REVIEW

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Mortality of Young Women due to Breast Cancer in Low, Middle and High-Income Countries: Systematic Literature Review and Meta-Analysis

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Abstract

Objective: To identify the difference in breast cancer mortality rates among young women according to countries' economic classification. **Methods:** A systematic literature review included retrospective studies on breast cancer mortality rates in women aged 20 to 49 years. Databases used were PubMed, Web of Science, Scopus, and Virtual Health Library, with articles selected in English, Portuguese, and Spanish. The study selection and analysis were conducted by two pairs of researchers. Data from 54 countries were extracted, including 39 high-income, 12 upper-middle-income, and 3 lower-middle-income countries. A meta-analysis was performed with the quantitative data from two studies. **Results:** Six articles met the inclusion criteria. Four were analyzed descriptively due to data diversity, and two were included in the meta-analysis. The pooled mortality rate for high-income countries was 10.2 per 100,000 women (95% CI: 9.8-10.6), while for upper-middle-income countries, it was 15.5 per 100,000 women (95% CI: 14.9-16.1). Lower-middle-income countries had a pooled mortality rate of 20.3 per 100,000 women (95% CI: 19.5-21.1). The decrease in mortality rates in high-income countries was statistically significant ($p<0.05$). **Conclusion:** Mortality rates for breast cancer among young women have decreased significantly in high-income countries but have increased in lower-income countries. This disparity underscores the impact of insufficient investment in preventive measures, health promotion, early diagnosis, and treatment on young women's mortality in lower-income countries.

Keywords: Breast neoplasms- epidemiology- country´s economic classification

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Introduction

Breast cancer is the most prevalent and highest mortality type of cancer in women worldwide. The incidence has increased in both developed and developing countries [1], but there is evidence of a higher incidence in developed countries, while mortality is higher in less developed ones [2]. The risk of a woman developing cancer during her lifetime is approximately 12.4% [3]. Despite cancer research and advances in diagnosis and treatment, breast cancer, incidence, and mortality, are expected to increase significantly in the coming years. There is evidence that breast cancer in women under the age of 45 is the leading cause of death from cancer, given the heterogeneity and complex nature of this type of cancer [4]. Worldwide, the highest breast cancer incidence rates are in Australia, New Zealand, Northern, Western, and Southern Europe, and Northern America [5]. As for breast cancer mortality, it is the main cause of death in Melanesia, Western Africa, Micronesia/Polynesia, and the Caribbean with Barbados having the world's highest mortality rate [5].

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Although the incidence of breast cancer is age-dependent, a constant increase in younger women diagnoses (under 40 years) has been reported in several countries [5, 1, 4]. This subgroup of women has different risk factors, tumor biology, clinical outcomes, and specific psychosocial issues, such as fertility preservation, family planning, and job reintegration [6]. The increase in mortality appears to be more significant in low and upper-middle-income countries when compared to countries classified as high-income [7].

Breast cancer prevention involves various measures, with mammography being one of the most effective tools for early detection. Mammography can reduce breast cancer mortality by up to 25% to 30% in women aged 50 to 69, enabling early diagnosis and timely treatment. In high-income countries, where screening programs are more widely implemented, breast cancer mortality has significantly decreased. In contrast, in low- and middle-income countries, where access to mammography and other preventive health services is limited, breast cancer mortality continues to rise. This disparity in mortality reflects not only the availability of screening but also the quality of healthcare services, access to treatment, and awareness of breast cancer. The World Health Organization (WHO) emphasizes the need to strengthen screening programs and early diagnosis in lower-income countries to reduce the global burden of breast cancer [8].

Breast cancer has the highest treatment cost of any cancer, accounting for 14% of all cancer treatment costs [9]. Therefore, understanding, if there is a difference in breast cancer mortality according to the economic classification of countries, is important to help build preventive strategies to lower breast cancer mortality rates among young women.

Materials and Methods

Eligibility and exclusion criteria

The inclusion criteria considered retrospective studies that described the breast cancer mortality rate in young women aged 20 to 49 years. Articles with mortality data for women under 20 and over 50 years were excluded, and studies that included data stratified in decades (20-29; 30-39; 40-49) were also excluded. Review studies, systematic reviews, meta-analyses, patents, comparative studies, comments, editorials, congress, integrative-comprehensive reviews, and studies in other languages (except English, Portuguese, and Spanish) and with no summary available were also excluded.

Research and study selection criteria

In the first phase of the study, four researchers (JDDS, KPS, ACD, and VDM) entitled Group 1, carried out an exhaustive search to define the MeSH and Emtree terms, which were validated by three specialists (RBP, LA, and SMP) entitled Group 2. The search strategy combined the terms: Vital Statistics, Epidemiologic Studies, Breast Neoplasms, and Adult. The complete search strategy is presented in Supplementary Information (Table 1). It is important to emphasize that the descriptors were defined independently, by the researchers, and always validated by consensus. The filters used (Pubmed) were summary, and publications between 07/03/2009 to 07/03/2018, studies with human beings, in English, Portuguese, and Spanish, adult women (20-49 years).

For the second phase, Group 1 screened the articles found in the databases by reading titles and abstracts. They conducted searches independently and any divergences were solved between them and/or between Group 2. For the third phase, the full text of the articles was randomly distributed to Group 1 researchers and, read in its entirety.

In case of disagreement, the inclusion or exclusion of the article was decided between researchers and specialists. In the third phase, the articles selected by Group 1 were distributed to three independent reviewers (RBP, LA, and SMP) for certification. The final selection of publications was made by mutual agreement between researchers from both groups.

Information sources

The following electronic databases were used: PubMed, Web of Science, Scopus, and Biblioteca Virtual da Saúde (Virtual Health Library). Only full articles published between 2009 and 2018, in English, Portuguese, and Spanish were included.

Data extraction

The reviewers from Group 1, divided into two groups (JDDS and KPS, ACD and VDM), performed independently, the data extraction, and the disagreements were solved by specialists. General characteristics of the studies were collected, such as year of publication, authors, city and country, mortality rate, study schedule, the age range of the mortality rate, and main conclusions.

Protocol and Registration

This systematic review is reported according to the Statement of Preferred Report Items for Systematic Review and Meta-analyzes (PRISMA) [10] and PRISMA Network Meta-analysis [11] (NMA) and is recorded in the PROSPERO database (https://www.crd.york.ac.uk/prospero/) under the number CRD42020108565.

Data analysis

To perform the meta-analyses, the Stata program (12.0, Stata Corporation, College Station, TX, USA) was used. For evaluation of the publications, the measure of estimated effect was combined with a 95% confidence range (CI). A subgroup analysis was done according to the presented information; two periods on the breast cancer mortality rate in young women, from the year 2002 and after 10 years, in 2012.

The measures of the estimated effect of the mortality rate were created to generate the measures of effect for the preparation of the forest plot (the year 2002/year 2012). Fixed and random effects were used. If the heterogeneity was greater than 50%, the random effects model was chosen. Statistical heterogeneity was performed according to Cochran's Q statistical test ($P < 0.010$) as indicative of significance. For publication analysis, the communication of Begg's [12] and Egger´s [13] methods was used, with a significance $P < 0.05$. Following the criteria of

50% or more significance as described by the Higgins and Thompson I statistics [14], the discrepancy of the publications was assessed [14]. To determine the weight of each study in the meta-analysis, the random effects of the DerSimonian-Laird model were used [15].

Evaluation of study quality

To analyze the quality of the included studies, a checklist to assess the quality of observational cohort and cross-sectional studies from the National Heart, Lung, and Blood Institute was used. The instrument consisted of 14 questions, with the possibility of answering "yes", "no" and "others". It was possible to verify that, in general, the included studies are of good quality.

Risk of bias between studies

To provide a better sense of the bibliographic search, all included articles listed references, were reviewed by Group 1. This was highly relevant because it allowed the identification of publications that were not found in the primary searches of the database.

Results

The PRISMA flowchart (Figure 1) shows the articles that were included in each step of this review. Initially, there were 6,167 articles identified, of which 32 were duplicates. After the title and abstract screening, 124 articles were considered relevant for reading in its fullness. From those, 118 articles were excluded because they did not meet the inclusion criteria. Therefore, six articles were included, and two were included for the meta-analysis.

General presentation of the studies

After reading and evaluating the six studies, data were extracted according to the aim of the research. Regarding the place of development, two were from Italy and Spain [16, 17], two were carried out by authors from the United States [18, 19], one from Brazil [20], and one from Switzerland [21]. Two were multicenter studies, carried out with collaboration between authors from Italy and Spain Spain [16, 17], that presented data from several countries.

The map (Figure 2) shows the spatial distribution of the six studies, as well as the breast cancer mortality rates in young women aged 20 to 49 years in the countries where the data presented in the articles were collected. Data showed a significant variation regarding the date that ranged from 1979 to 2013, with most of the data presented annually and just one study bringing only the average rate, in the period between 1996 and 2013 [20]. According to the information provided in Table 1, the publications were

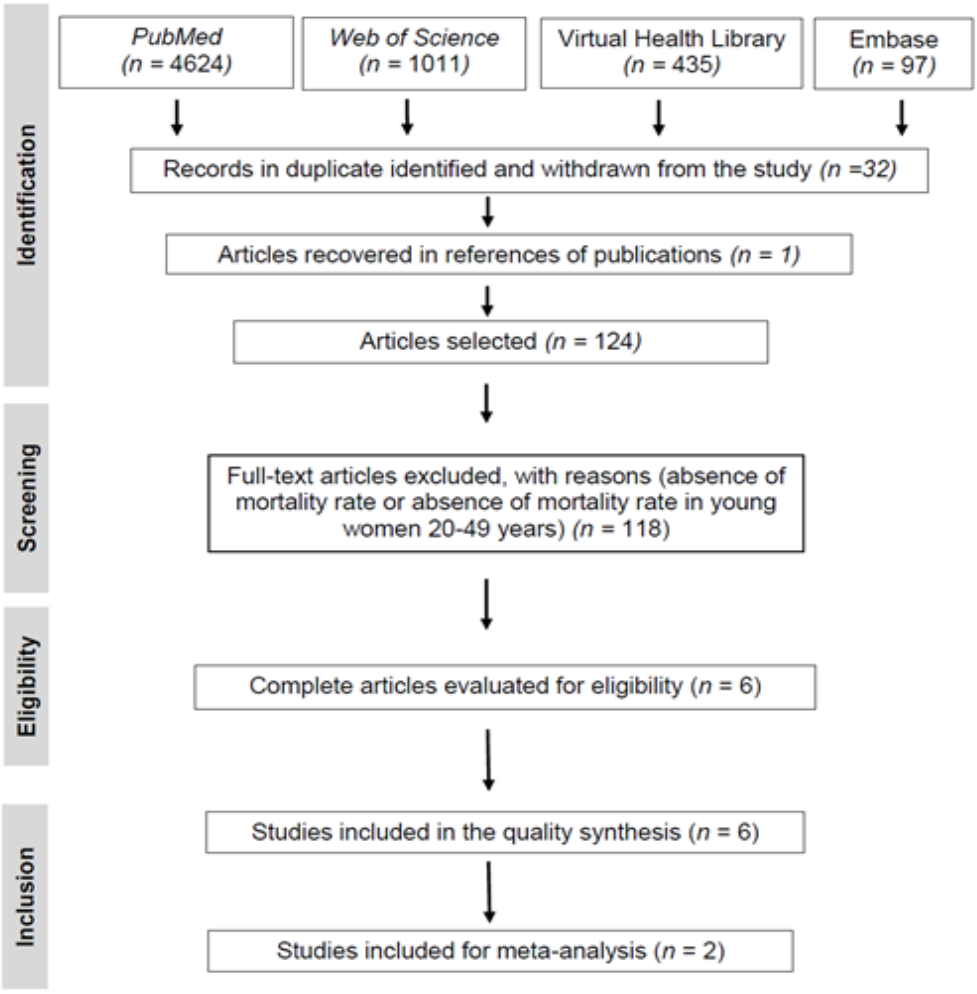

Figure 1. Flow Diagram of the Systematic Review Steps. Observational studies, that mentioned breast cancer mortality rate in young women (20-49 years) across the world.

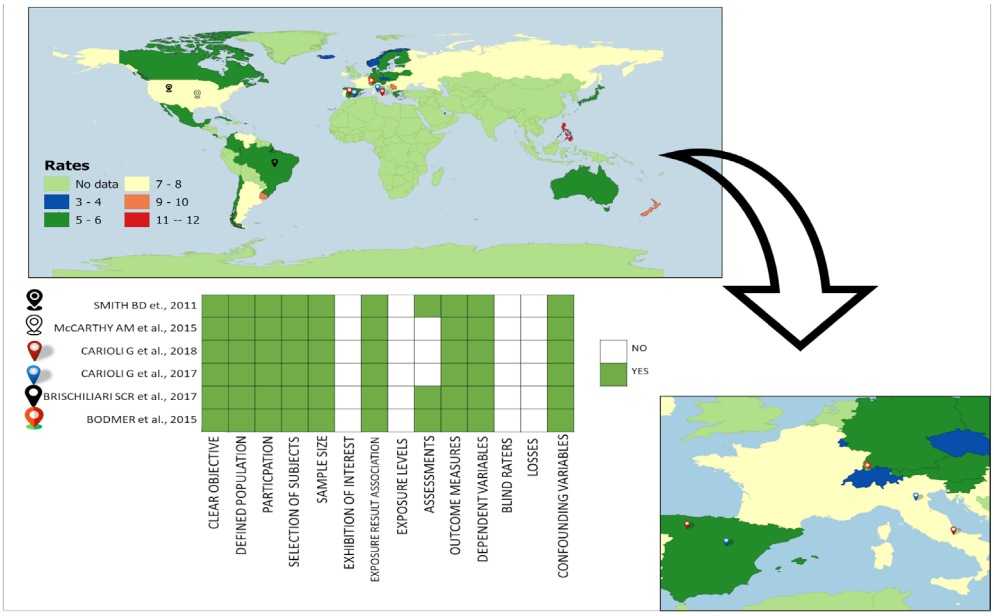

Figure 2. Distribution of Studies According to Country of Elaboration and Mortality Rate. Quality assessment of the included studies.

in 2011, 2015, 2016, 2017, and 2018 with mortality rates from 34 countries in Europe, 7 countries in Asia, 12 in America, and 1 in Oceania.

Only three of the six included studies were specific

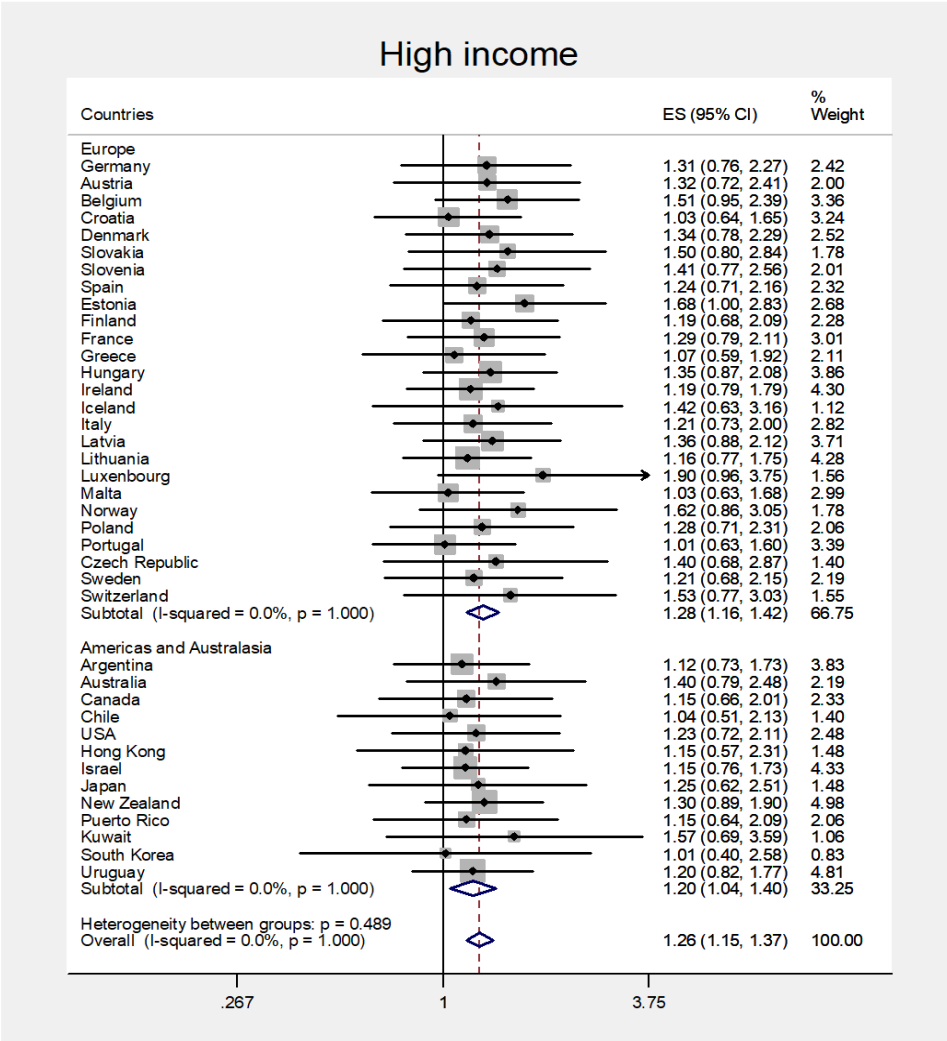

Figure 3. Forest Plot of the Mortality Rate of High-Income Countries (ES, effect size estimate); (CI, interval confidence).

Table 1. Data Synthesis from the Articles Included in the Study Regarding Breast Cancer Mortality in Women Aged 20 to 49 Years

Author/year	Place and number of countries involved	Age range and period included	Brief conclusion
Carioli G et al. [18]	Italy and Spain; 35 countries	20-49 Years: 2002, 2007 and 2012	In general, there was a decrease in the breast cancer mortality rate from 17.9 in 2002 to 15.2 in 2012. The decreases in mortality rates varied from 4.9% in Poland and 27% in the Czech Republic and Denmark. In the 20-49 age group, the overall drop in the European Union was 21.8%. It is noteworthy that the reduction in the mortality rate due to breast cancer occurred in the age group of 20 to 49 years.
Carioli G et al. [17]	Italy and Spain; 20 countries	20-49 Years: 2002, 2007 and 2012	Mortality rates dropped in most countries included in the study. Mortality in woman under 50 years old seems to have suffered a greater decrease in the studied period. The drop in mortality rates is due to better treatment, earlier detection. Breast cancer is no longer the leading cause of breast cancer in Europe. For 2020, the expectation is for a global rate of 13.5/100 thousand, where in the 90's it was more than 20/100 thousand.
McCarthy AM et al. [18]	United States; 01 country	20-49 Years: 1979 and 2010	In the 20 to 49 age group, breast cancer mortality was the second leading cause of death. The standardized rate was twice as high for black women (14.3) than for white women (7.1).
Bodmer et al. [21]	Switzerland; 01 country	20-49 Years: 1996 and 2009	Decrease in mortality during the study period, even in the face of increased incidence and decreased survival (in young women aged 20-39)
Brischiliari SCR et al. [20]	Brazil; 01 country	20-49 Years: 1996-2013	Mortality due to breast cancer in Brazil had a significant increase, where in 1996 it was 12.1, in 2013 it went to 15.7. In the 20-49 age group, the increase was more significant in all regions, with more emphasis on the central-west and northeast regions.
Smith BD et al. [19]	United States; 01 country	20-49 Years: 1980-2007	2.5%/year decrease in mortality in women aged between 20 and 49 years, from 1990 to 2007, due to improvements in screening and treatment. On the other hand, there was an increase in mortality in women over 75 years old.

to young women mortality and they were from Brazil, Switzerland, and United States. The others brought the mortality rate in the age group chosen, among other ages.

Two manuscripts that presented mortality trend analysis for the same time range and age (Figure 2) were developed by the same authors in three different continents (Europe, Australia and the Americas). The years investigated by the authors were 2002, 2007 and

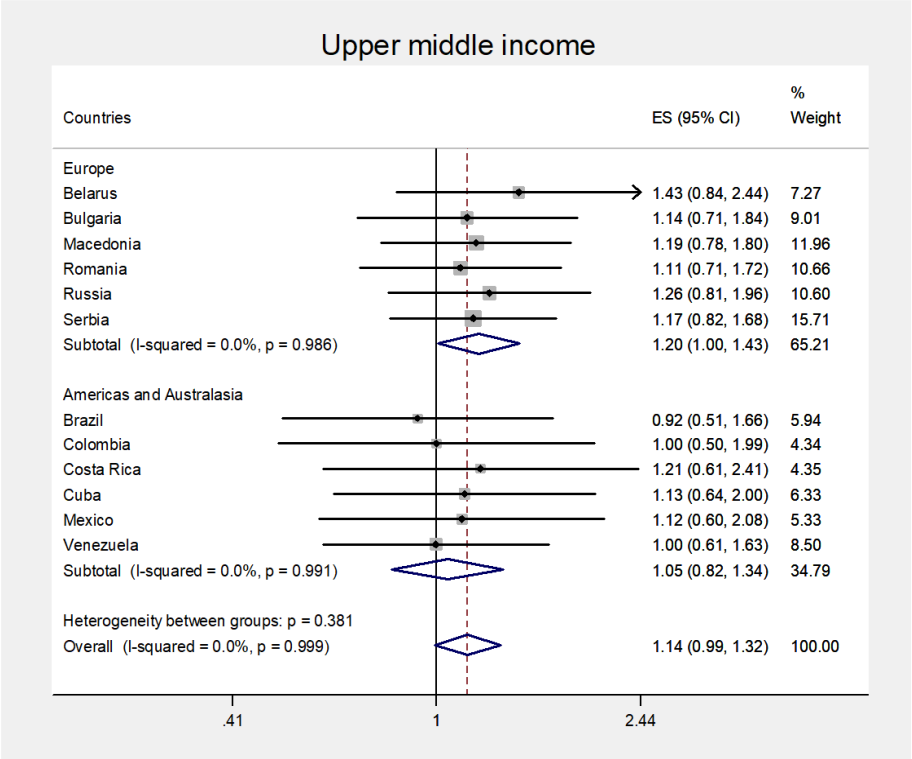

Figure 4. Forest Plot of the Mortality Rate of Upper-Middle-income Countries (ES, effect size estimate); (CI, interval confidence).

Table 2. The Meta-Analysis Data Synthesis from the Articles included in the study regarding breast cancer mortality in women aged 20 to 49 years.

			Test of association			Heterogeneity test	
	nº of studies	nº of countries	ES	95% Cl	p-value	p-value	I^2 (%)
High-income	2	39	1.26	1.15 - 1.37	<0.001	1	0
Europe		26	1.28	1.16 - 1.42	<0.001	1	0
Americas and Australasia		13	1.2	1.04 - 1.40	0.01	1	0
Medium-high-income	2	12	1.15	0.99 - 1.32	0.065	0.999	0
Europe		6	1.2	1.00 - 1.43	0.045	0.986	0
Americas and Australasia		6	1.05	0.82 - 1.34	0.704	0.991	0
Low-income	2	3	1.13	0.90 - 1.43	0.288	0.144	48.3
Europe		2	1.36	1.01 - 1.83	0.042	0.732	0
Americas and Australasia		1	0.85	0.58 - 1.23	0.389	NA	NA

ES, effect size estimate; CI, confidence interval; NA, not applicable.

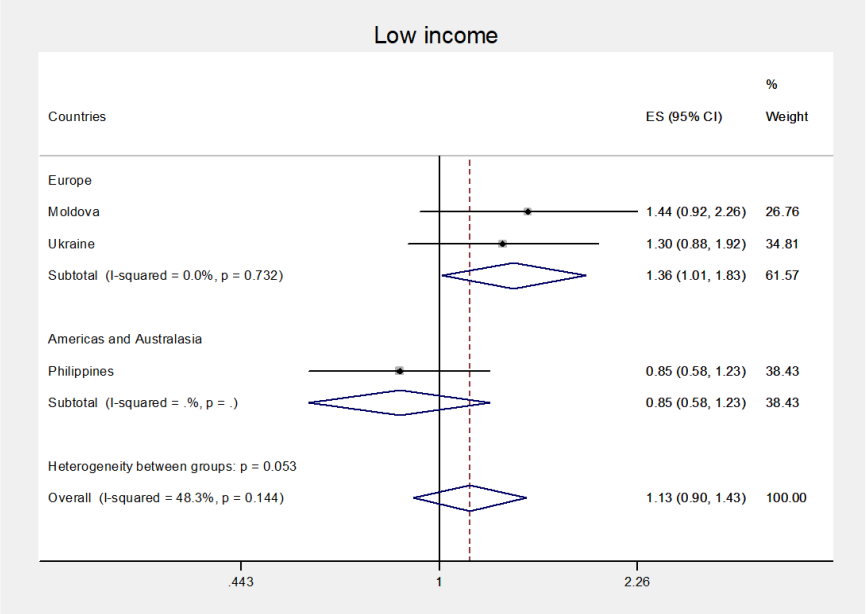

Figure 5. Forest Plot of the Mortality Rate of Low-Income Countries (ES, effect size estimate); (CI, interval confidence).

2012 for three age groups (20 to 49, 50 to 69 and 70 to 79) Spain [16, 17].

In the United States, a retrospective study from 1980 to 2007, published in 2011, found a decline from 14.9 to 7.9/100 thousand, that is, a significant decrease of 53% in the breast cancer mortality rate over 27 years [19]. According to the same author, this result is due to the better screening actions adherence, better treatment acceptance when compared to older women, in addition to having less comorbidities and better social support [19].

In the United States, in 1978 and 2010, the mortality rate was 1.76 and 2.0, respectively. Additionally, this same publication verified that mortality in black young women is twice as high as in white women [18]. In Switzerland, in 1996, the mortality rate was 10.2, and in 2009 it was 6.2, with a decrease of four cases/100 thousand women in a 13 years period [19]. In the article carried out in Brazil, there was an increase in the mortality rate between 1996 and 2013, with an increase in all regions of the country, being higher in the Northeast.

Economic classification

All the countries presented by the included articles, that granted mortality data were economic classified according to their income level. The World Bank assigns the world's economies to four income groups—low, lower-middle, upper-middle, and high income. The classifications are updated each year on July 1 and are based on the GNI per capita of the previous year.

In these, the mortality rate of 54 countries of different socioeconomic classifications was found, in which 39 were classified as high-income, 12 were of medium-high income and three of medium-low income. Among high-income countries, in the age group between 20 to 49 years, the lowest mortality rate found was 1.36/100 thousand in 1979 and the highest rate was 14.31/100 thousand in 1986, both in the United States. The maximum and minimum rates found in upper-middle-income countries were 11.7/100 thousand in Serbia in 2002 and 5.2/100 thousand in Costa Rica between the years 2007 and 2012. In low-income countries, the lowest rate in the 20 to 49 age

group was 7.4/100 thousand in Moldova and the highest was 11.5/100 thousand in Ukraine.

The study carried out with data from European countries, shows mortality rates from 34 countries, six of which are considered to be of medium-high income, two of medium-low income and 26 of high-income [16]. There was a gradual decrease in the mortality rate in women aged 20 to 49 years, in the three years studied (2002, 2007 and 2012), in most of the countries included. In high-income countries, the lowest rate found was 4.16 in Iceland and the highest was 10.6 in Hungary, both in 2007. In medium-low-income countries, the lowest rate was found in Moldova (7.4) in 2012 and the highest was in Ukraine (11.4) in 2002. Among the six medium-high-income countries, the lowest rate found was Belarus (6.2) in 2012 and the highest was in Serbia (11.7) in 2002.

Similarly, the survey carried out in Australia and the Americas, in the same period and age group, identified 13 countries classified as high income, six with high average, one with low average income. In high-income countries, the highest rate was in New Zealand (11.8) in 2002 and the lowest was in Kuwait (3.9) in 2012. In the Philippines, which is a medium-low-income country, there was an increase from 9.7 in 2002 to 11.4 in 2012. In the majority of the upper-middle-income countries, there was an increase in the rates, where the highest was in Venezuela (7.97) in 2012 and the lowest was 5.2 in Costa Rica, also in 2012 [17].

Meta-analysis

Two articles showed homogeneity for performing meta-analysis [16, 17], one performed with data from European countries and the other with data from Australasian and American countries. For the forest plot graph, the data were separated to according to the World Bank classification between in medium-low, medium-high, and high-income countries. Thus, making it possible to verify an increase or decrease in breast cancer mortality in young women according to the economic classification (Table 2). The analysis of publication bias was infeasible due to the number of articles.

In high-income countries (Figure 3), when comparing the mortality rate among young women with breast cancer in the years 2002 and 2012, it was possible to observe a pooled estimate of 26% reduction in mortality rates after a 10-year interval (1.26; 95% CI1 .15-1.37, p <0.001). Even when analyzed by subgroup in the European or American continents and Australasia, there was a reduction pooled estimate of 28% and 20%, respectively (Europe 1.28; 95% CI 1.16-1.42; p <0.001; Americas and Australasia 1.20; 95% CI 1.04-1.40; p = 0.01). The heterogeneity of data pooled was low (0.0%). The mortality rate among young women with breast cancer in medium-high-income countries (Figure 4) did not show statistical difference when comparing the years 2002 and 2012 (p = 0.06), even when analyzed by subgroup by European or American continent and Australasia (p = 0.045; p = 0.704). The heterogeneity of data pooled was low (0.0%).

Likewise, in Low-income countries (Figure 5), mortality rates among young women with breast cancer did not show a statistical difference when comparing the years 2002 and 2012 (p = 0.288), however, when analyzing the subgroup by continent, the European continent showed a reduction pooled estimate of 36% (1.36; 95% CI 1.01-1.83, p = 0.042). The American subgroup and Australasia did not show any difference between mortality rates (p = 0.389). Heterogeneity was moderate in the of data pooled analysis (48.3%) and in the European continent subgroup it was low (0.0%).

Discussion

The mortality due to breast cancer has been the subject of studies around the world, however, when related to young women, it is still incipient, since the rates are still relatively low in the age group below 50 years, when compared to the rates of death above that age.

In face of the results obtained in this study, it was found that the researchers' focus has been women over 50 years old, due to the higher incidence and mortality. Even in finding mortality data of women below 50 years old, in the majority, they are not mentioned in the discussions as a relevant aspect in the studies. As it can be seen in the meta-analysis that was carried out with two of the selected studies, in high-income countries there was a significant decrease in the mortality rate in young women, while in lower-income countries there were no results of a significant decrease in mortality. Among the lowest-income countries, only two showed a significant reduction in rates, Moldavia and Ukraine, both countries in Europe Spain [16, 17].

In Brazil, an analysis of overall breast cancer mortality by region was carried out and it was observed that in regions with greater economic development and better access to health services, the rates were higher, attributing to better conditions for diagnosis and access to oncology reference services [22]. In medium-low-income countries, 60 to 70% of the cases are diagnosed in more advanced stages, which decreases the chances of cure and increases the number of deaths. Late diagnosis and delay in starting treatment may explain the age difference of deaths, where 54% of low-income women die before age 54, whereas in high-income countries the percentage drops to 20% in the same age group [23].

The chance of survival for women with breast cancer in high-income countries is around 80%, 60% in middle-income countries and 40% in low-income countries [8]. Thus, the barriers imposed by economic struggles and health care have a strong influence on cancer mortality in young women worldwide [24]. Meanwhile, the preventable risk factors, cancer-related illness and death are increasingly concentrated in poor and disadvantaged populations. Although there was an improvement in early diagnosis measures and advances in treatment, breast cancer has still been the leading cause of death in women worldwide, and in 25% of these deaths occur in women under the age of 50 [23]. Between the 1980s and 2010, in medium-low-income countries, the increase in breast cancer incidence and mortality was 60 and 53%, respectively, while in high-income countries the increase was 47% in incidence and 30% in mortality [23].

The decrease in the mortality rate observed in several

studies has been relevant, since the prognosis of young women with breast cancer is worse than in older women. This is due to the aggressiveness of tumors in this age group, that involves lymph nodes, negativity for hormone receptors, high proliferation, among others. However, advances in diagnosis and treatment have been helpful to the survival of these women [25]. With this thought, WHO also highlights the decrease in the mortality rate in young women due to advances in treatment, unlike the public over 50 years old who also benefits from screening with mammography which increases the chances of early diagnosis [8].

Mammographic screening is still a discussion that has gaps, since the screening protocols are not performed in young women. This non-recommendation for screening in young women is due to several reasons, such as overdiagnosis and little evidence that mammography does indeed interfere with cancer mortality numbers in young women. Yes, it is believed that adequate treatment is the main responsible for the decrease in mortality, mainly in North America and Europe [26].

A study carried out in Norway showed that the balance of the benefits of screening by mammography is negative when compared to overdiagnosis, that is, screening reduces mortality by 15%, while overdiagnosis resulting from screening is 30% [23]. Likewise, a systematic review was carried out in Asia with the aim of evaluating the models of early detection associated with economic issues and, however attractive it may be to perform screening in women under 50 years old, there is still limited evidence regarding screening institution and early diagnosis [24].

Another factor is that in low-income countries, resources are limited and make the health system more expensive, since the organization of mammographic screening requires technological resources, training of professionals, education and adherence by the target audience. In these cases, the adoption of preventive measures and early identification with a clinical breast exam, as it has low cost, may be an option, since early detection is the cornerstone for decreasing mortality and increasing survival [8]. One of the limitations of the study was the heterogeneity found in the studies, with wide variations in the age group and year/period, thus making it difficult to carry out robust meta-analysis. In addition, only a few studies have been conducted specifically about mortality in young women due to breast cancer, highlighting that the subject is still underexplored in younger women.

In conclusion, it was observed that, from the studies included in this review, there was a significant decrease in mortality rates in high-income countries in the ten years analyzed in the meta-analysis. The same did not happen in lower-income countries. This scenario confirms the data already mentioned in the literature, highlighting that better screening actions, early diagnosis and adequate treatment are the factors that directly influence the decrease in breast cancer mortality. With this thought, it is necessary to have more investments and strategies aiming low-income countries, as well as new studies being carried out on breast cancer in young women.

Author Contribution Statement

All authors contributed to the study equally. All authors read and approved the final manuscript.

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Ethical Approval

This study did not involve the use of human or animalparticipants, therefore, ethical approval does not apply.

Availability of Data

Data are available by request to the corresponding author.

Study Registration

This systematic review is reported according to the Statement of Preferred Report Items for Systematic Review and Meta-analyzes (PRISMA) and PRISMA Network Meta-analysis (NMA) and is recorded in the PROSPERO database (https://www.crd.york.ac.uk/prospero/) under the number CRD42020108565.

Conflicts of Interest

The authors declare no potential conflicts of interest.

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