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Meta-Analysis

Meta Analysis: Effect of Mammography Screening on Breast Cancer Mortality

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ABSTRACT

Background: Breast cancer is the most common cancer experienced by women in developing and developed countries. One of the early detection of breast cancer is mammography. This study aims to analyze the effect of screening mammography on breast cancer mortality by using a meta-analysis study.

Subjects and Method: This was a systematic review and meta-analysis conducted using PRISMA flow diagrams. Search articles through journal databases including: Google Scholar, PubMed, and BMJ by selecting articles published in 2005-2020. The keywords used are "Mammography" AND "Mortality" AND "Breast Cancer". The inclusion criteria were full text articles with an observational study design, articles in English, multivariate analysis with adjusted Hazard Ratio. Eligible articles were analyzed using the Revman5.3 app.

Results: A meta-analysis of 11 cohort studies showed that screening mammography was 0.65 times lower in breast cancer mortality compared with women who were not screened for mammography (aHR= 0.65; 95% CI= 0.54 to 0.79; p=0.0001).).

Conclusion: Mammography screening reduces breast cancer mortality.

Keywords: Mammography Screening, Breast Cancer, Meta-analysis

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BACKGROUND

Non-communicable diseases are the largest contributor to death worldwide. The four largest non-communicable diseases are cardiovascular disease, diabetes mellitus, cancer and chronic respiratory disease (Bray et al., 2018). Cancer is the second leading cause of death globally. In 2018, about 9.6 million deaths, or one in six deaths, were caused by cancer (Bray et al., 2018). Breast cancer is the top cancer experienced by women in developing and developed countries (WHO, 2016). The estimated age standard incidence in 2020 for breast cancer is 47.8. Breast cancer also ranks second after lung cancer for an estimated mortality rate of 13.6 (GLOBOCAN, 2020). White and black women have the same chance of developing breast cancer. However, black women have a higher chance of dying from breast cancer (Richardson et al., 2016). Cancer in Indonesia shows a tendency to increase in incidence in recent years. As reported by Riskesdas that there was an increase in cancer prevalence from 1.4% in 2013 to 1.49% in 2018 (Riskesdas, 2018). The highest incidence rate for women is breast cancer, which is 42.1 per 100,000

population with an average death rate of 17 per 100,000 population (Ministry of Health of the Republic of Indonesia, 2019).

The incidence of delays in breast cancer patients conducting an initial examination of health services in Indonesia reaches more than 80%. This results in the incidence of breast cancer being found at an advanced stage. Hospital Information System (SIRS) data shows 60%-70% of patients who come to the hospital in advanced stages III and IV (Ministry of Health, 2016). Research shows that early detection of breast cancer has an important role in reducing mortality and improving disease prognosis (Rahimzadeh et al., 2014).

Breast cancer can be prevented if detected early. The most important and useful thing for self-protection from breast cancer is early detection of breast cancer (screening). Diagnosis of breast cancer at an early stage is associated with a reduction in breast cancer mortality and morbidity (Khatib, 2006). Most professional organizations in the United States recommend early detection by mammography with appropriate follow-up for abnormal screening tests (Winters et al., 2017). In a study it was said that the recommendation for mammography could reduce the mortality rate from breast cancer by 28% (Weedon-Fekjræ et al., 2014).

Several meta-analytical studies on mammography on breast cancer have also been conducted. A meta-analysis of studies conducted from databases from 1966–1993 found that mammography was effective in reducing breast cancer mortality in women aged 50–74 years after seven–nine years of follow-up, regardless of the screening interval or the number of mammographic views per screen. However, in the group of women aged 40–49 years, there was no decrease in breast mortality (Slawson& Coates, 1995). A meta-analysis conducted using the PubMed/MEDLINE database, OVID, COCHRANE, and the Educational Resources Information Center (ERIC) concluded that mammography screening was effective and reduced breast cancer mortality by 17% in women aged 39-49 years (Magnus et al., 2011). A meta-analysis study using a 1995–2006 databases in Australia also stated that there was a 49% reduction in breast cancer mortality in women undergoing mammography screening (Nickson et al., 2012). A quasi-experimental meta-analysis study suggests that mammography may have an effect on breast cancer mortality in the 50-69 year age range. However, for ages over 70 years, it has not shown a significant effect (Irvin and Kaplan, 2014). A European meta-analysis study by source Pubmed October 2019 said that there was a significant 22% reduction in breast cancer mortality by invitation to screening, with a relative risk of 0.78 (95% CI 0.75-0.82), and a significant 33% reduction with actual attendance at screening (RR= 0.67, 95% CI 0.61-0.75) (Dibden et al., 2020).

Various studies have been carried out to see the effect of mammography examination on mortality in breast cancer patients, but the results of the research still do not show consistent results. Further analysis is needed to arrive at a convincing conclusion. Therefore, researchers are interested in examining the effect of mammography examinations on mortality in breast cancer patients.

SUBJECTS AND METHOD

1. Study Design

The study design used in this research is a systematic review and meta-analysis, using PRISMA flow diagram guidelines. Article searches were conducted using journal databases including: PubMed, Google Scholar and BMJ. The keywords used are “mammography” OR “mammography

screening" AND "mortality" AND "breast cancer".

2. Inclusion Criteria

The inclusion criteria were full text articles in 2005-2021 using an observational study design, namely a cohort, articles in English, the analysis used was multivariate with adjusted Hazard Ratio, the research subjects were women aged 40 years, the intervention was screening mammography and the outcome is breast cancer mortality.

3. Exclusion Criteria

Exclusion criteria in this study included articles published before 2005 and languages other than English.

4. Operational Definition of Variable

In formulating the problem, the researcher here uses PICO. The population is women aged 40 years. Intervention is screening mammography, with comparison that is not screening mammography, and outcomes is breast cancer mortality.

Mammography examination is an imaging modality that uses low energy X-rays specifically for imaging breast tissue which is used as a screening tool to detect early breast cancer in asymptomatic women.

Mortality is the permanent loss of all signs of life at any time after live birth, i.e. the loss of life functions after birth, without the possibility of resuscitation.

Breast cancer is a disease in which cells in the breast grow out of control and are diagnosed by radiological examination.

5. Instrument

An assessment of the quality of research articles is carried out using the Critical Appraisal Skills Program (CASP) for Cohort Study).

6. Data Analysis

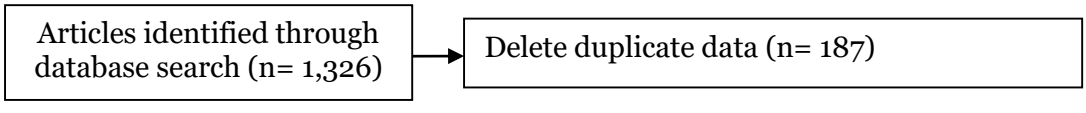
The Review Manager application (RevMen 5.3) was used in analyzing the data in this study. The results of data analysis are in the form of effect size values and study heterogeneity which later the results of the data that have been analyzed are interpreted in the form of forest plots and funnel plots.

RESULTS

Research from primary studies related to the effect of screening mammography on breast cancer mortality consisted of 11 studies originating from 1 study from the Asia, 5 studies from the Europe, and 5 studies from the North America. Figure 1 shows the region of the retrieved articles that fit the inclusion criteria. Furthermore, the researchers conducted an assessment of the quality of the articles and there were 11 cohort study articles. The results show that screening mammography has an effect on breast cancer mortality. The article search was carried out using a database based on the PRISMA flow diagram, which can be seen in Figure 1.

Forest plot

The forest plot provides a summary of the data entered and gives weights for each study, effect sizes, methods and models used to perform the meta-analysis, confidence intervals used, estimated impact of each study, overall effect estimates, and statistical significance of the analysis. Interpretation of the results of the meta-analysis process can be seen through the forest plot. Figure 2 shows that the results of the analysis in the cohort study, screening mammography examination 0.65 times reduced breast cancer mortality (aHR= 0.65; 95% CI= 0.54 to 0.79) and statistically signifycant (p= 0.001). The heterogeneity of the research data showed I^2= 91%. Therefore, the distribution of data is expressed by heterogeneous (random effect model).



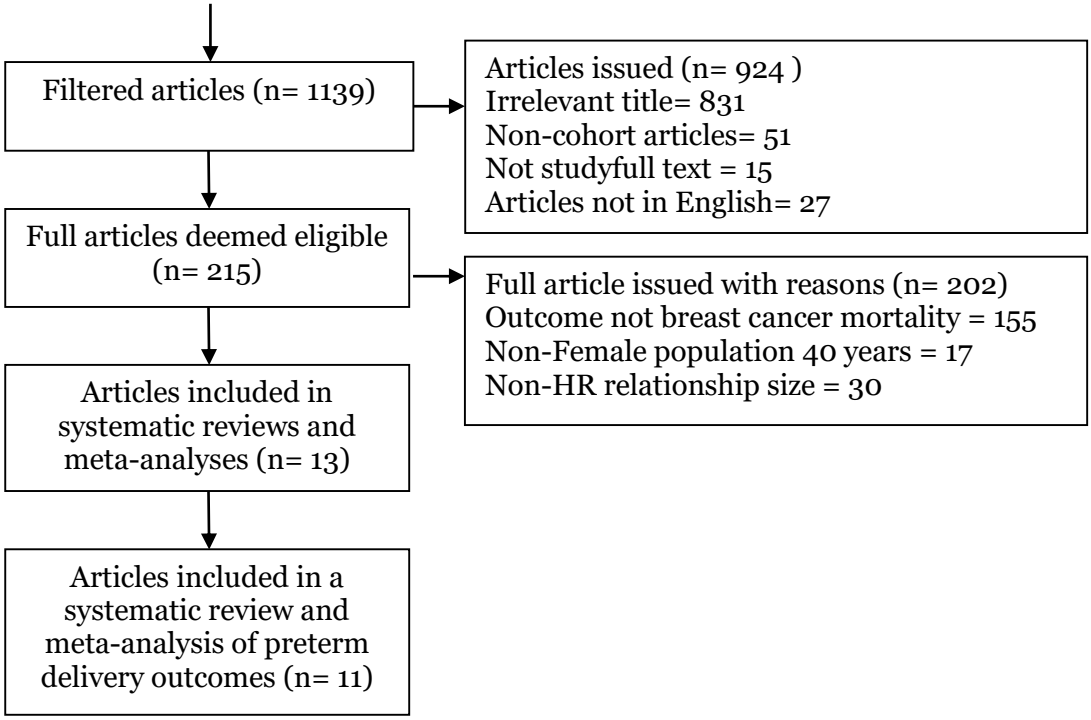


Figure 1. PRISMA flow diagram

Funnel Plot

A funnel plot is a plot that depicts the approximate size of the effect of each study on the estimate of its accuracy which is usually the standard error.

Based on Figure 3, the cohort study shows a publication bias indicated by the asymmetric distribution of right and left plots where 4 plots are on the right, and 7 plots are on the left. The plot on the left of the graph appears to have a standard error between 0 and 0.4 and the plot on the right has a standard error between 0 and 0.2.

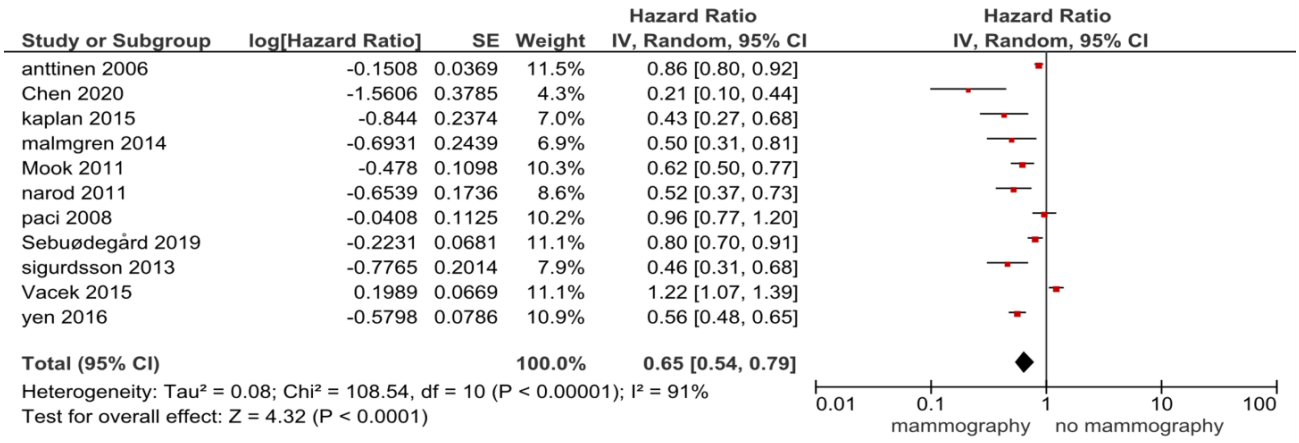


Figure 2. Forest plot of the effect of screening mammography on breast cancer mortality

Figure 3. Funnel plot of the effect of screening mammography on breast cancer mortality

DISCUSSION

This systematic study and meta-analysis discusses the effect of screening mammography on breast cancer mortality. The independent variables were analyzed by women aged 40 years who performed screening mammography. The dependent variable in this study was breast cancer mortality. The results of the primary study conducted showed that the epidemiological study design with a larger sample size, in addition to the demographic characteristics that vary in various countries, will serve as the basis for concluding that women who undergo screening mammography have a statistical effect on cancer mortality breast.

Breast cancer is the most common malignancy in women worldwide. Death from breast cancer is still a global problem, including Indonesia. The high mortality from breast cancer in Indonesia is still a special concern. Most breast cancers detected in Indonesia are in stages III-IV. The delay in breast cancer patients doing examinations, causes high rates of breast cancer morbidity and mortality (Ministry of Health, 2016).

Screening mammography is a specific type of breast imaging that uses low-dose x-rays to detect cancer early – before a woman develops symptoms – when the cancer is most treatable (RadiologyInfo.org, 2019). So far the only breast cancer screening method that has been shown to be effective in an organized population-based program is screening mammography. However, reports on the benefits and harms of screening mammography differ markedly in the context and intensity of screening examined, as well as in the interpretation of the available evidence. The majority of countries that have been able to apply this program are upper middle income countries (WHO, 2014).

Breast self-examination and routine clinical examinations are clinical ways to detect breast cancer early. However, because most breast cancers are not detected early, imaging has an important role (Yunus et al, 2004). Approximately 25-43% of cancers that are not palpable are detected on

mammography due to microcalcification (Zeeshan et al, 2018). The benefit of mammography is to detect all types of breast cancer, including invasive ductal cancer and invasive lobular cancer, as a supporting tool in helping doctors to detect small tumors. With early detection through mammography screening, it is hoped that the cancer detected is at an early stage, so that the treatment provided can be maximal. Early stage breast cancer has a good prognosis. (Brodersen et al., 2010; Løberg et al., 2015) (Løberg et al., 2015).

A study compared serial and non-serial screening mammography. The incidence of breast cancer that proved fatal within 10 years of diagnosis was 50% lower for serial mammography screening participants compared to non-serial mammography screening participants. Participants who attended two of the previous mammography screenings experienced a 29% reduction in breast cancer deaths compared to patients who attended only one screening. The protection provided by screening mammography does not last long so it is hoped that participants do not miss a single screening because it can increase the risk significantly (Duffy et al, 2021).

Other studies suggest that women who attend screening, and who usually have breast cancer diagnosed at an early stage, benefit significantly more from the advanced therapies available at the time of diagnosis than women who do not attend screening. Detection at an early stage through participation in screening mammography provides a significant reduction in the risk of death from breast cancer when modern adjuvant therapies are available (Duffy et al, 2020).

This study uses previous primary studies that control confounding factors, this can be seen based on the inclusion requirements of the study using multivariate analysis and the statistical results are adjusted hazard ratio (aHR). Confounding factors are mixed estimates of the effects of exposure being studied on the risk of disease by other factors related to exposure and are independent risk factors for the disease under study (Murti, 2018). These eleven research articles have several similarities in controlling for confounding factors. Several confounding factors that have been controlled for include age, tumor characteristics (tumor grade, node status, and tumor stage), ER status and adjuvant therapy. However, only one study included comorbid status as a confounding factor. Estimated association between screening mammography and breast cancer mortality was processed using the RevMan 5.3 application.

Effect of Mammography Screening on Breast Cancer Mortality

There are 11 research articles with cohort studies which are the source of meta-analysis of the effect of screening mammography examination on breast cancer mortality. The results of the forest plot of research articles with an observational cohort design showed that screening mammography was 0.65 times lower cancer mortality compared to not screening mammography and the results were statistically significant (aHR= 0.65; 95% CI = 0.54 to 0.79; p = 0.001).

The results of the analysis of 11 articles regarding the effect of screening mammography on breast cancer mortality reported that there was a high heterogeneity between experiments (I^2=91%; p <0.001) so the Random Effect Model (REM) was used population. In these 11 primary research articles, there is a fairly large range of samples (243-856,524 samples). Another difference is in the age criteria. The age used in the 11 primary articles is from the age of 40 to 82 years. Another difference is that

there is an intervention interval in each study, there are three studies that screen every two years, one study screens every year, and seven studies do not mention how many times the screening is done.

The systematic review and meta-analysis in this study aims to increase the generalizability of the findings and obtain convincing conclusions from the results of various similar studies regarding the effect of screening mammography on breast cancer mortality. In addition, a systematic review and meta-analysis in this study also uses research that controls confounding factors that can be seen from the research inclusion criteria, namely using a cohort design and the statistical results reported are Adjusted Hazard Ratio. Even so, there are still confounding factors from several primary studies that can influence the actual effect relationship.

(Beau et al., 2018) in their study stated that screening mammography has a clear long-term beneficial effect with a 20% reduction in breast cancer mortality in the invited population. However, this effect was only potential in women who were invited to mammography screening. Meanwhile, for women whose age has passed the screening period and diagnosed with breast cancer, the benefits obtained from screening mammography are very small (age-adjusted rate ratio= 0.80; 95% CI; 0.71 - 0.90).

Research conducted by (Taylor et al., 2004) found that reductions in breast cancer mortality in New South Wales went hand in hand with population screening. On the regression coefficient, at 70% biennial screening rate was associated with 32% lower mortality from breast cancer compared with no screening. At the municipal level, it was found that more screening was carried out in addition to other treatments such as breast self-examination and breast examination by a doctor. Factors associated with reduced mortality include age, geography, breast cancer incidence, and socioeconomic level.

In a study conducted by (Irvin et al., 2020) comparing interval breast cancer with breast cancer detected during mammography. The results of this study indicated that interval breast cancer had a higher risk of death than breast cancer detected on mammography (aHR = 1.64; 95% CI, 1.14-2.34). Interval breast cancer diagnosed within 1 year with a previous negative mammogram, had a higher proportion of invasive lobular carcinoma than breast cancer detected through screening. Mammography is known to be less sensitive for identifying lobular cancer, partly due to the fact that lobular tumor cells spread diffusely, and the lack of mammographic evidence of calcification due to possible loss of E-cadherin calcium-dependent transmembrane protein.

However, in a study conducted by (Autier et al., 2012) stated that breast cancer mortality statistics in Sweden are consistent with several studies that show limited or no impact of screening on breast mortality. In this study, the investigators could not consider the effect of risk factors on breast mortality that could mask the mortality effect of screening. In addition, differences in the availability of adjuvant therapy in each region also affect breast cancer mortality.

Ultrasonography (USG) and mammography are standard screening tools to detect and evaluate breast cancer. A study compared the sensitivity and specificity between ultrasound and mammography and stated that the sensitivity and specificity of mammography were 73% and 55%, and the false-negative rate was 17.27%, respectively. Mammography is more effective in women aged 50 years because the older a woman is,

the lower the breast density (Haghighi et al, 2017) (Luczynska et al, 2016).

Ultrasound can tell whether a lump is a solid mass or a fluid-filled cyst, but a large number of breast cancers are difficult to see using ultrasound because it is difficult to distinguish between fatty breast tissue and cancerous tissue (Mehnati and Tirtash, 2015). Ultrasound is recommended over mammography for women aged 45 years and younger and women with dense breasts. Dense fibrous glandular tissue is the most important inherent limitation of mammography in the diagnosis of breast cancer. Bilateral whole-breast ultrasound can be an effective adjunct imaging examination in the evaluation of women with dense breast tissue on mammography (Haghighi et al, 2017).

AUTHOR CONTRIBUTION

Bening Rahimi Titisari is the main researcher who chooses the topic, conducts a search for data collection in this study. Vitri Widyaningsih and Bhisma Murti conducted data analysis and review of research documents.

FUNDING AND SPONSORSHIP

This study is self-funded.

CONFLICT OF INTEREST

There is no conflict of interest in this study.

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