Obesity and Its Risk on Breast Cancer among Women: A Meta-Analysis

Ruth Apriyanti[1], Yulia Lanti Retno Dewi[2], Bhisma Murti[1]

[1]Masters Program in Public Health, Universitas Sebelas Maret
[2]Faculty of Medicine, Universitas Sebelas Maret

ABSTRACT

Background: Breast cancer is the most common type of cancer experienced by women which can cause the most deaths in both developed and developing countries. The risk of breast cancer severity in women with BMI obesity category increased up to 30% compared with women who had normal weight. This study aims to analyze the effect of obesity on breast cancer mortality in women, with a meta-analysis of primary studies conducted by previous authors.

Subjects and Method: This study is a systematic review and meta-analysis with the following PICO, population: breast cancer women. Intervention: obesity. Comparison: not obese. Outcome: mortality. The articles used in this study were obtained from four databases, namely Google Scholar, Pubmed, Science Direct and Springerlink. Keywords to search for articles "Obesity" OR "Obese Overweight" AND "Mortality" OR "Death" AND "Women with Breast Cancer" OR "Breast Cancer" OR "Breast Cancer Mortality" AND "Adjusted Hazard Ratio". The included articles are full-text English with an observational cohort study design from 2012 to 2021 and report on the aOR in multivariate analyses. Article selection is done by using PRISMA flow diagram. Articles were analyzed using the Review Manager 5.3 application.

Results: A total of 12 observational cohort studies from the United States, Denmark, Netherlands, UK, Spain, Malaysia and China were selected for systematic review and meta-analysis. The data collected showed that obesity increased the mortality risk of breast cancer women and was statistically significant (aOR = 1.23; 95% CI = 1.00 to 1.52; p = 0.050).

Conclusion: Obesity increases the risk of mortality in breast cancer women.

Keywords: obesity, breast cancer women, meta-analysis

Correspondence:
Ruth Apriyanti. Masters Program in Public Health, Universitas Sebelas Maret. Jl. Ir. Sutami 36A, Surakarta 57126, Central Java. Email: ruthyanti94.ras@gmail.com. Mobile: +6281375232120.

BACKGROUND

Cancer is ranked first as a cause of death and a barrier in increasing life expectancy in every country in the world based on estimates by the World Health Organization (WHO) in 2019. Breast cancer is the most common type of cancer suffered by women in the last 5 years with a prevalence of 7.8 million cases worldwide (15.4%). Globally, breast cancer is the most common cancer and the leading cause of cancer death in women. It is estimated that there were 2.09 million incident cases and 0.63 million deaths from breast cancer worldwide in 2018, which places a considerable burden on public health (Chan et al., 2019).

Breast cancer is the most common type of cancer found by women around the

world with 684,996 deaths in 2020. The Asian region is the most dominating breast cancer patient death (55%), this can be caused by some countries with large populations such as China, India, and Indonesia is in Asia. With 5 countries with the highest number of deaths, namely; China (17.1%), India (13.2%), USA (6.2%), Russia (3.4%), and Indonesia (3.3%). In Indonesia, with 3,353,448 new cases (24%) with 1,053,435 deaths (15.1%) (GLOBOCAN, 2020).

Obesity increases the risk of breast cancer through the performance of endogenous sex hormones, especially estradiol, which are likely to have tumor-inducing activity. Women who enter menopause age, adipose tissue is the main source of estrogen which can increase the risk of breast cancer is higher. The higher risk of postmenopausal breast cancer associated with obesity was mainly seen in estrogen and progesterone receptor-positive, and it was limited to women not taking hormone replacement therapy (Pischon and Nimptsch, 2016).

Breast cancer survivors gain weight primarily through sedentary activity and a sedentary lifestyle, with a peak in the third year, when followed for six years (Makari-Judson et al., 2014). Obesity is associated with an increased risk of developing breast cancer for women and an increased mortality from breast cancer in women of all ages. (Zeng et al., 2020). The mortality of cancer patients with obesity reaches 14% in men and 20% in women (Agha, 2017).

Based on this background, comprehensive research is needed from various primary studies on the effect of obesity on mortality in women with breast cancer. This study aims to analyze the effect of obesity on mortality in women with breast cancer.

SUBJECTS AND METHOD

1. Study Design
This research is a systematic review and meta-analysis. The articles used in this study were obtained from several databases, namely Google Scholar, PubMed, and Science Direct and Springerlink between 2012 and 2021. The selection of articles was carried out using PRISMA flow diagrams. Keywords to search for articles are as follows "Obesity" OR "Obese Overweight" AND "Mortality" OR "Death" AND "Women with Breast Cancer" OR "Breast Cancer" OR "Breast Cancer Mortality" AND "Adjusted Hazard Ratio".

2. Inclusion Criteria
The inclusion criteria in this research article are: full-text articles using a cohort study design, research subjects are breast cancer women, research outcomes are mortality, with multivariate analysis using adjusted Odds Ratio (aOR) values.

3. Exclusion Criteria
The exclusion criteria in this research article are: articles published in languages other than English, articles before 2012, and articles that are not free access.

4. Operational Definition of Variables
The search for articles was carried out by considering the eligibility criteria determined using the PICO model. Population: women with breast cancer. Intervention: obesity. Comparison: not obese. Outcome: mortality.

Obesity is a condition of being overweight in adults based on Body Mass Index (BMI) values. The measurement scale is categorical.

Mortality in women with breast cancer is defined as the mortality status of women diagnosed with breast cancer, with the categorization of dead or alive. The measurement scale is categorical.

5. Study Instruments

Research is guided by the PRISMA flow diagram and quality assessment using the Critical Appraisal for Critical Appraisal Skills Program (CASP, 2018).

6. Data Analysis

The data in the study were analyzed using the Review Manager application (RevMan 5.3). Forest plots and funnel plots were used to determine the size of the relationship and heterogeneity of the data. The fixed effect model is used for homogeneous data, while the random effect model is used for heterogeneous data.

RESULTS

The article search process is carried out through several journal databases including Google Scholar, PubMed, Science Direct and SpringerLink. The review process for related articles can be seen in the PRISMA flow diagram in Figure 1.

Research related to the effect of obesity on mortality in women with breast cancer consists of 12 articles from the initial search process yielding 1,630 articles, after the deletion process of published articles, 84 articles were found of which were eligible for further research. full text review. A total of 12 articles that met the quality assessment were included in the quantitative synthesis using a meta-analysis.

It can be seen in Figure 2 that the research articles come from 3 continents, namely: America, Europe and Asia with various countries namely the United States, Denmark, Netherlands, UK, Spain, Malaysia and China. Table 1 The researchers conducted an assessment of the quality of the study. Table 2 shows 12 articles from a cohort study as evidence of the effect of obesity on breast cancer mortality in women.
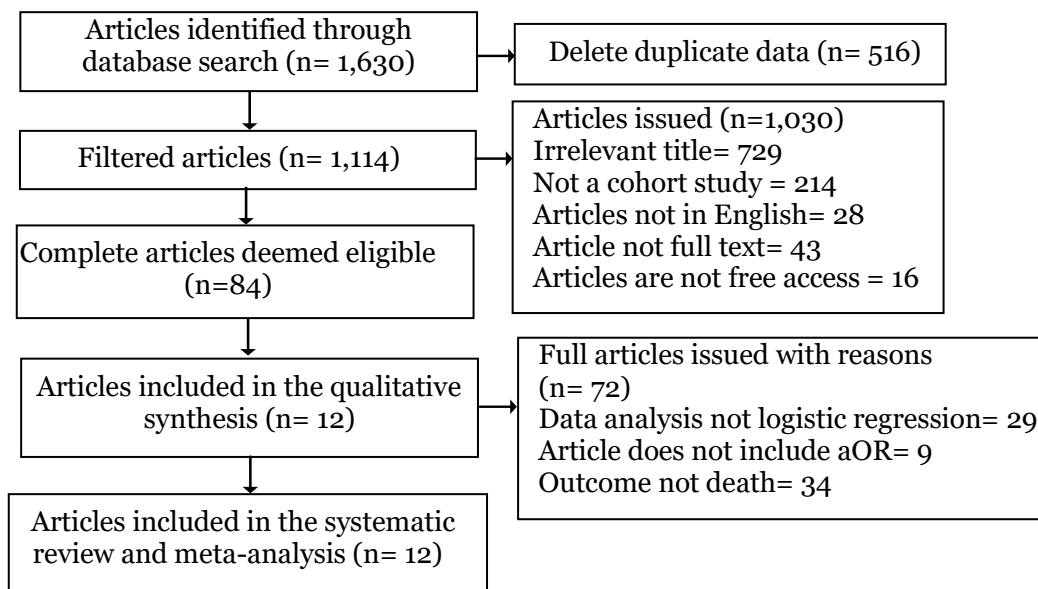

Figure 1. PRISMA flow diagram
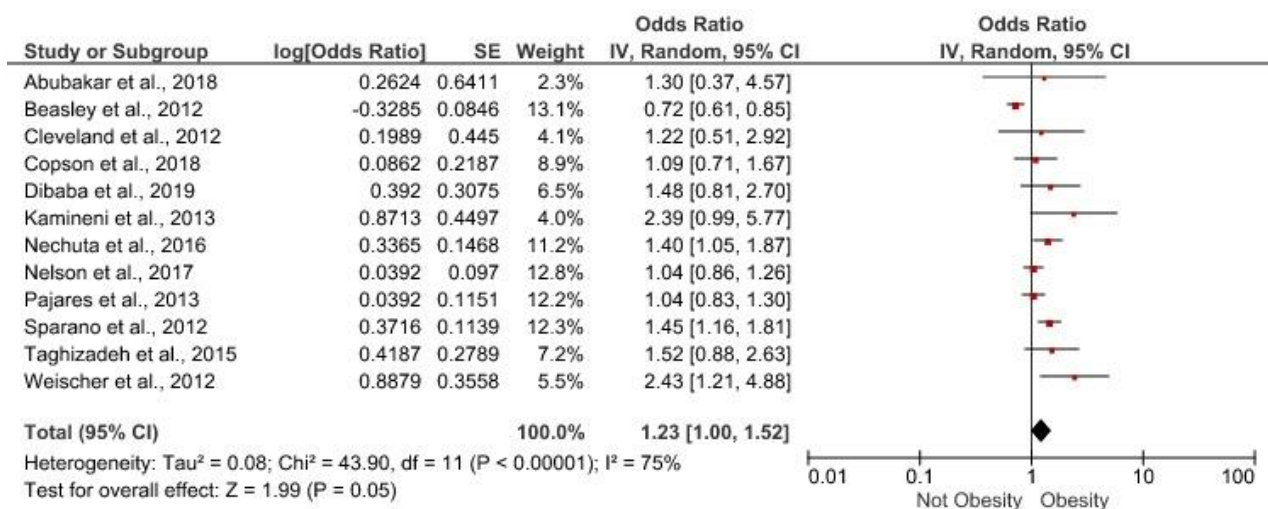
Figure 2. Map of the research area

**Figure 3. Forest plot The Effect of Obesity on Mortality
of Women with Breast Cancer**

Based on the results of the forest plot of the cohort study, obesity affected breast cancer mortality by 1.23 times compared to non-obese breast cancer women (aOR= 1.23; 95% CI= 1.00 to 1.52; p= 0.050) and the results were statistically significant. The heterogeneity of the research data shows I^2= 75% so that the distribution of the data is declared heterogeneous (random effect model).

The results of the funnel plot show publication bias with an overestimated effect which is characterized by an asymmetric distribution between the right and left plots. There are six plots on the right, four plots on the left, and two plots touching the vertical line. The plot on the right has a standard error (SE) between 0 and 0.6. The plot on the left side of the graph has a standard error (SE) between 0 and 0.4.
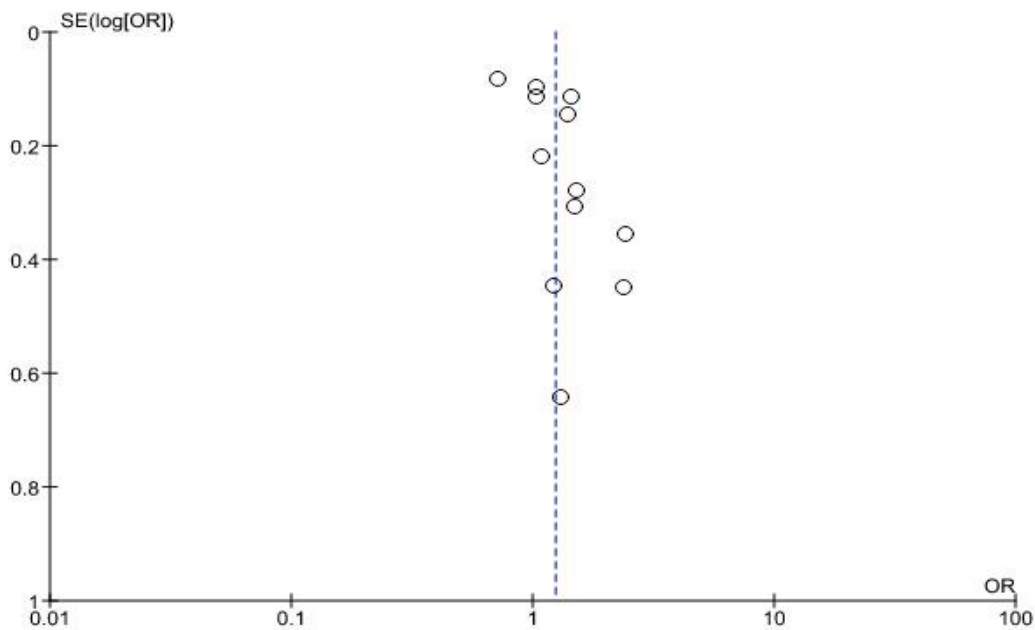
Figure 4. Funnel plot of the Effect of Obesity on Mortality of Breast Cancer Women

DISCUSSION

Systematic studies and meta-analyses raise the theme of the effect of obesity on mortality in women with breast cancer. This study discusses obesity which is considered to be one of the important factors because it can cause death in breast cancer women.

Breast cancer is a malignant neoplasm in which abnormal breast tissue grows regardless of the surrounding tissue, it grows infiltratively and destructively and can metastasize. The death rate from breast cancer is still a global problem, including Indonesia. The World Cancer Research Fund (WCRF) and American Cancer Society (ACS) cancer prevention guidelines recommend maintaining a healthy weight, getting at least 150 minutes of moderate-intensity exercise per week, limiting alcohol consumption, and eat plant foods. Obesity is a global problem associated with an increased risk of developing postmenopausal breast cancer and a poorer prognosis at the time of diagnosis (Harvie et al., 2015).

Obesity can increase the mortality risk of breast cancer women, these results are in accordance with the hypothesis. According to research by Anderson and Neuhouser, (2012) stated that obesity can contribute to the recurrence rate and mortality of breast cancer women. Breast cancer survivors by group whose weight continues to increase and have been shown to have a higher risk of mortality.

For breast cancer mortality, individual lifestyle models showed a significant association with very low physical activity. The category included in the study was lifestyle variables, very low physical activity was associated with a 22% increased risk of death from breast cancer (aHR= 1.22, 95% CI= 1.05, to 1.42) (Nelson et al., 2017).

Table 1. Assessment of study quality published by the Critical Appraisal Skills Program (CASP)

No	Indicators	Publication (Author and Year)					
		Abubakar et al., (2018)	Beasley et al., (2012)	Cleveland et al., (2012)	Copson et al., (2018)	Dibaba et al., (2019)	Nechuta et al., (2016)
1	Does the cohort study clearly address the clinical problem?	2	2	2	2	2	2
2	Were the cohorts (subjects in the exposed and unexposed groups) selected in the right way?	2	2	2	2	2	2
3	Is obesity exposure accurately measured to minimize bias?	2	2	2	2	2	2
4	Was the outcome (death status) measured accurately to minimize bias?	2	2	2	2	2	2
5	Did the researcher identify all the important confounding factors? Has the researcher taken into account confounding factors in the design and/or analysis of the data?	2	2	2	2	2	2
6	Did the research subject complete the full time of the study? Was there a long enough follow-up of the research subjects?	2	2	2	2	2	2
7	Are research results reported in Adjusted Odds Ratio (aOR)?	2	2	2	2	2	2
8	How precise is the result?	1	2	1	2	1	2
9	Are the results reliable?	2	2	2	2	2	2
10	Can the results be applied to the local (local) population?	2	2	2	2	2	2
11	Are the results of this study consistent with other available evidence?	2	2	2	2	2	2
12	What are the implications of this research for practice?	2	2	2	2	2	2
	Total	**23**	**24**	**23**	**24**	**23**	**24**

Description:

2: Yes; 1: Can't tell; 0: No

Table 2. Cont.

No	Indicators	Kamineni et al., (2014)	Nelson et al., (2017)	Pajares et al., (2013)	Sparano et al., (2012)	Taghizadeh et al., (2015)	Weischer et al., (2012)
		Publication (Author and Year)					
1	Does the cohort study clearly address the clinical problem?	2	2	2	2	2	2
2	Were the cohorts (subjects in the exposed and unexposed groups) selected in the right way?	2	2	2	2	2	2
3	Is obesity exposure accurately measured to minimize bias?	2	2	2	2	2	2
4	Was the outcome (death status) measured accurately to minimize bias?	2	2	2	2	2	2
5	Did the researcher identify all the important confounding factors? Has the researcher taken into account confounding factors in the design and/or analysis of the data?	2	2	2	2	2	2
6	Did the research subject complete the full time of the study? Was there a long enough follow-up of the research subjects?	2	2	2	2	2	2
7	Are research results reported in Adjusted Odds Ratio (aOR)?	2	2	2	2	2	2
8	How precise is the result?	1	2	2	2	1	1
9	Are the results reliable?	2	2	2	2	2	2
10	Can the results be applied to the local (local) population?	2	2	2	2	2	2
11	Are the results of this study consistent with other available evidence?	2	2	2	2	2	2
12	What are the implications of this research for practice?	2	2	2	2	2	2
	Total	**23**	**24**	**24**	**24**	**23**	**23**

Description:

2: Yes; 1: Can't tell; 0: No

Table 3. Description of the Main Study of the Relationship between Alcohol Consumption and Obesity

Author (Year)	Country	Study Design	Sample		P (Population)	I (Intervention)	C (Comparison)	O (Out-come)	aOR (95%CI)
			Breast Cancer	Obese (%)					
Abubakar et al. (2018)	Malaysia	Prospective Cohort	3,012	433 (13)	Breast cancer women aged 35 years	Breast cancer women with obesity	Breast cancer women are not obese	Dead	1.30 (0.37 to 4.52)
Beasley et al. (2012)	AS	Prospective Cohort	13,302	865 (13)	Breast cancer woman age 55 years old	Breast cancer women with obesity	Breast cancer women are not obese	Dead	0.72 (0.61 to 0.86)
Cleveland et al. (2012)	AS	Retrospective Cohort	2,900	522 (18)	Breast cancer woman age 65 years	Breast cancer women with obesity	Breast cancer women are not obese	Dead	1.22 (0.51 to 2.91)
Copson et al. (2018)	UK	Prospective Cohort	2,733	491 (19)	Breast cancer woman aged 40 years	Breast cancer women with obesity	Breast cancer women are not obese	Dead	1.09 (0.71 to 1.67)
Dibaba et al. (2019)	AS	Prospective Cohort	607	376 (62)	Breast cancer women aged 50 years	Breast cancer women with obesity	Breast cancer women are not obese	Dead	1.48 (0.81 to 2.72)
Kamineni et al. (2013)	AS	Retrospective Cohort	485	84 (17)	Breast cancer woman aged 40 years	Breast cancer women with obesity	Breast cancer women are not obese	Dead	2.39 (0.99 to 5.77)
Nechuta et al. (2016)	China	Prospective Cohort	6,596	1,036 (15)	Breast cancer women aged 20 to 83 years	Breast cancer women with obesity	Breast cancer women are not obese	Dead	1.40 (1.05 to 1.86)
Nelson et al. (2017)	AS	Retrospective Cohort	3,084	1,471 (13)	Women with breast cancer mean age 59 years	Breast cancer women with obesity	Breast cancer women are not obese	Dead	1.04 (0.86 to 1.27)
Pajares et al. (2013)	Spain	Retrospective Cohort	5,683	945 (16)	Breast cancer women ages 20 to 75	Breast cancer women with obesity	Breast cancer women are not obese	Dead	1.04 (0.83 to 1.29)
Sparano et al. (2012)	AS	Retrospective Cohort	4,817	1,745 (36)	Breast cancer women aged 50 years	Breast cancer women with obesity	Breast cancer women are not obese	Dead	1.45 (1.16 to 1.82)
Taghizadeh et al. (2015)	Nether-lands	Retrospective Cohort	3,469	569 (16)	Breast cancer women aged 20 to 65 years	Breast cancer women with obesity	Breast cancer women are not obese	Dead	1.52 (0.88 to 2.63)
Weischer et al. (2012)	Denmark	Prospective Cohort	14,524	1,933 (13)	Breast cancer woman age 53 years	Breast cancer women with obesity	Breast cancer women are not obese	Dead	2.43 (1.21 to 4.50)

Obesity is an independent risk factor for a number of diverse cancers including breast cancer. A meta-analysis study has reported a 30% increased risk of recurrence to severity in obese women compared to normal weight women diagnosed with breast cancer. In the US Cancer and Steroid Hormone study, weight gain increased the risk of developing premenopausal triple-negative breast cancer (TNBC) by 67% and the risk of premenopausal luminal B breast cancer by 73% compared with normal-weight women. TNBC is a subtype of breast cancer that does not express estrogen receptor (ER), progesterone receptor (PgR), and human epidermal growth factor receptor 2 (HER2). This is the breast cancer subtype with the worst prognosis, due to lack of targeted therapy and increased metastasis compared to other breast cancer subtypes (Kang et al., 2018).

The results of the study were in line with (Weischer et al., 2012) which linked the effect of obesity on the mortality of breast cancer women with populations from various races in Denmark, the results showed a significant effect (aOR= 2.43; 95% CI= 1.21 to 4.50; p= 0.021). Other similar studies were found in the United States (Cleveland et al., 2012; Sparano et al., 2012), and Malaysia (Abubakar et al., 2018).

In a normal cycle or before menopause symptoms for women, the primary site of the hormone estrogen is synthesized in the ovaries, but estrogen is also produced in adipose tissue. After menopause, when the ovaries stop producing hormones, fatty tissue (breasts, abdomen, thighs, and buttocks) becomes the most important source of estrogen, with estrogen levels in postmenopausal women being 50 to 100 percent higher than in normal/ideal weight women. Estrogen biosynthesis is catalyzed by the enzyme aromatase (P450 aroma-tase), a product of the CYP19 gene. Aroma-tase catalyzes the aromatization of ring A from the C19 androgen to the C18 phenol aestrogen ring. Aromatase enzymes also increase with increasing age and BMI (Lorincz and Sukumar, 2006).

However, Redaniel et al., (2012) which showed that obesity did not have a significant relationship with the risk of morbidity or mortality in breast cancer women (aHR= 1.12; 95% CI= 0.98 to 1.29; p= 0.100). Obesity is not associated with breast cancer-specific mortality among women who have Her2-overexpressing or triple-negative tumors (Blair et al., 2019). In another study by Makari-Judson et al., (2014) obesity is a global problem associated with an increased risk of developing postmenopausal breast cancer and a poorer prognosis at diagnosis but does not affect mortality in breast cancer women.

AUTHORS CONTRIBUTION

Ruth Apriyanti is the main researcher who selects the topic, searches for and collects research data. Yulia Lanti Retno Dewi and Bhisma Murti analyzed the data and reviewed research documents.

FUNDING AND SPONSORSHIP

CONFLICT OF INTEREST

There is no conflict of interest.

ACKNOWLEDGMENT

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