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The Impact of Screening and Surgery on Life Expectancy in Breast Cancer - A Mathematical Model Case Study in the European Union

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Rezumat

Impactul screeningului și tratamentului chirurgical asupra speranței de viață în cancerul de sân: studiu de caz al unui model matematic în Uniunea Europeană

Background: În ultimii 20 de ani speranța de viață în cadrul Uniunii Europene nu s-a modificat semnificativ, în intervalul 2012-2021 media acesteia fiind aproape constantă la 82 de ani. Cancerul mamar reprezinta principala cauză de deces prin cancer în rândul femeilor. Scopul acestei cercetări este de a identifica şi măsura influența unor proceduri şi intervenții medicale aplicate în neoplasmul mamar asupra speranței de viață. În cadrul acestui articol populația țintă este cea feminină din 27 de țări membre ale Uninunii Europene (UE).

Metodologie: Abordarea metolodogică utilizată pentru această analiză a folosit anumiți indicatori propuşi de către Eurostat precum: speranța de viață pentru populația feminina (variabilă dependentă), screeningul în cancerul mamar şi totalul intervențiilor chirurgicale utilizate în tratamentul acestui neoplasm (variabile independente). Această cercetare a utilizat un model matematic (panel de regresie) pentru 27 de state din cadrul UE pentru o perioadă de 10 ani, pentru a evalua impactul fiecărei

variabile independente asupra speranței de viață în cadrul Uniunii Europene ca întreg.
Rezultate: Din punct de vedere statistic , screeningul pentru neoplasmul mamar are o influență semnificativă asupra speranței de viață. Pe de alta parte, intervențiile chirurgicale au, de asemenea, un rol important în actul medical şi influențează speranța de viață. Modelul matematic aplicat a demonstrat faptul că intervențiile chirurgicale de tip conservator utilizate în tratamentul neoplasmului mamar contribuie mai puțin decât aplicarea procedurilor de screening în creşterea speranței de viață.
Concluzii: Dezvoltarea unor modele matematice în medicină este utilă în procesul de îmbunătățire a calității serviciilor medicale. În prezent, măsurarea şi cuantificarea unor metode medicale este dificilă în contextul multitudinii de variabile existente. În aceste circumstanțe, modelele matematice ar putea aduce un grad de claritate şi structură.

Cuvinte cheie: model matematic, politici de sănătate publică, speranță de viață, screening, neoplasm mamar, pandemie COVID-19, model de regresie randomizat EGLS

Abstract
Background: In the last 20 years in European Union states, the life expectancy did not change much. In the period 2012-2021 the average life expectancy remained almost constant at 82 years. Breast cancer represents the main cause of death by cancer in women The purpose of this research is to identify o identify and measure the influence of some medical interventions and procedures related to breast cancer on life expectancy. In our article, the target group is the feminine population from 27 EU countries.
Methodology: For the analysis several indicators provided by Eurostat were considered: life expectancy for female population as a dependent variable and breast cancer screenings, surgical operations and procedures performed in hospitals (partial and total excision) were used as independent variables. The research used a mathematical model (regression panel) for 27 EU countries, for a 10 year period, to evaluate the impact of each independent variable on the life expectancy in EU as a whole.
Results: From a statistical point of view, screening has a significant effect on life expectancy. On the other hand, surgical interventions have a role in the overall medical process and positively influence life expectancy. The panel model has shown that partial interventions contribute less than screening procedures to increase life expectancy.
Conclusion: The development of mathematical models in health care is useful in the process of improving health care quality. In our days, the measurement and quantification of some medical methods is particularly difficult due to so many variables and observations. In these difficult circumstances, the mathematical models could bring some clarifications and structure.

Key words: mathematical models, health care policy, life expectancy, screening procedures, breast cancer, partial and total surgical interventions, statistical analysis of indicators, random effect model-panel EGLS, COVID-19 pandemic

Introduction

This research paper intends to bring new quantifiable evidence that screening programs for breast cancer and surgical interventions have a positive impact over the life expectancy of feminine population. We are going to do this using a mathematical model called panel regression. During the advancement and refinement of public healthcare policies, the utilisation of novel and innovative mathematical models proves highly beneficial, offering new perspectives and valuable information. Life expectancy at certain ages represents the mean number of years that remain to be lived by a person who has reached a certain exact age, according to Eurostat definition, if subjected throughout the rest of his or her life to the statistically current mortality conditions. It is heavily influenced by various diseases among which cancer is an important negative factor.

Cancer is a major cause of disease burden in the world, and it seems that global malign burden will continue to grow in the next two decades.

Among women, breast cancer stands as the second most common cause of cancer-related deaths, with lung cancer taking the lead in mortality statistics. The way that breast cancer incidence and mortality influences life expectancy for women is still under debate.

Breast cancer is responsible of 1.8% of all women deaths in Europe. In the EU states, breast cancer deaths were highest in Ireland and Luxembourg (4.6%), while in Bulgaria, Latvia, Croatia, Lithuania, Romania, and Bulgaria were below 3% (1).

In 2017, the standardized mortality rate attributable to breast cancer among females in EU member states stood at 32.3 per 100,000 individuals. Among individuals aged 65 years and older, the standardized death rate in cancer is generally markedly higher than for younger age groups. However, in breast cancer, the standardized death rate among those aged 65 years and over was observed to be 9 times higher than for younger women. Conversely, for other cancer types, this rate was notably higher, reaching 13 times more for the same age group compared to younger individuals (2).

Highly developed nations have successfully implemented cutting-edge cancer care practices. However, there's a growing necessity to tailor and adopt these methodologies in low and middle-income countries through cost-effective approaches. In developed countries, breast cancer screening represents a standard of care to reduce mortality and detect asymptomatic patients. In low- and middle-income countries, strategies are developed mainly for early diagnosis in symptomatic patients through education, opportunistic screening and improved access to high quality and affordable cancer care (3).

Most women fall into the category of average risk for breast cancer development across their lifespan, estimated at a 12.4% lifetime probability of diagnosis. Age stands out as the primary risk factor within this group. In individuals under 40 years old belonging to this population with average risk, the likelihood of developing breast cancer remains relatively low, yet escalates with advancing age. Additionally, the effectiveness of mammography screening relies on age, exhibiting higher sensitivity and specificity in older women. Typically, the benefits derived from screening - despite associated costs, inconveniences, emotional strain, occasional physical harm, and the possibility of overtreatment - outweigh these downsides (4).

Regarding the treatment of breast cancer, there are three main components: surgery, systemic therapy (chemotherapy, targeted therapy, immunotherapy, hormonotherapy) and radiotherapy. One of the mainstays of curative treatment is surgery. In the past, radical mastectomy was the most frequent type of surgical intervention performed in breast cancer, considered for many years as the pinnacle of therapeutic approaches.

Breast conservative surgery with adjuvant radiotherapy has become standard of care in recent years for patients with no contraindication. Breast conservative surgery consist of preservation of noncancerous breast tissue obtaining a better cosmetic result, a lower rate of complication, better physical and psychological health, superior social function, and higher quality of life, comparing with radical mastectomy.

In Europe, according to the European Society for Medical Oncology guideline, 60-80% of breast cancer can be managed with breast conservative surgery (and post-operative radiotherapy) at diagnosis or after preoperative systemic treatment.

This study aims to assess the impact of breast cancer treatment procedures and screening on the life expectancy of women in Europe over one decade (2012-2021). It employs two mathematical models to estimate the influence of screening methods and surgical interventions. Specifically, the research examines the effects of total mastectomy and breast conservative surgery (partial mastectomy) on the life expectancy of women diagnosed with breast cancer, employing panel regression analyses. The hypothesis of this paper is that the procedures of breast cancer screening and surgical interventions (considered as independent variables) have a measurable influence on life expectancy.

Our paper navigates into a novel subject matter. As it is structured, the paper has, mainly, two parts. In the first part we provide some background about life expectancy, breast cancer screening and surgical interventions. The second part of the paper exclusively discusses the impact of screening and surgical procedures on life expectancy using mathematical models. The fact that the issue under discussion is new may be seen in how challenging it is to locate publications about it. When we investigated the literature, we discovered a sizable body of work that dealt with each subject separately, but there weren't many that addressed the relationship among the variables.

Materials and Methods

Literature Review

Life expectancy

According to some authors, life expectancy is defined as a statistical measure of life span. The prevailing method applied to quantify life expectancy involves assessing life expectancy at birth. There are two modalities to define life expectancy at birth: the cohort life expectancy, meaning the average length of life of a birth cohort and the period of life expectancy at birth, referring to the mean length of life for a hypothetical cohort that is exposed to the mortality rates observed each year. The first type of life expectancy measurement is implemented by international organizations (5).

Determining the life expectancy at a particular age within a demographic and contrasting this metric among individuals diagnosed with cancer versus those without enables the delineation of the gained years for non-cancer patients and the discernible impact of cancer within the population. The number of years of life accumulated in life expectancy in the absence of cancer can identify the importance of preventive measures, such as screening policies in certain cancers and earning years of life for the general population.

The moment of diagnosis is a critical factor influencing the impact of cancer on life expectancy, showing notably high excess mortality shortly after identification. Therefore, some authors calculated conditional measures to evaluate the impact of cancer for those who survived for a certain period after their initial cancer diagnosis. The influence of cancer over life expectancy and years of lost life is higher in the first years after diagnosis, but it depends on the cancer type (6).

Concerning breast-cancer cure rate, a very relevant study followed all invasive breast cancer patients aged 15-99 years old diagnosed between 1 January 1980 to 31 December 1995 in West Midlands (England) and New South Wales (Australia), with the purpose to determine the time elapsed from diagnosis until the moment when a patient can be considered cured. The results of this study showed that for women diagnosed from 1980 to 1987 the excess mortality rate in the 15th and 23rd year from diagnosis was higher than zero, for all extent of the disease groups, for women diagnosed before age 65. Therefore, these patients cannot be considered cured until 23 years from diagnosis. In the same trend, for women diagnosed from 1988 to 1995, excess mortality rate was higher than zero, between 10th and 15th years from their diagnosis. Nevertheless, breast cancer related mortality was negative for some groups diagnosed at an older age: 65-69, 70-79 and 80-99. This research holds significance as it elucidated the influence of breast cancer diagnosis on life expectancy across specific age cohorts for up to 23 years post-diagnosis (7). The authors concluded that early diagnosis of breast cancer using screening procedures, could influence this long-term impact of breast cancer diagnosis.

Screening for breast cancer

The aim of screening for breast cancer is to reduce mortality and morbidity associated with advanced stages of the disease through early detection in asymptomatic women. The way to obtain the highest potential effects from the screening is providing early access to effective diagnostic and treatment services (8).

The greatest value of screening is for individuals that are predisposed to develop breast cancer for whom early treatment is more effective compared with the application of treatment in later stages of the disease. Therefore, it is very important to determine the personal risk of an individual developing breast cancer, to establish the modality and frequency of screening and seek for patients who also benefit from genetic screening.

There is a limited number of published articles dedicated to assessing the influence of screening programs on life expectancy. One of them evaluated the life expectancy of feminine population every two years between 1975 and 2006. There were identified 858 breast cancer cases. It was observed that for the women diagnosed with a breast tumor smaller than 1.5 cm, life expectancy was not modified comparing with women diagnosed with larger tumors for which life expectancy was lower with 6 to 12 years (9).

According to a 2019 study, where women aged 40 to 69 years participated in organized screening, the program had a 60% reduced risk of dying from breast cancer within ten years from diagnosis and a 47% reduced risk of dying from breast cancer within twenty years after diagnosis, compared with women who did not participate in screening (10).

After publishing the results of many controlled randomized trials that demonstrated a reduction of breast cancer mortality, mammographic screening has become standard practice in high-income countries but unfortunately less used in Eastern and Central Europe. In these regions, breast cancer screening is mainly done by being promoted by advocacy groups and periodic campaigns to promote breast cancer education for the general population.

In 2002 the International Agency for Research on Cancer Working Group published a paper that sustained the efficacity of screening by mammography as the only mean of screening for reducing mortality from breast cancer in the age group 50-69 years and considered that it has limited benefits for age group 40-49 years and no benefit below 40 years (11).

The UK Age Trial, a randomized controlled trial involving 23 breast-screening units in Great Britain assigned women aged 40-48 years to yearly mammographic screening in a 1:2 ratio. More than 160,000 women were recruited between 1990 and 1997. These women were followed for a period of 22.8 years. A specific mortality reduction at ten years follow up was observed with 83 deaths of breast cancer in the mammography arm compared with 219 breast cancer deaths in the arm where screening was applied after the age of 50 years. After ten years, this reduction in mortality was not significant (12).

Surgical interventions

Although the implementation of screening programs for breast cancer has determined an important survival benefit, the patients that are diagnosed with breast cancer in these programs still need additional treatment. One of the most important treatments in breast cancer is surgery. There are two types of breast cancer surgery: the conservatory breast surgery (lumpectomy) or radical mastectomy. For many years radical mastectomy was considered safer and with a greater benefit on survival compared with partial mastectomy. In recent years, many clinical trials tried to compare these two approaches and eventually it seems that radical mastectomy is not superior to the conservative surgery of the breast. Treating cancer in a very early stage also determines conservative surgery approach.

In the past, between 1961 and 1993, several randomized controlled trials demonstrated that breast conserving surgery outcome is not inferior when it is compared with mastectomy (13). The next step was to prove that a conservative approach of breast cancer is superior to radical mastectomy in selected cases. A considerable volume of clinical trials conducted post-2013 revealed an improved survival rate among patients undergoing breast conserving surgery in comparison to radical mastectomy, regardless of tumor stage, age or cancer phenotype (14-16).

According to these data, the European Society of Medical Oncology Guideline recommends breast conservative surgery as the preferred approach in breast cancer management whenever there are no contraindications.

Two large studies followed patients for 20 years and confirmed the equivalence between conservative surgery and mastectomy. These studies are Milan and NSABP B-06 and practically they changed the paradigm of radical mastectomy that was performed in the past for every patient diagnosed with breast cancer, a highly mutilating surgery procedure (17).

At present, abundant conclusive datasets substantiate that breast conservative surgery does not compromise overall survival or the duration until recurrence in breast cancer. Certain patients may present contraindications for breast-conserving surgery due to various medical criteria, including multicentric disease, a substantial tumor size relative to the breast, persistently positive margins following attempts at re-excision, pregnancy, the existence of diffuse malignant-appearing calcifications detected through imaging (such as mammography or MRI) and a previous history of chest radiotherapy. Additionally, individuals with collagen vascular diseases, such as scleroderma or lupus erythematosus, may have contraindications if they cannot tolerate adjuvant radiotherapy.

One important question that researchers involved in breast cancer care concerns regarding adjuvant radiotherapy after breast conserving surgery and if irradiation can be omitted. This aspect was clarified by a large meta-analysis published in 2005 by Early Breast Trialists Group. In this study, the authors found that adjuvant radiotherapy after breast conservative surgery reduced breast cancer specific mortality and increased overall survival period at 15 years (18).

Individuals who undergo mastectomy typically include those diagnosed with breast cancer for whom breast-conserving surgery is contraindicated, as well as those who opt for mastectomy as their preferred treatment approach.

A negative impact on survival for patients that received total mastectomy surgical procedure was found reviewing the specialized literature. One of the most important studies is a Swedish study that revealed that surgical complications after mastectomy (reoperations and readmission in 30 days from initial surgery) were more frequent compared to breast conservative surgery. Additionally, having postoperative complication is associated with worse overall survival and breast specific survival (19).

Methodology

The methodology used in this research paper was designed to suit the hypothesis of this paper: the percentage of women that had undergone breast cancer screening and the type of surgical intervention have a measurable influence on life expectancy of women.

There are several methodological steps involved in this approach.

First, the following variables were selected and extracted from Eurostat database:

- Life expectancy for female population as a dependent variable (years);
- Breast cancer screenings – as independent variable (%);

Surgical operations and procedures performed in hospitals (partial and total mastectomy) as independent variables (number per hundred thousand inhabitants).

Second, we have analyzed the indicators in order to assess trends and dependencies among them. All statistical analyses were performed using EViews International Software version 12 and GraphPad Software version Prism 9. Categorical variables were described in frequencies and percentages. Continuous variables were represented as mean ±standard deviation (SD) or median and range, after checking for normality. Categorical variables were compared using the Chi-Square test. Continuous variables with quasi-normal distributions were compared using Student's T-test and those with a severe deviation from normality, with appropriate nonparametric tests.

Third, we processed the data using two panel regression models. The calculations were made with the EViews 12 software. The regression panel models have included 27 EU countries for a period of 10 years in order to evaluate the impact of each independent variable on the life expectancy. It is interesting to note that the model could be expanded so a regression line for each member state could be drawn. This will be carried out in another research. We used pooled crossed section data analysis giving the fact that the variables assessed were not on the same individuals nor on same cross-sectional units.

It is pertinent to note that the Eurostat database lacks uniformity, occasionally exhibiting discontinuities in time series, instances of missing data, and similar irregularities, causing the data to be unbalanced and heterogeneous. For example, in the case of the indicator Surgical operations and procedures performed in hospitals (Partial excision of mammary gland) there is no data at all for countries such as: Czechia, Greece, Latvia and Slovakia. Also, for the screening indicator, some countries as Spain, Austria, Poland, Portugal and Sweeden did not have any data on this topic. Some other countries did provide only limited sets of data etc. For other indicators some other countries did not have continuous data. In fact, this is a general situation regarding medical and health data. So, in these circumstances we have used all data available, considering common samples of the indicators.

Table 1. Stationarity check of the variables using Augmented Dickey-Fuller (ADF) test.

Variable	ADF - Fischer Chi-Square	p-value
Life Expectancy	97.83	0.00
Screening	55.65	0.01
Partial Mastectomy	77.13	0.00

Given the above mentioned, prior to further analysis we first checked for stationarity given is importance in the model validity, forecasting accuracy and statistical inference using Augmented Dickey-Fuller test. All variables are stationer as depicted in *Tabel 1.* We utilized random effects model for the pooled crossed section data analysis in order to account for unobserved heterogeneity, to allow and recognize the variation across individuals and time and also keep a balance between bias and variance.

Analysis of indicators; visual observations

In this section, the indicators selected are analysed from statistical point of view, as time series.

Life Expectancy for Women

As it was mentioned, life expectancy at a certain age is the mean additional number of years that a person of that age can expect to live, if subjected throughout the rest of his or her life to the current mortality conditions (age-specific probabilities of dying, i.e., the death rates observed for the current period).

In the last 10 years, in EU, life expectancy for women did not change much. In the period 2012-2021, the average life expectancy remained almost constant at 82 years, with some variations among EU member states (*Fig. 1*).

When we compare life expectancy for women in 2012 with the same indicator in 2021, we report that there are the extreme values that differ much. In 2021, the lowest value for life expectancy was 75.10 years compared with 77.9 years in 2012 and the

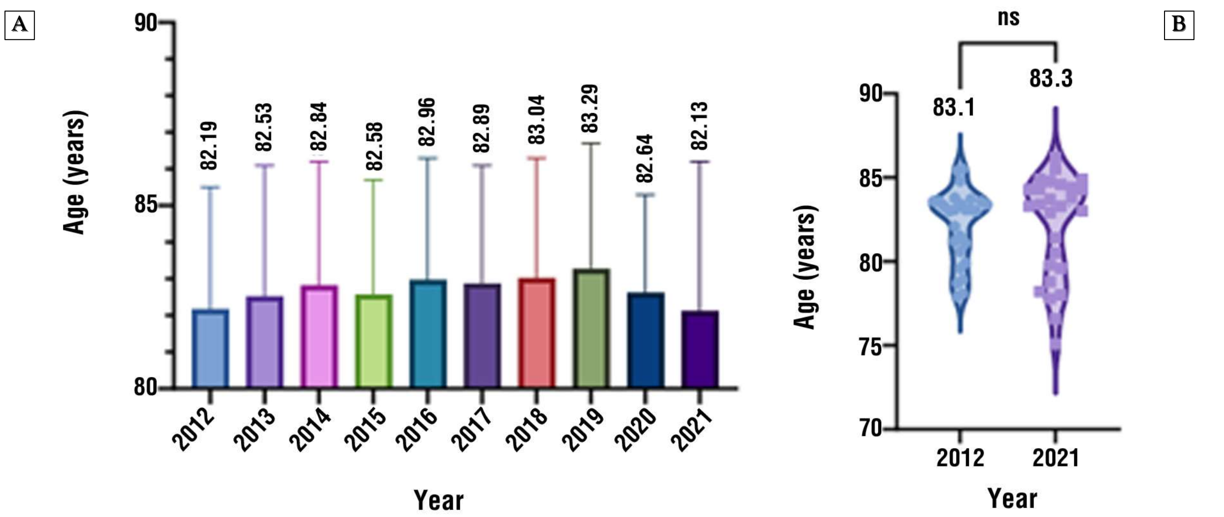


Figure 1. Life expectancy for women at in years, in EU (2012- 2021). **(A)** Mean Life expectancy for women during 2012-2021. **(B)** Median life expectancy for women 2012 and 2021 showing no statistically significant differences. Source: Own contribution, processing data from Eurostat.

maximum value for life expectancy was 86.2 years, comparing with 85.5 years in 2012. We observe a larger interval of life expectancy in 2021 (79.4-84.4 years). This change may be determined by the development of new therapies in non-communicable diseases and early detection programs that unfortunately are very well implemented in highly developed countries, but less available in some other EU states. Also, we need to take into consideration that the wide range for the 2021 may be caused by the COVID pandemic that started in 2020 and may have affected the life expectancy during the following period. Therefore, in 10 years we notice that the average of life expectancy is almost the same, but a larger variation of the age interval is present.

Breast Cancer Screening

The indicator for cancer screening is expressed in percentage for the period 2012 - 2021. The information provided by Eurostat is presented as a separate set of data for Malignant neoplasm of breast within a larger data set called Breast and cervical cancer screening. In our research only the data set for Malignant neoplasm of breast was used. The indicator is a ratio having at the numerator the Number of women aged 50-69 reporting having received a bilateral mammography in the past two years and at the denominator we have the Number of women aged 50-69 answering survey questions on mammography.

Fig. 2 presents the data processed from Eurostat database, concerning the percentage of feminine population that benefited from screening procedure in some EU countries between 2012 and 2021. The quantification was done by measuring the proportion of women who receive a mammography within the previous two years.

The purpose of these statistics is to identify the evolution of the screening programs in this ten-year period, in the EU member states. Unfortunately, there are countries for whom no data or limited data are available. One of the reasons that determined this situation is, probably, the absence of cancer registry and active screening programs in many countries.

However, a clear trend is not discerned to easy predict the evolution of screening in the EU member states during the ten years period. Examining the graphs, a variation of around 10% between 2012 until 2021 is observed, with

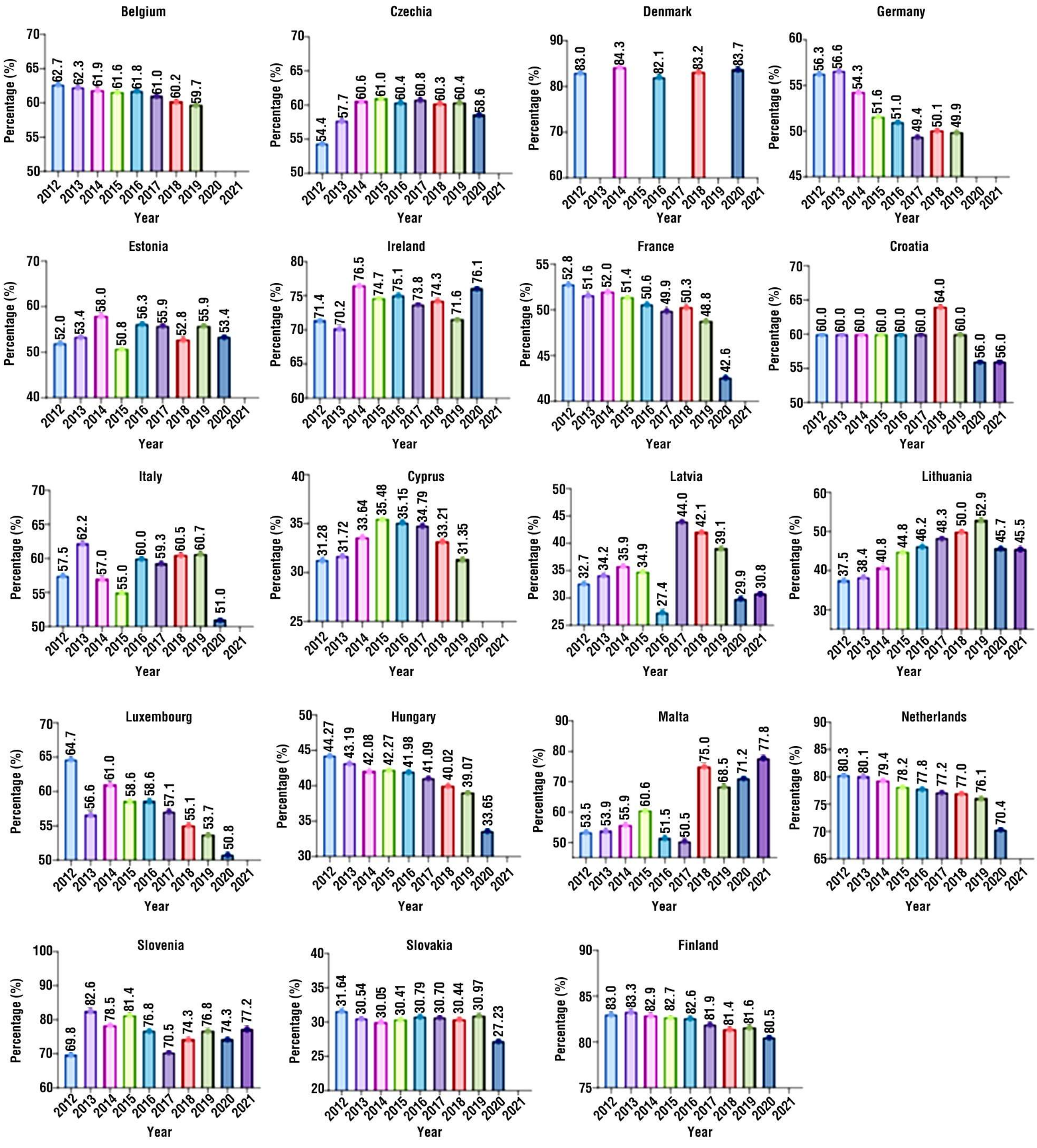


Figure 2. Screening for breast cancer - historical data (2012-2021) (%), Source: own contribution, processing data from www.eurostat.eu.

no specific pattern of increase or decrease of screened population percentage. The median percentage of screened women for breast cancer does not differ between 2012 (56.54%) and 2021 (56.73%) (Mann-Whitney U=59, p= 0.96). Also, we can see a drop in the screening process for the majority of the states in 2020 corresponding to the COVID pandemic's start.

Moreover, in Belgium, Italy, Croatia, Germany, Czech Republic, Estonia and France the percentage of breast screening is around 50-64% with the tendency to decrease in 2021 comparing to 2012. There is a high proportion of screened population in Ireland, Finland, Netherlands and Slovenia. In these countries, we observe that 70-84% women in the defined age interval were part of a screening program.

Malta has an interesting evolution of screening; there is a rise of the screening percentage from 50% in 2012 to 80% in 2021.

Also, there are EU states with lower screening rate like Cyprus, Latvia and Slovakia, with less than 50% screened feminine population.

For Romania and Bulgaria there are only few data available, only for 2014 and 2015 and for Denmark there is a scarcity of available data.

Surgical Interventions to Female Patients

Because total mastectomy is a surgical intervention with an important morbidity and impact on self-esteem, the European guidelines of medical oncology recommend conservative surgical intervention if there are no other contraindication.

According to Eurostat, in 2020, in EU states where data were available, 327,000 breast cancer conservative surgery, and 140,000 total mastectomy intervention were performed.

In *Fig. 3*, we analysed the Eurostat database to compare the existent data for a period of ten years (2012-2021) related to the type of surgery performed for breast cancer (measured as interventions/hundred thousand inhabitants). This data is illustrated by annually comparing the count of total mastectomies with breast cancer conservative surgery. No statistically significant discrepancies can be observed in the variance of the two types of surgery in the last ten years that we analysed.

The proportion of patients undergoing total mastectomy in most European Union states typically accounts for approximately one-third of those who have received breast cancer conservative surgery.

To evaluate the differences between surgical approaches in different EU countries, we developed two separate graphics: one for breast cancer conservative surgery and one for total mastectomy (*Fig. 4*).

When analysing these statistics, it can be observed that there are countries like Czech Republic for which there were no data available for either type of surgery. There are also countries like Greece where there are some data about total mastectomy but with no data about partial surgical intervention.

We could observe that the highest number of partial surgical interventions and total

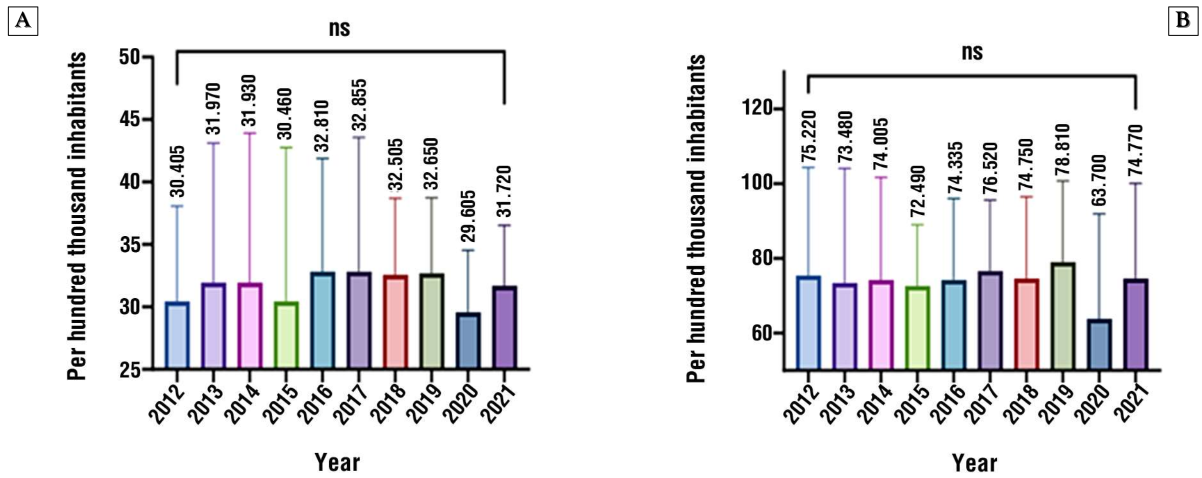
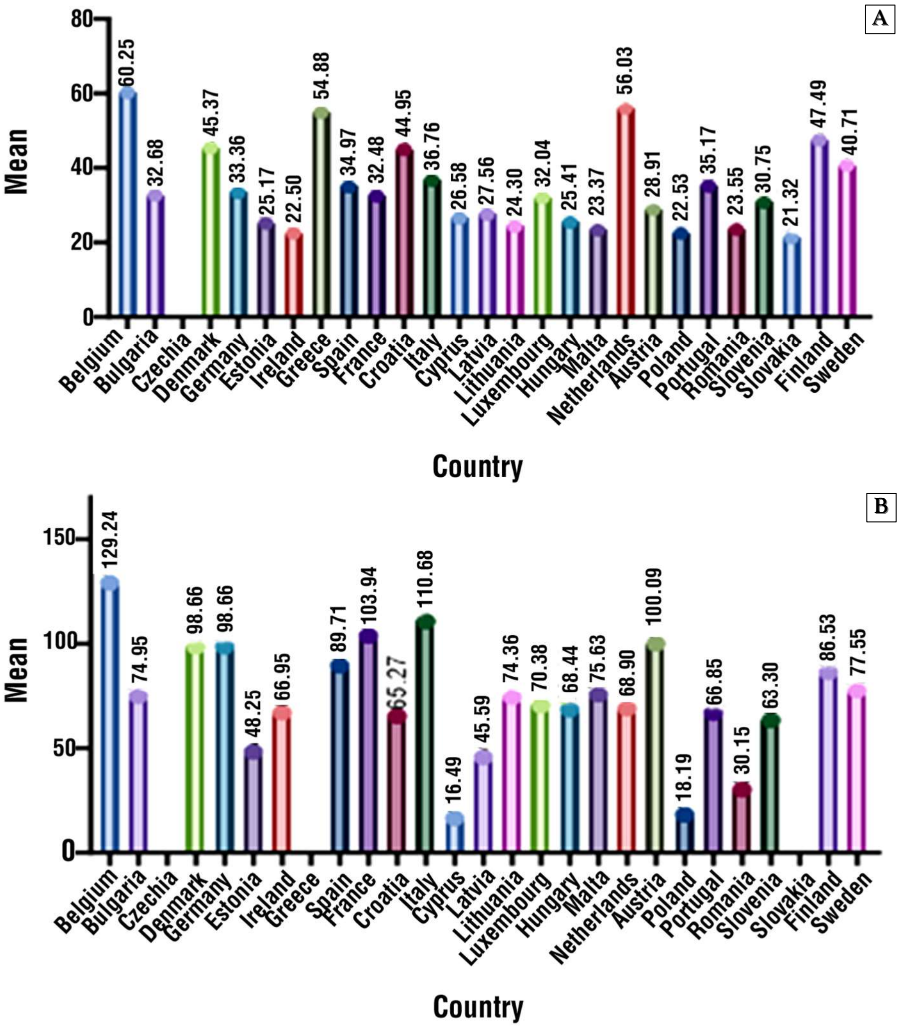


Figure 3. Surgical interventions and procedures performed in hospitals by ICD-9-CM, Source: processing data from www.eurostat.eu **(A)** Median with interquartile range of total mastectomies/hundred thousand inhabitants; **(B)** Median with interquartile range of partial mastectomies/hundred thousand inhabitants

Figure 4. Average count of surgical interventions to female patients, by countries (2012-2021) (partial and total mastectomy), Source: processing data from www.eurostat.eu

(A) Mean total mastectomies per hundred thousand inhabitants between 2012-2021;
(B) Mean partial mastectomies per hundred thousand inhabitants between 2012-2021;



mastectomies took place in Belgium. This aspect may correlate with the existence of many specialized breast cancer units that also determine patients from other EU countries to choose Belgium for the treatment of their disease. The significant number of partial surgical interventions for breast cancer reflects the high-specialized Belgian health care units. It is important to mention that a high percentage of conservative breast cancer surgery are a requirement for the accreditation of breast cancer units.

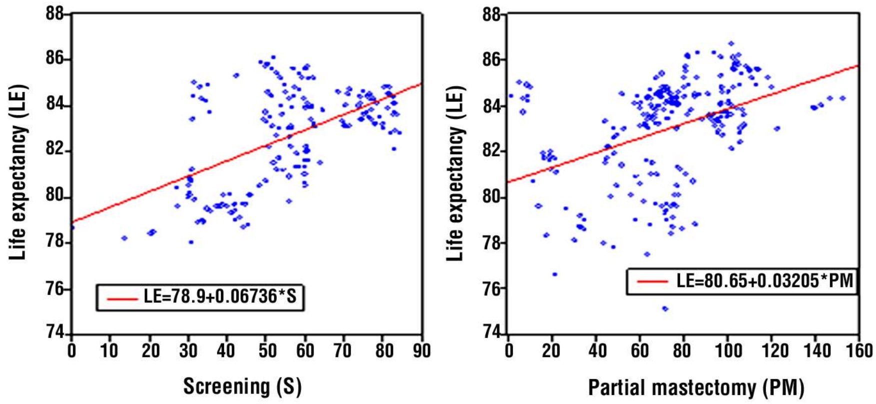
This two graphics give us information about total mastectomy and partial breast cancer surgery in the European Union. In most of these countries total mastectomy represents around one third to one half of the number of partial breast cancer surgery.

Visual Observation of Variables

As previously mentioned, our hypothesis is that breast cancer screening and surgical interventions (considered as independent variables) have a measurable influence on life expectancy. This is a preliminary analysis in order to further assess the time effect on life expectancy.

Visual observation of the scatterplots of the variables mentioned earlier strongly suggests that there is a significant correlation association between these variables (*Fig. 5*). Life

Figure 5. Visual observation of dependency among dependent and independent variables, Source: own compilation



expectancy is influenced not only by the screening procedure, but also by surgical intervention. On the left scatterplot below, the association between the breast cancer screening of feminine population (%) and life expectancy (years) can be noticed.

Visual observation of the right scatterplot for the second variable (PM) shows a positive influence on life expectancy induced by the surgical treatment (partial mastectomy). The association between partial surgical intervention in breast cancer and life expectancy is still significant and may be an important argument for employing this type of surgical approach.

The subsequent chapter contains an elaboration of the regression equations.

Outcomes and Discussions

In this section we are going to apply the methodological steps presented earlier and discuss the results.

Modelling

To assess the impact of independent variables on the dependent variable (life expectancy), a regression panel model was constructed. Data Panel is a regression model that uses a combination of cross section data (in our case country data) and vertical time data (years) (34). Thus, our variables will have two dimensions: i is the cross-section (country) dimension and t is the time dimension. Our variables are the next:

- Y_{it} = life expectancy (dependent variable) (years);
- $X_{1, it}$ = Screening (%);
- $X_{2, it}$ = Surgical interventions (p-partial and t-total) (no./per hundred thousand inhabitants);
- β_0 is the intercept and β_1 and β_2 are the slopes of the independent regressors;
- ν_{it} is the error term.

Equation 1 describes the regression panel model.

EQ 1. $$Y_{it} = \beta_0 + \beta_1 X_{1, it} + \beta_2 X_{2, it} + \nu_{it}$$

Results

As explained in the methodology, the investigation carried out has used two models (see *Fig. 6*).

The first model has used the independent variable *Screening* and the second model has used two independent variables.

First model

The method used to determine Model 1 was Panel EGLS (Estimated generalized least square) with Cross-section weights. The regression equation for this model is next:

EQ. 2 LE_FEMALE = 78.9 + 0.06736 * SCREENING

The model has a strong explanatory power: >97% for the variation of the Life expectancy

Model 1

Dependent Variable: LIFE_EXPECTANCY
Method: Panel EGLS (Cross-section random effects)
Sample: 2012 2021
Periods included: 10
Cross-sections included: 21
Total panel (unbalanced) observations: 174
Swamy and Arora estimator of compoent variances

Variable	Coefficient	Std. Error	t-Statistic	p-value
SCREENING	0.036441	0.008383	4.346872	0.0000
C	80.48551	0.590307	136.3453	0.0000
Effects Specification				
			S.D.	Rho
Cross-section random			1.774768	0.9385
Idiosyncratic random			0.454464	0.0615
Weighted Statistics				
R-squared	0.097670	Mean dependent var		7.221367
Adjusted R-squared	0.092424	S.D. dependent var		1.158403
S.E. of regression	0.457842	Sum squared resid		36.05448
F-statistic	18.61755	Durbin-Watson stat		1.209974
Prob(F-statistic)	0.000027			
Unweighted Statistics				
R-squared	0.239804	Mean dependent var		82.64483
Sum squared resid	589.2964	Durbin-Watson stat		0.074029

Model 2

Dependent Variable: LIFE_EXPECTANCY
Method: Panel EGLS (Cross-section random effects)
Sample: 2012 2021
Periods included: 10
Cross-sections included: 24
Total panel (unbalanced) observations: 222
Swamy and Arora estimator of compoent variances

Variable	Coefficient	Std. Error	t-Statistic	p-value
PARTIAL_MASTECTOMY	0.012661	0.004067	3.112849	0.0021
TOTAL_MASTECTOMY	0.010125	0.007984	1.268112	0.2061
C	81.52591	0.547844	148.8122	0.0000
Effects Specification				
			S.D.	Rho
Cross-section random			2.07663	0.9385
Idiosyncratic random			0.531607	0.0615
Weighted Statistics				
R-squared	0.060604	Mean dependent var		6.899822
Adjusted R-squared	0.052025	S.D. dependent var		0.945155
S.E. of regression	0.535669	Sum squared resid		62.84007
F-statistic	7.064301	Durbin-Watson stat		1.084024
Prob(F-statistic)	0.001064			
Unweighted Statistics				
R-squared	0.114591	Mean dependent var		83.01532
Sum squared resid	967.2637	Durbin-Watson stat		0.0740426

Figure 6. Main statistics of the Model 1 and Model 2. Source: own calculations.

variable (LE_FEMALE). More than 98% of its variation is explained by the independent variable (*Screening*);

The probability resulted from F-Statistic value is near zero indicating that the coefficient of the *SCREENING* variable is statistically very significant; the coefficient is higher than zero (+0.06736) indicating a positive influence on dependent variable.

This value indicates that an increase of 10% in screening will produce a rise of 0.6 years (7 months) of the Life expectancy for the screening age interval (50-69 years).

This result shows the importance of preventive measures such as screening.

Second Model

The second model (Panel EGLS- Estimated generalized least square) has used two independent variables: Partial Mastectomy and Total Mastectomy.

The model shows some peculiarities:

- The variable Total Mastectomy is statistically not significant and has little explanatory power; as a consequence, this variable will be removed from the model.
- The variable Partial Mastectomy is statistically significant and is retained in the model.
- This value (+0.03) means an increase of 100 partial interventions/100 000 women will result in a Life expectancy increase of 0.3 year (4 months) for the feminine population in EU diagnosed with breast cancer.

The equation for the Model 2 is next:

EQ. 3 LE_FEMALE = 80.65 + 0.03205*Partial Mastectomy

Discussions

The application of panel regression models enabled us to discern and analyze the influence of the independent regressors on the Life Expectancy specifically for women. The Model 1 has an intercept of 78.9 and a slope of 0.06 while the Second Model has an intercept of 80.65 and a slope of 0.03.

The intercept shows us the value for Life expectancy if the regressor is zero. In the case of Model 1 we have 78.9 years (approx. 79 years) and in the case of Model 2 we have 80.65 years. The difference between them is not significant (approximately 1 year). More significant is the difference of the slope. In the Model 1 we have a slope of 0.06 and in the case of Model 2 we have a slope of 0.03. That means the slope of Model 1 is much higher than the slope of the Model 2. Consequently, the influence of the regressor Screening on the dependent variable Life expectancy is higher than the influence of the regressor Partial mastectomy. Not to mention that screening is far cheaper than surgical interventions. This is one of the arguments to promote screening as a matter of health care policy.

The model described is very versatile and can be applied to many other interrogations using the data available. For instance, if we want to see if the Covid period (2020-2021) had a statistical influence on the model we may proceed like this. We take the Model 1 and apply the method OLS (ordinary least square). Next, we introduce 10 dummy variables representing each year of the period considered (2012-2021) and eliminate the C parameter. We get the next result (*Table 2*).

From *Table 1*, we can notice that all dummy variables that represent the years for the period 2012-2021 are statistically significant. T-statistic is elevated, so probabilities are zero for all coefficients. We are very confident that the coefficients of the model are not null. The equation that resulted is *EQ. 4*.

EQ. 4

LE_female = 0.06*SCREENING + 78.39*(Years=2012) + 78.76*(Years=2013) +78.98*(Years=2014) + 78.73*(Years=2015) + 79.07*(Years=2016) + 79.07*(Years=2017) + 79.15*(Years=2018) + 79.55*(Years=2019) + 78.86*(Years=2020) + 77.07*(Years=2021)

The model exhibits user-friendly characteristics. If, for instance we want to find out the equation for a specific year, then the dummy variable is 1 for that year and zero for the rest. The slope remains constant for all years. As an example, for the year 2017 we get the next equation:

EQ. 5.

LE_FEMALE2017 = 0.06*SCREENING + 79.07*1

In the period Covid-19 pandemic (2020-2021) we notice the evolution of the values for the dummy variables. For the period 2012-2019 we could observe an increase trend of the intercept values from 78.399 to 79.557 (as we have mentioned before, the intercept represents the life expectancy if the Screening does not exist). After this period, in 2020 and 2021 we notice a decrease to 78.86 in 2020 and to 77.07 in 2021. The value of the intercept for the year 2021 is lower than the value recorded in 2012. The evident impact of the COVID-19 pandemic is discernible. *Fig. 7* displays the scatterplot showing the SARS-COV-2 virus effect. We may see only some regression lines are drawn in the scatterplot in order not to complicate the figure. There are regression lines for some periods: a separate regression line for the whole period (2012-2021) and regression lines for each of the years 2012, 2019 and 2021. The regression line for the year 2021 has the lowest position among the regression lines draw illustrating the influence of COVID pandemic.

In the literature, the paper published by Thaddäus Tönnies et. Al (16) has a model that estimates life expectancy for patients with type 2 diabetes. The authors managed to determine the type 2 diabetes life expectancy and years of life lost in Germany for the year 2015 until 2040 due to this disease. The purpose of this model was conceived to demonstrate the influence of type 2 diabetes on life expectancy and years of life lost.

This proposed model demonstrated that women and men aged 40 years with type 2 diabetes, diagnosed in 2015, will be expected to lose between 1.6 and 2.7 years of life, respectively, compared to a same aged person without the same disease.

The article shows that, in 2040, it is expected to be a reduction by approximately 0.9 years and 1.6 years of the values determined earlier.

Table 2. Time effects in the Model 1 (OLS method)

Dependent Variable: LE_FEMALE				
Method: Panel Least Squares				
Sample: 2012 2021				
Periods included: 10				
Cross-sections included: 21				
Total panel (unbalanced) observations: 174				
Variable	Coefficient	Std. Error	t-Statistic	p-value
SCREENING	0.067	0.00	8.74	0.00
YEARS=2012	78.39	0.59	131.88	0.00
YEARS=2013	78.76	0.59	131.74	0.00
YEARS=2014	78.98	0.57	136.44	0.00
YEARS=2015	78.73	0.55	141.12	0.00
YEARS=2016	79.07	0.57	136.44	0.00
YEARS=2017	79.07	0.57	136.53	0.00
YEARS=2018	79.15	0.60	130.80	0.00
YEARS=2019	79.55	0.60	132.49	0.00
YEARS=2020	78.86	0.61	127.53	0.00
YEARS=2021	77.07	0.9	85.48	0.00

Source: own calculations.

This translates to 10.8 million and 6.4 million lives lost due to premature death in Germany (16.) and is supported in another research (33-35).

Conclusions

The main goal of the article was to estimate the influence on the women life expectancy of two of the most used treatment methods to deal with breast cancer. These two methods,

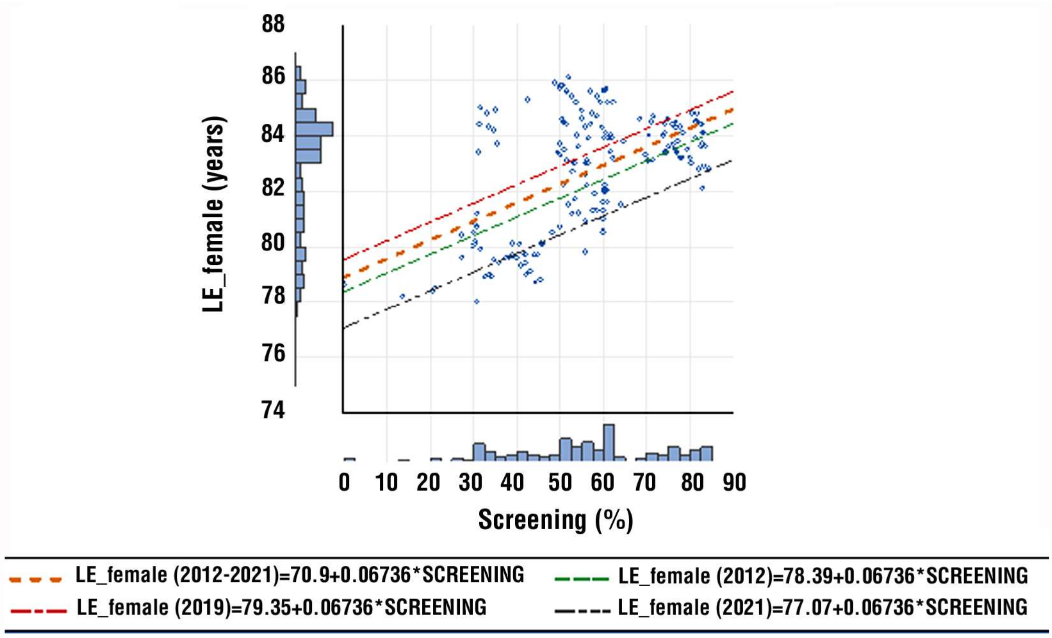


Figure 7. Regression lines for Model 1 with time effects, Source: own calculations.

screening and surgery, are widespread and could be found data and statistical information for the EU member states. The estimate of the influence was carried out using mathematical models (panel regression).

In EU countries, in the period 2012-2021, life expectancy for women altered slightly; the average value is the same (82.2 years) with more extreme values in 2021 (minim of 75 years and maxim of 86 years).

For estimating the influence on life expectancy of the two most used methods for breast cancer treatment, a regression panel model was used. With this model the goal was to estimate the influence of some independent variables (screening, partial surgery, and total surgery) in the treatment of breast cancer, in the period 2012 – 2021. This model showed clear dependence relations for all 27 EU countries, as a group.

From a statistical point of view, Screening is the variable with the highest influence on life expectancy; an increase of 10% in screening will produce an increase of 0.6 years (7 months) of the Life expectancy for the European population in the group age 50-69 years, eligible for breast cancer screening. The importance of screening has been evaluated in multiple prospective and retrospective clinical trials. This research paper brings new statistical evidence, using mathematical models, that screening programs implementation would have a positive impact over the life expectancy of feminine population.

Our research shows that the variable Total Mastectomy is statistically not significant; as a consequence, this variable was removed from the model. Although in this study this variable did not demonstrate an influence on life expectancy, there are still some clinical situations in which total mastectomy is indicated. The absence of influence on life expectancy of this treatment modality might be related also to the fact that radical surgery is more often performed in advanced stages of breast cancer and the overall survival rate of these patients is already lower.

The second variable Partial Mastectomy is statistically significant and was kept in the model; the estimated value shows an increase of 100 partial mastectomies/100 0000 women would result in a Life expectancy increase of 0.3 years (4 month) for the feminine population. Significantly augmenting the number of partial breast cancer surgery procedures in EU states may determine increasing of the life expectancy for the feminine population diagnosed with breast cancer.

The article explains that using mathematical models in health care is useful in the process of improving health care quality. In our days, the measurement and quantification of some medical methods is particularly difficult due to so many variables and observations. In these difficult circumstances, the mathematical models could bring some clarifications and structure.

Limits and Further Research

The limits of the research are due to some shortcomings in the data structure, based on practical constraints that the authors faced. These shortcomings limited what we could process and conclude, but at the same time, the findings present a foundation for future research.

We are aware that more advanced and more effective treatment methods are available for cancer treatment. Still, the availability of these methods is not widespread, there are high costs associated and the results are not included yet in official general statistics. Any mathematical model and statistical analysis depend on reliable data that could be available for processing and interpretation.

The mathematical model developed by authors is flexible. If more data are available, new independent variables could be included in the analysis and more complex and mature results will be uncovered as the influence of COVID-19 pandemic. As well, this model could be used in some future research to derive dependency relations for each country of the group analyzed to show country specificity.

More data and information would be needed in regard with other determinants of life expectancy in EU as: age groups, eating habits, smoking, alcohol drinking, physical exercises, body mass index, etc. With more data, the model presented could be expanded.

Author's Contributions

Conceptualization: Iuliana Pantelimon; Methodology: Victor Platon; Project administration: Andreea Constantinescu; Resources: Corina-Aurelia Zugravu; Software: Laurentia Gales; Visualization: Loredana Sabina Cornelia Manolescu; Writing – original draft: Iuliana Pantelimon and Victor Platon; Writing – review & editing: Corina-Elena Minciuna, Dragos Eugen Georgescu and Victor Platon. All authors have read and agreed to the published version of the manuscript.

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Conflicts of Interest

The authors declare no conflict of interest. The funders had no role in the design of the study; in the collection, analyses, or interpretation of data; in the writing of the manuscript; or in the decision to publish the results.

Informed Consent Statement

Not applicable.

References

1. Eurostat. Cancer statistics. Internet. 2023 Aug. Available from: https://ec.europa.eu/eurostat/statistics-explained/index.php?title=Cancer_statistics.
2. Eurostat. Cancer statistics – specific cancer. Internet. 2023 Aug. Available from: https://ec.europa.eu/eurostat/statistics-explained/index.php?title=Cancer_statistics__specific_cancers#Breast_cancer.
3. Autier P, Boniol M, La Vecchia C, Lars Vatten, Anna Gavin, Clarisse Héry, et al. Disparities in breast cancer mortality trends between 30 European countries: retrospective trend analysis of WHO mortality database. BMJ. 2010;341:c3620. doi: 10.1136/bmj.c3620.
4. Giaquinto AN, Sung H, Miller KD, Kramer JL, Newman LA, Minihan A, et al. Breast Cancer Statistics. CA A Cancer J Clin. 2022;72:524-541.
5. Julian Buxton. Period and cohort life expectancy explained. Office for National Statistics (ONS) (Internet). 2023 Jan. Available from: www.ons.gov.uk
6. Rutherford MJ, Andersson TML, Björkholm M, Lambert PC. Loss in life expectancy and gain in life years as measures of cancer impact. Cancer Epidemiology. 2019;60:168-173.
7. Woods LM, Rachet B, Lambert PC, Coleman MP. 'Cure' from breast cancer among two populations of women followed for 23 years after diagnosis. Ann Oncol. 2009;20(8):1331-6.
8. Von Karsa L, Dean P, Arrossi S, Sankaranarayanan R. Screening - principles. In: Stewart BW, Wild CP, editors. World cancer report. Lyon, France: IARC Press; 2014. p. 322-9
9. Otten JDM, Broeders MJM, Den Heeten GJ, Holland R, Fracheboud J, De Koning HJ, et al. Life expectancy of screen-detected invasive breast cancer patients compared with women invited to the Nijmegen Screening Program. Cancer. 2010;116:586–91
10. Tabár L, Dean PB, Chen TH, Yen AM, Chen SL, Fann JC, et al. The incidence of fatal breast cancer measures the increased effectiveness of therapy in women participating in mammography screening. Cancer. 2019;125(4): 515-523.
11. Lauby-Secretan B, Scoccianti C, Loomis D, Benbrahim-Tallaa L, Bouvard V, Bianchini F, et al. International Agency for Research on Cancer Handbook Working Group. Breast-cancer screening--viewpoint of the IARC Working Group. N Engl J Med. 2015;372(24):2353-8.
12. Duffy SW, Vulkan D, Cuckle H, Parmar D, Sheikh S, Smith RA, et al. Effect of mammographic screening from age 40 years on breast cancer mortality (UK Age trial): final results of a randomised, controlled trial. Lancet Oncol. 2020;21(9):1165-1172.
13. Fisher B, Anderson S, Bryant J, Margolese RG, Deutsch M, Fisher ER, et al. Twenty-year follow-up of a randomized trial comparing total mastectomy, lumpectomy, and lumpectomy plus irradiation for the treatment of invasive breast cancer. N Engl J Med. 2002;347(16):1233.
14. Arriagada R, LêMG, Rochard F, Contesso G. Conservative treatment versus mastectomy in early breast cancer: patterns of failure with 15 years of follow-up data. Institut Gustave-Roussy Breast Cancer Group. Clin Oncol. 1996;14(5):1558.
15. Chu QD, Hsieh MC, Yi Y, Lyons JM, Wu XC. Outcomes of Breast-Conserving Surgery Plus Radiation vs Mastectomy for All Subtypes of Early-Stage Breast Cancer: Analysis of More Than 200,000 Women. J Am Coll Surg. 2022;234(4):450
16. Tönnies T, Baumert J, Heidemann C, von der Lippe E, Brinks R, Hoyer A. Diabetes free life expectancy and years of life lost associated with type 2 diabetes: projected trends in Germany between 2015 and 2040. Popul Health Metr. 2021;19(1):38.
17. Veronesi U, Cascinelli N, Mariani L, Greco M, Saccozzi R, Luini A, et al. Twenty-year follow-up of a randomized study comparing breast-conserving surgery with radical mastectomy for early breast cancer. N Engl J Med. 2002;347(16):1227-32.
18. Clarke M, Collins R, Darby S, Davies C, Elphinstone P, Evans V, et al. Early Breast Cancer Trialists' Collaborative Group (EBCTCG). Effects of radiotherapy and of differences in the extent of surgery for early breast cancer on local recurrence and 15-year survival: an overview of the randomised trials. Lancet. 2005;366(9503):2087-106.
19. de Boniface J, Szulkin R, Johansson ALV. Major surgical postoperative complications and survival in breast cancer: Swedish population-based register study in 57152 women. Br J Surg. 2022;109(10):977-983.
20. Eurostat. Breast cancer and cervical cancer screenings - historical data

(2000-2021). Internet. 2022 Jul. Available from: https://ec.europa.eu/eurostat/databrowser/view/hlth_ps_scre/default/table?lang=en.
21. Wooldridge JM. Econometric Analysis of Cross Section and Panel Data. Cambridge, MA: The MIT Press; 2002.
22. Niță I, Nițipir C, Toma SA, Limbău AM, Pîrvu E, Bădărău AI, et al. Correlation between Androgen Receptor Expression and Immunohistochemistry Type as Prognostic Factors in a Cohort of Breast Cancer Patients: Result from a Single-Center, Cross Sectional Study. Healthcare (Basel). 2021;9(3):277.