squares	df	Mean Square	F	Sig.
Between Groups	14567.659	1	14567.659	33.547	.000
Within Groups	21712.631	50	434.253		
Total	36280.290	51			

Note: ASR is the incidence of breast cancer based on Age-standardized rate (ASW);

Table 10 shows the significance value of the *F* test in the ANOVA that is less than 0.001. Thus, we must reject the hypothesis H_0 that average incidence of breast cancer based on Age-standardized rate (ASW) is equal across sets of countries in temperate and non temperate zone. Although the "variability within groups" is 59.85% of the total, the "variability between groups" displays a considerably high value, equal to 40.15%. Hence, the systematic effect of greater incidence of breast cancer based on Age-standardized rate (ASW) could be due to higher GDP per capita that may spur behavior and style of life of populations that contribute to increase the breast cancer risk of woman.

If ANOVA is repeated, *mutatis mutandis*, per three sets of countries: non temperate zone, temperate zone north and temperate zone south, results are in table 11.

Table 11. ANOVA of countries of temperate zone North and South vs. Non temperate zone based on ASR_W_2008

	Sum of Squares	df	Mean Square	F	Sig.
Between Groups	15491.632	2	7745.816	18.257	.000
Within Groups	20788.657	49	424.258		
Total	36280.290	51			

Note: ASR is the incidence of breast cancer based on Age-standardized rate (ASW);

Table 11 confirms, *de facto*, previous results; the significance value of the *F*-test in the ANOVA table that is less than 0.001: we must also here reject the hypothesis H_0 that average incidence of breast cancer based on Age-standardized rate (ASW) is equal across these sets of countries in North/South temperate and non temperate zone. In this case "variability within groups" is 57.30% of the total, whereas the "variability between groups" displays a higher value than previous binomial case, equal to 42.70%. In addition the cumulative risk of breast cancer is higher in temperate zone about 6.35 (average between North and South) *vs.* 2.6 of countries in non temperate zone Hence, this analysis seem to display that the systematic effect of higher incidence of breast cancer based on Age-standardized rate (ASW) could be due to some drivers of socio-economic factors, mainly localized in richer countries that will be discussed in the next section. In addition, ANOVA can provide an alternative interpretation of the theory of Oh *et al.* (2010) on the influence of latitude on breast cancer, focusing on socio-economic factors rather than biologic root causes.

5. Discussion on socio-economic determinants of breast cancer incidence

Studies have estimated that approximately 50% of breast cancer incidence can be due to genetic, physiologic, environmental, or behavioral risk factors (alcohol consumption,

smoking, etc.) with genetic risk factors accounting for 5-10% of breast cancer cases (*cf.* Evans and Howell, 2007; Madigan *et al.*, 1995; Geber *et al.*, 2003). Empirical evidence shows that the breast cancer incidence tends to be higher across richer countries, measured by GDP per capita and number of Computed Tomography. The drivers of these findings can be due to several factors, mainly localized in richer countries that are group in three main areas:

- The wealth, well-being and current socio-economic changes of richer countries are prone to a higher demand of two main innovations for fertility control and post-menopausal treatments represented by Oral Contraceptive pill (OCs) and Hormone Therapy (HT).

  Exogenous exposures to estrogen, presents in OCs and HT, increase the breast cancer risk (Klassen and Smith, 2011, p. 219). Travis and Key (2003) discuss about the epidemiological and experimental evidence of estrogen in the etiology of breast cancer (p.239). They show that women currently using OCs and/or who had used them in the past 10 years have a slightly higher risk of breast cancer. Instead, the breast cancer risk among women that use HT for 5 years or longer is 35% (Travis and Key, 2003, p. 238.). Gaffield *et al.* (2009) evidence as women who took OCs in the period before the 1975 may be at greater risk (p. 372). Because of high adverse effects of OCs, there has been a reduction of hormone in their content. In fact, estrogen dose greater than 50µg characterizes pills between 1964 and 1971, for instance at the beginning Envoid (the first contraceptive pill) contained 150µg estrogen and 9.85µg progestin, in 1965 the content was 100µg estrogen and 2.5µg progestin (Tyrer, 1999, p. 13S). Since 1983 the majority of pills has a dose of about 50µg. Higher risk of breast cancer in richer countries may be due to several factors. First of all, the industrialization process in many countries has increased the wealth and well- being with affluent social class, mainly in western countries. The improvement of average social class is "the fundamental driver of material and social resources, and occurs 'logically and materially prior its expression in the distribution of occupation, income, wealth, education and social status' "(Klassen and Smith, 2011, p. 231). Since 1960s, the use of OCs has had an exponential growth and the worldwide users of contraceptive pill was greater 12.5 million in 1967 (Tyrer, 1999, p. 12S) and about 200 million women worldwide in 1996. Nowadays OCs is widely used across all countries. Tyrer (1999, p. 15S) claims that: "by the end of reproductive years, >80% of United States women have used the pill for an average of about 5 years". Recent medical literature confirms a possible association between breast cancer and OCs either overall or especially in subgroups of women. For instance, Travis and Kay (2003) show

that women who were currently using combined oral contraceptives (containing an estrogen and a progestogen) or who had used them in the past 10 years, they have a slightly higher risk of having breast cancer diagnosed. In particular, some: "Experimental data suggest that conventional estrogen treatment regimens, both as oral contraceptives (OCs) and hormone therapy (HT). . ., upset the normal estrogen/androgen balance and promote 'unopposed' estrogenic stimulation of mammary epithelial proliferation and, hence, potentially breast cancer risk" **(**Dimitrakakis and Bondy, 2009, original emphasis). Barnes *et al.* (2011) argue that hormone therapy has the highest "population attributable risks . . . . of 19.4%" for overall invasive tumors (p. 345). Other research shows different results: OCs are not associated to an increased risk of breast cancer (cf. Rosenblatt *et.al.* 2009, p. 32). Although several changes in doses and biochemical structures have taken place over time, there is a hot scientific debate about the possibility that oral contraceptives (OCs) may increase the risk of breast cancer (Brinton *et al.*, 1997; Marchbanks *et al*., 2002; Marchbanks *et al*., 2011). Industrialization has also driven a modernization of societies, improving the role of women and the introduction of the OCs has had a high impact in terms of social life, careers of woman, fertility control, gender relations, feminist movement and sexual approaches. Botha *et al.* (2003) find higher rate of breast cancer into well-developed countries of Northern and Western Europe that are the first to receive the fruitful effects of industrialization and modernization in terms of widespread wellbeing and also some health concerns. They also argue that in these countries the main risk factors are: "use of hormonal contraception and replacement therapy, changes in menstrual history and obesity" (Botha *et al.*, 2003, p. 1727). In addition, they confirm an increasing time trends in breast cancer incidence. The increasing role of women in advanced societies is showed not only with the use of OCs, but also with other socio-economic behaviors that are main cancer risk factors such as smoking, alcohol, etc. (Brinton *et al.*, 1996p. 201). Regan (2010), studying Sweden context, shows that the effect of culture, historical factors, women's level of literacy and religious composition are economically significant determinants of demand for the oral contraceptive pill. As far as the research on global breast cancer seasonality by Oh *et al.* (2010) is concerned, these authors find that breast cancer increases as the latitude of population residence increases (*i.e.* distance from equator increases) and "suggest biologic rather than social root causes" This interesting result can be explained by an alternative socio-economic interpretation represented by the distribution of richer

countries mainly in the temperate zone (with greater latitude) that has apt geo-ambient conditions for living. In fact, countries in the temperate zone have been mainly affected by industrialization waves that have generated socio-economic transformations and modernization of societies with a general improvement of wellbeing and wealth of nations. These factors have spurred a higher technological progress, which has improved the role of women in the society, but also changed their reproductive patterns and style of life that are prone to increase the breast cancer risk of woman. ANOVA has confirmed the statistical significant diversity of the arithmetic mean of breast cancer incidence between countries of temperate zone (rich) and non temperate zone (poorer). Hence, the higher incidence of breast cancer associated to higher latitudes might be traced back to socio-economic factors of countries rather than biological root causes of the theory of Oh *et al.* (2010).

However, it is important to note that the scientific literature is vast with different and ambiguous results and considering the current social change that has also driving a technological change, further breast cancer research is therefore crucial because the relationship can change over time and across space with the patterns of technological innovation and economic growth.

- Other factors spread in richer countries are more difficult to analyze and are suspected of increasing breast cancer risk, such as pollution, food habits, psychological stress, etc. (Miller, 2008; DeRoo *et al.*, 2010; Barnes *et al.*, 2011; Gammon *et al.*, 2004). Narod (2011, p. 127) claims that high risk of breast cancer for women with a family history or a mutation in BRCA1 or BRCA2 gene is 1-2% (cf. also Jones *et al.*, 2011). Barnes *et al.* (2011) discuss of "modifiable risk factors" (p. 2011, *passim*) represented by hormone therapy use, physical inactivity, alcohol consumption and high body mass index. Physical inactivity has a higher population risk equal to 12.8% for overall invasive tumors (p. 345), in particular low physical activity and a higher body mass index are associated with ER+/PR+ tumors (p. 348). De Roo *et al.* (2010, p. 497ff) find that Geneva women have a greater consumption of cigarette, oral contraceptive use, hormone replacement therapy, that is associated to an increased risk of breast cancer in comparison with Shanghai women that have different habits and a longer duration of breastfeeding than Geneva women. Hamajima *et al.* (2002) claim that for breast cancer, alcohol consumption is one of the major risk factor. Soerjomataram *et al.* (2010, p. 2617) suggest, by a dynamic model applied on Danish data, that government interventions to reduce alcohol

consumption may lower breast cancer by 7%. Gammon *et al.* (2004 p. 176) assess the relationship between environment tobacco smoke and breast cancer incidence and data suggest that the positive association between these two variables is focused on a specific group of women that have a long-run exposure from a smoking spouse (cf. also Miller, 2008). Instead, Conlon *et al.*, (2010, p. 142) show that a long duration of passive smoking is associated with an increased risk of breast cancer as well as among active women smokers, and the effects can be affected by N-acetyltransferase 2 phenotype. Other causes can be related to physiological factors of richer countries and Kruk *et al.* (2004) claim an association between major life events and breast cancer: "women with major life events, stress of daily activity, and depression had 3.7 times higher risk for breast cancer, compared to those which did not experience such stress . . . . A higher proportion of cases (89.1%) . . . reported that their job was stressful, very fretful or very responsible or experienced a major life event" (p. 399). According to Antonova *et al.* (2011): "Stress exposure has been proposed to contribute to the etiology of breast cancer. However, the validity of this assertion and the possible mechanisms involved are not well established". Nevertheless, the interaction of these factors on breast cancer incidence across countries deserves further research.

- Richer countries have routine mammographic screening as an accepted standard for the early detection of breast cancer. Mammographic screening national plans and other medical equipment increase the incidence of breast cancer but also play a vital role to reduce the mortality from breast cancer, in particular among women ages 50 to 69 years (cf. Harris *et al.*, 2011, p. 108; Coldman and Phillips, 2011, p.117). The main role of mammographic screening has been underlined recently by several researches, although prevention may play a vital role for future breast cancer control (Miller, 2011; Miller 2011a, p. 147). Lakkis *et al.* (2010) show in Lebanon the high rate of incidence of breast cancer among women in comparison with other Arab countries and this result is attributable to wide implementation of screening program. Botha *et al.* (2003) claim that countries with national screening programs have a decline of mortality such as in England and Wales (–3.1%), Scotland (–2%), The Netherlands (–1%). Similar consideration for Sweden where women aged 40-74 years are screened. Yip *et al.* (2011) argue that detection programs (breast examination and mammography) are important in countries with middle-resource but this should be associated to awareness programs about breast cancer risk. Despite the improved availably of health services (surgery, pathology,

radiology, etc.), the implementation in some countries of screening programs have financial barriers associated to cultural resistance and should be important a higher educational efforts to reduce these effects of friction. In fact, Mittra (2011) argues that screening program can be successfully implemented in developing countries if, *a priori*, there is a high level of compliance based on a high level of awareness. Developing countries have several socio-economic problems and it is difficult to select, considering the available resources, the apt examination for detection of breast cancer. Hence, although the importance of early detection, breast cancer management in some countries with low economic resource countries is affected by several factors. The lack of regional pathology services, medical oncologists and surgeons play a vital role for detecting breast cancer and applying apt anticancer treatments (Saghir *et* al., 2011). In general, countries have different results in terms of incidence also due to early detection and screening programs associated to socio-economic-cultural factors.

Although the incidence of breast cancer in women tends to be higher in richer countries, as showed by empirical evidence, the higher R&D investment fosters vital scientific advances in the research fields of genomics and cell biology that have been spurring more effective and less toxic treatments for breast and other cancers based on targeted therapies for patients (cf. Coccia, 2012). These new scientific and technological trajectories have been generating a revolution in clinical practice across countries to treat and we hope to cure this and other typologies of cancer in not-to-distant future.

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Appendix

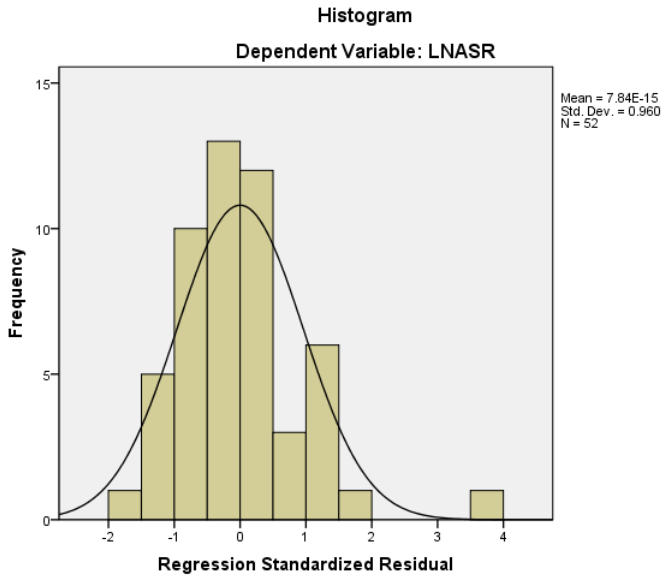

Figure 1A: Z residuals Histogram

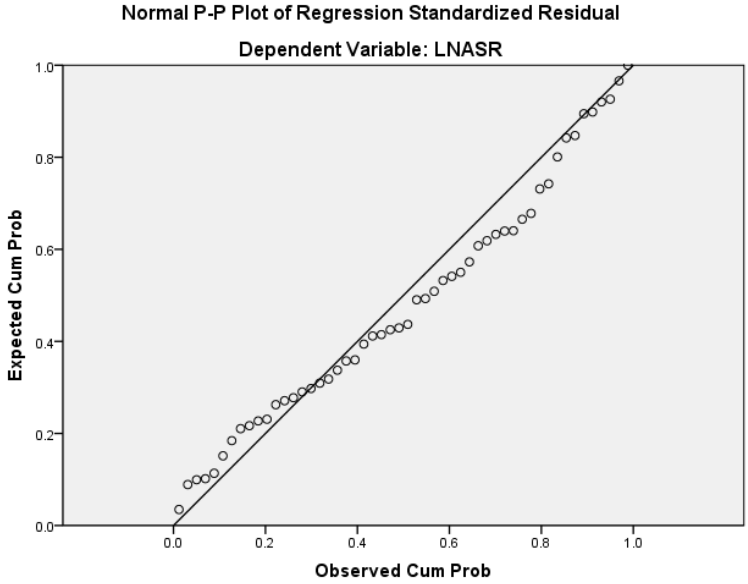

Figure 2A: Z residuals Normal P-P Plot