FACULTAD DE MEDICINA
UNIVERSIDAD DE CANTABRIA

GRADO EN MEDICINA

TRABAJO FIN DE GRADO

Relationship between socio-economic level and breast cancer prognosis: a meta-analysis

(Relación entre el nivel socioeconómico y el pronóstico en el cáncer de mama: Metaanálisis)

Autora: Cristina Corrales Selaya

Directora: Inés Gómez Acebo

Santander, junio 2019

CONTENTS

ACKNOWLEDGMENTS

This work has been funded by a grant from the Ministerio de Educación.

ABSTRACT

Introduction: Breast cancer prognosis has been improving during the last decades, differences in mortality rates seem to be influenced by socioeconomic status. However, the relationship and trends between socioeconomic status and breast cancer prognosis is still controversial. For this reason, the objective of this meta-analysis is to summarize all papers published in PubMed, SCOPUS and Web of Science-databases before November 2018. We did a broad search strategy including cohort studies that provided at least one association measurement (OR, HR) with confidence interval 95%. In total Twenty-two studies published. Pooled RR were estimated by weighting individual OR/RR by the inverse of their variance. In addition, we stratify by European, Public Health System, considering in each group if they were retrospective or prospective.

Results: Our study showed a risk effect between educational level and breast cancer mortality, but only in retrospective studies (OR=1.07, 95% CI: 1.00-1.14). Considering only retrospective studies conducted in Europe or those carried out in Public Health systems, we obtained similar association (OR= 1.06, 95% CI: 1.00-1.13). However, when we consider the temporary period, the OR of prospective studies conducted before 1980 was 1.18 (95% CI: 1.08-1.30) meanwhile, the OR of prospective studies conducted after 1980 show a protective effect between educational level and mortality from breast cancer (OR=0.75, 95% CI: 0.70-0.81).

Conclusions: this meta-analysis suggest that in retrospective studies exist increased risk of mortality between people of higher economic status with breast cancer in Europe and in Public Health Systems. On the other hand, prospective studies suggest a change in trend before 1980 so that, from that time, higher socioeconomic status tends to be a protective factor from breast cancer mortality.

Keywords: Breast cancer, Socioeconomic Status, Educational Level, Prognosis and Mortality.

RESUMEN

Introducción: El pronóstico en el cáncer de mama ha mejorado durante las últimas décadas y las diferencias observadas en las tasas de mortalidad parecen estar influenciadas por el nivel socioeconómico, aunque está relación es aún controvertida. El objetivo de este trabajo es analizar todos los artículos publicados en PubMed, SCOPUS y Web of Science antes de noviembre de 2018. Para ello se incluyeron todos aquellos estudios de cohortes que proporcionaron al menos una medición de asociación (OR, HR) con intervalo de confianza del 95%. En total se han publicado veintidós estudios. La OR combinada se estimó ponderando la OR o RR individual por el inverso de su varianza. Además, se analizaron de forma independiente por una parte los estudios europeos, y por otra los realizados en países con sistemas públicos de salud, diferenciando dentro de cada grupo si eran estudios prospectivos o retrospectivos.

Resultados: Este estudio mostró un incremento del riesgo de mortalidad por cáncer de mama en relación con el nivel educativo, pero solo en estudios retrospectivos (OR = 1.07, IC 95%: 1.00-1.14). Teniendo en cuenta solamente los estudios retrospectivos realizados en Europa o los realizados en los sistemas de salud pública, obtuvimos una asociación similar (OR = 1,06, IC 95%: 1.00-1.13). Sin embargo, cuando consideramos los resultados en función del tiempo, la OR de los estudios prospectivos realizados antes de 1980 fue de 1.18 (IC 95%: 1.08-1.30), mientras que la OR de los estudios prospectivos realizados después de 1980 sugiere un efecto protector del nivel educativo con respecto a la mortalidad por cáncer de mama (OR = 0.75, IC 95%: 0.70-0.81).

Conclusión: Este metaanálisis sugiere que el nivel educativo sería un factor de riesgo para la mortalidad por cáncer de mama en los estudios retrospectivos llevados a cabo en Europa o en sistemas públicos de salud. Sin embargo, los estudios prospectivos realizados después de 1980 sugerirían que, a partir de este de momento, el nivel educativo comenzaría a ser un factor protector.

Palabras clave: Cáncer de mama, nivel socioeconómico, nivel educativo, pronóstico y mortalidad.

INTRODUCTION

Breast cancer (BC) is the most commonly diagnosed cancer worldwide. In 2018, about 2.1 million females were diagnosed from breast cancer accounting for almost 1 in 4 cancer cases among women (1). Nevertheless, in the last decades, breast cancer prognosis has improved due to medical and technological advances in early detection methods, standardization in the interpretation of tests, use of less invasive surgical techniques, improvement in systemic treatments and new discoveries in the field of genomics. On the other hand, disease awareness has increased worldwide, which has led to greater economic investment in early detection strategies (2). Thus, since 1980, screening programs have been established in many developed countries. This meant an increase in the number of cases of breast cancer, especially at the expense of early forms, which stabilized years later (3). Similarly, according to a statement issued by the IARC, early detection methods would have caused a decrease in mortality of 23% in women between 50-69 years who were invited to the screening programs, and that amounted to 40% considering only the women who really participated (4). However, some authors (3) consider that survival increased considerably earlier than expected, so mammography would not have been the only reason. Moreover, in the 1980s, the use of chemotherapy treatments and hormone therapy was also increased, becoming systematic in many developed countries. This issue has been proposed for some authors as the reason of the decreasing in mortality at a time when screening was still beginning (5). A meta-analysis published in 2005 (6) showed that these treatments reduced both the risk of recurrence at 5 years and the mortality rate at 15 years. The mortality rate was decreased by 38% for women under 50 years of age and by 20% among women between 50 and 69 years of age. In this way, since the beginning of the 21st century, new changes have been introduced in the treatment, such as neoadjuvant chemotherapy, new chemotherapy regimens, biological drugs (7), mastectomy has been replaced by conservative surgery and axillary emptying by selective sentinel lymph node biopsy (8,9), whose impact on mortality will be seen over the next few years.

Otherwise, other factors apart from early detection or treatment have been proposed as prognosis factors for breast cancer survival. Some of the factors are inherent of the patient such as age at diagnosis, age of menopause, comorbidities, period of diagnosis, race and other are related with the tumor: tumor size, histological type, histological grade regional lymph node involvement, lymphovascular invasion and molecular markers of angiogenesis (10). In addition to these factors, traditionally, breast cancer has been considered as a “disease of privilege” due to the association between higher socioeconomic level and breast cancer incidence. This relationship continues to be shown in recently published studies (11,12). Reproductive factors (nulliparity, late age at first birth, fewer children), factors related to menstruation (early age at menarche, later age at menopause), mammography screening, hormone replacement therapy and life style factors (alcohol intake, weight gain during adulthood) have been proposed as some of the factors that could explain this association (13). On the other hand, physical activity and breastfeeding have been considered as protective factors specially in estrogen and progesterone receptor negative subtypes (14,15).

However, mortality rates are higher in many low-middle income countries (LMICs) than in high income countries (HICs). In HICs breast cancer mortality rates have been decreasing due to mammography screening (identifying tumors at earlier stages when treatment has a greater likelihood of success) and better treatments (16). In contrast, the higher mortality rates in LMICs may be the consequence of more often late stage diagnosis and poorer access to treatment. Apart from higher probability of mortality, women of LMICs more often suffer from lasting physical effects from surgery and radiation treatment including lymphedema of the arm or pain in chest region due to invasive treatments. Long-term effects of breast cancer treatment including increased risk of osteoporosis, cognitive impairment, chronic fatigue, hot flashes, and vaginal dryness are more frequent also in this population (17).

In recent years interest has grown in the relationship between individual socioeconomic status and prognosis in breast cancer. Several studies have been published on this subject, but the relationship remains unclear. The main objective of this paper is to summarize the published literature on the relation and trends between socioeconomic level and breast cancer mortality in three period (prior to 1975, from 1975 to 1980 and more than 1980), using studies with different types of socioeconomic level measurement.

METHODS

2.1 Search strategy.

Firstly, the following inclusion criteria were defined: we looked for cohort studies performed in humans, which reported, at least, one hazard risk (HR) or odds ratio (OR) with 95% confidence interval (95% CI). We included only articles that were published in English before November 2018.

We start our bibliographic search in Pub-Med, Scopus and Web of Science databases. The keywords of the search were ““Breast cancer” AND ("Area-level Deprivation" OR “socioeconomic level” OR “socioeconomic status” OR “education level” OR “education status” OR "SES" OR “income” OR “occupation”) AND (“Prognostic” OR “Survival”)”. We found 2093 articles after having entered the search terms in the three databases (PubMed, Scopus and WOS) and checking for duplicates. Subsequently, we looked for previous meta-analysis in our research and added 31 references that were not included. After having read the title, we selected 466 articles, and 235 after reviewing the abstracts. Next, we carried out a more exhaustive and complete reading, which allowed us to reject, all that were not cohort studies and obtained 108 references for full text reading. Finally, we selected 40 studies which included association measures (OR or HR) between socioeconomic status and breast cancer mortality to perform the meta-analysis (some of them include 2 socioeconomic factors measurement). Classifying them according to the socioeconomic factor that is used in the study, we obtain 22 of Education level (18-39), 5 Occupational level (40-44), 5 Area of residence (45-49), 8 of Income (18, 25, 31, 51-54) and 4 of Urban vulnerability (22,39,55,56). Figure 1 describes the methodology of selection of the articles and Table 1 summarizes the main characteristics of the studies that use educational level as SE measurement. Tables with characteristics of the rest of selected articles (income, occupational level, area of residence and urban vulnerability) are some in supplementary materials.

2.2 Data extraction.

The following step consisted of creating a database to gather all relevant information extracted from each article: year of publication, author, journal, follow up, country, sample size, exposure levels, units of measure, data for the creation of the contingency table and HR/OR with 95% CI.

2.3 Statistical analysis.

Statistical analysis was performed separately for retrospective and prospective cohort studies. A sensitivity analysis was carried out, separating articles prior to 1980 and articles subsequent to 1980. In the same way, articles from a public health system were analyzed separately from a private health system.

We performed independent analyses according to the socioeconomic factor that is used in the study: Education level, Occupational level, Area of residence, Income, and Urban vulnerability.

The ways in which socioeconomic status were reported in each individual article were not standardized across studies (for instance, some papers reported three levels,

others four levels, another in quartiles; others in tertiles, and so on), making it difficult to extract them in an analyzable form. Therefore, in order to provide a consistent criterion of comparability, we selected the HR/OR reported for the highest category compared to the lowest one.

Regarding the type of breast cancer, we analyzed all invasive breast cancers together. Pooled HR/OR were estimated by weighting individual OR/HR by the inverse of their variance. HR/OR heterogeneity was measured using Q and I2 statistics (57) A fixed-effect model was preferred if the Q statistic was higher than 0.1 or I2 lower than 25%, indicating no relevant heterogeneity; a random-effect model was otherwise chosen (58). The presence of small-study bias was explored with Rosenthal model and with Egger test (59); due to the low sensitivity of Egger test, the cut-off was set at p = 0.1. Funnel plots (60) were applied to detect publication bias.

An analysis of influence was performed via the re-estimation of pooled OR/HR by removing one study at a time. Studies that, when removed, strongly changed the OR/HR would be considered as highly influential. Results are displayed as forest plots showing RR obtained by combining OR and HR and their 95% confidence intervals for each individual study and for the pooled result. Cumulative meta-analyses were carried out to deem the stability of the OR/RR estimates. In order to do that, all studies considered were arranged from oldest to newest. Then an OR/HR estimate was obtained for the two eldest studies; another for the three eldest, and so on, adding a study each time. Results are reported as forest plots.

All the analyzes were carried out for all the studies and, separately, dividing the studies into three large periods (prior to 1975, from 1975 to 1980 and more than 1980). All the statistical analyses were carried out with the package Stata 14/SE (Stata Corporation, College Station, TX, US).

RESULTS

Initially we conducted a broad search with several types of measures of socioeconomic level (educational level, occupational level, income, urban vulnerability and area of residence). Each type of socioeconomic status measurement was analyzed individually, however, due to the low number of articles found of other types of socioeconomic status measurement, only conclusive results were obtained with the educational level group, and therefore, only these results are shown in this article. Results about occupational level, income, urban vulnerability and area of residence have been included in the supplementary material. (Supplementary table 1-4)

3.1 Relationship between Educational level and breast cancer mortality.

Twenty-two cohort studies provided results on educational level and breast cancer mortality (18-39) obtaining a pooled RR of 1.03 (95% CI: 0.96-1.12). This value was calculated using the random effects model because of the high heterogeneity (84.79%). Therefore, our study did not find significant association between mortality from breast cancer and educational level. However, analyzing independently retrospective cohort studies (21-26,28-30,33,35,37-39) and prospective cohort studies (18-20,27,31,32,34,36) we obtained a pooled RR of 1.07 (95% CI:1.00-1.14) with retrospective cohort studies using aleatory effects model which suggests significant borderline association. Symmetric distribution of studies in the funnel plot and Egger test (p=0.524) suggest that there is not publication bias. Furthermore, the Rosenthal model suggest that there would be needed 9 more articles in order to lose statistical significance. However, this association was not shown when analyzing prospective cohort studies pooled RR 0.93 (95% CI: 0.72-1.19). (Figure 2) (Supplementary figure Figure 1a-1b)

3.2 Relationship between Educational and Breast Cancer mortality in Europe.

Fourteen articles (18,21-29,31,32,35,38) provided results on breast cancer mortality and educational level in European population. Combined HR/OR of these articles was 1.03 (95% CI: 1.00-1.06) using fixed effects model with an I2 value of 83,16% but aleatory effects model OR was 1.05 (95% CI: 0.97-1.13), showing no statistical significance.

Analyzing only retrospective cohort studies (21-26,28,29,35,38), we obtained a OR of 1,06 (95% CI: 1,00-1,13) using aleatory effects model, meanwhile the OR of prospective cohort studies (18,27,31,32) was 0.96 (95% CI: 0.66- 1.40) using the same analytic method. Considering only retrospective studies, the Funnel plot and Egger test (p=0.703) did not identify publication bias. Rosenthal model suggests that 78 studies would be needed in order to lose statistical significance. Therefore, we only found significant association between mortality from breast cancer and educational level in retrospective studies conducted in Europe. (Figure 3) (Supplementary figure 2a-2b)

3.3 Relationship between Educational and Breast Cancer mortality in Public Health System.

Fifteen articles (18,20-29,31,32,35,38) provided data of the association between breast cancer mortality and educational level of public health system. Combined RR of these articles was 1.03 (95% CI: 1.00-1.06) using fixed effects model with an I2 value of 82,41% but significant association disappeared when using aleatory effects model 1.06 (95% CI: 0.99-1.14).

Considering only retrospective articles (21-26,28,29,35,38) that were conducted in Public Health System we obtained the same result as considering European retrospective articles OR of 1.06 (95% CI: 1.00-1.13). Nonetheless, OR of prospective Public Health System articles (18,20,27,31,32) was 0.90 (95% CI: 0.84-0.97) using fixed effects model with a I2 value of 93.16% and OR 1.08 (95% CI:0.80-1.47) using aleatory effects model. (Figure 4)

3.4 Educational and Breast Cancer mortality before 1980.

Six studies (22,32-35,38) provided results on breast cancer mortality and educational level before 1980. Combined HR/OR of these articles was 1.10 (95% CI 0.95-1.29) using aleatory effects model.

Retrospective articles (22,33,35,38) have a pooled RR of 1.07 (95% CI:0.84-1.37) using aleatory effects model due to high heterogeneity found with fixed effects model I2 86,30%. In prospective articles (32,34), we utilized fixed model effects because the value of I2 was 13.73 and we obtained a pooled RR of 1.18 (95% CI: 1.08-1.30). Funnel plot did not identify publication bias showing symmetric distribution of the studies and so did Egger test (p=0.921). Rosenthal model suggest that 11 articles would be needed in order to lose statistical significance. (Figure 5) (Supplementary figure 3a-3b)

Making the subdivision of this group previously commented in the methods, five articles provided results of studies conducted before 1975 (22,32,33,35,38). Combined RR of these five articles was 1.06 (95% CI: 0.85-1.33) using aleatory effects model. Analyzing independently retrospective (22,33,35,38) and prospective articles (32), pooled RR of retrospective was 1.05 (95% CI: 0.71-1.55) using aleatory effects model, meanwhile the OR of the only prospective article found had was 1.14 (95% CI: 1.02 – 1.27). (Figure 6)

We found three articles (34,35,38) which provided data of the relation between breast cancer mortality and educational level in studies conducted between 1975-1980. The combined RR obtained was 1.20 (95% CI: 1.08-1.33) using fixed effects model. Two of them were retrospective (35,38) and the OR was 1.16 (95% CI: 1.03-1.30), meanwhile only one article was prospective (34) with an OR of 1.33 (95% CI: 1.10-1.62). (Figure 7)

Thus, all OR or HR obtained from prospective articles conducted before 1980 suggest that higher educational level would be a risk factor for breast cancer mortality.

3.5 Educational and Breast Cancer mortality after 1980.

Eighteen articles (18-21,23-31,35-39) provided results on breast cancer mortality and educational level after 1980 and their combined HR/OR was 1.00 (95% CI: 0.92-1.09).

Twelve of them were retrospective (21,23-26,28-30,35,37-39) and six prospective (18-20,21,27,31). Analyzing retrospective articles, we obtained a OR of 1.05 (95% CI: 0.99-1.11) using aleatory effects model. Meanwhile, the OR analyzing prospective articles was 0.75 (95% CI: 0.70-0.81) using fixed model effects with an I2 value of 86.45. Most of the heterogeneity disappeared when using random effects model obtaining an OR of 0.86 (95 CI: 0.68-1.09). (Figure 8)

Thus, analyzing comparatively the studies carried out before and after 1980, it seems that the prospective studies conducted after this date suggest that higher educational level would be a protective factor against what happened with the studies carried out before 1980.

TABLES AND FIGURES

Figure 1. Flowchart which describes the methodology of selection of the articles

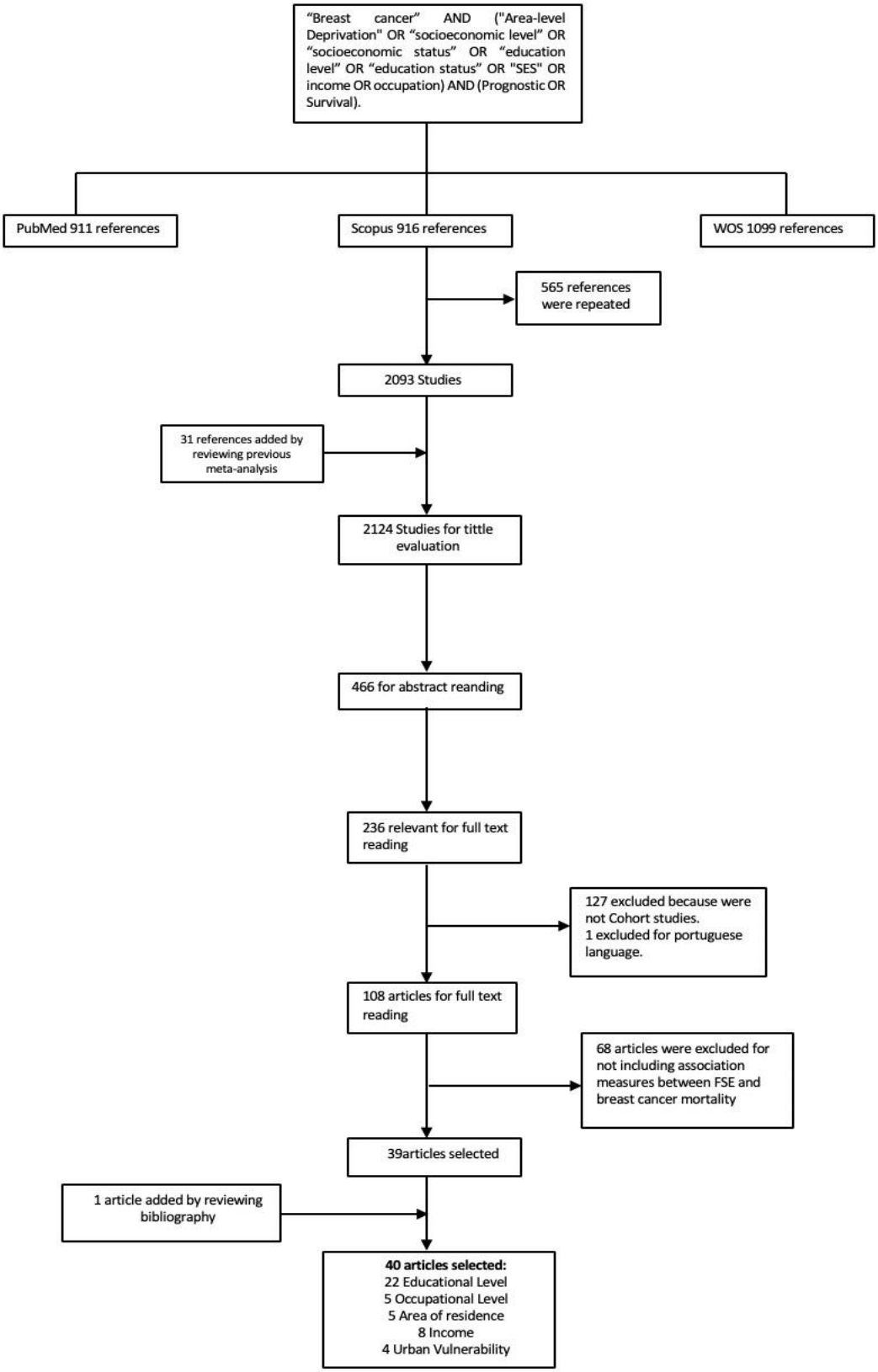


Table 1. Articles included with educational level as measure of SE status

Article	Journal	Author	Publication year	Country	Year	Number of participants
EDUCATIONAL LEVEL						
Educational inequality in cancer mortality: a record linkage study of over 35 million Italians. (29)	Cancer causes and control	Alicandro et al.	2017	Italy	2012	11966
Social inequality and incidence of and survival from breast cancer in a population-based study in Denmark, 1994-2003. (18)	European Journal of Cancer	Carlsen et al.	2008	Denmark	1994	25855
Influence of socioeconomic factors on survival after breast cancer--a nationwide cohort study of women diagnosed with breast cancer in Denmark 1983-1999. (25)	International Journal of Cancer	Dalton et al.	2007	Denmark	1983	25897
Trends in educational inequalities in mortality, seven types of cancers, Norway 1971-2002. (38)	European journal of public health	Elstad et al.	2012	Norway	1971	3593
Cancer mortality by educational level in the city of Barcelona. (24)	British Journal of Cancer	Fernandez et al.	1999	Barcelona	1992	174
Does birth history account for educational differences in breast cancer mortality? A comparison of premenopausal and postmenopausal women in Belgium. (28)	International Journal of Cancer	Gadeyne et al.	2012	Belgium	1991	2247699
Effect of socioeconomic status as measured by education level on survival in breast cancer clinical trials. (19)	Psycho-oncology	Herdorn et al	2013	CALGB	1991	5146
Influence of education level on breast cancer risk and survival in Sweden between 1990 and 2004. (27)	International Journal of Cancer	Hussain et al.	2007	Sweden	1990	1571511
Education Level Is a Strong Prognosticator in the Subgroup Aged More Than 50 Years Regardless of the Molecular Subtype of Breast Cancer: A Study Based on the Nationwide Korean Breast Cancer Registry Database. (36)	Cancer research and treatment: official journal of Korean Cancer Association	Hwang et al.	2017	Korea	1987	64129
The Influence of Education Level On the Survival of Breast Cancer (30)	European Journal of Cancer	Hwang et al.	2012	Korea	1987	36299
Is Education Associated with Mortality for Breast Cancer and Cardiovascular Disease Among Black and White Women? (34)	Gender Medicine	Kim et al.	2005	USA	1979	207625
Socio-economic factors and breast cancer survival--a population-based cohort study (Sweden). (23)	Cancer causes and Control	Lagerlund et al.	2004	Sweden	1993	2926
Survival probability and prognostic factors for breast cancer patients in Vietnam. (37)	Global health action	Lan et al.	2013	USA	2001	1584
Influence of metabolic indicators, smoking, alcohol and socioeconomic position on mortality after breast cancer. (31)	Acta Oncologica	Larsen et al.	2015	Sweden	1993	1229
Relationship of ethnicity and other prognostic factors to breast cancer survival patterns in Hawaii. (33)	Journal of the national cancer institute	LeMarchand et al.	1984	Hawaii	1960	2956
Education and breast cancer mortality: experience from a large Norwegian cohort study. (32)	Cancer causes and Control	Lund et al.	1991	Norway	1970	425884
Socio-economic status and survival from breast cancer for young, Australian, urban women. (20)	Cancer	Morley et al.	2010	Australia	1992	1029

EDUCATIONAL LEVEL						
Social inequalities in breast cancer mortality among French women: disappearing educational disparities from 1968 to 1996. (35)	British Journal of Cancer	Menvielle et al.	2006	UK	1968	94734
Impact of educational differences as measure of socioeconomic status on survival for breast cancer patients. (21)	Wspolckesna Onkol.	Nowara et al.	2012	Poland	2001	810
Weak associations between sociodemographic factors and breast cancer: Possible effects of early detection (22)	European Journal of Cancer Prevention	Robsahn et al.	2005	Norway	1964	589521
Sociodemographic Factors and Late-stage Diagnosis of Breast Cancer in India: A Hospital-based Study. (39)	Indian journal of medical and pediatric oncology.	Sathwara et al.	2017	India	2008	1210
Is birth history the key to highly educated women's higher breast cancer mortality? A follow-up study of 500,000 women aged 35-54. (26)	International Journal of Cancer	Strand et al.	2005	Norway	1990	512353

Figure 2. Meta-analysis of all articles of Educational level as SE measurement

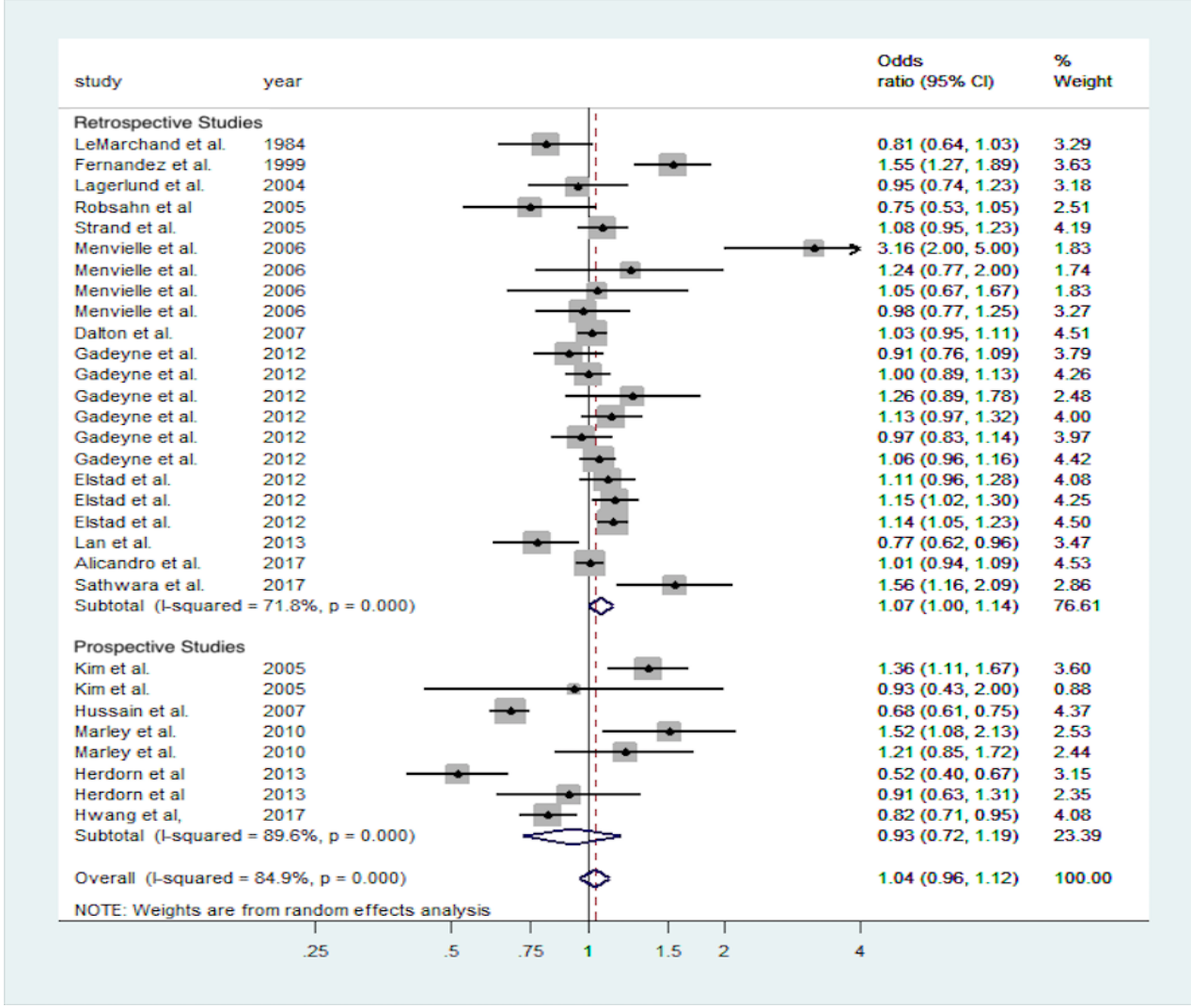


Figure 3. Meta-analysis of all studies with Educational level as measurement of SE conducted in Europe

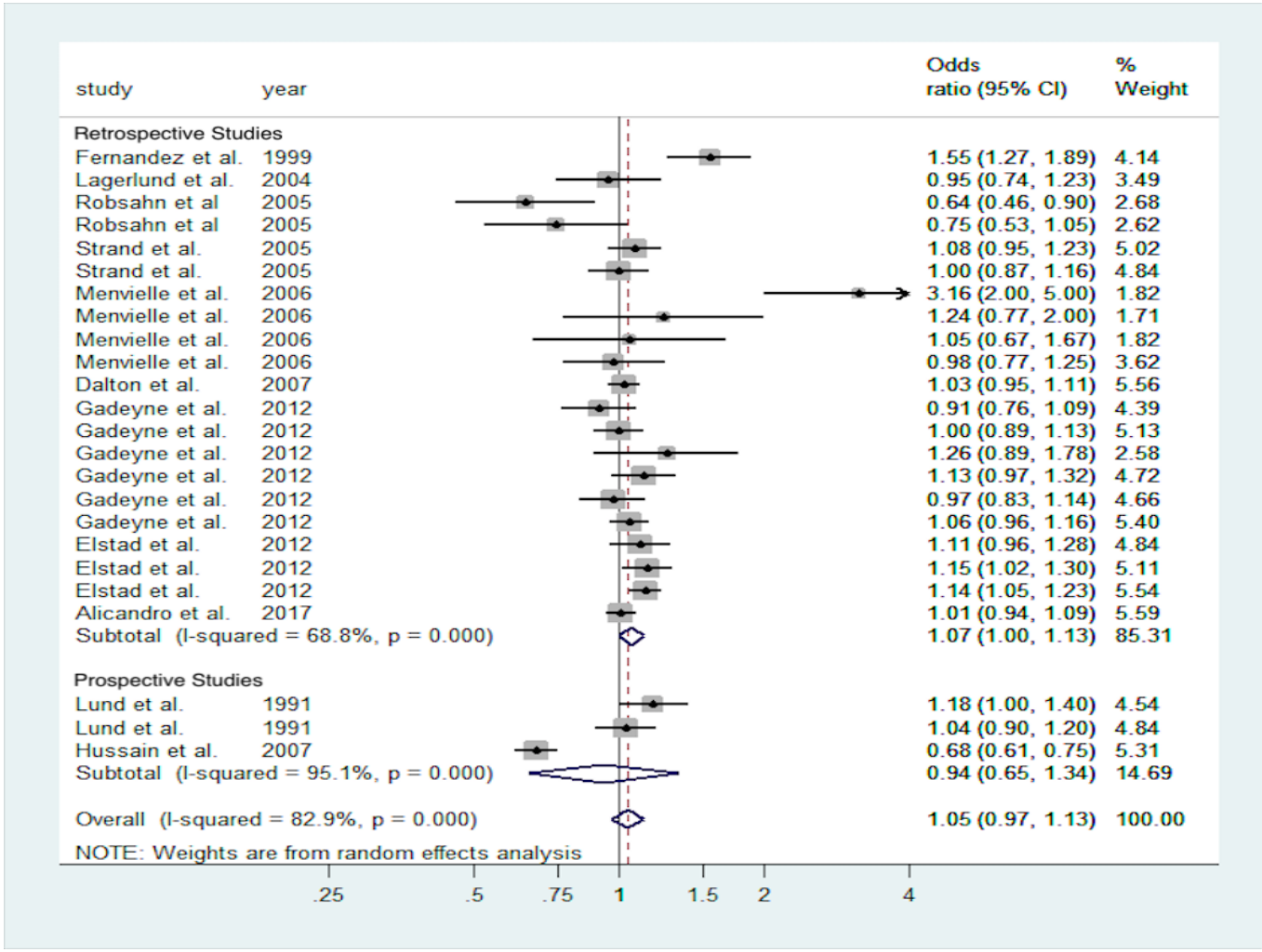


Figure 4. Meta-analysis of all studies of Public health system studies

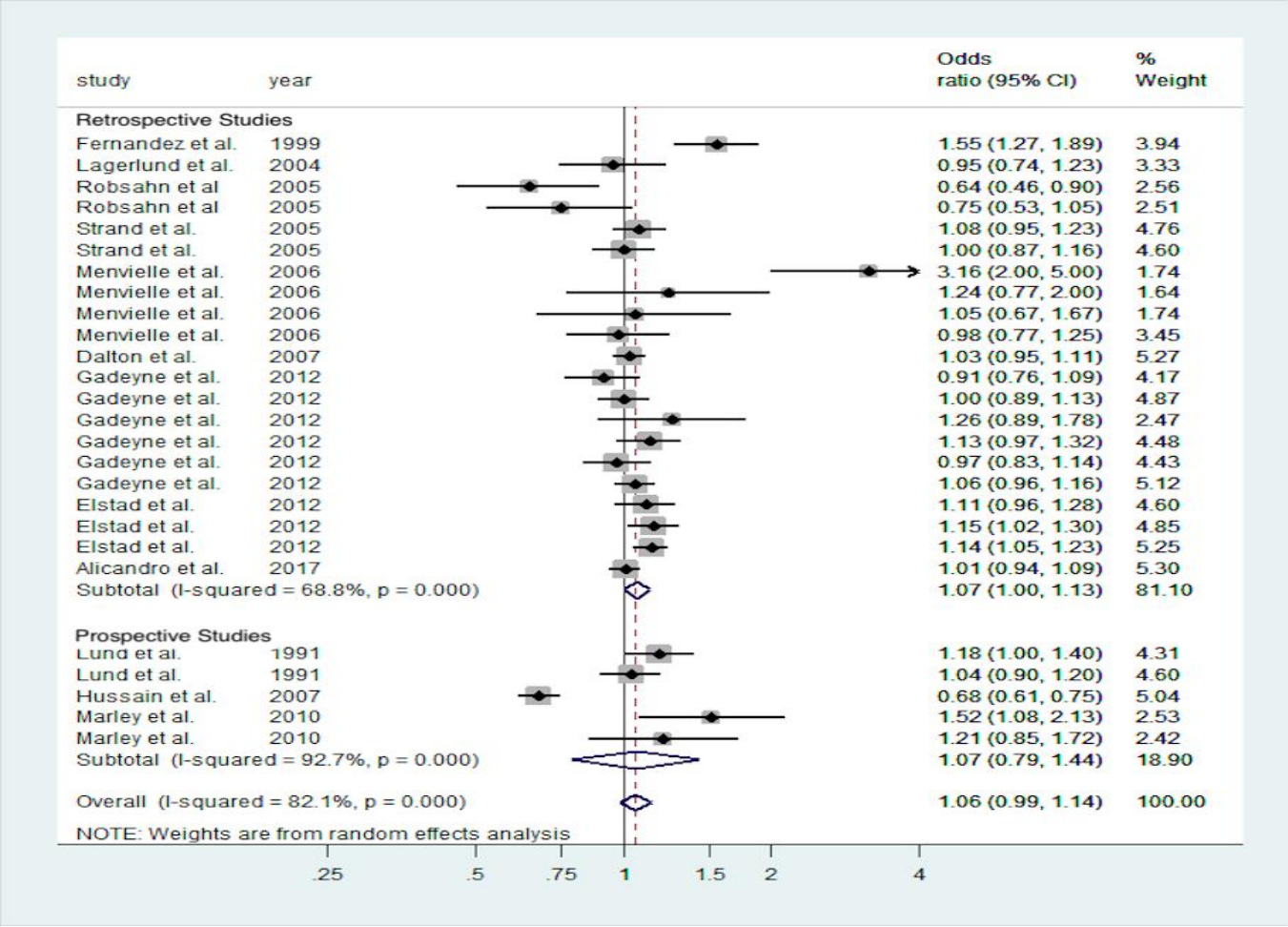


Figure 5. Meta-analysis of all studies conducted before 1980

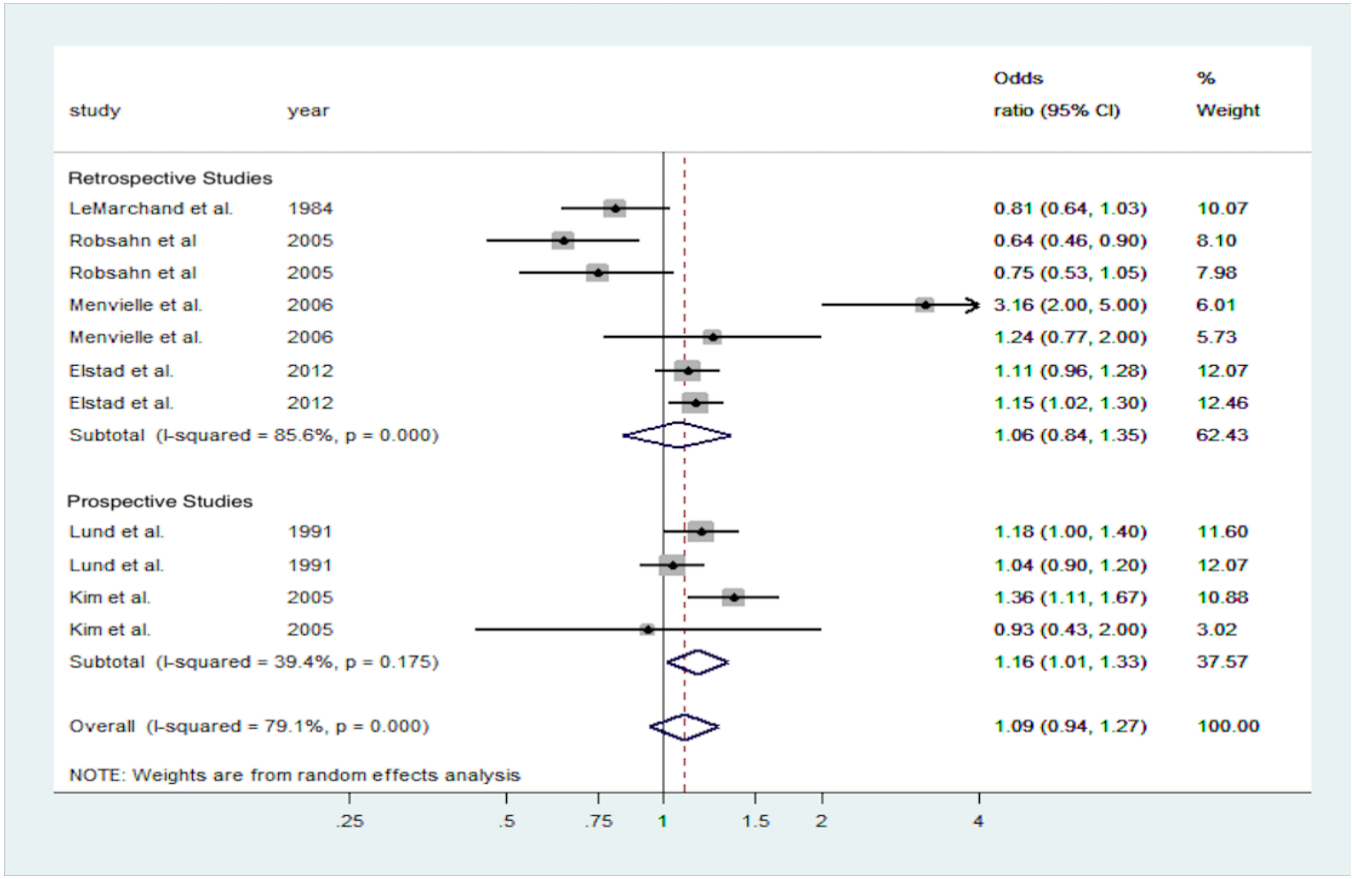


Figure 6. Meta-analysis of Studies conducted before 1975

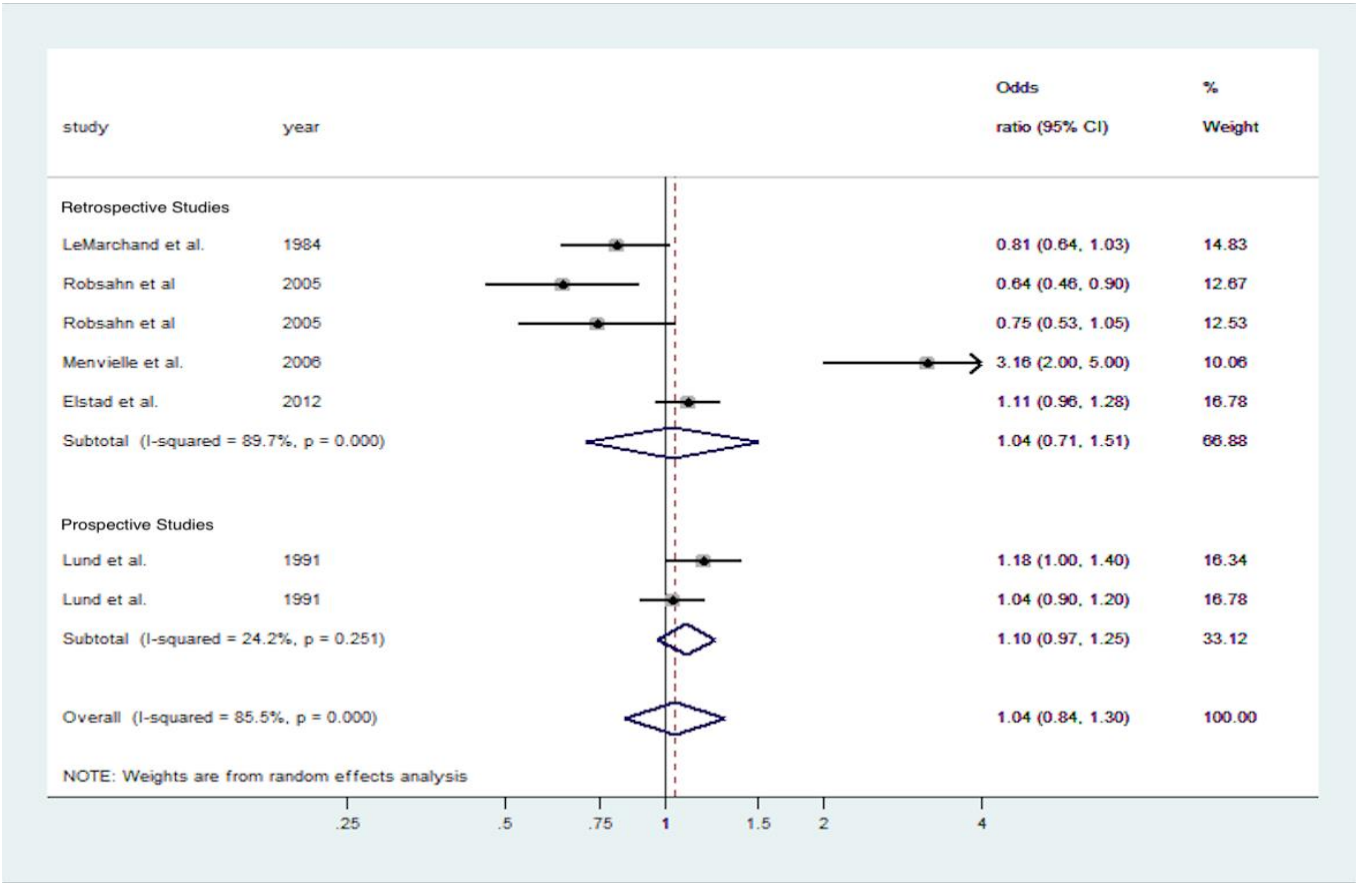


Figure 7. Meta-analysis of Studies conducted between 1975-1980

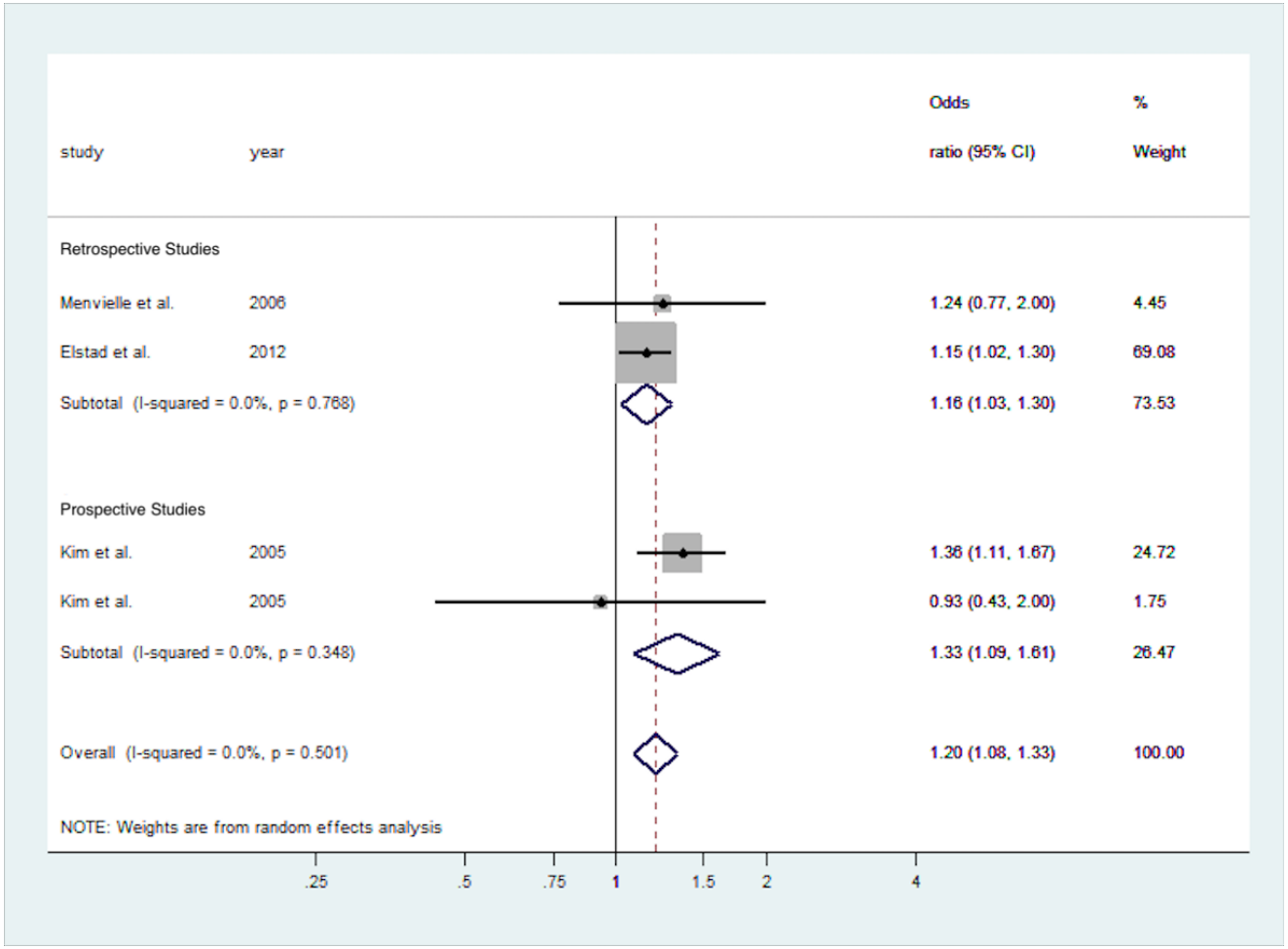
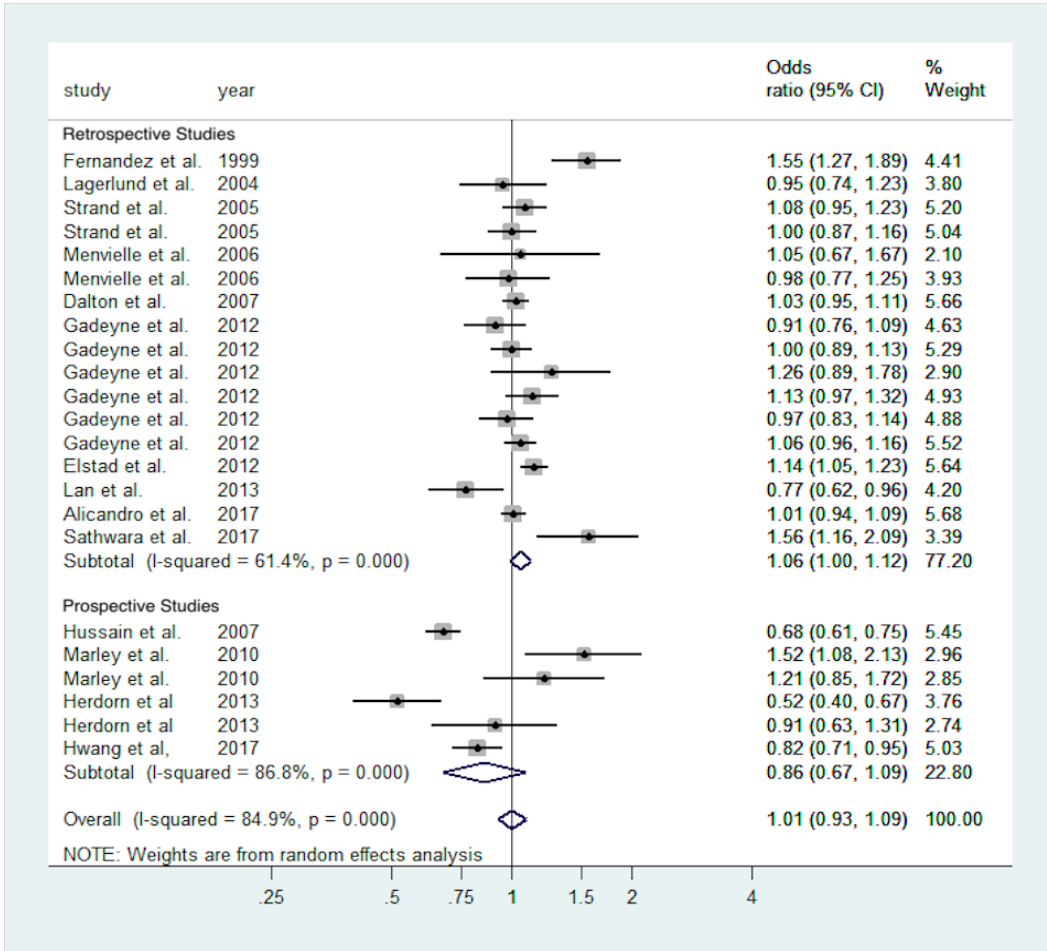


Figure 8. Meta-analysis of Studies conducted after 1980



Supplementary table 1. Articles included with income as measure of socioeconomic status

Article	Journal	Author	Publication year	Country	Beginnig of follow up.	Number of participants.
INCOME						
Race, income, and survival from breast cancer at two public hospitals.	Cancer Journal	Ansell et al	1993	Illinois	1973	1089
Worsened oncologic outcomes for women of lower socio-economic status (SES) treated for locally advanced breast cancer (LABC) in Pakistan.	The breast.	Aziz et al.	2008	Pakistan	2000	237
Social inequality and incidence of and survival from breast cancer in a population-based study in Denmark, 1994-2003.	European Journal of Cancer.	Carlsen et al.	2008	Denmark	1994	25855
Influence of socioeconomic factors on survival after breast cancer--a nationwide cohort study of women diagnosed with breast cancer in Denmark 1983-1999.	International Journal of Cancer.	Dalton et al.	2007	Denmark	1983	25897
Differences in breast cancer stage at diagnosis and cancer-specific survival by race and ethnicity in the United States.	JAMA.	Iqbal et al.	2015	USA	2004	373563
Influence of metabolic indicators, smoking, alcohol and socioeconomic position on mortality after breast cancer.	Acta Oncologica.	Larsen et al.	2015	Sweden	1993	1229
Disparities in survival after female breast cancer diagnosis: a population-based study.	Cancer causes and control.	Tannenbaum et al.	2013	Florida	1996	127754
Differences in mortality among women with breast cancer by income - a register-based study in Finland.	Scandinavian Journal of Public Health.	Vehko et al.	2016	Finland	1998	43439

Supplementary table 2. Articles included with occupational level as measure of socioeconomic status

Article	Journal	Author	Publication year.	Country	Beginning of follow up.	Number of participants
OCCUPATIONAL LEVEL						
The influence of socio-economic and surveillance characteristics on breast cancer survival: a French population-based study.	British Journal of Cancer	Gentil-Brevet et al.	2008	France	1993	1150
Social class is an important and independent prognostic factor of breast cancer mortality.	International Journal of Cancer	Bouchardy et al.	2006	Switzerland	1980	3920
Social class as a prognostic factor in breast cancer survival.	Cancer	Karjalainen et al.	1990	Finland	1971	10181
Socioeconomic Position in Childhood and Early Adult Life and Risk of Mortality: A Prospective Study of the Mothers of the 1958 British Birth Cohort	American Journal of Public Health	Power et al	2005	Uk	1958	266
Socio-economic status and overall and cause-specific mortality in Sweden.	Bmc public health	Weires et al.	2008	Sweden	1960	23138

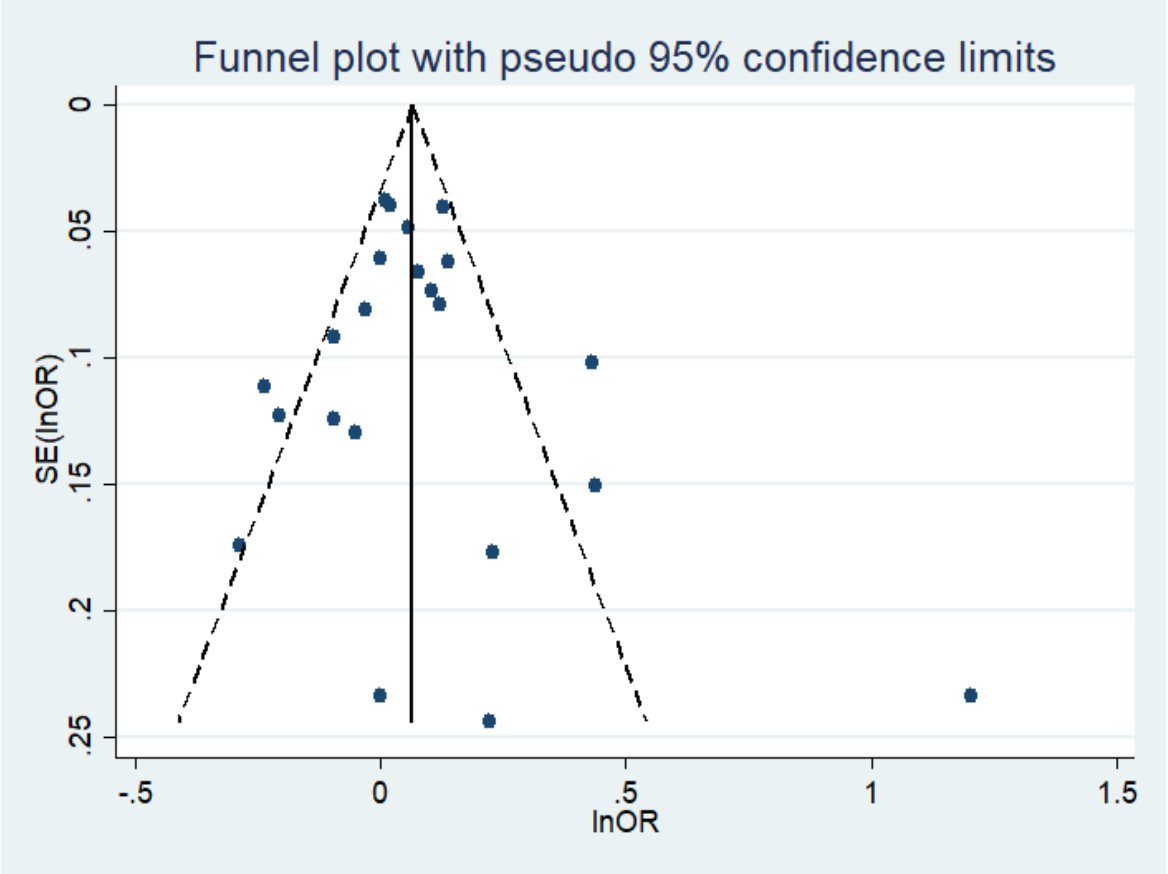
Supplementary table 3. Articles included with urban vulnerability as measure of socioeconomic status

Article	Journal	Author	Year of Publication	Country	Beginning of follow up.	Number of participants.
URBAN VULNERABILITY						
Why are death rates higher in rural areas? Evidence from the Australian Longitudinal Study on Women's Health.	Australian and New Zeland Journal of Public Health	Dobson et al.	2010	Australia	1996	12400
Disparities in late stage diagnosis, treatment, and breast cancer-related death by race, age, and rural residence among women in Georgia.	Women and health	Markossian et al.	2012	Georgia US	1992	23500
Weak associations between sociodemographic factors and breast cancer: Possible effects of early detection	European Journal of Cancer Prevention	Robsahn et al	2005	Norway	1964	589521
Sociodemographic Factors and Late-stage Diagnosis of Breast Cancer in India: A Hospital-based Study.	Indian journal of medical and paediatric oncology.	Sathwara et al.	2017	India	2008	1210

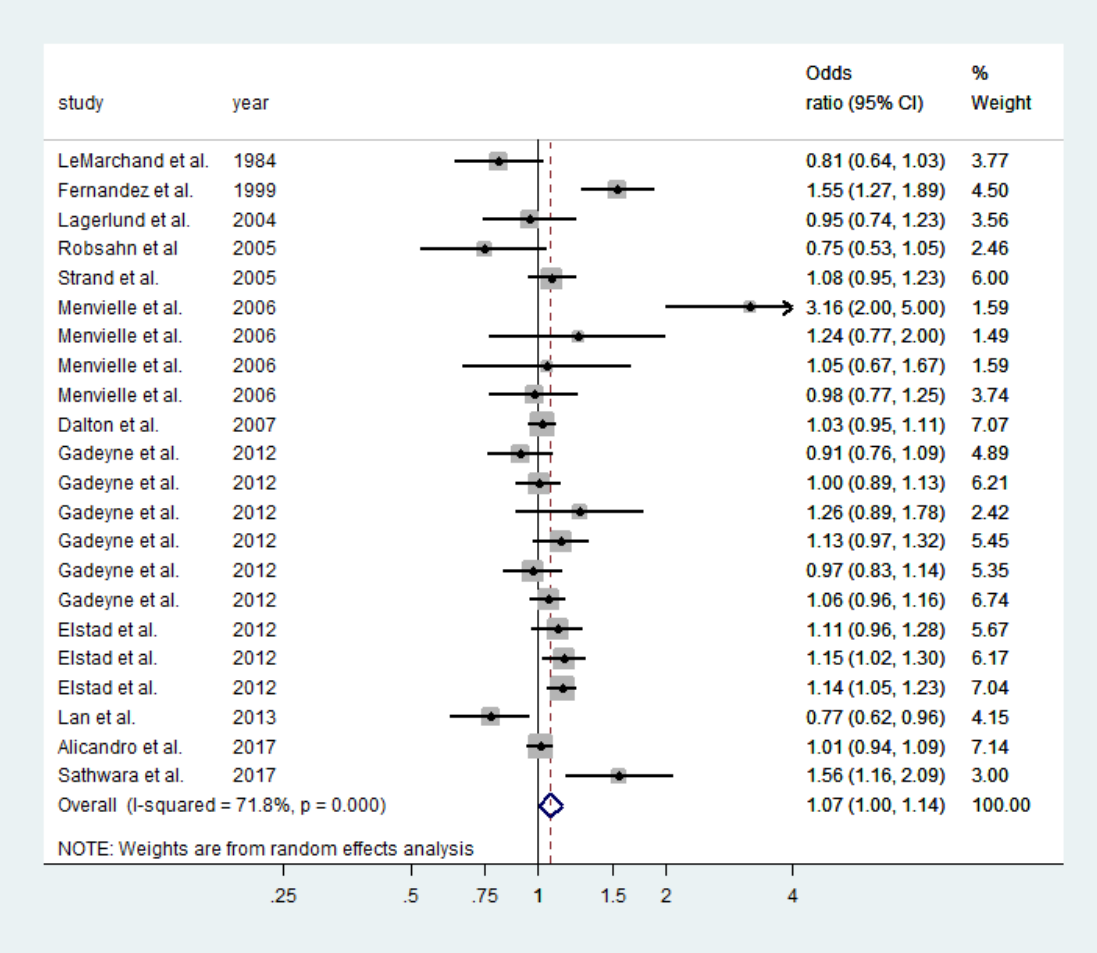
Supplementary table 4. Articles included with area of residence as measure of socioeconomic status

Article	Journal	Author	Publication year	Country	Beginning of follow up	Number of participants
AREA OF RESIDENCE						
Socioeconomic effects on breast cancer survival: proportion attributable to stage and morphology.	British Journal of Cancer	Kaffashian et al	2003	UK	1992	10865
Breast cancer survival in ontario and california, 1998-2006: socioeconomic inequity remains much greater in the United States.	Annals of epidemiology	Gorey et al.	2009	Ontario	1998	1913
An international comparison of breast cancer survival: Winnipeg, Manitoba and Des Moines, Iowa, metropolitan areas.	Annals of epidemiology	Gorey et al.	2003	Canada	1984	2383
Mediation of the effects of living in extremely poor neighborhoods by health insurance: Breast cancer care and survival in California, 1996 to 2011	international journal of equity in health	Gorey et al.	2013	California	1996	6300
Prognostic factors in women with breast cancer: distribution by socioeconomic status and effect on differences in survival.	J. Epidemiol Community Health	Thomson et al.	2001	Scotland	1978	21751

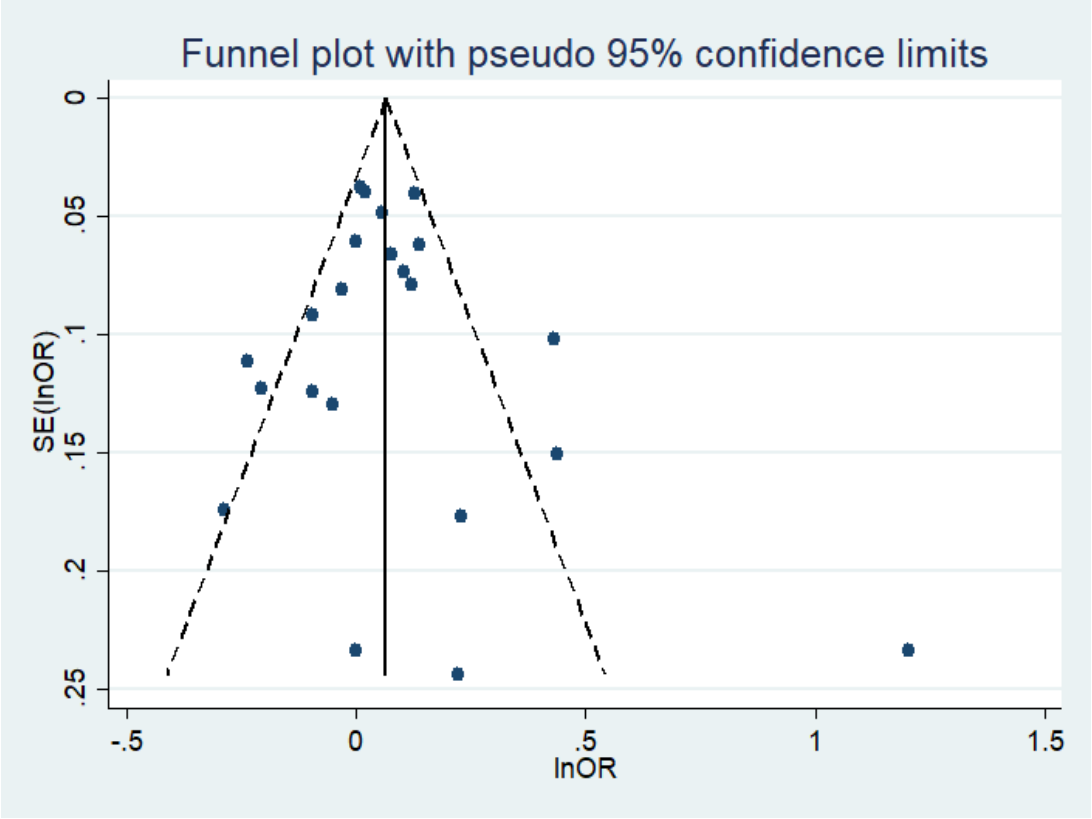
Supplementary figure 1. Funnel plot educational level and breast cancer mortality retrospective



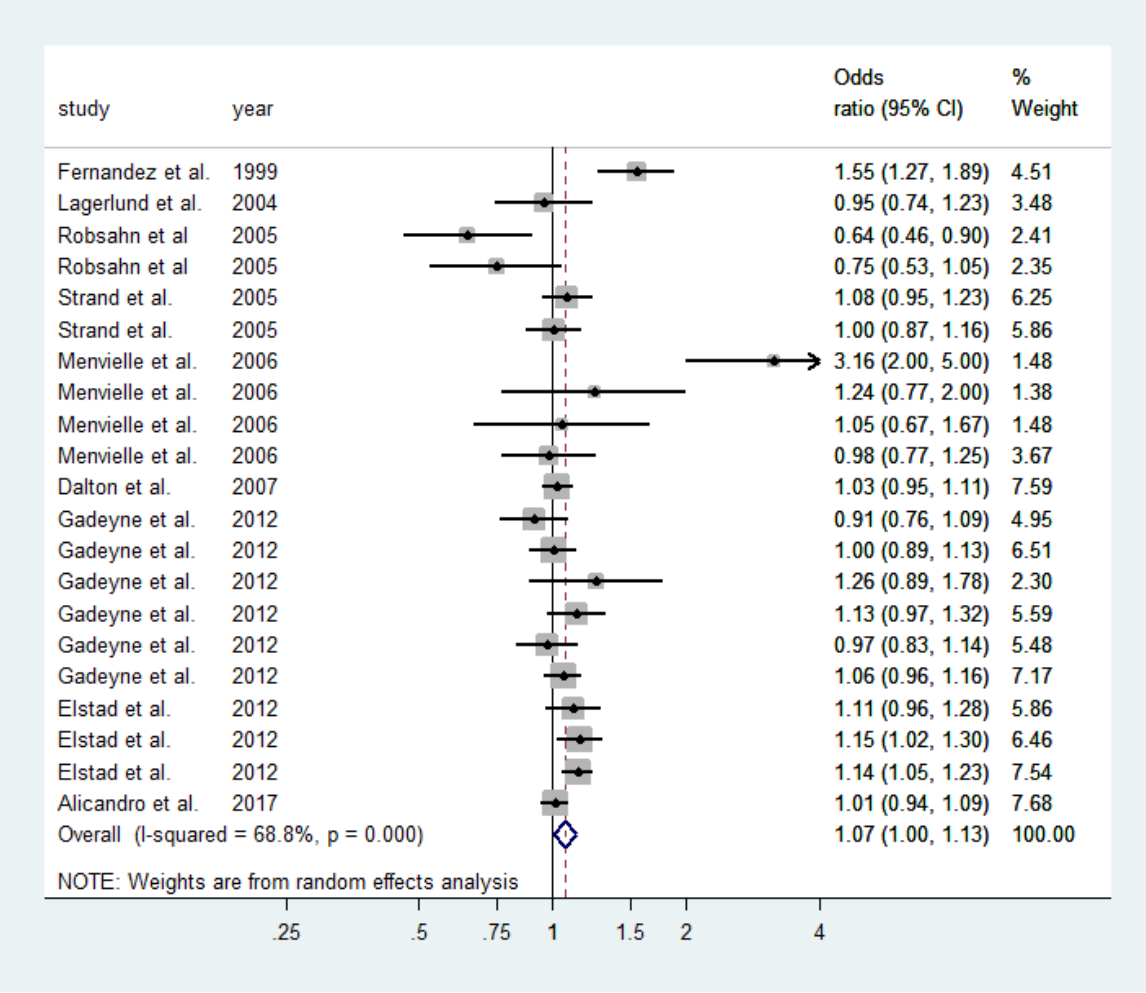
Supplementary figure 2. Forrest plot educational level and breast cancer mortality retrospective



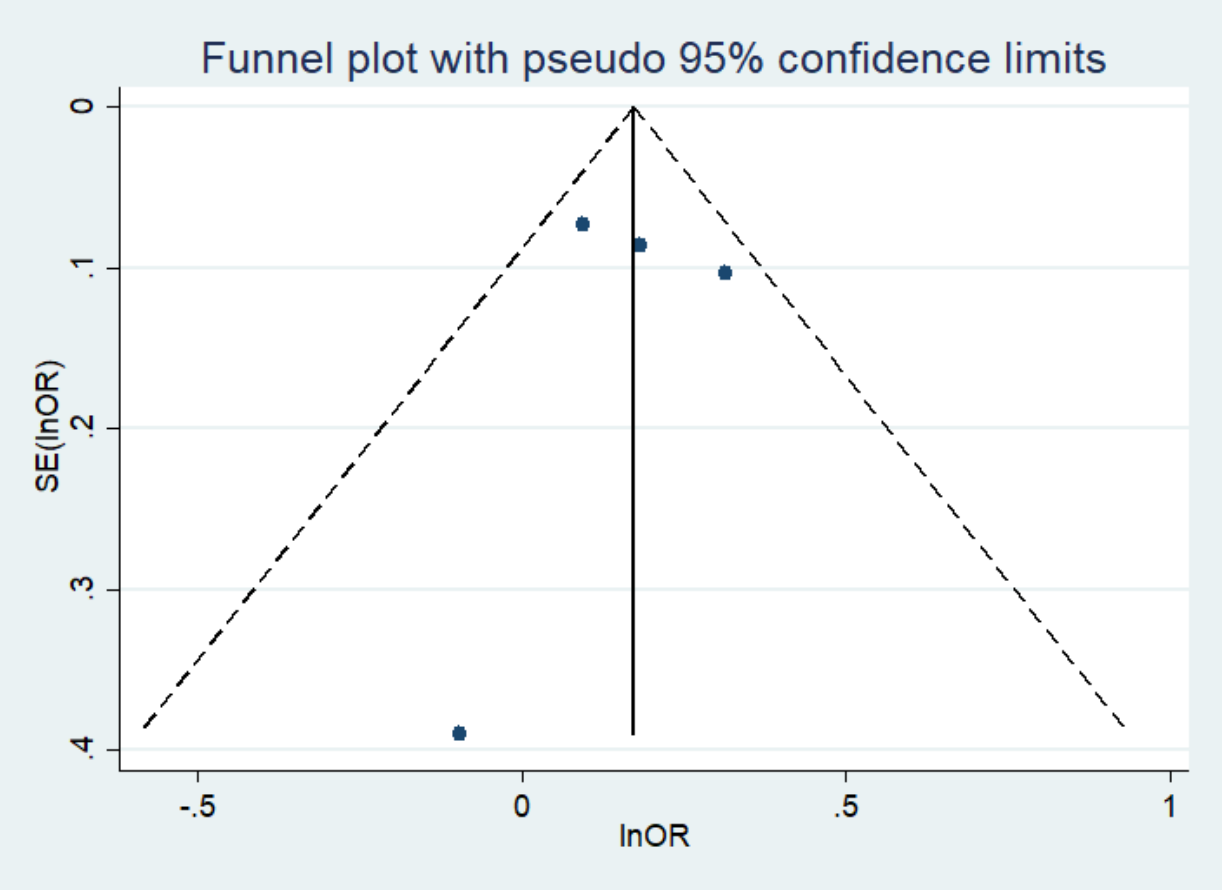
Supplementary figure 3. Funnel plot educational level and breast cancer mortality retrospective Europe



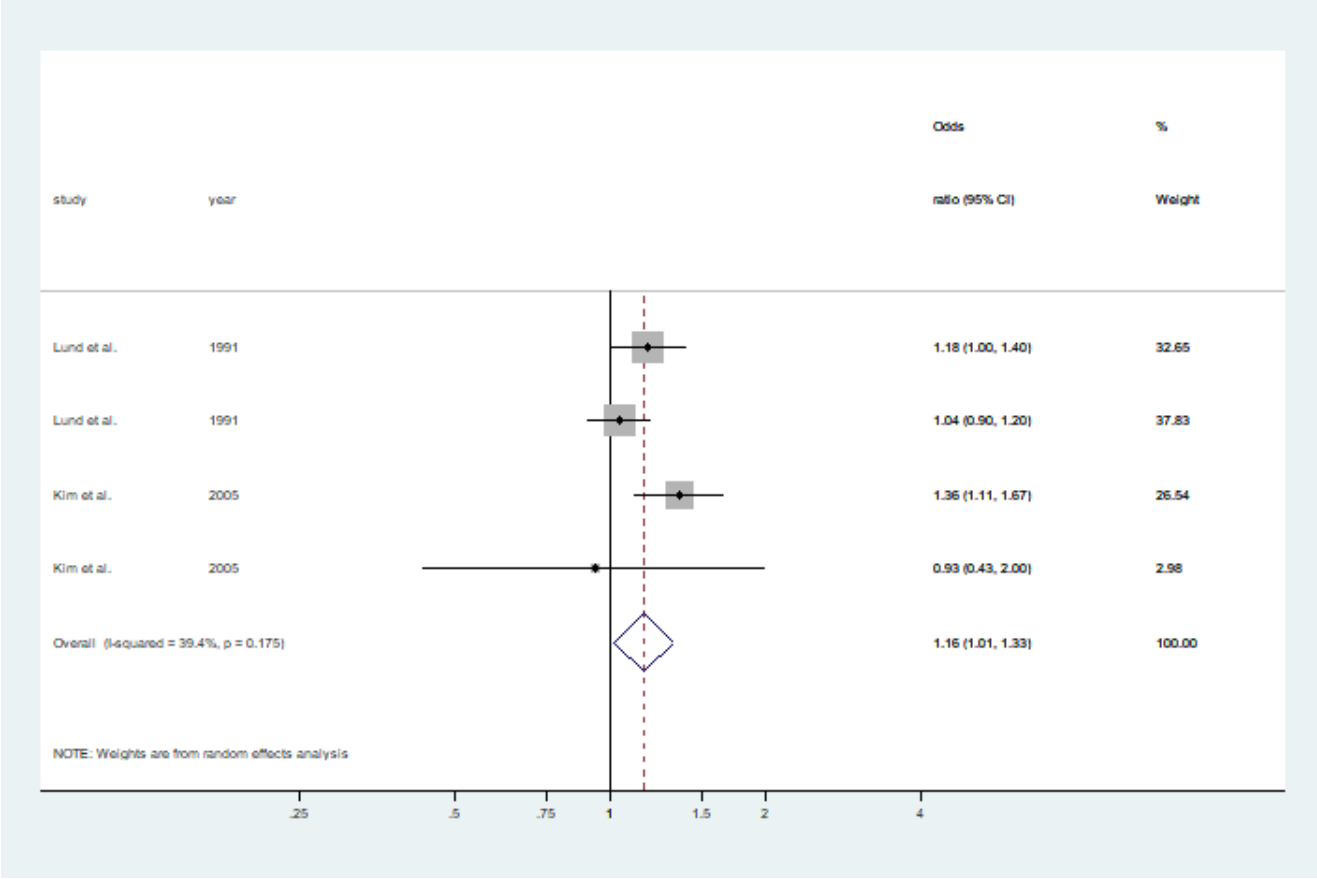
Supplementary figure 4. Forrest plot educational level and breast cancer mortality retrospective Europe



Supplementary figure 5. Funnel plot of prospective studies conducted before 1980



Supplementary figure 6. Forrest plot of prospective studies conducted before 1980



DISCUSSION

Analyzing all the articles found that relate educational level to mortality from breast cancer, only a statistically significant association was only found in those who used retrospective cohorts (21-26,28-30,33,35,37-39). The pooled RR obtained 1.07 (95% CI: 1.00-1.14) suggests that higher socioeconomic status measured by educational level would be a risk factor for mortality from breast cancer. As far as we know, there is no previous meta-analysis published with educational level as unique socioeconomic status measure with differentiation between prospective and retrospective data in the literature.

When we analyze the association between these two factors only in European countries, we did not find statistically significant association combined RR =1.05 (95% CI: 0.97-1.13). This goes against the findings that were published in previous meta-analysis in 2016 (4). Lundqvist meta-analysis (4) included only studies that were conducted in Europe with education and occupation as socioeconomic status measures. They obtained a combined HR/OR of 1.16 (95% CI: 1.10-1.23) including data of 5 articles (26,28,35,38,44) and OR of 1.05 (95% CI: 1.02-1.08) after controlling for reproductive factors including 3 articles (26,28,43) that would suggest a positive association between breast cancer mortality and high socioeconomic status. Our study analyzed all the articles included in the previous meta-analysis, however, we grouped the studies according to the socioeconomic factor used and showed only those corresponding to the educational level as previously explained. Thus, Weires (43) and Power (44) are not included in the results because they correspond to the occupational level. We could find this association when analyzing only retrospective cohort studies (21-26,28,29,35,38) OR 1.06 (95% CI: 1.00-1.13), but no with combined HR/OR of prospective (18,27,31,32) selected articles 0.96 (95% CI: 0.66- 1.40). The same happened when we analyzed association between breast cancer mortality and educational level in Public Health Systems. Only combining retrospective (21-26,28,29,35,38) studies the OR suggests that there is an association between mortality from breast cancer and a higher level of education [(OR=1.06 (95% CI: 1.00-1.13)], while combining all studies OR 1.06 (95% CI: 0.99-1.14) nor the OR of the prospective studies (18,20,27,31,32) [(OR= 1.08 (95% CI:0.80-1.47)] suggested no such association. Usually, prospectively conducted studies are more reliable in collecting data and this previous meta-analysis did not differentiate between retrospective and prospective cohort studies, so in the future, more prospective studies would be needed to try to clarify whether socioeconomic status is really a prognostic factor of breast cancer in Europe and in Public Health Systems.

When we stratified as a function of time, a change of trend was found between studies conducted before and after 1980. Considering prospective studies conducted before 1980 (32,34), high socioeconomic level women suffering from breast cancer were more likely to have worse outcomes than those of low socioeconomic level OR 1.19 (95% CI: 1.07-1.32). However, prospective studies conducted after 1980 (18-20,21,27,31) showed higher socioeconomic status could be a protective factor OR 0.75 (95% CI: 0.70-0.81) with fixed effects model but the OR with random effects model was 0.86 (95% IC 0.68-1.09).

As we commented in the introduction, 1980 is an important date because it was the moment from which the screening of breast cancer began to establish (3) in developed countries and also new forms of treatment such as chemotherapy and hormone therapy began to be used (5). From this point breast cancer patient survival increased considerably, and although these two important advances are highly related to it, other factors could have been involved.

The results found in this meta-analysis suggest that the socioeconomic status could be related in some way to the increase in survival observed after 1980. We considered that the change in trend observed after 1980 in our study could be associated, at least in part, with lifestyle changes that would be conditioned in turn by the economic possibilities of each family. For this reason, some of known risk factors breast cancer incidence could be conditioning the prognosis too.

Age, family history of breast cancer, estrogen exposition, reproductive factor and lifestyle are all breast cancer risk factors (61). While the first two are independent of socioeconomic level, exposure to estrogen, reproductive factors and lifestyle could be conditioned, at least in part, by socioeconomic status.

In this way, obesity and physical activity are two of the lifestyle factors that could be involved in breast cancer prognosis. There are a lot of articles established the relation between SES and obesity. For example, in a review of 191 articles that related obesity and Diabetes (62), which conclude that central obesity is more common between individuals of low SES. Moreover, the quality of food seems to be lower because they tend to consume more fat and simple carbohydrates and less fruits and vegetables than high SES individuals. On the other hand, they tend to live in unsafety neighborhoods with less areas to exercise, which also contributes to overweight and obesity. Protani (63) and Niraula (64) meta-analyses conclude that the mortality from breast cancer is higher between obese than non-obese individuals. Chan (65) studied the relation between mortality in women with breast cancer and obesity, obtaining RR of 1.41 (95% CI: 1.29-1.53) for obese (BMI >30.0), and RR 1.07 (95 CI: 1.02-1.12) for overweight women (BMI 25.0-30.0).

On the other hand, breastfeeding has been demonstrated to be more common between individuals of high educational level, however this association does not occur with high income or occupational level (66). One study (67) conducted in Sao Paulo and published in 1980 show that breastfeeding at that time was more common in lower socioeconomic classes considering a sample of 200 children. 39% of low socioeconomic status women of the study breastfed for 6 months meanwhile only 19% of high socioeconomic women did. On the other hand, Gilbert (68) studied social disparities in maternal smoking and breastfeeding in Canada comparing periods between 1992-1996 and 2005-2008. Breastfeeding initiation increased in both groups (high and low socioeconomic status) over the time, but the percentage of high socioeconomic level women who breastfed (from 83.8 % (95 % CI: 81.9-85.6 %) to 91.5 % (95 % CI: 90.2-92.8 %)) was considerably higher than those of lower socioeconomic status (from 63.1 % (95 % CI: 58.9-67.4 %) to 74.7 % (95 % CI: 69.8-79.7 %)). Fortner (69) studied the association between breastfeeding and incidence of more aggressive breast cancer subtypes (ER-)

utilizing Nurses Health Studies, establishing that the risk of ER- breast cancer was significantly high between women who had never breastfed. Millikan (70) established that longer duration of breastfeeding, increasing number of children breastfed, and increasing number of months breastfeeding per child were each associated with reduced risk of basal-like breast cancer. So, women who never breastfed were more likely to have more aggressive subtypes of breast cancer and consequently, more likely to have worse outcomes.

Smoking has been associated with worse prognosis in breast cancer survival (71). Current smoker women with breast cancer have increased probability of death OR 1.84 (95% CI: 1.44-2.34) than those who never smoke. This increase in risk is also maintained if we compare them with ex-smokers (OR 1.60 (95% CI: 1.04-2.46).One study conducted in Chile (72) compared the rate of smokers in two cohorts: born between 1974-1978 and born between 1988-1992. This study shows that compared with people of high socioeconomic level, young people of low SES tend to smoke more usually (OR 3.00 (95% CI: 1.85 -4.88)) than people of 1974-1978 cohort [OR 1.01 (95% CI: 0.54-2.23)]. So, it seems that young people with high socioeconomic status tend to smoke less than low SES people do, and this could play a role in improving the prognosis of breast cancer.

Our study has some limitations firstly, each article uses different cutoff points according to education levels. To analyze it we restricted our analysis to the comparison between the highest vs. lowest category of exposure. This analysis strategy does not allow for a dose-response analysis. Although our intention was to establish the relationship between breast cancer mortality and socioeconomic level using different forms of measurement (income, area of residence, urban vulnerability and occupational level), we could not find a sufficient number of articles to obtain representative results in some ways of measuring. Finally, we could not differentiate the association between the socioeconomic level and mortality from breast cancer depending on the histological type because it was not specified in most articles.

Despite these limitations, our study also has several strengths; firstly, we have gathered all the observational studies published in the last twenty years using the data from the most adjusted model of those offered in each study. In addition, we have focused the analysis on different types of strata, assessing the differences found when analyzing European or Public studies, conducted before or after 1980 and comparing in all of them whether they were retrospective or prospective. This strategy allows us to obtain a more detailed analysis of the relationship between socioeconomic level and prognosis of breast cancer.

CONCLUSIONS

In conclusion, our meta-analysis supports the hypothesis that high education levels would be a risk factor of mortality from breast cancer when analyzing only retrospective studies conducted in Europe or in Public Health Systems. However, there is no significant association when analyzing prospective studies. Moreover, a change in trend has been observed between studies conducted before and after 1980, so that higher socioeconomic status would have been a risk factor for breast cancer mortality before 1980 and a protective factor after 1980. However, new prospective studies are needed to confirm these findings.

REFERENCES

1. Bray F, Ferlay J, Soerjomataram I, Siegel RL, Torre LA, Jemal A. Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin. 2018 Sep;

2. Merino Bonilla JA, Torres Tabanera M, Ros Mendoza LH. Breast cancer in the 21st century: from early detection to new therapies. Radiologia. 2017 Sep;59(5):368–79.

3. Jatoi I, Miller AB. Why is breast-cancer mortality declining? Lancet Oncol. 2003 Apr;4(4):251–4.

4. Fitzgerald SP. Breast-Cancer Screening--Viewpoint of the IARC Working Group. Vol. 373, The New England journal of medicine. United States; 2015. p. 1479.

5. Vervoort MM, Draisma G, Fracheboud J, van de Poll-Franse L V, de Koning HJ. Trends in the usage of adjuvant systemic therapy for breast cancer in the Netherlands and its effect on mortality. Br J Cancer. 2004 Jul;91(2):242–7.

6. Effects of chemotherapy and hormonal therapy for early breast cancer on recurrence and 15-year survival: an overview of the randomised trials. Lancet (London, England). 2005 May;365(9472):1687–717.

7. Slamon D, Eiermann W, Robert N, Pienkowski T, Martin M, Press M, et al. Adjuvant Trastuzumab in HER2-Positive Breast Cancer. N Engl J Med [Internet]. 2011;365(14):1273–83. Available from: https://doi.org/10.1056/NEJMoa0910383

8. Clarke M, Collins R, Darby S, Davies C, Elphinstone P, Evans V, et al. 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 (London, England). 2005 Dec;366(9503):2087–106.

9. Veronesi U, Galimberti V, Mariani L, Gatti G, Paganelli G, Viale G, et al. Sentinel node biopsy in breast cancer: early results in 953 patients with negative sentinel node biopsy and no axillary dissection. Eur J Cancer. 2005 Jan;41(2):231–7.

10. Soerjomataram I, Louwman MWJ, Ribot JG, Roukema JA, Coebergh JWW. An overview of prognostic factors for long-term survivors of breast cancer. Breast Cancer Res Treat. 2008 Feb;107(3):309–30.

11. Klassen AC, Smith KC. The enduring and evolving relationship between social class and breast cancer burden: a review of the literature. Cancer Epidemiol. 2011 Jun;35(3):217–34.

12. Lu G. The fluctuating incidence, improved survival of patients with breast cancer, and disparities by age, race, and socioeconomic status by decade, 1981–2010. Cancer Manag Res. ::10 4899–4914.

13. Lundqvist A, Andersson E, Ahlberg I, Nilbert M, Gerdtham U. Socioeconomic inequalities in breast cancer incidence and mortality in Europe-a systematic review and meta-analysis. Eur J Public Health. 2016 Oct;26(5):804–13.

14. Collaborative Group on Hormonal Factors in Breast C. Breast cancer and breastfeeding: collaborative reanalysis of individual data from 47 epidemiological studies in 30 countries, including 50302 women with breast cancer and 96973 women without the disease. Lancet. 2002;360:187-95.

15. Islami F, Liu Y, Jemal A, Zhou J, Weiderpass E, Colditz G et al. Breastfeeding and breast cancer risk by receptor status--a systematic review and meta-analysis. Ann Oncol. 2015;26:2398-407.

16. Althuis MD, Dozier JM, Anderson WF, Devesa SS B LA. Global trends in breast cancer incidence and mortality 1973-1997. Int J Epidemiol. 2005;34:405-12.

17. Jemal A Torre LA, Siegel RL WE. Global cancer incidence and mortality rates and trends- an update. CacnerEpidemiolBiomarkersPrev. 2016;25(1):16-27.

18. Carlsen K, Hoybye MT, Dalton SO, Tjonneland A. Social inequality and incidence of and survival from breast cancer in a population-based study in Denmark, 1994-2003. Eur J Cancer. 2008 Sep;44(14):1996–2002.

19. Herndon JE 2nd, Kornblith AB, Holland JC, Paskett ED, Herndon II JE, Kornblith AB, et al. Effect of socioeconomic status as measured by education level on survival in breast cancer clinical trials. Psychooncology. 2013 Feb;22(2):315–23.

20. Morley KI, Milne RL, Giles GG, Southey MC, Apicella C, Hopper JL, et al. Socio-economic status and survival from breast cancer for young, Australian, urban women. Aust N Z J Public Health. 2010 Apr;34(2):200–5.

21. Nowara E, Suwinski R. Impact of educational differences as measure of socioeconomic status on survival for breast cancer patients. Contemp Oncol (Poznan, Poland). 2012;16(4):345–9.

22. Robsahm TE, Tretli S. Weak associations between sociodemographic factors and breast cancer: Possible effects of early detection. Eur J Cancer Prev [Internet]. 2005;14(1):7–12. Available from: https://www.scopus.com/inward/record.uri?eid=2-s2.0-15444370971&doi=10.1097%2F00008469-200502000-00002&partnerID=40&md5=db7cc1a598d6204bb7a07b6cda90ba40

23. Lagerlund M, Bellocco R, Karlsson P, Tejler G, Lambe M. Socio-economic factors and breast cancer survival--a population-based cohort study (Sweden). Cancer Causes Control. 2005 May;16(4):419–30.

24. Fernandez E, Borrell C. Cancer mortality by educational level in the city of Barcelona. Br J Cancer. 1999 Feb;79(3–4):684–9.

25. Dalton SO, Ross L, During M, Carlsen K, Mortensen PB, Lynch J, et al. Influence of socioeconomic factors on survival after breast cancer--a nationwide cohort study of women diagnosed with breast cancer in Denmark 1983-1999. Int J cancer. 2007 Dec;121(11):2524–31.

26. Strand BH, Tverdal A, Claussen B ZP. Is birth history the key to highly educated women's higher breast cancer mortality? A follow-up study of 500,000 women aged 35-54. Int J Cancer. 2005;117:1002–6.

27. Hussain SK, Altieri A, Sundquist J, Hemminki K. Influence of education level on breast cancer risk and survival in Sweden between 1990 and 2004. Int J cancer. 2008 Jan;122(1):165–9.

28. Gadeyne S, Deboosere P, Vandenheede H, Neels K. Does birth history account for educational differences in breast cancer mortality? A comparison of premenopausal and postmenopausal women in Belgium. Int J CANCER. 2012 Dec;131(12):2878–85.

29. Alicandro G, Frova L, Sebastiani G, El Sayed I, Boffetta P, La Vecchia C. Educational inequality in cancer mortality: a record linkage study of over 35 million Italians. CANCER CAUSES Control. 2017 Sep;28(9):997–1006.

30. Hwang KT, Han W, Shin HC, Kang HS, Bae YT, Jung YS, et al. The Influence of Education Level On the Survival of Breast Cancer. Eur J Cancer. 2012 Mar;48(1):S131–2.

31. Larsen SB, Kroman N, Ibfelt EH, Christensen J, Tjonneland A, Dalton SO. Influence of metabolic indicators, smoking, alcohol and socioeconomic position on mortality after breast cancer. Acta Oncol. 2015 May;54(5):780–8.

32. Lund E, Jacobsen BK. Education and breast cancer mortality: experience from a large Norwegian cohort study. Cancer Causes Control. 1991 Jul;2(4):235–8.

33. LeMarchand L, Kolonel LN, Nomura AM. Relationship of ethnicity and other prognostic factors to breast cancer survival patterns in Hawaii. J Natl Cancer Inst. 1984 Dec;73(6):1259–65.

34. Kim C, Eby E, Piette JD. Is education associated with mortality for breast cancer and cardiovascular disease among black and white women? Gend Med. 2005 Mar;2(1):13–8.

35. Menvielle G, Leclerc A, Chastang J-F, Luce D. Social inequalities in breast cancer mortality among French women: disappearing educational disparities from 1968 to 1996. Br J Cancer. 2006 Jan;94(1):152–5.

36. Hwang K-T, Noh W, Cho S-H, Yu J, Park MH, Jeong J, et al. Education Level Is a Strong Prognosticator in the Subgroup Aged More Than 50 Years Regardless of the Molecular Subtype of Breast Cancer: A Study Based on the Nationwide Korean Breast Cancer Registry Database. Cancer Res Treat. 2017 Oct;49(4):1114–26.

37. Lan NH, Laohasiriwong W, Stewart JF. Survival probability and prognostic factors for breast cancer patients in Vietnam. Glob Health Action. 2013 Jan;6:1–9.

38. Elstad JI, Torstensrud R, Lyngstad TH, Kravdal O. Trends in educational inequalities in mortality, seven types of cancers, Norway 1971-2002. Eur J Public Health. 2012 Dec;22(6):771–6.

39. Sathwara JA, Balasubramaniam G, Bobdey SC, Jain A, Saoba S. Sociodemographic Factors and Late-stage Diagnosis of Breast Cancer in India: A Hospital-based Study. Indian J Med Paediatr Oncol. 2017;38(3):277–81.

40. Gentil-Brevet J, Colonna M, Danzon A, Grosclaude P, Chaplain G, Velten M, et al. The influence of socio-economic and surveillance characteristics on breast cancer survival: a French population-based study. Br J Cancer. 2008 Jan;98(1):217–24.

41. Bouchardy C, Verkooijen HM, Fioretta G. Social class is an important and independent prognostic factor of breast cancer mortality. Int J cancer. 2006 Sep;119(5):1145–51.

42. Karjalainen S, Pukkala E. Social class as a prognostic factor in breast cancer survival. Cancer. 1990 Aug;66(4):819–26.

43. Weires M, Bermejo JL, Sundquist K, Sundquist J, Hemminki K. Socio-economic status and overall and cause-specific mortality in Sweden. BMC Public Health. 2008 Sep;8:340.

44. Power C, Hyppönen E, Smith GD. Socioeconomic position in childhood and early adult life and risk of mortality: a prospective study of the mothers of the 1958 British birth cohort. Am J Public Health. 2005 Aug;95(8):1396–402.

45. Kaffashian F, Godward S, Davies T, Solomon L, McCann J, Duffy SW. Socioeconomic effects on breast cancer survival: proportion attributable to stage and morphology. Br J Cancer. 2003 Nov;89(9):1693–6.

46. Gorey KM, Luginaah IN, Holowaty EJ, Fung KY, Hamm C. Breast cancer survival in ontario and california, 1998-2006: socioeconomic inequity remains much greater in the United States. Ann Epidemiol. 2009 Feb;19(2):121–4.

47. Thomson CS, Hole DJ, Twelves CJ, Brewster DH, Black RJ. Prognostic factors in women with breast cancer: distribution by socioeconomic status and effect on differences in survival. J Epidemiol Community Health. 2001 May;55(5):308–15.

48. Gorey KM, Holowaty EJ, Fehringer G, Laukkanen E, Richter NL, Meyer CM. An International comparison of cancer survival: Metropolitan Toronto, Ontario, and Honolulu, Hawaii. Am J Public Health [Internet]. 2000;90(12):1866–72. Available from: https://www.scopus.com/inward/record.uri?eid=2-s2.0-0033697040&doi=10.2105%2FAJPH.90.12.1866&partnerID=40&md5=31a4b6c93962d4ad6d09d6b1cd62fd04

49. Gorey KM, Luginaah IN, Holowaty EJ, Zou G, Hamm C, Balagurusamy MK. Mediation of the effects of living in extremely poor neighborhoods by health insurance: Breast cancer care and survival in California, 1996 to 2011. Int J Equity Health [Internet]. 2013;12(1). Available from: https://www.scopus.com/inward/record.uri?eid=2-s2.0-84872126317&doi=10.1186%2F1475-9276-12-6&partnerID=40&md5=3923c57bd9147bc076e3b2eb5755829a

50. Ansell D, Whitman S, Lipton R, Cooper R. Race, income, and survival from breast cancer at two public hospitals. Cancer. 1993 Nov;72(10):2974–8.

51. Vehko T, Arffman M, Manderbacka K, Pukkala E, Keskimaki I. Differences in mortality among women with breast cancer by income - a register-based study in Finland. Scand J Public Health. 2016 Nov;44(7):630–7.

52. Aziz Z, Iqbal J, Akram M, Anderson BO. Worsened oncologic outcomes for women of lower socio-economic status (SES) treated for locally advanced breast cancer (LABC) in Pakistan. Breast. 2010 Feb;19(1):38–43.

53. Iqbal J, Ginsburg O, Rochon PA, Sun P, Narod SA. Differences in breast cancer stage at diagnosis and cancer-specific survival by race and ethnicity in the United States. JAMA. 2015 Jan;313(2):165–73.

54. Tannenbaum SL, Koru-Sengul T, Miao F, Byrne MM. Disparities in survival after female breast cancer diagnosis: a population-based study. Cancer Causes Control. 2013 Sep;24(9):1705–15.

55. Dobson A, McLaughlin D, Vagenas D, Wong KY. Why are death rates higher in rural areas? Evidence from the Australian Longitudinal Study on Women's Health. Aust N Z J Public Health. 2010 Dec;34(6):624–8.

56. Markossian TW, Hines RB. Disparities in late stage diagnosis, treatment, and breast cancer-related death by race, age, and rural residence among women in Georgia. Women Health. 2012;52(4):317–35.

57. Higgins JPT, Thompson SG. Quantifying heterogeneity in a meta-analysis. Stat Med. 2002 Jun;21(11):1539–58.

58. DerSimonian R, Laird N. Meta-analysis in clinical trials. Control Clin Trials. 1986 Sep;7(3):177–88.

59. Egger M, Davey Smith G, Schneider M, Minder C. Bias in meta-analysis detected by a simple, graphical test. BMJ. 1997 Sep;315(7109):629–34.

60. Light RJ, Pillemer DB. Summing Up: The Science of Reviewing Research Harvard University Press: Cambridge, MA, 1984, xiii+191 pp. Educ Res [Internet]. 1986;15(8):16–7. Available from: https://doi.org/10.3102/0013189X015008016

61. Sun Y-S, Zhao Z, Yang Z-N, Xu F, Lu H-J, Zhu Z-Y, et al. Risk Factors and Preventions of Breast Cancer. Int J Biol Sci. 2017;13(11):1387–97.

62. Volaco A, Cavalcanti AM, Filho RP, Precoma DB. Socioeconomic Status: The Missing Link Between Obesity and Diabetes Mellitus? Curr Diabetes Rev. 2018;14(4):321–6.

63. Protani M, Coory M, Martin JH. Effect of obesity on survival of women with breast cancer: systematic review and meta-analysis. Breast Cancer Res Treat. 2010 Oct;123(3):627–35.

64. Niraula S, Ocana A, Ennis M, Goodwin PJ. Body size and breast cancer prognosis in relation to hormone receptor and menopausal status: a meta-analysis. Breast Cancer Res Treat. 2012 Jul;134(2):769–81.

65. Chan DSM, Vieira AR, Aune D, Bandera E V, Greenwood DC, McTiernan A, et al. Body mass index and survival in women with breast cancer-systematic literature review and meta-analysis of 82 follow-up studies. Ann Oncol Off J Eur Soc Med Oncol. 2014 Oct;25(10):1901–14.

66. Heck KE, Braveman P, Cubbin C, Chavez GF, Kiely JL. Socioeconomic status and breastfeeding initiation among California mothers. Public Health Rep. 2006;121(1):51–9.

67. Sigulem DM, Tudisco ES. [Breast feeding in different income classes in the Municipality of Sao Paulo]. Arch Latinoam Nutr. 1980 Sep;30(3):400–16.

68. Gilbert NL, Bartholomew S, Raynault M-F, Kramer MS. Temporal trends in social disparities in maternal smoking and breastfeeding in Canada, 1992-2008. Matern Child Health J. 2014 Oct;18(8):1905–11.

69. Fortner RT, Sisti J, Chai B, Collins LC, Rosner B, Hankinson SE, et al. Parity, breastfeeding, and breast cancer risk by hormone receptor status and molecular phenotype: results from the Nurses' Health Studies. Breast Cancer Res. 2019 Mar;21(1):40.

70. Millikan RC, Newman B, Tse C-K, Moorman PG, Conway K, Dressler LG, et al. Epidemiology of basal-like breast cancer. Breast Cancer Res Treat. 2008 May;109(1):123–39.

71. Warren GW, Kasza KA, Reid ME, Cummings KM, Marshall JR. Smoking at diagnosis and survival in cancer patients. Int J cancer. 2013 Jan;132(2):401–10.

72. Amigo H, Ale D, Varela N, Peruga A, Bustos P. [Pattern of smoking and socioeconomic status in two cohorts of young adults]. Rev Med Chil. 2018 Feb;146(2):168–74.