Report

UNIVERSITY OF SKÖVDE

META-ANALYSIS OF WHETHER MAMMILLA TUMOR METASTASIS CAN BE MITIGATED BY MASS-TESTING

Thesis in Bioscience G2E 30 credits

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Abstract

Tumors are mutated abnormal groups of cells that develop at any stage of life in any part of the body. Mammilla tumors appear in chest tissue that contain malignant cells in the terminal ductal-lobular unit, where the risk of the development of a mammilla tumor increases with age with a probability of 14.7%. Previous reviews have only focused on radiotherapy and digital mammography, while this review is, to the best of the author´s knowledge, the first review that encompasses the tomosynthesis and presumptive magnetic resonance using digital mammography. The aim of the meta-analysis was to determine the extent in which mass-testing of mammilla tumor metastasis can lead to its mitigation in adult females of all age-groups. The research question was the following: To what extent can mammilla tumor metastasis be mitigated by mass-testing of adult females of all age-groups? As part of the meta-analysis, a literature review was conducted using a selection of keywords in search queries on Pubmed, Libsearch and Academic Search Elite. In conclusion, mass-testing of mammilla tumor metastasis does not lead to a mitigation in adult females of all age-groups, since there was not a statistical significance of pooled value as indicated by the forest plot and the funnel plot indicated that the publication bias had some effect and the Mann-Whitney U-test also indicated that there was not a significance difference. Future research may consist of whether adult females within the age-range of 60-80 benefit from the test.

Abbreviation table

LCIS	lobular carcinoma *in situ*
DISC	ductal carcinoma *in situ*
FSM	film-Screen mammography
FFDM	Full-Field Digital Mammography

Table of content

1 Introduction

1.1 Problem specification

Late-onset mammilla carcinoma has a high mortality rate and low survival rate, which decreases the quality of life in the patients and is an alarming problem (Bryfonski, 2016). Currently, screenings for mammilla carcinoma are mainly performed for 50-60 year old adult females (Saunders & Jassal, 2009). However, the earlier the carcinoma is detected, the higher the survival rate becomes (Taghian & Halyard, 2012). To decrease the risk of developing late-onset mammilla carcinoma even further, it has to be evaluated whether screenings for mammilla carcinoma has a substantial effect in adult females of all ages.

The incidence rate of mammilla carcinoma increases by 0.3% every year, where the probability of mortality from mammilla carcinoma is 2.6%. Nearly 276 480 new cases of mammilla carcinoma has been estimated for women in the U.S. during 2020, where 48 530 of the cases are for the non-invasive form and 42 170 will die as a consequence of the invasive-form. The survival rate is improving as the technological advancements has enabled diagnosis and treatment of mammilla carcinoma to be detected earlier and treated better (American Carcinoma Society, 2020). The invasive form of mammilla carcinoma is called lobular carcinoma *in situ* (LCIS) and is frequent in the age-group 40-50. The non-invasive form is called ductal carcinoma *in situ* (DISC) and is frequent from the age-group 50-60 and beyond (Hameed, 2015). Mammilla carcinoma is a carcinoma caused by the epithelial cells´s lining close to the breast ducts, which is formed from permanent changes in the base sequence. When a base-sequence has been altered, the stop-codon in the base-sequence during translation has also been changed, which in-turn changes the amino acid sequence and the conformation of the protein (Allott & Mindorff, 2014). When the base sequence of a gene has acquired a permanent change, a mutation has occurred (Bryfonski, 2016). Various mutations are prevalent in carcinoma cells and accumulate into tumors through metastasis. The inactivation of apoptosis during metastasis enable the carcinoma cells to survive regardless of cell damage by mutating the gene p53 (Bryfonski, 2016).

Mammilla tumors appear in chest tissue that contain malignant cells in the terminal ductal-lobular unit, where the risk of the development of a mammilla tumor increases with age with a probability of 14.7% (Taghian & Halyard, 2012). There are several risk factors associated with mammilla carcinoma. One factor is the genetic history of the biological family, where other family members' acquisition of the carcinoma is also a strong likelihood for their offspring. Mutations in the germ-line can be inherited by the next generation of offspring, which is called hereditary mutations (Taghian & Halyard, 2012), via epigenetics. The hereditary mutations are inflicted to the tumor suppressor genes called BRCA1 and BRCA1 (Weinberg, 2014), which yields a 60-85% likelihood of acquiring a mammilla tumor during a lifetime. The BRCA1- and BRCA2-mutations are prevalent in the age-group 20-30 (Hameed, 2015). Another factor is the mammographic mammilla density, where a positive feedback has been established, which is not desired as it is an indicator for the tumor´s growth. Another factor is the usage of postmenopausal hormone therapy consisting of estrogen and progestin, which also established an increased risk (Saunders & Jassal, 2009). Any potential factors has to be taken into consideration during an evaluation when deciding for screenings for mammilla tumors (Bryfonski, 2016).

1.2 Literature review

Previous reviews have only focused on radiotherapy and digital mammography (Shah et al. 2016). This review is, to the best of the author´s knowledge, the first review that encompasses tomosynthesis and presumptive magnetic resonance using digital mammography (Hovda et al., 2019). These could be used in clinical practice to acquire more accurate readings during screening procedures of mammilla tumors in attempts to decrease the risk of malignant mammilla carcinoma-types even further (Huzarski et al., 2017).

Screenings for mammilla tumors currently yields a 20-30% reduced mortality rate from mammilla tumor metastasis when screenings are implemented since the carcinoma could be removed and its progression was halted (Warwick et al, 2003). The carcinoma did not return or re-grow (Nordenskjöld et al., 2002). For adult females in the age-range 40-49 the effect is not as substantial (Waller et al, 2006). This is attributed to the tumour´s proportion and increase in incidence later in the lifespan (Chen et al., 1995). The substantial effect in the age-range 40-49 is still debated (Lubbe et al, 1986; Djulbegovic & Lyman, 2006). More than one screening per year does not have a significant impact in decreasing the risk (Baines et al., 2002; Feig, 2000). This has to be taken into account before implementing screening programs.

Furthermore, screening-programs have apparent advantages and disadvantages. Women who participated in screening programs had the lethality risk of mammilla carcinoma reduced (Massat et al,. 2015; Duffy et al., 2010; Nyström et al., 2016) and reduced mortality rates (Woźniacki et al., 2017; Heywang-Köbrunner et al., 2015; Puvanesarajah et al., 2019) where increased screening rates are correlated with decreased rates of carcinoma diagnosis and increased survival rates (Seneviratne et al., 2015; Tabar et al., 2011; Chen et al., 2013). When the screenings using mammography was performed, there was a significantly higher likelihood of detecting any potential mammilla tumors (Copeland et al.,2017; Shen & Chai, 2001) which resulted in an increased rate of early treatment to the benign carcinoma (Chandler et al., 2019; Laake, 2016). In comparison to the control group who was not screened, the incidence of late-stage mammilla carcinoma was significantly higher (Munck et al., 2018) and the non-screened control group had a lower net survival rate (Poiseuil et al., 2019; Tabar et al., 2015). However, screenings on a national-scale are the most effective for benign carcinoma rather than malignant ones, because the latter yields greater damage prior to its removal (Lilleborge et al., 2019). In addition, the detections of the early stages of mammilla carcinoma had a high incidence when screenings were conducted at set time intervals (Kayhan et al., 2016). Late-stage mammilla carcinoma saw a significant reduction when consecutive screenings for cancerous cells were implemented, since the number of cases that developed into late-stage mammilla carcinoma decreased (Foca et al., 2013; Massat et al., 2015). However, some say that the effect of chemotherapy for mammilla carcinoma was limited (Loehberg et al., 2010; Ellis, 2009).

Additionally, whether screenings have an effect for all age-groups is contested. While the effect of screening was substantive and significant for the age-group of 50-60 year olds with a 9.6% reduced risk after continuous participation of screenings, the effect as negligible and insignificant for the age-groups younger than 50 and older than 60 (Ourti et al., 2019). Screenings for the age-range 50-70 also revealed an estimated 21% reduced mortality rate of mammilla carcinoma after screening (Bleyer et al., 2015; Abdolell et al., 2020). However, the decreased mortality rate of mammilla carcinoma when mammography screenings were implemented may have been overestimated. The effect may have been attributed because of the design of the trials (Autier et al., 2015; Chen et al., 2012; Pollan et al., 2013). Older women would benefit to a larger extent using preoperative MRI (Goodrich et al., 2016; Lee, 2016) while in younger women the specificity is low (Vreeman et al., 2018; Ripping et al. 2015; Lynge et al., 2019). Decreased screenings for older women is correlated with increased carcinoma diagnosis and thus poorer quality of life (Vacek & Skelly, 2014; Bennet & Moss, 2011; Randall et al., 2009)

The recent emergence of more accurate technology in mammography, such as bioimpedance spectroscopy and perimetry, has allowed for more sensitive measurements and even earlier detection of mammilla carcinoma. This reduces the risk of acquiring permanent invasive malignant carcinoma versions and increases the likelihood of treating benign carcinoma. This encourages the use of screening programs (Shah et al. 2016), which have a higher detection rates of the carcinoma when digital breast tomosynthesis is used (Hovda et al., 2019; Huzarski et al., 2017). The digital mammography had a significantly decreased recall rate in comparison radiotherapy according to the interim analysis of the screenings, however for the radiation dose the effect was negligible (Aase et al., 2018; Inari et al., 2018), which supports the use of digital

mammography during screenings. However 2D mammography did not yield a signifiant reduction in the recall rate (Rees, 2014). As part of digital mammography in recent screening-programs, MRI-scans of the breast has been shown to detect mammilla carcinoma at an even earlier stage of development and determine its type in women who have a high risk, which increases the specificity (Whitaker et al., 2020; Panourgias et al., 2018) and is enhanced using machine-learning image-identification computer software in the screening-procedure (Dempsey, 2005). In comparison to FSM (Film-Screen Mammogrpahy), FFDM (Full-Field Digital Mammography) was able to significantly detect tumors, both low-risk and high-risk ones, caused by mammilla carcinoma at a greater frequency during screenings and has resulted in an increase in the total number of detections since its inception (Drukker et al., 2014).

1.3 Method overview

The methodology of a metaanalysis was selected to acquire an overall assessment from all studies pertaining to mammilla carcinoma. This can be done by performing a forest plot, which illustrates the overall direction of the combined effect sizes from the studies, and a funnel plot, which highlights whether publication bias is present. All studies are collected by performing searches in databases based on a set inclusion- and exclusion criteria, which assures reproducibility in the findings (Cochrane, 2020).

1.4 Ethics

The following ethical considerations were followed during this meta-analysis followed: The studies were not invasive to the participants. Deception was not required. The participants´ right to confidentiality was respected. Any implications from the result of this meta-analysis will not result in clinical outcomes to the target population.

1.5 Aim

The aim of the meta-analysis was to determine the extent in which mass-testing for late-onset mammilla tumor metastasis can lead to its reduction in adult females of all age-groups. This should lead to evidence supporting whether or not screening of adult females from all age-groups should be implemented. The research question was the following: To what extent can mammilla tumor metastasis be mitigated by mass-testing of adult females of all age-groups? The objectives were the following: To identify whether there is a significant difference between the studies for and against determining the carcinoma-risk is all adult females of all age-groups, a Mann-Whitney U test was performed. To identify the relative risk and pooled-value from each study, a forest plot was created. To identify publication bias, a funnel plot based on the natural logarithm of relative risk and the standard error of the natural logarithm of relative risk was created. This study will investigate publication bias, the combined effect sizes and the significant difference in the collected studies about mammilla carcinoma in adult females.

2 Method

2.1 Metaanalysis

A metaanalysis was performed. A metaanalysis is used to summarize the findings from various studies and draw an overall conclusion from the combined effect estimates using statistical tools. This can be illustrated in a forest plot and a funnel plot, which are established practices in metaanalysis, to make an overall assessment. Each study is acquired through systematic searches in databases with a pre-defined inclusion- and exclusion-criteria and a pre-defined scope (Cochrane, 2020).

Various searches in databases such as Pubmed, Libsearch, Springer Link and Academic Search Elite were conducted to acquire each study (Appendix A). The inclusion-criteria included randomly-allocated controlled quantitative mammilla carcinoma studies that focused on the mortality and survival rate. The exclusion-criteria excluded non-mammilla carcinoma lifestyle intervention uncontrolled non-randomly allocated non-adult female non-screening procedure qualitative studies that did not have a focus on survival rate or mortality rate or risk (Table 1). Non-published non-English articles were not taken into account because of the limited resources allocated to this study. The searches' scope was set between the years 2009-2020, due to the emergence of preoperative tomosynthesis and MRI in screening procedures for mammography.

Table 1. The inclusion- and exclusion-criteria.

Inclusion	**Exclusion**
Mammilla carcinoma	Non-mammilla carcinoma
Mammilla carcinoma	Lifestyle intervention
Controlled	Uncontrolled
Random allocation	Non-random allocation
Adult females	Non-adult females
Screening	Non-screening procedure
Quantitative	Not focusing on risk
Mammography	Not focusing on mortality rate
Risk	Not focusing on survival rate
Mortality rate	Qualitative
Survival rate	

2.2 Query

In Pubmed, one search query was used, which took into account mammilla carcinoma and screening programs. In the search in Pubmed, the following query (Query 1) was used with a filter for the years 2009-2020 and a filter for English and a filter for fulltext (see Appendix A for further details):

$$breast\ AND\ carcinoma\ AND\ screening\ AND\ program\ AND\ trial \qquad (Query\ 1)$$

In Libsearch, four variations of a search query were used, where mammilla carcinoma and screening procedures in adult females were configured into the search queries. In the first search in Libsearch, the following query (Query 2) was used with a filter for the years 2009-2020:

$$breast\ AND\ carcinoma\ AND\ screening\ AND\ program\ AND\ trial \qquad (Query\ 2)$$

In the second search in Libsearch, the following query (Query 3) was used with a filter for the years 2009-2020:

$$"mammilla\ carcinoma"\ AND\ "screen-detected"\ AND\ (women\ OR\ woman\ OR\ female) \quad (Query\ 3)$$

In the third search in Libsearch, the following query (Query 4) was used with a filter for the years 2009-2020:

$$\text{mammilla carcinoma screening trials}\ AND\ \ woman*\ AND\ mammography* \quad (Query\ 4)$$

In the fourth search in Libsearch, the following query (Query 5) was used with a filter for the years 2009-2020:

$$metaanalysis\ AND\ "mammilla\ carcinoma"\ AND\ screening \quad (Query\ 5)$$

In Springer Link, one search query was used, which took into account mammilla carcinoma and screenings. In the search in Springer Link, the following query (Query 6) was used with a filter for English and a filter for article and a filter for the subjects biomedicine and oncology:

$$\text{mammilla carcinoma } AND \text{ screen-detected } AND\ woman* \quad (Query\ 6)$$

In Academic Search Elite, one search was conducted. In the search in Academic Search Elite, the following query (Query 7) was used with a filter for the years 2009-2020:

$$\text{mammilla carcinoma } AND \text{ screen-detected } AND\ woman* \quad (Query\ 7)$$

2.3 Equations

From all the studies that were collected from the searches, a forest plot was drawn to indicate whether there was an effect of the early detection of early-onset carcinoma at mitigating late-onset carcinoma. A forest plot is used in a metaanalysis to collectively assess the direction of the findings and whether an effect is evident (Cochrane, 2020), which has previously been used in a study by Massat et al. (2015) to assess the lethality of mammilla tumors. In this study, the forest plot had 95% confidence interval based on the Relative Risk of each study and a pooled value from all of them on the x-axis. One disadvantage with forest plots is that they cannot reveal whether publication bias is present (Campbell, Machin & Walters, 2017). To account for this, a funnel plot was drawn. A funnel plot is used in a metaanalysis to assess whether the findings have been skewed by publication bias and whether any relevant studies have been excluded (Campbell, 2017). In this study, the funnel plot had natural log of relative risk (ln(RR)) on the x-axis and standard error of the natural log of relative risk (SE ln(RR)) on the y-axis.

To acquire natural log of relative risk (ln(RR)) for the x-axis of the funnel plot, various equations have to be employed. Firstly, the risk was calculated to determine the probability to acquire a disease if in presence of risk factors (Equation 1):

$$Risk = individuals\ with\ condition\ /\ total\ number\ of\ indivudals \quad (Equation\ 1)$$

In addition, the Relative Risk (RR) was calculated, based on the risk (Equation 2) :

$$Relative\ Risk = risk\ of\ condition\ A /\ risk\ of\ condition\ B \quad (Equation\ 2)$$

The natural log of Relative Risk (RR) was thereafter calculated, based on the Relative Risk (Equation 2), by taking the natural log of Relative Risk.

To acquire the standard error of the natural log of relative risk (SE ln(RR)) (Equation 3) for the y-axis of the funnel plot, it was calculated based on the Relative Risk (RR) (Equation 2) and the Lower Limit (LL) of the 95% confidence interval that were calculated previously:

$$SE\ ln\ (RR) = (ln(LL)\ -\ ln(RR))\ /\ (-1.96) \quad (Equation\ 3)$$

To acquire the relative risk pooled and its upper limit and lower limit values for the x-axis of the forest plot, various equations have to be employed. To begin with, the weight (Equation 4) was calculated to estimate the treatment effect, based on the standard error of natural log of relative risk (SE ln(RR)) (Equation 3) that was calculated previously:

$$Weight = 1\ /\ SE\ \ln(RR)\text{^}2 \quad (Equation\ 4)$$

This was followed by the calculation of the standard error pooled (Equation 7), based on the sum of the weight:

$$SE_{pooled} = \pm\sqrt{(1 / \sum Weight)} \qquad (Equation\ 7)$$

After this the natural log of Relative Risk pooled (Equation 5) was calculated, based on the Relative Risk (RR) (Equation 2) and the weight (Equation 4) and sum of the weight that were calculated previously:

$$ln(RR_{pooled}) = \sum(ln(RR) * Weight) / \sum Weight \qquad (Equation\ 5)$$

Furthermore, the Relative Risk pooled (RR_{pooled}) (Equation 6) was calculated, based on natural log of Relative Risk pooled that was calculated previously, and was used on the y-axis of the forest plot:

$$RR_{pooled} = e\hat{}ln(RR_{pooled}) \qquad (Equation\ 6)$$

In addition, the natural log of Lower Limit pooled (ln(LL)) (Equation 8) was calculated, based on the Relative Risk pooled (RR_{pooled}) (Equation 6) and the negative value of standard error pooled ($-SE_{ooled}$) (Equation 7) that was calculated previously:

$$ln(LL)_{pooled} = ln(RR_{pooled}) - 1.96 * (-SE_{pooled}) \qquad (Equation\ 8)$$

Additionally, the natural log of Upper Limit (ln(UL)) (Equation 9) was calculated, based on Relative Risk pooled (Equation 6) and the positive value of standard error pooled (Equation 7):

$$ln(UL)_{pooled} = ln(RR_{pooled}) + 1.96 * (+SE_{pooled}) \qquad (Equation\ 9)$$

Thereafter, the Lower limit (LL) pooled (Equation 10) was calculated, based on the natural log of Upper Limit (Equation 8), and was used on the x-axis of the forest plot:

$$LL_{pooled} = e\hat{}ln(LL) \qquad (Equation\ 10)$$

This was followed by calculation of the Upper Limit (UL) pooled (Equation 11), based on the natural log of Upper Limit (Equation 9), and was used on the x-axis of the forest plot:

$$UL_{pooled} = e\hat{}ln(UL) \qquad (Equation\ 11)$$

To determine whether there was a significant difference between the article for and against screenings, a Mann-Whitney U-test was conducted (Equation 12; Equation 13), where *n* stands for the sample size and *U* stands for the U-value and *Rank* stands for the ranked-values:

$$U1 = n1 * n2 + (n1 * (n1 + 1)/2) - \Sigma Rank1 \qquad (Equation\ 12)$$

$$U2 = n2 * n1 + (n2 * (n2 + 1)/2) - \Sigma Rank2 \qquad (Equation\ 13)$$

3 Results

3.1 Calculated values

Table 3 presents the resulting calculations of Relative Risk (Equation 2), 95% Confidence Interval, natural log of Relative Risk, Standard Error of log Relative Risk (Equation 3), weight (Equation 4) and natural log of Relative Risk multiplied by weight from the included studies. The study by Aase et al. (2018) has the highest weight, followed by Abdolell et al. (2020). As the

relative risk decreases, the natural log of relative risk increases, where the highest has Randall et al. (2009). As relative risk increases, the 95% Confidence Interval increases and the standard error of natural log of relative risk increases.

Table 4 presents Relative Risk pooled, Standard Error pooled, natural log of Lower Limit, natural log of Upper Limit, Lower Limit pooled and Upper Limit pooled. Since the pooled-value does not exceed 1, the forest plot indicate a significant effect in the difference between the control group and the experimental group. The funnel plot had natural log of relative risk (ln(RR)) on the x-axis and standard error of the natural log of relative risk (SE ln(RR)) on the y-axis. The forest plot had 95% confidence interval based on the Relative Risk of each study and a pooled value from all of them on the x-axis.

Table 3. Name of the study, relative risk, 95% confidence interval, natural log of relative risk, standard error of natural log relative risk, weight and log of relative risk multiplied by weight.

Study	Relative Risk	95% CI	natural log Relative Risk	Standard error of log Relative Risk	Weight	ln(RR)*Weight
Bleyer et al. (2015)	0,78	0,56 - 1,08	-0,25	0,17	34,99	-8,69
Chen et al. (2012)	0,79	0,32 - 0,83	-0,24	0,37	7,17	-1,69
Vreeman et al. (2018)	0,97	0,74 - 1,27	-0,03	0,14	52,45	-1,60
Huzarski et al. (2017)	1,7	0,2 - 1,2	0,53	0,42	5,55	2,95
Vacek & Skelly (2014)	0,82	0,81 - 0,82	-0,20	0,03	970,55	-192,61
Munck et al. (2018)	0,92	0,85 - 0,99	-0,08	0,19	29,17	-2,43
Seneviratne et al. (2015)	0,82	0,62 - 1,09	-0,20	0,29	11,50	-2,28
Lake (2016)	1,72	0,87 - 2,56	0,54	0,49	4,19	2,27
Massat et al. (2015)	0,4	0,31 - 0.51	-0,92	0,13	59,13	-54,18
Copeland et al. (2017)	1,56	1,27 - 1,93	0,44	0,10	90,82	40,39
Autier et al. (2015)	0,83	0,71 - 0,97	-0,19	0,08	157,53	-29,35
Loehberg et al. (2010)	1,74	1,20 - 2,53	0,55	0,19	27,83	15,41
Aase et al. (2018)	0,71	0,52 - 0.97	-0,34	0,16	39,61	-13,57
Duffy et al. (2010)	1,06	1,04 - 1.08	0,06	0,01	10587,77	616,94
Foca et al. (2013)	1,35	1,03 - 1.41	0,30	0,14	52,48	15,75
Massat et al. (2015)	0,61	0,44 - 0,85	-0,49	0,17	36,00	-17,79
Drukker et al. (2014)	2,33	1,73 - 3,15	0,85	0,15	43,33	36,65
Goodrich et al. (2016)	0,99	0,67 - 1,5	-0,01	0,20	25,20	-0,25
Abdolell et al. (2020)	0,91	0,89 - 0.92	-0,09	0,01	7778,60	-733,61
Inari et al. (2018)	0,94	0,75 - 1,17	-0,06	0,12	75,34	-4,66
Chandler et al. (2019)	1,32	0,72-2,4	0,28	0,31	10,46	2,90
Nyström et al. (2016)	0,85	0,73-0,98	-0,16	-0,08	145,45	-23,64
Tabar et al. (2014)	0,78	0,72-0,84	-0,25	-0,13	62,23	-15,46
Schoor et al. (2011)	0,35	0,19-0,64	-1,05	-0,54	3,49	-3,66
Randall et al. (2009)	1,04	0,85-1,27	0,04	0,02	2497,36	97,95
Ellis (2009)	0,58	0,36-0,92	-0,54	-0,28	12,95	-7,05
Pollan et al. (2013)	0,81	0,63-1,04	-0,21	-0,11	86,52	-18,23
Lynge et al. (2019)	0,56	0,53-0,58	-0,58	-0,30	11,43	-6,63
Toth et al. (2018)	0,68	0,37-1,25	-0,39	-0,20	25,83	-9,96

Table 4. Natural log of relative risk pooled, relative risk pooled, standard error pooled, log of lower limit pooled, log of upper limit pooled, lower limit pooled and upper limit.

log Relative Risk pooled	Relative Risk pooled	SE pooled	log Lower Limit pooled	log Upper Limit pooled	Lower Limit pooled	Upper Limit pooled
-0,30	0,74	0,03	-0,35	-0,24	0,86	0,87

3.2 Forest plot and funnel plot

The forest plot indicate a significant effect of the detection of early-onset carcinoma at mitigating

late-onset carcinoma (Figure 1). Since the pooled-value does not exceed 1 (Table 4), the forest plot indicate a significant effect in the difference between the control group and the experimental group. The length of the confidence interval´s horizontal line is influenced by the sample size of the study, where Poiseuil et al. (2019)´s study has the greatest horizontal line, while Munck et al. (2018)´s study has the smallest horizontal line. The largest box is held by Vacek & Skelly et al. (2014)´s study, while the smallest box is held by Autier et al. (2015)´s study (Figure 1), which indicates larger and smaller effect size respectively. If the boxes are located to the left of the vertical line, the result favors the experiments-condition, since the experimental group occurred more frequently in comparison to the control-group. Screenings are supported and have an effect in reducing late-stage mammilla carcinoma according to the forest plot (Figure 1), since the majority of the boxes are to the left of the vertical line in the forest plot. Over time, the direction of the boxes have generally not shifted and did have a significant difference but remained to the left and remained with an significant difference instead. To analyze whether there was a skewed distribution in one direction in the forest plot over another and there was publication bias, a funnel plot was constructed. The funnel plot indicated that publication bias was present (Figure 2). Since the lower left part of the funnel plot had an absence in points, the shape is asymmetrical, which indicate that publication bias was present and decreased the reliability of the results.

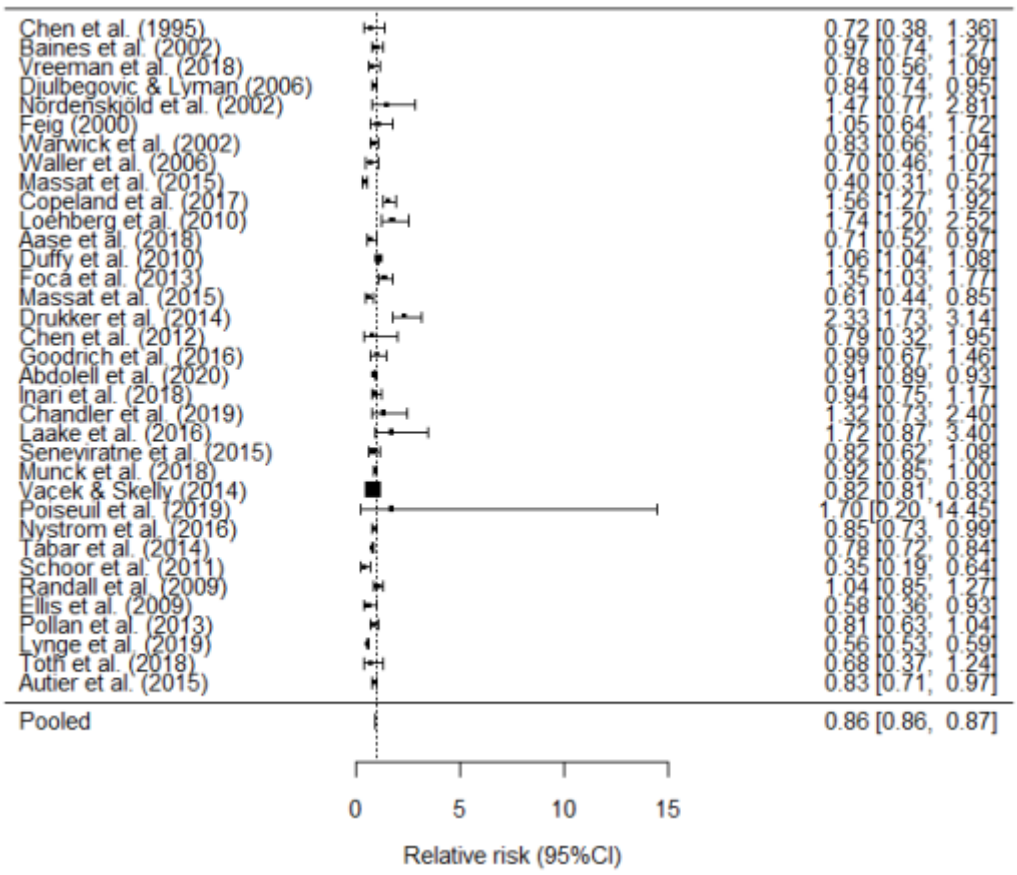

Figure 1. Forest plot with the various studies' effect sizes indicated by the boxes and 95% confidence interval indicated by the horizontal line, where the diamond indicate the pooled-value. The horizontal line indicate the relative risk´s confidence interval, where the greater the line is, the less reliable the result is. The boxes indicate effect size. The larger the boxes are, the smaller the effect size is. If the boxes are located to the left of the vertical line, the result favors the experiments-condition, since the experimental group occurred more frequently in comparison to the control-group. If the boxes are located to the right of the vertical line, the result conversely favors the control-condition. The diamond indicate the pooled-value, where the greater the diamond is, the less reliable the result is. If the diamond touches the dotted vertical line and exceeds the confidence interval value of 1, there is an insignificant effect. Since the majority of the

boxes are to the left of the vertical line, the screenings have an effect.

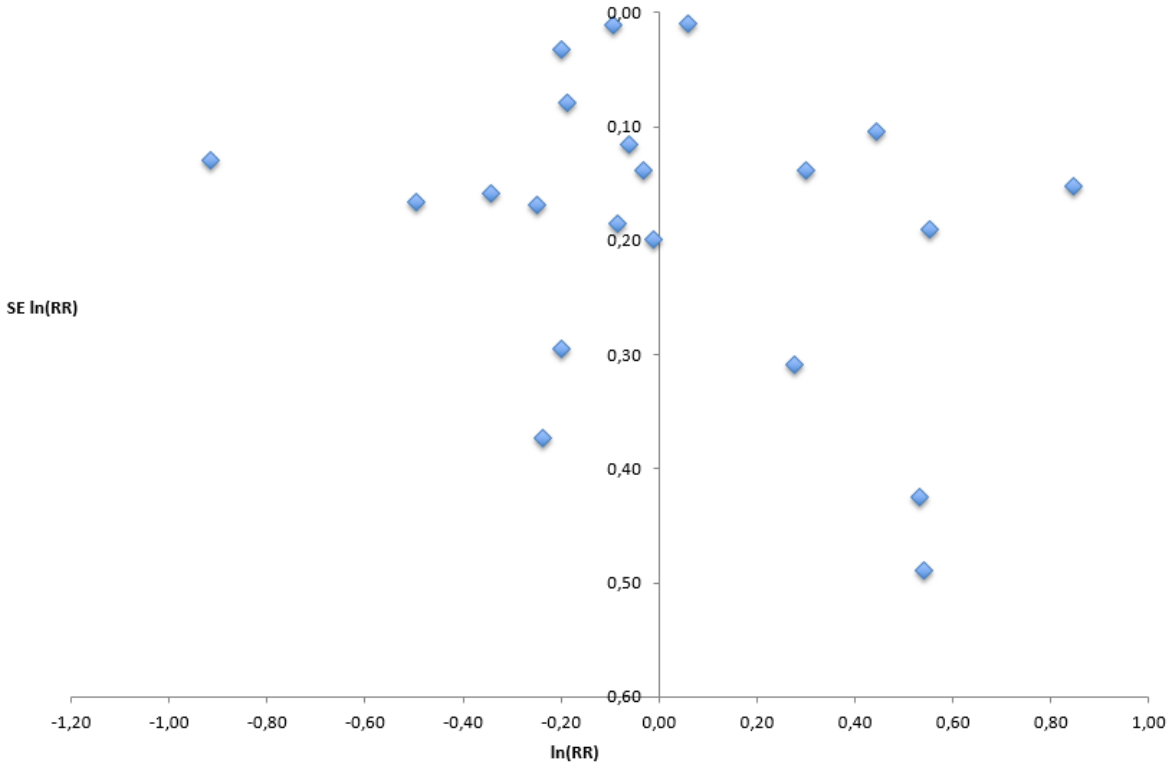

Figure 2. A funnel plot with the standard error of the natural log of relative risk (SE ln(RR)) as a function of the natural log of relative risk (ln(RR)). If publication bias is present, the shape will be asymmetrical with an absence of points at one side in the funnel plot. Since the lower left part of the funnel plot had an absence of points, the shape is asymmetrical, which indicate that publication bias was present.

3.3 Significant difference

To evaluate whether there was a significant difference between the studies supporting and not supporting the value of determining the carcinoma-risk is all adult females of all age-groups, a Mann-Whitney U test was conducted. The Mann-Whitney U test indicated that there was a not significant difference (p-value>0.05) (Table 5) between the studies supporting and not supporting the effect in screening all adult females of all age-groups.

Table 5. Mann-Whitney U test results showing the number of studies support, the number of studies not support, the U-value, the U critical-value, the Z-score and p-value.

# studies support	# studies not support	U-value	U critical-value	Z-score	P-value
16	28	224	6	0.0122	0.496

4 Discussion

The aim of the meta-analysis was to determine the extent in which mass-testing for late-onset mammilla tumor metastasis can lead to its mitigation in adult females of all age-groups, This should lead to evidence supporting whether or not screening of adult females from all age-groups should be implemented. The objectives were the following: To identify whether there is a significant difference between the studies supporting and not supporting the effect, a Mann-Whitney U test was performed. To identify the relative risk and pooled-value from each study, a forest plot was created. To identify publication bias, a funnel plot based on the natural logarithm

of relative risk and the standard error of the natural logarithm of relative risk was created.

Screening-programs have apparent advantages and disadvantages. Women who participated in screening programs had the lethality risk of mammilla carcinoma reduced (Massat et al,. 2015; Duffy et al., 2010; Nyström et al., 2016) and reduced mortality rates (Woźniacki et al., 2017; Heywang-Köbrunner et al., 2015; Puvanesarajah et al., 2019), which is in alignment with the findings of this study. Both this study´s forest plot (Figure 1) and the forest plots in the studies by Duffy et al. (2010) and Nyström et al. (2016) indicate that screenings have an effect in reducing the carcinoma, however neither Duffy et al. (2010) or Nyström et al. (2016) have an effect size that exceeds Vacek & Skelly´s study in the forest plot (Figure 1) and neither had publication bias indicated in their funnel plot which contrast this study´s funnel plot (Figure 2) does indicate publication bias. When screening using mammography was performed there was a significantly higher likelihood of detecting potential mammilla tumors in comparison to the control group (Copeland et al.,2017; Shen & Chai, 2001). This is in alignment with the findings with the study according to the forest plot´s overall direction and effect size (Figure 1). Copeland et al. (2017)´s forest plot also have a direction that indicates that screening have an effect. This is a similarity with this study´s forest plot (Figure 1). However, their funnel plot does not indicate publication bias while this study´s funnel plot (Figure 2) does indicate publication bias. Copeland et al. (2017)´s statistical test did illustrate a significant effect while this study´s statistical test did not illustrate a significant effect (Table 5). However, the reduction of the risk from acquiring mammilla carcinoma as an effect of mammography screenings is also shown to be an insignificant effect for all age-groups (Autier et al., 2015; Chen et al., 2012; Pollan et al., 2013), which is not in alignment with the findings of this study and may have been caused by the unreported studies that show an insignificant effect, by the differed breadth of the search criteria or by the differed degree of publication bias. Autier et al. (2015)´s forest plot does not have a direction that favors the experimental-condition, which contrasts with this study´s forest plot (Figure 1) whose direction favors the experimental-condition, however both Autier et al. (2015)´s statistical test and this study´s statistical test illustrate an insignificant effect (Table 5).

The length of the confidence interval´s horizontal line is influenced by the sample size of the study, where Poiseuil et al. (2019)´s study has the greatest horizontal line, while Munck et al. (2018)´s study has the smallest horizontal line. The reason for Poiseuil et al. (2019)´s larger 95% confidence interval values may be because of sampling error, where a small sample size leads to a large 95% confidence interval value. One limitation is that a test of heterogeneity was not conducted using a I^2-test to determine whether the variations in the experimental conditions are due to sampling error and whether there was an independent measures design. One improvement could be to use a Mantel-Hanzal weight, instead of invariance weight, to minimize the standard error. Another improvement could be to use meta-regression to determine the association of the characteristics and the treatment effect by using a linear regression and estimate the covariate effects. Another improvement could be to include a certain sample size as an inclusion-criteria. The largest box is held by Vacek & Skelly et al. (2014)´s study, while the smallest box is held by Autier et al. (2015)´s study (Figure 1), which indicates larger and smaller effect size respectively. The reason that Vacek & Skelly´s study has the largest box and hence largest effect size, as seen by the large weight-value (Table 1), may be because the reduction of the risk from acquiring mammilla carcinoma as an effect of mammography screenings may have been overestimated and the effect may have been attributed because of the design of the trials. The overestimation may also have caused more studies in the forest plot to favor the experimental condition and indicate an effect when there is none in reality as illustrated by the Mann-Whitney U test´s p-value (Table 5). The wide range of the effect size may have influenced the pooled value (Table 4) and caused the pooled value to be lower than it should be. This would result in a pooled value that does not exceed 1 and indicate that the screenings have an effect when they may not have had it in reality.

One reason for the difference in conclusions could be that articles that indicate an insignificant effect or written in non-English have a lower opportunity of being published by a journal. One consequence is publication bias, as illustrated in the funnel plot (Figure 2), since it would decrease the number of published articles against the hypothesis. One strength with the funnel plot however is that standard error was plotted on the y-axis instead of sample size. The statistical power would otherwise be influenced by the sample size or the standard deviation. In contrast, standard error enables a triangular region to be illustrated using the points which is more accurate. Another strength is that the x-axis of the funnel plot has a logarithmic scale, which assures that the magnitude is the same while keeping opposite directions. One limitation with the funnel plot is that the funnel plot is in part interpreted in the eye of the beholder. The absence of studies may not have been entirely absent because of publication bias but because they simply do not exist, which would make the funnel plot less reliable and may not be true publication bias as seen in the lower left part of the funnel plot (Figure 2). Another reason may be that the search criteria may have been too narrow by excluding non-English articles and non-published articles, which were excluded because of limited resources allocated for this study, and including only full-text availability of the articles and thus cause other related articles to be excluded, which would increase the likelihood of acquiring publication bias as seen in the lower left part of the funnel plot (Figure 2). One improvement could be to conduct an adjusted rank correlation-test instead to determine publication bias, since it is more accurate in comparison to a funnel plot. Another improvement to minimize the effect of publication bias could be to use a linear regression test or a trial sequential analysis or Cochrane risk of bias tool.

Another consequence of having unreported articles that illustrate an insignificant effect is a p-value of the Mann-Whitney U-test (Table 5) that is lower than it should be. Another limitation is the Mann-Whitney U-test, since the risk of type 1-error is increased when heteroscedasticity is present. One improvement could be to conduct a goodness of test, such as Poisson distribution test or negative binomial test. Another improvement could be to conduct Cohens´ d or Glass´s delta. According to the findings of this study it appears that screenings can in fact mitigate risk of mammilla tumor metastasis, however there was not a significant difference according to the Mann-Whitney U-Test.

Another consequence of having unreported articles that illustrate an insignificant effect is that the direction in the forest plot (Figure 2) could have become more in favor of the experimental-group than it should. This also causes the effect more significant that it should be. The advantages of a forest plot are that it successfully depicts whether heterogeneity is present in the different studies and the pooled value from the combined effect sizes. The disadvantages of a forest plot are that it does not depict whether publication bias is present (Campbell, Machin & Walters, 2007). The advantages of a funnel plot are it successfully depicts whether publication bias is present. The disadvantages of a funnel plot are that it cannot illustrate heterogeneity or a pooled value and that it is to an extent in the eye of the beholder (Campbell, Machin & Walters, 2017). One strength is that the results from the various studies are combined in order to acquire an overview of the effect by conducting a forest plot and pooling the values. Another strength is that the experimental and control condition are separated from each other, which minimizes the skewing of the results. Another strength is that the inclusion of the risk ratio takes into account the varying sampling error and sample size.

4.1 Impact to society

In conclusion, mass-testing of mammilla tumor metastasis does not lead to a mitigation in adult females of all age-groups. There was not a statistical significance of pooled value as indicated by the forest plot. The funnel plot indicated that the publication bias had some effect. The Mann-Whitney U-test also indicated that there was an insignificant difference. The scope of study may

have been too broad by taking into account all age-ranges of adult females, which may have resulted in some values favoring the control condition. This project finding´s impact to society is that the screening procedures for mammal tumors has not been thoroughly evaluated for all age-groups, as there are uncertainties for multiple age-groups, and more studies have to be performed to validate the current screening procedures. This may avoid unnecessary economical losses and side-effects from the treatments. This project´s findings could also enable a decreased mortality rate as early-onset of mammilla carcinoma could be detected earlier, which increases survival rate and cause mother and grandmother´s to survive and not leave their children and grandchildren early, which increases the quality of life. Future research may consist of how adult female within the age-range of 60-80 benefit from the test and whether there is a significant impact on the mitigation of the carcinoma to that age-group. In the future, how magnetic resonance imaging could be incorporated into the screening procedure to detect the carcinoma and how the treatments of the carcinoma impacts the quality of life in patients could be explored. Future research may also focus on which magnetic resonance imaging is the most efficient for which age-group, which may increase the detection rate. The following ethical considerations were followed during this meta-analysis followed: The studies were not invasive to the participants. Deception was not required. The participants´ right to confidentiality was respected. Any implications from the result of this meta-analysis will not result in clinical outcomes to the target population.

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Appendix A

Table 2. The number of searches, the search query, the number of hits, selected sources and the date of the search in Pubmed, Libsearch, Springer Link and Academic Search Elite for the various searches. The searches were organized chronologically, with the first search at the top and the last search at the bottom

Pubmed

- Search query: breast AND carcinoma AND screening AND program AND trial
  Filter(s): Years 2009-2020. Language English. Fulltext.
  Total hit(s): 1039
  Reason for excluding hit(s): Non-mammilla carcinoma, lifestyle intervention, not focusing on mortality rate qqqqqqqqqqqqqqqqqqqqqand not focusing on screening procedures.
  Date: 20/08/2020.
  Selected source(s):
  1. Impact of Screening on Mammilla carcinoma Mortality: The UK Program 20 Years On.
  Conclusion -
  2. Effectiveness of Interventions for Mammilla carcinoma Screening in African American Women: A Meta-Analysis.
  3. The impact of early detection and intervention of mammilla carcinoma-related lymphedema: a systematic review.
  4. Effect of screening mammography on mammilla carcinoma mortality: Quasi-experimental evidence from qqqqqqrollout of the Dutch population-based program with 17-year follow-up of a cohort.

Libsearch

- Search query: breast AND carcinoma AND screening AND program AND trial
  Filter(s): Years 2009-2020.
  Total hit(s): 1550
  Reason for excluding hit(s): Non-mammilla carcinoma, lifestyle intervention, not focusing on mortality rate qqqqqqqqqqqqqqqqqqqqqand not focusing on screening procedures.
  Date: 20/08/2020.
  Selected source(s):
  1. Letter in response: mammilla carcinoma screening of women aged 70–74 years
  2. Mammilla carcinoma risk assessment in a mammography screening program and participation in the IBIS-II chemoprevention trial
  3. A randomized controlled trial of digital breast tomosynthesis versus digital mammography in population-based screening in Bergen: interim analysis of performance indicators from the To-Be trial
  4. The impact of the Polish mass mammilla carcinoma screening program on prognosis in the Pomeranian Province
  5. Dynamic contrast-enhanced magnetic resonance imaging for risk-stratified screening in women with BRCA mutations or high familial risk for mammilla carcinoma: are we there yet?
  6. Maximum of the Weighted Kaplan-Meier Tests with Application to Carcinoma Prevention and Screening Trials
  7. Measuring the Mortality Impact of Mammilla carcinoma Screening
  8. Radiologic findings of screen-detected carcinomas in an organized population-based screening mammography program in Turkey.
  9. No mammilla carcinoma subgroup can be spared postoperative radiotherapy after breast-conserving surgery. Fifteen-year results from the Swedish Mammilla carcinoma Group randomised trial, SweBCG 91 RT
  10. Absolute numbers of lives saved and overdiagnosis in mammilla carcinoma screening, from a randomized trial and from the Breast Screening Programme in England
  11. metananalysis - Test Sensitivity in the Computer-Aided Detection of Mammilla carcinoma from Clinical Mammographic Screening: a Meta-analysis

12. Decreasing incidence of late-stage mammilla carcinoma after the introduction of organized mammography screening in Italy.
13. Impact of Screening on Mammilla carcinoma Mortality: The UK Program 20 Years On.
14. Mammographic screening detects low-risk tumor biology mammilla carcinomas
15. Conclusions for mammography screening after 25-year follow-up of the Canadian National Mammilla carcinoma Screening Study (CNBSS)
16. A Stochastic Model for Calibrating the Survival Benefit of Screen-Detected Carcinomas.

- Search query: "mammilla carcinoma" AND "screen-detected" AND (women OR woman OR adult female)
  Filter(s): Years 2009-2020.
  Total hit(s): 1358
  Reason for excluding hit(s): Non-mammilla carcinoma, lifestyle intervention, not focusing on mortality rate and not focusing on screening procedures.
  Date: 20/08/2020.
  Selected source(s):
  1. Risk of mammilla carcinoma by prior screening results among women participating in BreastScreen Norway.
  2. The Role of Preoperative Magnetic Resonance Imaging in the Assessment and Surgical Treatment of Interval and Screen-Detected Mammilla carcinoma in Older Women.
  3. Assessing mammilla carcinoma risk within the general screening population: developing a mammilla carcinoma risk model to identify higher risk women at mammographic screening
  4. Comparison of screening CEDM and MRI for women at increased risk for mammilla carcinoma: A pilot study.
  5. Mode of detection and mammilla carcinoma mortality by follow-up time and tumor characteristics among screened women in Carcinoma Prevention Study-II
  6. Correction to: A comparison of clinicopathological characteristics and long-term survival outcomes between symptomatic and screen-detected mammilla carcinoma in Japanese women
  7. Review of mammilla carcinoma diagnoses in women aged over 70 years in Wales: A comparison between screen-detected and symptomatic presentations between 2010-2012 with 5 year follow-up.
  8. A randomised trial of screening with digital breast tomosynthesis plus conventional digital 2D mammography versus 2D mammography alone in younger higher risk women.
  9. The added value of mammography in different age-groups of women with and without BRCA mutation screened with breast MRI
  10. Towards personalized screening: Cumulative risk of mammilla carcinoma screening outcomes in women with and without a first-degree relative with a history of mammilla carcinoma.
  11. Are international differences in mammilla carcinoma survival between Australia and the UK present amongst both screen-detected women and non-screen-detected women? survival estimates for women diagnosed in West Midlands and New South Wales 1997–2006
  12. Impact of mammographic screening on ethnic and socioeconomic inequities in mammilla carcinoma stage at diagnosis and survival in New Zealand: a cohort study.
  13. Is the incidence of advanced-stage mammilla carcinoma affected by whether women attend a steady-state screening program?
  14. Screening outcome for consecutive examinations with digital breast tomosynthesis versus standard digital mammography in a population-based screening program.
  15. A Prospective Study of the Use and Effects of Screening Mammography in Women Aged 70 and Older.

16. Deprivation and mass screening: Survival of women diagnosed with mammilla carcinoma in France from 2008 to 2010.
17. Screening with magnetic resonance imaging, mammography and ultrasound in women at average and intermediate risk of mammilla carcinoma.
18. Screening outcomes in women over age 70 who self-refer in the NHSBSP in England.

- Search query: "mammilla carcinoma screening trials" AND (women OR woman OR adult female) AND mammography*
  Filter(s): Years 2009-2020.
  Total hit(s): 8
  Reason for excluding hit(s): Non-mammilla carcinoma, lifestyle intervention, not focusing on mortality rate qqqqqqqqqqqqqqqqqqqqqand not focusing on screening procedures.
  Date: 20/08/2020.
  Selected source(s):
  1. Reduced mammilla carcinoma mortality after 20+ years of follow-up in the Swedish randomized controlled mammography trials in Malmö, Stockholm, and Göteborg.
  2. Insights from the Mammilla carcinoma Screening Trials: How Screening Affects the Natural History of Mammilla carcinoma and Implications for Evaluating Service Screening Programs.
  3. Increasingly strong reduction in mammilla carcinoma mortality due to screening.
  4. Systematic review of the mammilla carcinoma screening trials is error-ridden.

- Search query: metaanalysis AND "mammilla carcinoma" AND screening
  Filter(s): Years 2009-2020.
  Total hit(s): 18
  Reason for excluding hit(s): Non-mammilla carcinoma, lifestyle intervention, not focusing on mortality rate qqqqqqqqqqqqqqqqqqqqqand not focusing on screening procedures.
  Date: 20/08/2020.
  Selected source(s):
  1. Assessment of the effects of decision aids about mammilla carcinoma screening: a systematic review and meta-analysis.

Springer Link

- Search query: "mammilla carcinoma" AND "screen-detected" AND (women OR woman OR adult female)
  Filter(s): within English. Biomedicine. Oncology. Biomedicine, general. Article.
  Total hit(s): 15263
  Reason for excluding hit(s): Non-mammilla carcinoma, lifestyle intervention, not focusing on mortality rate qqqqqqqqqqqqqqqqqqqqqand not focusing on screening procedures.
  Date: 20/08/2020.
  Selected source(s):
  1. Annual or biennial mammography screening for women at a higher risk with a family history of mammilla carcinoma: prognostic indicators of screen-detected carcinomas in New South Wales, Australia
  2. Molecular profiles of screen detected vs. symptomatic mammilla carcinoma and their impact on survival: results from a clinical series
  3. Prognosis of screen-detected mammilla carcinomas: results of a population based study
  4. Mammographic density and risk of mammilla carcinoma by tumor characteristics: a case-control study

Academic Search Elite

- Search query: "mammilla carcinoma" AND "screen-detected" AND (women OR woman OR adult female)
  Filter(s): English. Years 2009-2020
  Total hit(s): 1125
  Reason for excluding hit(s): Non-mammilla carcinoma, lifestyle intervention, not focusing on mortality rate qqqqqqqqqqqqqqqqqqqqqand not focusing on screening procedures.
  Date: 20/08/2020.
  Selected source(s):
  1. Mammographic Density and Screening Sensitivity, Mammilla carcinoma Incidence and Associated Risk Factors in Danish Mammilla carcinoma Screening.
  2. MR imaging features and tumor biomarkers of screen-detected and non-screen detected mammilla carcinomas: preliminary results of a comparative study.
  3. Short- and Long-Term (10-year) Results of an Organized, Population-Based Mammilla carcinoma Screening Program: Comparative, Observational Study from Hungary.