Systematic review and health economic evaluation of expanding the Norwegian breast cancer screening program to screen all women between the ages of 40 and 69

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1. Abstract:

Background

The Norwegian breast cancer screening program started in 2005 inviting all Norwegian women aged between 50 and 69 to attend biennial mammography screening. More than 10 years after its implementation, the high cost-effectiveness of the current Norwegian mammography program has been established by other studies.

Objectives

This thesis looks at the potential cost-effectiveness of expanding the national breast cancer screening program to include women between the age of 40 and 49 in Norway.

Methods and results

To reach a conclusion, I first conducted a systematic review on the topic. My systematic review of the topic shows that national mammography programs in western countries that screen women between the ages of 40 and 69 were cost-effective in 7 out of 9 studies (78%). In addition, a six-state Markov model was also developed to evaluate the cost effectiveness of the Norwegian breast cancer program if the program expands to invite women between the ages of 40 and 69 to biennial screening. Cost effectiveness is estimated to be 51313 Euros per QALY gained when comparing the hypothetical program that screens women between the ages of 40 and 69 with the current mammography program that screens women aged 50 to 69.

Conclusion

With the Norwegian national threshold value being around 700000 NOK(73020 Euros) per QALY gained, it appears that it is in fact cost effective to expand the national breast cancer screening program to screen women between the ages of 40 and 69 biennially for breast cancer in Norway. The results show decent external validity as the calculated expected remaining life years for a 40-years-old Norwegian woman in my model is very similar to the expected remaining life years for a 40-years-old Norwegian woman estimated by Statistics Norway.
2. Introduction:

Breast cancer is the cancer that develops from breast tissue, and it is one of the most prevalent types of cancer for women in both the developing and the developed world. (2) In Europe alone, an estimated 464000 women were diagnosed with breast cancer in 2012, accounting for 29% of all new female cases that year. In the same year, 131000 women were estimated to die from breast cancer, accounting for 17% of all female cancer deaths in Europe and making it the most common cause of female cancer death in Europe. (3)

The breast cancer incidence rate has continued to rise in almost all European countries in recent decades, while mortality rate of breast cancer have fallen in many countries since the mid-1990s due to advances in breast cancer treatment. (3) The increase in breast cancer incidence rate is largely due to the increase in life expectancy as health technologies advance. As people get to live longer, their chances of getting breast cancer in their lifetime also increase.

Breast cancer used to have a very low survival rate due to the lack of proper treatment. However, survival rate for breast cancer has improved drastically in the past half century. Nowadays, “the five-year survival rate of women with breast cancer is 82% in Europe with variations from 74% in Eastern Europe to 85% in Northern Europe” (3, European breast cancer screening guideline 2016)

As with all cancers, the five-year survival rate of breast cancer for an individual is much higher if breast cancer is detected early, which is often achieved through breast cancer screening. The most commonly used screening test for early breast cancer detection is mammography. Mammography (also called mastography) is the process of using low-energy X-rays (usually around 30 kvp) to examine the human breast for diagnosis and screening. The goal of mammography is the early detection of breast cancer, typically through the detection of characteristic masses or micro calcifications. (41)

On the basis of several randomized clinical trials, the World Health Organization concluded in 2002 that screening mammography for women between the ages of 50
and 69 reduced the rate of death from breast cancer by 25%. (44)

However, breast cancer screening is still a hotly debated subject at the moment. Many studies have casted doubts on the benefits of breast cancer screening program, warning that it save fewer lives than previously thought. This is partly due to the high rate of over-diagnosis, and the high specificity associated with mammography programs. In addition, the actual effect of mammography on mortality reduction is often questioned. The estimated breast cancer mortality reduction associated with mammography screening ranges from almost zero to 30% in different papers.(42,43,57) This fluctuation of results is often due to the fact that it is hard to provide valid comparison groups when doing economic evaluations on mammography screening programs. “Although historical, prescreening control groups are often used, such a comparison has important limitations because it does not take into account confounding by chronological trends in breast-cancer mortality, reflecting such factors as advances in breast-cancer awareness and treatment.”(44)

However despite of these doubts and uncertainties, most European countries including Norway has implemented national breast cancer screening program for all women aged between 50 and 69 in the past 20 years, following the recommendation by the European Commission. This recommendation is based on the assumption that earlier diagnosis of breast cancer can lead to better prognosis. Confirming this assumption, studies done in the past 20 years evaluating the cost effectiveness of different national breast cancer screening programs in Europe have shown that most of these programs are in fact cost effective in respective country settings. (17, 20-23) Studies have also overwhelmingly shown that the benefits-to-harm ratio for women aged between 50 and 69 to receive screening is high enough to justify the implementation of national mammography programs. (18, 23)

Data shows that the incidence rate of breast cancer as well as the benefit-to-harm ratio of mammography is the highest for women aged between 50 and 69, (49, 18, 23) and therefore this age group is chosen as the standard age group to receive mammography screening in most national breast cancer screening programs in Europe. Since the results of many current breast cancer screening program have shown that
these programs are in fact a very cost effective method to reduce breast cancer mortality for the 50 to 69 age group women, countries are now beginning to look into the possibilities of expanding the national mammography program to invite women in other age groups to screening. Even though other age groups will not benefit from screening as much as the 50-69 age group, it may still be cost effective for certain age group to be screened. By including more age groups that are cost effective to be screened for breast cancer, the national mammography program can further improve its effectiveness, and further improve the total social welfare of that country.

3. Objective of the master thesis:

Very recently, the European Commission made an update on the recommendations for breast cancer screening. Previously, average risk women aged 45-49 were weakly recommended to have no mammography screening over screening for breast cancer. But now, they started to weakly recommend mammography screening over no screening for women aged 45-49 in a new round of voting based on new evidences on the effect of breast cancer screening. The European commission’s decision is “a result of a balance of health effects that probably favors mammography screening, despite only moderate certainty in the evidence about these effects”(1). This means that the recommendation is not based on the cost effectiveness of mammography programs, but based on the benefits-to-harm ratio of mammography programs.

This decision made by the European commission may have an effect on the future of the Norwegian mammography program as the European commission has suggested that screening women below the age of 50 may have more benefits than harm in Europe. If the Norwegian mammography program can remain cost effective after expanding the program to include women below the age of 50, then it will be welfare improving to the society to include these women for biennial mammography screening in Norway.

Therefore, **the objective of this thesis is to find out the cost effectiveness of**
including average risk Norwegian women aged between 40 and 49 into the Norwegian national mammography program based on the new recommendation by the European commission comparing with the current program. Is the expansion cost effective in the Norwegian setting? How much will the total cost effectiveness of the national mammography program decrease/increase if these additional women are to be included? The result of this study may help provide some information on the possibilities of expanding the current breast cancer screening program to invite and benefit more people in Norway.

Given the higher level of threshold for accepting new health interventions in Norway compared with the European average, my hypothesis is that it will be cost effective to expand the program in Norway. However, the final outcome of my study may provide a different conclusion since the per patient cost of mammography as well as breast cancer treatment cost are also higher in Norway compared with the European average because of Norway’s higher labor cost.

4. Background Information:

4.1 The breast

“The human breast for both male and female are developed from the same embryological tissues. At puberty, estrogens, in conjunction with growth hormone, causes breast development in females”. (39) For female, the breast serves as the mammary gland, which produces and secretes milk to feed infants. “The mammary gland is composed of fatty cells which store fat, and in adult lactating women, lobules produce milk. There are complex networks of branching ducts within the mammary gland. These ducts transport milk from the lobules out to the nipple. The size of a normal breast on average is 10-12 cm in diameter and in thickness 5-7 cm” (40).
4.2 Breast Cancer and its development

Cancer occurs as a result of mutations in the genes responsible for regulating the growth of cells and keeping them healthy. With these genes losing the ability to regulate cell growth, some cells will start to keep dividing without control, producing more cells just like it, forming a tumor. (38) A tumor can be either benign or malignant. A tumor is considered benign when it grows slowly, and does not invade nearby tissues spreading to other parts of the body. A benign tumor is not dangerous to our health, and is not considered to be cancerous in medical science. On the other hand, a tumor is malignant when it invades other parts of our body or metastasizing. A malignant tumor is life-threatening and is the focus of this thesis.

Breast cancer means the malignant cancer that develops from the breast cells. “Breast cancer most commonly develops in cells from the lining of milk ducts and the lobules that supply the ducts with milk.” (Wikipedia, 2018) Breast cancer is generally asymptomatic in its early stages, making it hard to be detected early. However, if it is left untreated, cancer cells will find its way into the lymphatic system of our body. Lymphatic system filters out foreign substances in our body, and it runs pass most of our organs. Using the lymphatic system as a highway, breast cancer cells are now free to metastasize to other parts of our body.

4.3 Stage classification of breast cancer

The stage classification of breast cancer is decided based on how far from the breast cancer cells have managed to travel. Although there are other staging systems like the TNM (Tumor, Node, and Metastasis) system, numerical staging system is the most commonly used. In this system, breast cancer is classified into five big stages.

In stage 0, the cancer is still non-invasive meaning that there is no evidence of the cancer cell breaking out of the part of the breast in which they started. (38) Ductal carcinoma in situ (DCIS) is a common representation of a stage 0 breast cancer.

In stage 1, the cancer becomes invasive, which means that cancer cells have broken through the lining of the duct or lobule of its original breast area, and have started to invade neighboring tissues. Although in stage 1, this invasion is often
microscopic, and is still very treatable. In terms of its size, the maximum length of the tumor is 2 centimeters for stage 1 breast cancer.

When the breast cancer tumor grows larger than 2 centimeters, but smaller than 5 centimeters, breast cancer have entered stage 2. In stage 2, cancer has spread to the lymphatic system of our body. Tumors can now be found in 1 to 3 lymph nodes under the arms or in the lymph nodes near the breast bone. (38) Breast cancer cells may have begun to metastasize so that sometimes no tumor can be found in the breast. In stage 2, breast cancer tumor is likely to have grown to a noticeable size, and about 55.6% of all breast cancers diagnosed in women who didn’t undergo any prior breast cancer screening are in stage 2. (35)

When breast cancer has reached stage 3, the tumor may have spread to the chest wall or the skin of the breast. Up to 9 lymph nodes will have cancer cells in them, and the tumor may have grown to be larger than 5 centimeters. In this stage, breast cancer becomes quite symptomatic as patients will start to develop ulcer and inflammation. Inflammation will cause the reddening of the breast skin, and the breast may also be swollen. In stage 3, at least 10 lymph nodes now have cancer cells in them.

Finally, in stage 4 breast cancer, the cancer cells have metastasized past the breast. Through the lymphatic system, cancer cells have spread to other organs such as bones, skins, brain, and so on. Stage 4 breast cancer is extremely life-threatening, and its five-year survival rate is very low. As a result, stage 4 cancer is also known as advanced breast cancer.

4.4 Treatment options of breast cancer

There are generally three categories of treatment available for breast cancer:

First is surgery, which is also the most commonly used. (39) The purpose of the surgery is to remove the part of the breast that contains the tumor. Depending on the size and stage of the tumor, breast cancer surgery can be categorized into lumpectomy (removal of a lump), mastectomy (removal of the whole breast), and quadrantectomy (removal of a quarter of the breast). (39)

After surgery, there may still be cancer cells left in the patients. Therefore, in
addition to surgery, there are also many drugs for breast cancer available in the market. Most of these drugs are to be used in combination with the surgery, and are therefore a part of the adjuvant therapy. Three main groups of medications are hormone-blocking agents, chemotherapy, and monoclonal antibodies. Chemotherapy is the most common method for breast cancer from stage 2 to stage 4, and are suitable for all subtypes of breast cancer. “Most chemotherapy works by destroying fast-growing cancer cells in our body.”(39) While it is effective at killing fast growing cancer cells, chemotherapy also kills fast growing normal cells such as bone marrow, hair and heart muscles. As a result, chemotherapy is often associated with adverse side-effects. Hormone blocking therapy, on the other hand, is only suitable for certain types of breast cancer that requires estrogen to reproduce. It works by either blocking the estrogen receptors of cancer cell or blocking the production of estrogen in the patient’s body. Lastly, monoclonal antibodies are also only suitable for a certain subtypes of breast cancer that have very active HER2 cells. “When stimulated by certain growth factors, HER2 causes cellular growth and division.”(39) In some breast cancer cases, HER2 are overexpressed causing the fast growth of the cancer cells. Monoclonal antibodies “work by preventing growth factors from being able to bind to the HER2 in breast cancer cells, blocking the growth of the cancer cells”. (39)

Last category of treatment is radiation, which is also to be used in combination with surgery. The purpose of radiotherapy is to kill off remaining cancer cells that was not removed by surgery. These cancer cells are usually microscopic, and are the main cause of recurrence of breast cancer. Studies estimate that “radiotherapy after surgery can reduce the risk of recurrence by 50-60% when delivered in the correct dose.”(39) Radiotherapy is especially important when the patient choose to perform lumpectomy as there is a high chance of microscopic cancer cells left in the part of the breast is not removed.

Overall, there are no standard way of treating breast cancer. Almost all breast cancer patients will undergo surgery to remove most of the cancer cells in the breast, and treatment options after that vary depending on the patient’s age, his/her cancer subtype, his/her breast cancer stages as well as his/her available resources.
4.5 Risk factors of breast cancer

Aside from being a women, age is considered to be the single biggest risk factor of breast cancer. (40) Our body goes through countless cell divisions every day. As we live longer, there are simply more chance of genetic mutations in our body, which leads to a higher chance of breast cancer. In addition, our immune system becomes less effective as we get older. Immune system acts as a check in our body to get rid of mutated genes before it further mutates. Therefore, a weaker immune system as we become older increases the likelihood of us getting breast cancer. According to the data from Norwegian cancer registry, the incidence rate of breast cancer is only 23 per 100000 women in age group 30-34 for Norwegian women. While the incidence rate of breast cancer becomes 175.4 per 100000 women in 45-50 age groups. (49)

Race is also an important risk factor of breast cancer. The overall breast cancer incidence rate is slightly lower for Asian women and African women compared with White women. In addition, age range with the highest breast cancer incidence rate is different between races. Breast cancer incidence rate peaks in their fifth decade between the ages of 40 and 49 for Asian women while White women generally have the highest breast cancer incidence rate between the ages of 54 and 65. (33)

Family history and genetics are also important risk factors for breast cancer. “About 5-10% of breast cancers are thought to be hereditary, caused by abnormal genes passed from parent to child.”(39) Most of the hereditary breast cancers are associated with mutations in BRCA1 and BRCA2 genes. This mutation greatly increases a woman’s risk of getting breast cancer in her lifetime. According to one study, “an average risk American woman has a 12% chance of getting breast cancer in her lifetime, while a woman with BRCA1 or BRCA2 mutations has a 80% chance of getting breast cancer in her lifetime”.(39) Taken into account of the importance of family history on the risk of breast cancer, the Norwegian mammography program invites women with a family history of breast cancer to attend biennial mammography screening much earlier than the age of 50, which is the normal starting age of invitation to screening for the rest of the population.
In addition to inherent genetic mutations, women also inherit her breast density from her family members. Dense breast means that instead of mostly made of fatty tissues, a patient’s breast contains a large amount of fibrous and glandular tissues. If her family members all have dense breast, then the patient is more likely to have dense breast. Dense breast is considered an important risk factors to breast cancer, and women with dense breast are 6 times more likely to develop breast cancer. (39) This is probably due to the fact that breast cancer develops from ductal and glandular tissues. The more ductal tissues there are, the more likely genetic mutations happen. In addition, dense breast makes it harder for mammography to detect the tumor, which reduces the chance of the patient getting breast cancer detected early.

Moreover, because many types of breast cancer depends on estrogen to replicate, high estrogen level is associated with a higher risk of breast cancer. Therefore menstrual history, breastfeeding history, pregnancy history are all important risk factors for breast cancer. Women who start menstrual cycle before the age of 12 or who go through menopause older than the age of 65 are at a higher risk of breast cancer. This is due to the fact that these women would remain at the high estrogen level for a longer period of their lives. Moreover, a short breastfeeding time is also a risk factor for breast cancer as menstrual cycle is stopped when the mother is breastfeeding. The reduction in menstrual cycle will help reduce estrogen level in the mother’s body, which helps to reduce the risk of breast cancer. Similarly, a woman without a full term pregnancy or have her first baby late in life are at a higher risk of breast cancer. This is partly because pregnancy reduces the total number of menstrual cycles in a woman’s life time. This is also partly due to the fact that woman’s breast only become fully mature and grow in a regular way after a full term pregnancy when the breast produces milk to feed the baby. Without a full term pregnancy, woman’s breast will never be fully developed, and the immature ducts are at a higher risk of developing breast cancer.

Lastly, people living unhealthy lifestyles are also at a higher risk of breast cancer. Smoking, excessive drinking, lacking exercise, eating unhealthy food, and living in polluted environment are all associated with a higher rate of getting breast cancer.
4.6 Breast cancer prevention

In addition to try and reduce the controllable risk factors such as lifestyle changes and longer breastfeeding time, the risk of dying from breast cancer can also be reduced through breast cancer screening. Breast cancer screening is the medical screening of asymptomatic women for breast cancer in an attempt to detect breast cancer in its early stages. “The benefits of breast cancer screening in terms of reduced mortality rates primarily comes from the detection of pre-clinical cancer (the detection of cancers before they present with clinical symptoms, and the more favorable prognosis associated with early-stage cancers.”(13) In its early stages, breast cancer is only localized and it is very treatable by removing a part of the breast containing cancer cells. The five year survival rate is very high if breast cancer is detected early.

However, if breast cancer is detected at an advanced stage such as in stage 3 or 4, then the cancer has already metastasized to other parts of the body, and surgery will no longer be very effective at curing breast cancer. The existing drugs and radiotherapy will not cure the cancer at this stage, but merely try to extend the life of the patient. As a result, breast cancer screening is widely accepted as the most effective way to reduce breast cancer mortality until a miracle drug that can cure breast cancer in advanced stages gets developed.

5. Breast Cancer screening by mammography

5.1 What is mammography?

There are many imaging technologies to conduct breast cancer screening including mammography, ultrasound, magnetic resonance imaging, molecular breast imaging and so on. Among them, mammography is the most commonly used, and national mammography programs have been widely implemented all over the world. Mammography stands out amongst others because of its relative low cost, fast process, and the already common and abundantly available X-ray machines.

During mammography, women will have their breasts X-rayed on an X-ray machine. The resulting image will then be sent to a specialized physician for evaluation
and interpretation either on a computer screen (digital mammography) or on a photographic film. If the physician finds anything suspicious in the image, the women will be recalled for a second mammography test. If physicians again find a suspicious lump in the second mammography, a biopsy will generally be performed on the breast to determine the nature of the lump. If biopsy result comes back positive, the patient will be confirmed to have developed breast cancer, and will then undergo the full course of treatment for breast cancer.

5.2 Norwegian breast cancer screening program

In Norway, the national screening program for breast cancer is called: “Mammografiprogrammet”. It

- invites all women between 50 and 69 years of age to mammography every two years
- is a governmental, nationwide and voluntary health service administrated by the Cancer Registry of Norway
- detects every year about 1000 cases of breast cancer or precancerous lesions
- has a participation rate of around 75%. (4)

In Norway, “the screening program is organized with 26 stationary units at different hospitals and 4 mobile screening units using biennial mammography buses. The Central Population Registry of Norway identifies eligible women on the basis of their national registration number. Invitations are mailed to each eligible woman, suggesting a time for an appointment. Overall, 77% of all women who are invited participate in the program. In accordance with European guidelines, mammograms are obtained in two views, which are independently read by two radiologists.” (8, Mette Kalager et al 2010) Women are invited to participate in the screening program by a posted personal letter where time and place for the screening test is given. About 80% of the screening takes place in stationary units, while the other 20% of the screening was undertaken in buses.

5.3 Sensitivity and specificity of mammography

Sensitivity is the also known as the recall rate. Sensitivity refers to a screening test’s ability to correctly identify a diseased individual as having the disease. (60) The
sensitivity of a screening test is calculated by dividing the number of true positives by the sum of the number of true positives and the number of false negatives. (Sensitivity = TP / (TP+FN)) If a mammography screening test has a high sensitivity, then the test has a strong ability to correctly pick up most of the patients who have breast cancer. The sensitivity of mammography program differs from country to country. Hofvind S has estimated the sensitivity of the Norwegian breast cancer screening program to be 91.0% for initial assessment, and 90.7% for final assessment given a 2-year screening interval. (16) This means that for every 100 women with breast cancer, the Norwegian breast cancer screening program has the ability to identify around 91 of them in the initial assessment. The other 9 out of the 100 women who in fact have breast cancer will not get positive results from the initial round of screening. In addition, out of the 91 women who were correctly identified in the first round, 9.3%(6.37 women on average) will be cleared of having breast cancer in the second round of screening even if they in fact have breast cancer. As a result, low sensitivity will cause 15.37(9+6.37) women in every 100 women screened who has breast cancer to miss their opportunity to be detected of breast cancer early, significantly reducing the effectiveness of the screening program in Norway.

On the other hand, specificity measures the percentage of healthy people that are correctly identified as not having the condition. (60) It is calculated by dividing the number of true negatives by the sum of the number of true negatives and the number of false positives. (Specificity = TN / (TN+FP)) The specificity of mammography programs also vary from country to country. In the same article, Hofvind estimated the specificity of the Norwegian breast cancer screening program to be 97.8% for initial assessment, and 99.5% for the final assessment. (16) This means that after the final assessment, the Norwegian breast cancer screening program will be able to correctly identify almost all of the women who does not have breast cancer. Only roughly 2 out of 100 healthy women will be wrongly diagnosed to have breast cancer after the first round, and only 0.5 out of the remaining 98 women who does not have breast cancer will be detected as having breast cancer in the second round. As a result, on average a total of around 2.5 out of every 100 healthy women will be wrongly diagnosed to have
breast cancer during mammography screening in Norway.

The Norwegian breast cancer screening program, therefore, has a fairly high specificity level, and a low sensitivity level. A high specificity is very important for a screening program. One can even argue that it is more desirable for a medical intervention to have a high specificity than to have a high sensitivity. This is because of the Hippocratic Oath of “first do no harm”. If the specificity of a screening program is low, then many women who are cancer free will be wrongly diagnosed of having breast cancer. These women will have to go through radioactive breast cancer treatments, which are very harmful to the body. In addition, high specificity can also assure that the effect of the mammography program is not overestimated. Healthy patients who are wrongly diagnosed of cancer will find themselves be magically “cured” of cancer after going through intensive treatments. However, studies will still count the recovery of these people as the effects of the mammography program, causing overestimation of the effect of the screening program.

5.4 Controversies surrounding mammography

There are so many debates, chaos and controversies associated with the effectiveness of mammography. Almost every academic paper on this issue will yield a different number, and no consensus has been reached on this topic yet. The controversy can be categorized into three main parts: low specificity, mortality reduction and over-diagnosis.

(1) Low specificity

To start off, the effectiveness of mammography has been under heavy questioning in recent years. Many national mammography programs have a relatively low specificity. Hofvind estimated the specificity of the mammography program in Vermont, USA to be only 90%. (16) This means that for every 100 healthy women, 10 will be wrongly diagnosed of having breast cancer. However, these healthy women will have no problem surviving for a long time, causing studies to overestimate the benefits of the screening program. The specificity of the screening program is most likely to be even lower in less developed countries, creating an even bigger overestimation of the
effect of mammography.

(2) Mortality Reduction

Moreover, “the benefits of breast cancer screening in terms of reduced mortality rates primarily comes from the detection of pre-clinical cancer (the detection of cancers before they present with clinical symptoms), and the more favorable prognosis associated with early-stage cancers.” (13) The underlying assumption of breast cancer screening is that detecting cancer at early stages will lead to better prognosis. It sounds logical, and promising. However, many authors have casted doubts on this assumption arguing that the benefit of mammography is in fact very limited. In a systematic review on the topic, Harris concluded that “when the analysis included only the least biased trials, women who had regular screening mammograms were just as likely to die from all causes, and just as likely to die specifically from breast cancer, as women who did not.” (42) His result shows that mammography doesn’t seem to reduce breast cancer mortality, and his result was confirmed by the 2013 Cochrane review, in which the absolute risk reduction associated with screening 50-75 years old women using mammography is only 0.05. (43) In these studies, the mammography program is not very effective at reducing the mortality rate of breast cancer, and the assumption that early diagnosis leads to better prognosis comes under questioning. According to the results of these studies, the effect of the mammography program is small, and the money for the program might be better spent in other areas of the health-care system.

However, another group of authors came up with a complete different picture about the mortality reduction associated with mammography programs. Over the past two decades, many western countries have implemented national breast cancer screening program for the 50-69 age group women. Many studies evaluating these national screening programs concluded that the benefits of mammography screening outweighed the harm for this age group. After analyzing the data for the mammography trial in the Basque county, Spain for the 50 to 69 age group, Arrospide estimated that “the screening program yielded a 16 % reduction in breast cancer mortality and a 10 % increase in the incidence of breast cancer through 2011. 2 % of
all the women in the program had a false positive result during the evaluation period.”(24) In addition, Gunsoy estimated the breast cancer mortality reduction and over-diagnosis rate to be 18.1% and 5.6% respectively for triennial screening in women aged 47-73 in the UK. (59) It seemed the Spanish program as well as the British program have a large effect of mortality reduction, with an acceptable level of over-diagnosis. The high benefit-to-harm ratio indicated that national mammography programs were very beneficial and effective.

With both sides telling a good story, which side should we trust? Nobody knows for sure. However, most European governments seem to have believed in the effectiveness of mammography programs at reducing breast cancer mortality, and many countries have implemented national mammography program for women between the ages of 50 and 69. As a result, I will also assume that breast cancer screening is in fact effective at reducing mortality rates of breast cancer, and write my thesis based on this assumption.

(3) Over-diagnosis

In addition to its effectiveness at reducing mortality rate, mammography also becomes controversial because of its high rate of over-diagnosis. Many people question the benefits of mammography because they believe that mammography causes a lot of over-diagnosis. Over-diagnosis is defined as the detection of a breast cancer tumor that would not have been detected and would not be harmful to the woman’s health in her lifetime. Without screening, some women would have died from another diseases despite having a benign breast tumor in her body. In 2013, the Cochrane review reported the rate of over-diagnosis to be 30%. (10) Another review found the rate of over-diagnosis to be 19% among screened women in the 50-69 age group. (11)

Over-diagnosis is costly. After a tumor suspect finding is wrongly detected during the first round of mammography, the patient is then recalled for a repeat examination. When repeat examination wrongly confirms that the patient has breast cancer, she will undergo the treatment process for breast cancer. All of this is a big waste of money in
an increasingly budget constraint world because these cancers would have no effect on the patient’s life if it was not detected by screening. Not only does the society suffer financial wastes, the patient also suffers mentally and physically.

In addition, the patient will have to take time off work, and travel long distances to the hospitals. In the worst case scenario, the over-diagnosis will cause the patient to undergo the full radioactive cancer treatment. Not only will the patient suffer enormous physical and mental pain, the risk of the patient actually getting a life threatening cancer increases as she receives more radioactive treatments. Because of over-diagnosis, it has been argued that the benefit of the mammography program is overestimated. One study calculated that this type of over-diagnosis accounts for 6.5% of all the breast cancer detected by mammography. (8)

However, there are always two sides to a debate. One Norwegian study done in 2017 casted doubts on the prevalence of over-diagnosis (9). In the study, they found that screened women had a 1.1% increased cancer incidence rates of breast cancer diagnosis compared with women who had never had a mammography. The increase was statistically significant. However, they also found that invasive cancers were significantly smaller in screened versus unscreened women. When accounting for this, the difference between breast cancer incidence rates was reduced to -0.2%. (9) In addition, screened population seemed to have a significant decrease in lymph node positive cancer. As a result, the authors concluded that the prevailing view of over-diagnosis in the mammography program in Norway should be challenged. (9)

Again, nobody can be certain which side of the story to trust. However, I will assume that over-diagnosis does not have a significant effect on the Norwegian breast cancer screening program in my model.

5.5 Cost effectiveness of screening 50-69 women

Nowadays, most European countries have implemented the national mammography program to invite women between the ages of 50 and 69 to screening as studies have shown that this age group has the highest breast cancer incidence rate. (49) Studies evaluating the cost effectiveness of the current mammography program
of screening 50-69 age group in several European countries have shown that organized mammography programs are mostly cost effective in European countries for the 50-69 age group even though the ICER ratios vary significantly across countries. In the UK, Pharaoh found that screening 50-69 years old costed $20800 per QALY gained, which is slightly above the lower boundary of the threshold for the NHS in UK. The results is confirmed by other UK studies showing that the breast cancer screening program in the UK is borderline cost effective.

The current Norwegian breast cancer screening program was also found to be highly cost effective. Van Lujit estimated that screening women aged 50-69 in Norway reduced breast cancer specific mortality by 16-30% at the cost of 112162 NOK per QALY gained in 2017. It is well below the suggested Norwegian threshold of 700000 NOK per QALY gained in the same year. However, this paper didn’t take into account of the harms caused by over-diagnoses and overtreatment. Thus, the paper may have overestimated the cost effectiveness of the Norwegian breast cancer program.

Moreover, screening 50-69 years old women is found to be cost effective for many middle income countries. In a study done for Turkey, the incremental cost effectiveness ratio for the 50-69 age group was estimated to be $2423 per life year saved. The program was considered highly cost effective as Turkey has a threshold of around $10000 at the time of their study. Ernesto Ulloa-Pérez also found that it was highly cost effective to implement national mammography program for 50-69 age group in Mexico.

5.6 Benefits and harm of mammography screening in 50-69 women

To determine whether a health intervention should be introduced, it is not enough to just know its cost effectiveness. Instead, both its cost effectiveness and its benefit-to-harm ratio need to be considered before making the decision.

One Danish study found that the benefit-to-harm ratio of screening the 50-69 women was estimated to be 2.5 in the mammography program of Denmark. This meant that for every Danish woman being over-diagnosed, 2.5 women would be
prevented from dying from breast cancer due to the introduction of mammography program. Moreover, in a study done for the Norwegian breast cancer screening program, Hofvind found that “for every 10,000 biennially screened women, followed until age 79, they estimated that 53-61 (average 57) women were saved from breast cancer death, and 45-126 (average 82) were over-diagnosed. The benefit-detrimen\textregistered{}t ratio using average estimates was 1:1.4, indicating that the program saved about one life per 1-2 women with epidemiologic over-diagnosis”.(23) The benefit-to-harm ratio was lower than the Danish study. However, I believe that this is still a good rate, and the current national mammography program that screen women between 50 and 69 in Norway should be beneficial to the society.

5.7 Benefits and harm of mammography screening in 40-49 women

Since the benefits of having organized mammography screening for the 50-69 women seem to outweigh the harm caused, and the high cost effectiveness of screening 50-69 has been widely established in most European countries, will it be a good idea to expand the mammography program to include women aged 40 to 49?

Studies have shown that women in the 50-69 age group have the highest breast cancer incidence rate. (49) However, data published by the Norwegian cancer registry also shows that breast cancer incidence rate begins to significantly increase for women over the age of 40. This change is especially drastic for women between the ages of 45 and 49 where the incidence rate increases to 175.4 per 100000 women. (49) Although still slightly less than the incidence rate of 50-69 age group, the incidence rate is still quite high making the mammography program potentially beneficial to 40-49 age group in Norway.

Screening the 40-49 age group will have a lower benefit-to-harm ratio comparing with screening the 50-69 age group. This is due to the lower incidence rate as well as the higher rate of over-diagnosis amongst 40-49 women comparing with 50-69 women. In a study done for the U.S, the author found that “women aged 40 to 49 years with a 2-fold increased risk had similar harm-benefit ratios for biennial screening mammography as average-risk women aged 50-74. (12)
However, many studies find that screening 40-49 women still seem have large benefits despite having a lower benefit-to-harm ratio in this age group. Meta-analysis including the most recent follow-up data from all eight RCTs involving women aged 40-49 at entry demonstrated a statistically significant mortality reduction due to regular screening mammography in women of this age group.(4) In addition, the Edinburgh RCT of breast cancer screening found that after 10-14 years of follow-up, breast cancer mortality had been reduced by 12% (adjusting for social economic status) to 18% (without adjusting for social economic status) for 40-49 age group. (6)

Moreover, Charles looked at all the available studies and found that, “combining all current data on women ages 40 to 49 years at entry yielded a 14% benefits from screening mammography, without statistical significance at 95% CI”. (5) In the neighboring Sweden, results also showed that women aged 40-49 could in fact benefit from mammography screening as “combining all current follow-up data on women aged 40-49 at entry into the five Swedish RCTs yielded a statistically significant 29% mortality reduction among women invited to screening (relative risk: 0.71; 95% confidence interval: 0.57-0.89).” (5) Evidently, the mortality reduction associated with screening 40-49 women is probably high enough to justify the expansion of mammography programs despite some uncertainties about the level of harms caused when screening this age group. From all these evidences above, it is highly possible that screening women between the ages of 40 and 49 is beneficial in the Norwegian setting, and I will write my thesis based on this assumption.

Under such assumption, expanding the Norwegian breast cancer screening program to invite 40-69 age group women for biennial screening can potentially be welfare improving if the cost effectiveness of including this age group to screening is below the national threshold value. I will calculate the cost effectiveness of screening 40-69 women in Norway in the chapters below using both a systematic review and a Markov model.

6. Systematic review
6.1 Method:

I used the article, “preferred reporting items for systematic reviews and meta-analysis: the PRISMA statement” (15) as my guideline when doing the systematic review.

6.2 Objective:

To summarize the current knowledge on the cost effectiveness of screening women between the ages of 40 and 69 in national breast cancer screening programs.

6.3 Search Strategy:

I used the following search items in PubMed: 1. breast cancer screening 2. Cost effectiveness or cost utility or ICER. I chose to only look at articles from the past 15 years as there are systematic reviews on similar topic done 15 years ago.

6.4 Results:

Searching the combination of the two terms in PubMed gives me a result of 676 articles. Finally, I picked out 15 articles that are relevant to this topic from all the results. In addition, I included 4 relevant articles about the expansion of age limits from a previous systematic review (37) on the cost-effectiveness of breast cancer screening programs 15 years ago. Together, I was able to produce a table summarizing all the studies done for the past 25 years on the cost effectiveness of starting breast cancer screening for women below the age of 50.

I separated 19 articles into 2 groups. First group includes articles talking about the overall cost effectiveness of the breast cancer screening programs after lowering the starting age from 50 to 40. (Screening offered to women between 40 and 69)

The second group includes studies that discuss the cost effectiveness of women in their 40s undergoing breast cancer screening. (Screening offered to women between 40 and 49 only)

(1) Group 1: Overall cost effectiveness group (40-69):

<table>
<thead>
<tr>
<th>Author</th>
<th>Year</th>
<th>Perspective</th>
<th>Model</th>
<th>Age group</th>
<th>Interval</th>
<th>Country</th>
<th>Results</th>
<th>Outcomes</th>
<th>Threshold</th>
</tr>
</thead>
</table>

(continued)
<table>
<thead>
<tr>
<th>Study</th>
<th>Year</th>
<th>Domain</th>
<th>Model</th>
<th>Age</th>
<th>Frequency</th>
<th>Location</th>
<th>Cost per Life Year Gained</th>
<th>DALY Averted</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hall et al. (7)</td>
<td>1992</td>
<td>Health care</td>
<td>Decision tree</td>
<td>45-69</td>
<td>Biennial</td>
<td>Australia</td>
<td>$7190</td>
<td></td>
</tr>
<tr>
<td>Carter et al. (19)</td>
<td>1993</td>
<td>Health care</td>
<td>MISCAN</td>
<td>40-69</td>
<td>Biennial</td>
<td>Australia</td>
<td>$20300</td>
<td></td>
</tr>
<tr>
<td>Szeto et al. (13)</td>
<td>1996</td>
<td>Health care</td>
<td>MICRO LIFE</td>
<td>45-64</td>
<td>Biennial</td>
<td>New Zealand</td>
<td>$15169</td>
<td></td>
</tr>
<tr>
<td>Rosenquist et al. (37)</td>
<td>1994</td>
<td>Health care</td>
<td>Markov</td>
<td>40-69</td>
<td>Biennial</td>
<td>U.S.A</td>
<td>$20000</td>
<td></td>
</tr>
<tr>
<td>Nooshin Zehtab et al. (28)</td>
<td>2014</td>
<td>Health care</td>
<td>Decision Tree</td>
<td>35-69</td>
<td>Biennial</td>
<td>Iran</td>
<td>$6264</td>
<td>DALY Averted</td>
</tr>
<tr>
<td>Schiller-Freuhwirth I et al. (27)</td>
<td>2014</td>
<td>Health care</td>
<td>Markov</td>
<td>45-69</td>
<td>Biennial</td>
<td>Austria</td>
<td>$20010</td>
<td></td>
</tr>
<tr>
<td>Mittmann N et al. (25)</td>
<td>2018</td>
<td>Health care</td>
<td>Breast cancer simulation</td>
<td>40-74</td>
<td>Biennial</td>
<td>Australia</td>
<td>$73647</td>
<td>QALY Gained</td>
</tr>
<tr>
<td>Mittmann N et al. (26)</td>
<td>2015</td>
<td>Societal</td>
<td>Wisconsin CISNET model</td>
<td>40-69</td>
<td>Annual 40-49, Biennial 50-69</td>
<td>Canada</td>
<td>$146333 or $97006 if only biennial 50-69</td>
<td>QALY Gained</td>
</tr>
<tr>
<td>Riberto RA et al. (29)</td>
<td>2013</td>
<td>Health care</td>
<td>Markov</td>
<td>40-69</td>
<td>Biennial</td>
<td>Brazil</td>
<td>$4162</td>
<td>QALY Gained</td>
</tr>
<tr>
<td>Laurens M et al. (30)</td>
<td>2014</td>
<td>Health care</td>
<td>Markov</td>
<td>40-69</td>
<td>Biennial</td>
<td>Costa Rica</td>
<td>$6965</td>
<td>DALY Averted</td>
</tr>
<tr>
<td>Mo M et al. (31)</td>
<td>2015</td>
<td>Health care</td>
<td>Decision Tree</td>
<td>35-69</td>
<td>Biennial</td>
<td>China</td>
<td>$21396</td>
<td>QALY Gained</td>
</tr>
<tr>
<td>Zelle et al. (32)</td>
<td>2013</td>
<td>Health care</td>
<td>WHO-CHOICE guidelines</td>
<td>40-69</td>
<td>Annual</td>
<td>Peru</td>
<td>$8426</td>
<td>DALY Averted</td>
</tr>
</tbody>
</table>

*NOTES:*
- DALY: Disability Adjusted Life Years
- QALY: Quality Adjusted Life Years
- CISNET: Comprehensive Information System for Networked Epidemiology and Technology
Table 1 Systematic Review (40 to 69 women)

In the past 25 years, there were 17 studies done on the overall cost effectiveness of breast cancer screening program that start from age 40 or 45 until age 69 or 74 in the world. The results are shown in Table 1. Within these 17 studies, 6 studies were performed on middle or low income countries. The remaining 11 studies were performed on high income countries.

In terms of the model, 4 studies used decision tree model; 8 studies used various Markov models; and the rest used other complex models such as the MISCAN model for breast cancer or the Wisconsin CISNET model. In terms of the unit of outcome, 7 studies used cost per life year saved; 3 studies used cost per DALY (Disability Adjusted Life Year) averted; and 7 studies used cost per QALY gained. Among the 17 studies, the cost effectiveness ranges from $3468 per QALY gained in India (36) to $146333 per QALY gained in Canada. (26) In terms of cost per life year saved, results range from $8709 per life year saved in Catalonia (34) to $36435 per life year saved in South Korea. (37) Among papers using disability adjusted life year, outcomes range from $6264 per DALY averted in Iran (28) to $8426 per DALY averted in Brazil. (29)
The threshold values for cost effectiveness in my review are based on the national GDP per capita of the country in the year when the study was conducted. This is based on the recommendation by the WHO. In its guidelines, the WHO recommends thresholds value for new health interventions in a country to be around the GDP per capita of that country. (61)

In terms of cost effectiveness, results are different between developing and developed countries. Amongst the 6 articles on developing countries, the ICERs in 2 studies are well below their respective threshold values, thus very cost effective. The ICERs in 2 other studies are roughly the same as their respective threshold values, thus borderline cost effective. However, another 2 studies found their ICERs to be higher than their respective threshold values, making screening women aged 40 to 69 using mammography not cost effective in these 2 studies. As the results are evenly mixed, it remains quite uncertain whether it is cost effective to expand national mammography programs to screen women aged 40 to 69 in developing countries.

Amongst the 11 studies on developed countries, 6 studies have their ICERs below their respective threshold values, thus having cost effective results. 1 study has its ICER very close to its threshold value, thus borderline cost effective. The remaining 4 studies have their ICERS well above their respective threshold values, thus not cost effective. The results are also a bit mixed. However, it is important to note that neither of the 2 studies on developed countries in Asia have cost effective results, while most studies on western developed countries have their ICERs below their respective threshold values. Therefore, there seems to be big differences in terms of the cost effectiveness of mammography programs between western developed countries and Asian developed countries. Since this thesis is conducted in the Norwegian setting, I will only look at articles from western countries. If considering only developed countries in the West, then 7 out of 9 studies (78%) have cost effective results.
In western developed countries, lowering the starting age of the breast cancer screening program to age 40 is not cost effective in only 2 out of 9 studies. For the rest of the studies on western developed countries (78%), national breast cancer screening programs remain cost effective after expanding the program to include women in their 40s. In previous chapters, I have shown that many studies have shown that screening women between the age of 40 and 49 probably have more benefits than harm. If the overall cost effectiveness of the mammography program remains cost effectiveness when women aged 40 to 69 are screened, then it is recommended for the government of that country to expand the national mammography program to invite more women in order to create more social welfare.

Given that Norway is a welfare state, and the fact that Norway has an extremely high threshold of cost effectiveness for new health interventions compared with other countries, it is very likely that the Norwegian breast cancer screening program will remain cost effective after expanding the mammography program to include women in their 40s.

(2) Group 2: Cost effectiveness of screening 40-49 age group:

<table>
<thead>
<tr>
<th>Author</th>
<th>Year</th>
<th>Perspective</th>
<th>Model</th>
<th>Age group</th>
<th>Interval</th>
<th>Country</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Madan et al.(37)</td>
<td>2010</td>
<td>Health care</td>
<td>Decision tree</td>
<td>47-49</td>
<td>Triennial</td>
<td>UK</td>
<td>$44692 per QALY gained</td>
</tr>
<tr>
<td>Rosenquist et al.(37)</td>
<td>1994</td>
<td>Health care</td>
<td>Markov</td>
<td>40-49</td>
<td>Annual/Biennial</td>
<td>U. S. A</td>
<td>$26200/$14000 per life years gained</td>
</tr>
</tbody>
</table>

Table 2 Systematic Review for 40-49 women

Among the 19 articles, only 2 articles talked purely about the cost effectiveness of screening women in their 40s. The results were shown in Table 2. In Madan et al.(37), the article estimates the incremental cost effectiveness of screening the 47-49 age group to be $44692 in 2010 for the UK, which is about the same as the
domestic gross product per capita for the UK in that year. Comparing with the WHO recommended threshold for ICER of around 1 times that of the domestic gross product (61), screening 47-49 age group in the NHS seems to be cost effective according to this study. If this result is to be believed, then it is cost effective for the English NHS to expand its current breast cancer screening program to invite women aged 47-49 to screening. In the other study done for women in their 40s, Rosenquist (37) estimated that the cost effectiveness of screening women aged between 40-49 in the U.S biennially would be only around $14000 per life years gained, well below the GDP per capita of the U.S in 1994. Even though the study didn’t calculate the quality-adjusted life year gains, the results were most likely to be in favor of screening the 40-49 age group in the U.S.

Based on the evidences from these two studies, it appears that even though women in their 40s are less cost effective to be screened comparing with the 50-69 age group, it is indeed still cost effective to start screening women at an age younger than 50 in western countries, and the government should consider lowering the starting age limit of the breast cancer screening program.

6.5 Discussion:

In the previous systematic review by Rashidian et al. (37) 15 years ago, the author summarized all the articles on the cost effectiveness of breast cancer screening programs from 1993 to 2003. The author’s objective was to summarize the cost effectiveness of breast cancer screening programs in countries around the world, and all studies were categorized into 3 age groups: 50-69, 40-49, 40-69. Majority of the studies were conducted on women under age 70 and above age 50, which was the most commonly used age range for national mammography program around the world. Among all the studies the author reviewed, only 2 studies calculated the cost effectiveness of screening women in their 40s, and both of these studies resulted in high ICERs.
From the review, the author concluded that screening 50-69 age group was the most cost effective range. Screening women in their 40s had less benefits and a higher chance of doing harm to the patient. As a result, the author didn’t think that it was cost effective to screening this age group.

However, as more and more countries have implemented the national breast cancer screening program for the most cost effective 50-69 age group women with success in the past 15 years, countries are increasingly looking into options to expand the program to benefit more women. Especially in Asian countries, where women’s breast cancer incidences rate peaks at women’s fifth decade due to biological and social factors (33), many studies have attempted to figure out the cost effectiveness of the screening program if women were to start being screened in their 40s. From Table 2, it was clear that mammography programs are still mostly cost effective when women in their 40s were included although the ICERs increased when women in their 40s were included.

It is also worth noting that there are other ways of calculating the threshold value of a new health intervention aside from following the recommendation from the WHO, which is often criticized for not reflecting the opportunity costs that are imposed on health care systems. To account for this, Woods estimated that the threshold value to be 1%-51% of the country’s GDP per capita for low income countries; 4%-51% of the country’s GDP per capita for low-middle income countries; 11%-51% of the country’s GDP per capita for upper middle income countries; 33%-59% of the country’s GDP per capita for high income countries; and 39%-129% of the country’s GDP per capita for extremely wealthy countries. (62)

When using Woods’ rules for calculating the threshold value, only 2 out of 6 studies done on developing countries in Table 1 will still have cost effective results, while the 2 borderline cost effective studies when using the original threshold will no longer be cost effective. Using Woods’ rule, only 3 out of 9 (30%) studies done on western developed countries in Table 1 will still have cost effective results, comparing
with 7 out of 9 (78%) studies on western developed countries having cost effective results using the original threshold. Therefore, if I use Woods’ rule for calculating the threshold values, then expanding the national mammography program to screen women aged 40 to 69 is more likely to be not cost effective than cost effective for both developed and developing countries.

However, I will refer only to the threshold value recommended by the WHO in this thesis to avoid confusion.

### 6.6 Conclusion

To conclude, studies in the systematic review have shown that the benefits-to-harm ratio for women in their 40s was less than women in the 50-69 age group. However, the benefits of screening women in their fifth decades was probably still bigger than the harm dealt. In addition, 7 out of 9 relevant studies (78%) done on western countries showed that the cost effectiveness of screening women between the ages of 40 and 69 was below the national threshold value in their respective countries. Therefore, there seems to be enough evidence for the Norwegian government to start considering the possibility of expanding the breast cancer screening program to include women aged 40-49.

### 7. Modelling

#### 7.1 Model Structure

A 6-state Markov model was developed to calculate the cost effectiveness of expanding the national mammography program in Norway to include women aged between 40 and 49. (Figure 2) The model takes a societal perspective calculating the burden of the program on the society as a whole. The discount rate is assumed to be 4% for both cost and health outcomes, in line with the Norwegian guidelines. (64) In this model, the screening interval for all age groups is assumed to be two years as
studies have shown that biennial screening has the highest cost effectiveness. (34) In addition, the procedure of screening as well as the subsequent treatment for breast cancer after diagnosis for the 40-49 age group are assumed to be the same as the 50-69 age group. The model simulates an average Norwegian women in perfect health starting at the age of 40. The model tracks her probability of getting breast cancer as well as her estimated survival rate until the age of 100. Each cycle length is one year.

(Figure 2)

The model includes three strategies: screening women aged 40 to 69; screening women aged 50 to 69; and no screening program in place. I also made three comparisons based on the strategies. Firstly, the strategy of providing mammography screening to women aged between 40 and 69 is compared with the current mammography program, which screens women between the ages of 50 and 69. Secondly, the strategy of screening women aged between 40 and 69 for breast cancer is compared with the strategy where no national mammography program exists. Lastly, the current mammography program (50-69) is compared with the strategy where no national mammography program exists.

The Markov model has six health states: Healthy, Stage 1 breast cancer, Stage 2 breast cancer, Stage 3 breast cancer, Stage 4 breast cancer, and Death. The stage
classification follows the guidelines of the Cancer registry of Norway where “stage I represents localized breast cancer; stage II represents regional breast cancer; stage III represents breast cancer fixed to either skin or chest wall; and stage IV represents breast cancer with distant metastases.” (49)

The hypothetical woman who is going to be screened is assumed to start off from the healthy state at the age of 40. From the healthy state, she can die from other causes aside from breast cancer, and the probability is captured by the natural rate of death of the Norwegian population by age. The data is obtained from the Statistics Norway (49). From the healthy state, she can also go to one of the four disease states. The distribution of stages at diagnosis is different for the woman in a year where she is screened, and in a year where she is not screened. (Table 3) If the woman is not screened this year, the stage distribution at diagnosis will be 0.316/0.556/0.099/0.029 for stage 1/2/3/4 breast cancer obtained from Wong et al (35). If the woman is screened this year, the stage distribution at diagnosis will be 0.521/0.382/0.057/0.04 for stage 1/2/3/4. (35) The data was collected from a randomized trial in Hong Kong, and the author assumed the rate to be the same for both the U.S and Hong Kong. Due to a lack of European data on this, I will assume that the stage distribution is the same between different countries.

Then, the probability of the woman going from the healthy state to each breast cancer stage equals the stage distribution at diagnosis times the breast cancer incidence rate in Norway for her age. I obtained this data from the Cancer in Norway website, (63) and the rate is grouped by five year age groups. For this model, I will assume that the breast cancer incidence rate is the same for every age within each five-year age group. For example, the breast cancer incidence rate is all 106.1 per 1000 women for women aged 40, 41,42,43,44 and 45. To get the rate for each individual, I divided the numbers from the website by 100000.

Furthermore, one can go from stage 1 breast cancer to stage 4; stage 2 breast cancer to stage 4; and stage 3 breast cancer to stage 4. (Table 3) These three transition probabilities are obtained from Wong et al. (35) I assume that stage 1, 2, 3
can only transit to stage 4, which means that no transitions from localized (stage 1) to regional (stage 2) or distant (stage 3) or from regional (stage 2) to distant (stage 3) breast cancer were included in the model. These transitions do exist in reality, but the effect of these transitions after diagnosis can be largely captured by the difference in mortality rate and costs between breast cancer stages.

Moreover, patients in each disease stage health state may die, and the mortality rate of breast cancer by stages is obtained from Groot et al. The data is from North America, but the rate is assumed to be the same across continents in Groot’s article. Therefore, I will assume that the morality rate of breast cancer by stages is the same between Norway and North America.

Table 3 Key input parameters

Early diagnosis leads to improved prognosis for breast cancer patients, and the main function of breast cancer screening is to help detect cancer early. As a result, the effect of mammography screening is represented in the model by the shifting of the stage distribution of breast cancer at diagnosis of cancer between the screened years and the unscreened years of the woman. As stage 1 and stage 2 breast cancer has a significant lower mortality rate than stage 3 or 4 breast cancer, the resulting difference in the expected remaining life year between the control group (50-69 women) and the intervention group (40-69 women) will be the effect of expanding the screening program.

7.2 Method
Threshold value for cost effectiveness:

The outcomes of the model will be compared with the threshold value in Norway. The threshold value for incremental cost effectiveness ratio can be seen as the maximum amount of money a country is willing to pay to save one additional outcome of interest. The threshold value varies across countries as every country has different levels of resources. If the incremental cost effectiveness ratio of a new health intervention is below the national threshold limit, the national government will generally approve the introduction of the new intervention into the national healthcare system if there are enough resources/budget to make it happen. On the other hand, if the incremental cost effectiveness ratio of an intervention is above the national threshold value, then the national government is likely to decline the introduction of this new health intervention in favor of other interventions that have a lower incremental cost effectiveness ratio. Of course, this will lead to some health interventions that are beneficial to many citizens being left out of the healthcare system, but this is the tradeoff that every country needs to make in this resource constraint world.

Many countries in the world, most notably the United Kingdom, have a specific threshold value for cost effectiveness of health interventions, and this threshold value is often made aware of by the general public. This is called a hard threshold, and it leaves little room for negotiation. However, there are also many countries that use a soft threshold, including Norway. Countries using a soft threshold don’t have a clear threshold value for incremental cost effectiveness. The threshold value is usually not given explicitly by the government. The authorities have a rough range of the threshold in mind, but the cutoff is not so black and white. The acceptance of new health interventions is on a case-to-case basis if the incremental cost effectiveness ratio of this intervention is close to the threshold range.

In many countries, the threshold value is close to the GDP per capita of the country. However, in a commentary written by Torbjørn Wisloff, the author
estimated that the willingness to pay (threshold) was around 700000 NOK or 73157 Euros in practice for Norway in 2017 (54), which was higher than the GDP per capita for Norway for that year (549887 NOK). This estimate is based on the article by Woods et al. (62) According to Woods’ paper, Norway’s threshold should be between 39%-129% of the GDP per capita as Norway belongs to the wealthiest category of countries in her article as mentioned in Chapter 6 of my thesis. This means that the maximum threshold value for Norway should be around 700000 NOK per QALY gained.

There are also other ways of calculating the threshold value of a country. It also has been suggested by the WHO guidelines that the threshold value should be between 1 and 3 times the national GDP per capita, which stood at 1926366 NOK in 2016 as used by P.A Van Lujit in their paper. (55) However, almost no one uses this threshold in Norway, and I will only use the 700000 NOK per QALY gained as the threshold value for this model.

(2)What is ICER?

The results of the model is represented using the ICER. The incremental cost effectiveness ratio, or the ICER is a commonly used statistics in cost-effectiveness/cost-utility analysis. It “represents the average incremental cost associated with 1 additional unit of the measure of effect.” (58) The effect can be either in life years gained or quality adjusted life years gained. The ICER is calculated by dividing the difference in cost between the two interventions (the cost of the new intervention minus the cost of the control group intervention) by the difference in effect between the two interventions (the effect of the new intervention minus the effect of the control group intervention). The resulting ICER is then compared with the threshold value of the country. The threshold value represents the country’s willingness to pay for new interventions per unit of increased effect. If the ICER is below the threshold value, then the new intervention is below the willingness-to-pay level, which means that the new intervention is cost effective. If the ICER is above the threshold value,
then it is too costly for the country to implement the new intervention given its current resources.

7.3 Data Acquisition:

(1) Health related quality of life

Different from quality of life (QOL) which shows the quality of a person’s daily life, health related quality of life (HRQoL) is defined as “an assessment of how the individual’s well-being may be affected over time by a disease, disability, or disorder.”(47) A patient in perfect health will assume to have a HRQoL of 1, and a dead person will have a HRQoL of 0. It is also possible to have a negative HRQoL when a person’s suffering from the disease makes the patient feels worse than death. In healthcare research, health related quality of life is often thought of as the utility or preference weight for a health status, and is widely used in cost utility analysis of economic evaluation.

There are many ways to measure the health related quality of life of a disease, mostly by the means of conducting surveys. One of the simplest and most frequently used form of survey is known as EQ-5D, and researchers have reported that the EQ-5D form have good validity and reliability. “The EQ-5D questionnaire is made up for two components: health state description and evaluation. In description part, health status is measured in terms of five dimensions (5D): mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. In evaluation part, the respondents evaluate their overall health status using the visual analogue scale.” (37)

EQ-5D form also has 2 subtypes: EQ-5D-3L and EQ-5D-5L. The difference is that patients can choose from 3 health levels in each dimension in EQ-5D-3L while patients can choose from 5 health levels in each dimension in EQ-5D-5L. Both subtypes are widely used in economic analysis, and the decision to use either one depends on the situation and availability.
(2) HRQoL Data

The data for health related quality of life is given in Wong et al (35). The health related quality of life for stage 1/2/3/4 is estimated to be 0.9/0.8/0.7/0.3 in the article. The data was acquired in Hong Kong. However, in the paper, the author assumed that the quality of life for each stages of breast cancer is the same between Hong Kong and U.S.A. Since I cannot find any quality of life data for Norway, I will use this data in my model assuming that the real Norwegian HRQoL for breast cancer patient is the same as it is in Hong Kong.

(3) Cost Data

The cost data is collected from two papers published by the department of health economics, evaluation and management at the University of Oslo. One paper calculated the cost of the national mammography program, (52) while the other paper calculated the average cost of treating a breast cancer patient in Norway. (53)

Mammography in Norway has two rounds. All women attending screening will go through first round of mammography. When a tumor suspect finding is discovered in the first round of mammography on a patient, she is then recalled for a repeat examination. In the repeat examination round, patients “may undergo a clinical examination (palpation) and additional clinical mammography (with new images) and/or an ultrasound examination. Also, approximately 50% of the women have a biopsy taken.” (55) In Norway, this applies to 3.5% of the screened women. (48) Therefore, for women participating in the program, 100% will be screened for the first time. 3.5% will be screened a second time.

<table>
<thead>
<tr>
<th>Stage</th>
<th>Total Cost</th>
<th>95% Confidence Interval</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>lower Bound</td>
</tr>
<tr>
<td>Stage 1</td>
<td>23570</td>
<td>22470</td>
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<tr>
<td>Stage 2</td>
<td>46550</td>
<td>44610</td>
</tr>
<tr>
<td>Stage 3</td>
<td>55230</td>
<td>47950</td>
</tr>
<tr>
<td>Stage 4</td>
<td>60430</td>
<td>51250</td>
</tr>
</tbody>
</table>
Table 4 Costs of breast cancer treatment in Norway in Euros

The cost of mammography program includes both direct and indirect cost. 64% of the total costs of one screening round were health care costs, and 36% of the total costs were travel costs and productivity losses. In total, Moger estimated that the cost of first round of mammography screening per patient to be 1262 NOK, and the cost of second round of repeat examination per patient to be 3655 NOK. (53) In the second paper, Moger estimated the per patient treatment cost for 10 years after being diagnosed of cancer to be 31940 Euros on average. In addition, Moger calculated the 10 year treatment cost for each breast cancer stages. Unsurprisingly, the cost increases by stages, with stage 4 breast cancer having an average 10 year treatment cost of 60430 Euros. (53)

The treatment cost is the highest for a patient in her first 12 months of diagnosis. Then, the treatment enters a continuous phase, during which the cost is relatively cheap at around 300 Euros per month. However, before the patient dies from breast cancer, the end-of-life treatment cost rises again. Adding them up, Moger then calculated the 10 year treatment cost of an average breast cancer patient in Norway. Due to the lack of data on how long the patient on average will survive after diagnosis, I assume that the 10 year treatment cost given in Moger’s paper is the lifetime treatment cost for a patient diagnosed with breast cancer in Norway.

The only difference between the real cost and the 10 year cost is in the length of the continuous cost. Since the continuous cost is not so high compared with the initial cost and the end-of-life cost, the discrepancy between the cost input in my model and the cost in the real world will not be very big.

7.4 Results:

(1)Screening the 50-69 age group:

Firstly, I evaluate the cost and effect of the current mammography program in Norway, which screens women between the ages of 50 and 69 biennially. In this
strategy, for the 40-49 group as well as the over 70 age group, there is no screening. For the 50-69 age group, women are invited to be screened. The effect of the screening strategy is captured by the shifting of the stage distributions at diagnosis for the screened age group comparing with the unscreened age group.

In terms of cost, there will be no cost for mammography when the woman is between the ages of 40 and 49, and when the women is over 70 years old. When the woman is between the ages of 50-69, she will incur the cost of first round of mammography. In addition, 3.5% of the time the patient will incur the cost of the second round of repeat screening. In addition, when the woman is in the four disease states (Stage1, Stage 2, Stage 3, and Stage 4), she will incur the average treatment cost for breast cancer per patient depending on stages at diagnosis in Norway obtained from Moger et al. (53)

Consequently, in the current Norwegian mammography program which screens Norwegian women between the ages of 50 and 69 biennially for breast cancer, the average estimated cumulative cost on breast cancer for a woman starting from the age of 40 until the age of 100 is 60283 Euros before discounting, and 23246 Euros after discounting. (Figure 3) The average expected remaining life years for a Norwegian woman aged 40 is estimated to be 44.62 before discounting, and 24.02 after discounting. After adjusting for health related quality of life, the expected QALY remaining for a Norwegian woman aged 40 is estimated to be 44.28 before discounting, and 23.89 after discounting. (Figure 3)

(2)Screening the 40-69 age group:

Then, I test the cost and effect of expanding the current national mammography program in Norway to offer biennial screening to women aged 40 to 69. In this strategy, women aged 40 to 69 will be screened, while women aged 70 will remain unscreened. The effect of the screening strategy is also captured by the shifting of the stage distributions at diagnosis for the screened age group comparing with the unscreened age group.
In terms of cost, a woman will incur the cost of the first round of mammography every two years from age 40 to 69. Again, 3.5% of the time the patient will need to be recalled for a repeat screening. When the woman is over the age of 70, she will incur no mammography cost. In addition, when the woman is in the four disease states (Stage 1, Stage 2, Stage 3, and Stage 4), she will incur the average treatment cost for breast cancer per patient depending on stages at diagnosis in Norway obtained from Moger et al. (37)

Consequently, for the strategy that screens Norwegian women between the ages of 40-69 biennially for breast cancer, the average estimated cumulative cost on breast cancer for a woman starting from the age of 40 until the age of 100 is 61481 Euros before discounting, and 23904 Euros after discounting. (Figure 3) The average expected remaining life years for a Norwegian woman aged 40 is estimated to be 44.65 before discounting, and 24.03 after discounting. After adjusting for health related quality of life, the expected QALY remaining for a Norwegian woman aged 40 is estimated to be 44.31 before discounting, and 23.90 after discounting. (Figure 3)

(3) No screening program:

Lastly, I test a hypothetical situation where there is no national mammography program in place in Norway. In this strategy, no women will be invited to breast cancer screening in Norway. As there is no breast cancer screening, there is no cost for the mammography program. All the cost comes from the expected treatment cost for breast cancer patient.

Consequently, for the strategy where there is no national screening program, the average estimated cumulative cost on breast cancer for a woman starting from the age of 40 until the age of 100 is 57457 Euros before discounting, and 22259 Euros after discounting. (Figure 3) The average expected remaining life years for a Norwegian woman aged 40 is estimated to be 44.51 before discounting, and 23.98 after discounting. After adjusting for health relate quality of life, the expected QALY
remaining for a Norwegian woman aged 40 is estimated to be 44.17 before discounting, and 23.85 after discounting. (Figure 3)

(4) Deterministic incremental cost effectiveness ratio

Figure 3 ICERs of three screening strategies comparing with each other

Figure 4 Cost effectiveness of the three strategies

From Figure 4, it is clear that screening 50 to 69 women is the most cost effective strategy. Screening 40 to 69 women is less cost effective than screening only 50 to 69 women. However, it is still cost effective to screen women aged 40 to 69 in Norway biennially for breast cancer since the slope of the “40-69 vs no screening” line is still flatter than the slope of the WTP curve.

In terms of numbers, it is clear that the incremental cost effectiveness ratios of the all three strategies are below the threshold of 73157 Euros per QALY. (Figure 3)
When the current mammography program is compared with the hypothetical situation where there is no screening, the ICER is 27186 Euro per QALY gained. (Figure 3) The results show that the current mammography program is highly cost effective comparing with the situation if there is no screening program.

Furthermore, when the hypothetical program where women aged between 40 and 69 are screened is compared with the current national mammography program (50-69), the ICER is 51313 Euro per QALY. (Figure 3) The results show that it is in fact cost effective to expand the current biennial national mammography program in Norway to screen women between the age of 40 and 69. The expansion will further increase the benefits of the screening program at an acceptable cost in Norway.

7.5 Probabilistic sensitivity analysis

I conducted a probabilistic sensitivity analysis on the input parameters in Table 3 by running a Monte Carlo simulation 1000 times, and the results are shown in Table 5. The resulting cost effectiveness acceptability curve, cost effectiveness acceptability frontier as well as cost effectiveness plane are shown in Figure 5, Figure 6, and Figure 7 respectively.

From the cost effectiveness plane (Figure 5), each dot represents the ICER of one iteration of the Monte Carlo simulation. With 1000 iterations of the Monte Carlo simulation, there are a total of 1000 dots in the plane. The majority of the ICERS from the Monte Carlo simulation lies below the threshold value of Norway, which is represented as the line in Figure 5. This means that screening 40-69 women biennially for breast cancer is very likely to be cost effective comparing with screening women aged 50 to 69 biennially for breast cancer after accounting for uncertainties surrounding the parameters. The results give a robust confirmation that it is indeed cost effective to expand the national mammography program to invite women aged 40 to 69 to screening biennially.
Table 5 PSA results

<table>
<thead>
<tr>
<th></th>
<th>50-69</th>
<th>40-69</th>
<th>50-69</th>
<th>40-69</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean</td>
<td>23907</td>
<td>24179</td>
<td>23.90</td>
<td>23.91</td>
</tr>
<tr>
<td>Min</td>
<td>14941</td>
<td>20020</td>
<td>23.85</td>
<td>23.65</td>
</tr>
<tr>
<td>Max</td>
<td>27773</td>
<td>28160</td>
<td>24.05</td>
<td>24.07</td>
</tr>
<tr>
<td>Std dev</td>
<td>1203</td>
<td>1285</td>
<td>5.96</td>
<td>6.96</td>
</tr>
<tr>
<td>2.5th percentile</td>
<td>23100</td>
<td>21765</td>
<td>23.78</td>
<td>23.78</td>
</tr>
<tr>
<td>97.5th percentile</td>
<td>35411</td>
<td>26615</td>
<td>24.00</td>
<td>24.02</td>
</tr>
</tbody>
</table>

Figure 5 Cost effectiveness plane (screening 40-69 versus screening 59-69)

Figure 6 CEAC Curve
In addition to the cost effectiveness plane, one can also report the results of the Monte Carlo Simulation using the cost effectiveness acceptability curve (CEAC) and the cost effectiveness acceptability frontier (CEAF). CEAC represents the probability that the new intervention is cost effective according to increasing threshold values. From the CEAC figure (Figure 6), screening only 50 to 69 women is more likely to be cost effective comparing with screening women from 40 to 69 if the threshold is below 55000 Euros per QALY gained. If the threshold is above 55000 Euros per QALY gained, screening women 40 to 69 becomes more likely to be cost effective comparing with screening women from 50 to 69. Since the threshold value for Norway is around 73000 Euro per QALY gained, screening women aged between 40 and 69 biennially will be cost effective when comparing with the current mammography program that screens women aged between 50 and 69.

Similarly, the CEAF curve represents the alternative with the highest probability of being cost effective according to the threshold values. From CEAF figure(Figure 7), it is clear that the new intervention(screening 40 to 69 biennially) will start to become more likely to be cost effective comparing with the current program when the national threshold value is above 55000 Euros per QALY gained. This further shows that it is cost effective to screen women aged 40 to 69 biennially in Norway given that the threshold value for Norway is above 55000 Euro per QALYs.

![Figure 7 CEAF curve](image)
7.6 Scenario Analysis (data on stage distribution from another source)

During literature reviews, I came across two sets of data on the shifting of stage distribution of breast cancer at diagnosis caused by screening. I used the set of data from Wong et al in the original model. (35) However, the data from Groot et al (51, Table 6) has quite different probabilities comparing with data from Wong et al in Table 2. Therefore, it is important to test the model again by inputting data on stage distribution at diagnosis stages from Groot’s paper instead of Wong’s paper, and the results are shown in Figure 7. In Table 6, the first column of data is for North America, while the second column is for Asia. Since the author assumed that North America and Asia have the same probability, it is also logical to assume that the probability is applicable to Europe.

Table 6 alternative data from Groot et al (51)

<table>
<thead>
<tr>
<th>Stage distribution of incident cases in absence of an extensive program, 2000–2010 and the whole population thereafter (%)</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Stage I</td>
<td>9.40</td>
</tr>
<tr>
<td>Stage II</td>
<td>14.20</td>
</tr>
<tr>
<td>Stage III</td>
<td>56.00</td>
</tr>
<tr>
<td>Stage IV</td>
<td>18.40</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Stage distribution of incident cases in presence of an extensive program; 2000–2010 (%)</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Stage I</td>
<td>49.00</td>
</tr>
<tr>
<td>Stage II</td>
<td>37.40</td>
</tr>
<tr>
<td>Stage III</td>
<td>8.60</td>
</tr>
<tr>
<td>Stage IV</td>
<td>5.00</td>
</tr>
</tbody>
</table>

Figure 7 ICERs when using alternative data from Groot et al.

From the results in Figure 7, it is clear that the ICERs are significantly lower when using the alternative data from Groot et al. The ICER is only 31874 Euro per QALY using alternative data for the first comparison where screening 40-69 is compared with screening 50-69, while it is 51313 Euro per QALY in the original model. The
model using alternative data shows that expanding the screening program in include women 40-49 is highly cost effective.

An increase in the effect of screening contributes to the lower ICERs and higher cost effectiveness. This is plausible as the probability of having stage 1 and 2 cancer if the woman is screened this year is much higher in the alternative data. Since early detection leads to better prognosis, the effect of screening estimated using alternative data set will have higher effect, thus higher cost effectiveness.

Regardless of which data set used, the model shows consistent conclusion that it is indeed cost effective for the Norwegian government to expand the breast cancer screening program to include women aged between 40 and 69.

7.7 Discussion

(1) Validity of the model:

Since the national mammography program was introduced in Norway, a total of 3 studies have been done to estimate the cost effectiveness of the program before my study. All of these studies focused on the current program that screened women aged 50 to 69. In the first paper, Norum estimated the cost effectiveness to be 8561 Euros in 1999. After adjusting for annual inflation of 2 % (56), the cost effectiveness is 12227 Euro per QALY. It is difficult to compare our results as Norum estimated the effect of screening using an assumed 30% mortality reduction accordant with the aim of the Norwegian mammography project, while I estimated the effect of screening using the shifting of stage distributions as a result of screening.

In another paper, Wong estimated the cost effectiveness to be merely 3024 Euro per life year gained. (57) This is due to the fact that the author didn’t include treatment cost, and the discount rate was 5%. I believe that this result is not very reliable, as most studies from other European countries estimated the cost effectiveness of screening 50-69 women to be over 10000 Euros per life years gained.
Given that Norway has a higher labor cost than most countries, one should feel skeptical about the extremely high cost effectiveness in this article.

Lastly, there was a paper written by Van Lujit et al (55) on the cost effectiveness of the current mammography program in Norway in 2017, the author estimated the ICER to be 112162 NOK per QALY gained (11737 Euro per QALY gained in 2018 exchange rate). His result has a higher estimate of the cost effectiveness of the current mammography program comparing to the result from my study (27186 Euro per QALY gained). However, our results are not comparable as our paper use very different models. I used a Markov model, while Van Lujit used the complex MISCON model for breast cancer developed by the Erasmus University of Rotterdam.

Despite differences in method and results, all the studies including mine have shown that the current breast cancer screening program in Norway is highly cost effective comparing with when there is no screening program. In addition, my study shows that it is cost effective to invite women aged between 40 and 69 to biennial screening. As my model has the highest incremental cost effectiveness ratio among the 4 studies on the cost effectiveness of 50-69 age group, all the other studies would have come to the same conclusion with an even lower cost-effectiveness ratio if they conducted evaluations on women aged 40-69.

In addition to the consistency of results across relevant studies, my model also displays external validity through the calculation of estimated life years gained. According to Statistics Norway website, the estimated remaining life year for a 40-year-old Norwegian woman is 44.9. My calculation (44.62) is quite close to this number, which shows that my model has convincing external validity.

(2) Limitations:

In this model, I have to make some assumptions due to the lack of data from literature reviews that fits in the Norwegian setting. Firstly, I assume that it is not possible to reverse the stages of breast cancer or become healthy again after being
diagnosed of cancer. For example, it is not possible to go from stage 3 back to stage 2 breast cancer or stage 1 breast cancer in my model. In reality, it is possible to be fully cured of breast cancer, especially in the early stages. Since screening helps detect cancer early, my model will underestimate the effect of screening because of this assumption.

In addition, I assume that the natural rate of death for the Norwegian population by age will not change even if the breast cancer screening program is extended to include 40 to 49 women. In reality, the expansion of the screening program will reduce the natural rate of mortality by a little, which will cause my model to deviate from reality a bit.

More importantly, I assumed 100% participation in the repeat examination after the first examination. The participation rate in the first mammography round doesn’t matter in the model as the model simulates the cost effectiveness of an average woman being screened from 40 to 69 comparing with being screened from 50 to 69. The participation rate doesn’t have an effect on the outcome of the model as long as we assume that participation rate has the same effect on both cost and QALYs. However, the situation becomes more complicated when a patient doesn’t show up for a repeat examination. Say a patient participates in the first round of mammography screening, and is recalled for a repeat examination. If she doesn’t show up for the second examination, then mammography program will have no effect on her. Nevertheless, she already used a bit of the resources in the first round of screening. This kind of non-compliance do happen in reality, and it will reduce the effectiveness of the screening program.

Furthermore, I assumed that stage 0 breast cancer (DCIS) is harmless to health, and will not have an effect on a woman’s life if it is unnoticed. This is due to the fact stage 0 breast cancer is non-invasive, and the five year relative survival rate of stage 0 breast cancer is close to 100% if properly treated.(50) However, in reality, having DCIS will increase a woman’s chance of getting breast cancer in the future if it is not
detected early. (35) Screening will help detect DCIS, and early detection will reduce the risk of future invasive breast cancer. Although not health-damaging itself, DCIS is a risk factor of invasive breast cancer. Since my model did not include a stage 0 breast cancer health state due to the lack of data, my model will underestimate the effect of screening. The real ICER should be even lower than the one calculated by the model, making screening 40-49 age group even more cost effective.

Moreover, the cost data I obtained from Moger paper is the average ten year treatment cost per patient in Norway. This cost includes initial cost, continuous cost, as well as end-of-life cost for a patient. However, not all patients will finish their treatment after 10 years. Some patient will die before reaching 10 years. Some patient will still be alive after 10 years, and will continue to require treatment. I assume that the 10 year treatment cost is the overall cost per patient in their lifetime due to lack of alternative data. Therefore, my model may deviate a bit from reality.

In addition, my data for QALY as well as my data for the mortality of breast cancer by stages was not obtained from Norwegian sources. QALY data was obtained from a study in Hong Kong, while the mortality rate by stages was obtained from a study in the U.S. However, in both article, the author used the same QALY and mortality rate for different countries assuming that these rate don’t change across countries. As a result, I will assume that the mortality rate as well as QALY data in their articles are applicable to Norway as well. In reality however, different countries will have slightly different mortality rates as well as QALYs due to difference in the quality of national healthcare system, causing my model to deviate from reality.

Lastly, there are many other ways of modelling the effect of screening. In my model, the effect of screening is captured by the shifting of stage distributions at diagnosis when a woman is screened comparing with when a woman is not screened. But, other studies have used mortality reduction associated with screening to capture the effect of screening. (55) The effect of screening can also be captured using relative effect or relative risk of screening. Due to time and data constraint, I
can only produce one model in my thesis. In a perfect world, it will be optimal to develop one model for each ways of capturing the effect of screening mentioned above, and then to compare the results to reach a more robust conclusion.

(3) Other ways of improving the mammography program

In this thesis, I look at the effect of including women aged 40 to 49 to screening instead of women aged 45 to 49 as recommended by the European Commission. This is because in biennial screening, including women aged 45 to 49 only means 2 extra screening rounds per women, and the effect may be too small. By evaluating the effect of including the 40 to 49 women, there will be 5 extra screening rounds per women, and the effect will be more apparent. Since the results of both the systematic review and the model show that including women aged 40 to 49 is cost effective in Norway, including women aged 45 to 49 to the screening program is also cost effective in Norway.

Expanding the mammography program in Norway to include women aged 40 to 49 is only one of the ways to increase the benefit and cost effectiveness of mammography program. What about increasing the upper age limit of mammography screening to 74 years old? In Gemma et al, authors estimated the impact of expanding the Australian breast cancer screening program to include 70-74 age group. They found that “when compared with stopping at age 69, screening 1,000 women to age 74 was likely to avert one more breast cancer death, with an additional 78 women receiving a false positive result and another 28 women diagnosed with breast cancer, of whom eight would be over-diagnosed and over-treated. The extra 5 years of screening resulted in approximately 7 more over-diagnosed cancers to avert one more breast cancer death. Thus extending screening mammography in Australia to older women resulted in a less favorable harm to benefit ratio than stopping at age 69.”(1) The harm-to-benefit ratio seems less favorable for the 70-74 years old comparing with either the 50-69 age group or the 40-49 age group. However, it may also be worth investigating whether screening women aged 70 to 74 is cost effective in the
Norwegian setting.

Moreover, it may be possible to improve the cost effectiveness of the mammography program through patient heterogeneity. In the era of personalized care and big data, it is becoming increasingly possible to track a patient’s lifestyle, family history, pregnancy history, and even breastfeeding history. Through these data, the government can know who is at a greater risk of developing breast cancer, and who is not. As a result, instead of the current one-size-fits-all age-based invitation criteria for screening, the government could potentially come up with a stratified invitation system of mammography screening that maximizes the potential benefits of the screening program.

Furthermore, it may also be worth investigating whether mammography is the best breast cancer screening method for Norway. “Study to date has focused on individual screening interventions, and interactions among interventions are largely ignored.”(38) Combining different screening modalities can potentially lead to a higher cost effectiveness of the breast cancer screening program. Alternative methods includes CBE (doctors feeling the breast by hand), ultrasound, and so on. In a study done in China, the most cost effective screening modality is concluded to be a biennial CBE followed by ultrasound and mammography after comparing various screening modalities. (16) Of course, this result is not applicable to other nations due to difference in labor cost in every country. However, this study shows that it is worth studying whether it is more beneficial for Norway to use a combination of different screening methodologies instead of simply the mammography.

8. Conclusion

In the past 20 years, many European countries have implemented national breast cancer screening programs. Currently, most European programs screen women between the age of 50 and 69 as women in this age group have the highest incidence rate of breast cancer, and thus having the highest benefits from screening.
Many studies have shown that the program that screens women between the age of 50 and 69 is cost effective in most developed countries as well as many middle income countries.

With success in screening women aged 50 to 69, countries are considering expanding the program to invite more women. Although not as much as women between 50 and 69 years old, studies have also shown that women aged between 40 and 49 can also benefit from breast cancer screening programs. Even though women in the 40 to 49 age group have a lower incidence rate and a higher chance of over-diagnosis, the benefits are still likely to outweigh the harms caused by mammography.

Prior to my study, there has been attempts to estimate the cost effectiveness of screening women aged 40 to 69 for breast cancer. My systematic review shows that the overall mammography program remains cost effective in most studies (78%) done on western developed countries after expanding the national program to include women aged 40 to 69. Combined with the assumption that screening 40-49 women have more benefits than harm, I conclude that screening 40 to 69 age group is highly likely to be cost effective for Norway.

After the systematic review, I also conducted a Markov model to calculate the cost effectiveness of including women aged 40 to 49 into the Norwegian mammography program. Both the deterministic results as well as the subsequent probabilistic sensitivity analysis confirm that it is in fact cost effective to screen Norwegian women aged between 40 and 69 for breast cancer every two year comparing with the current mammography program. The ICER is 51313 Euros per QALY gained if I use the data on stage distribution at diagnosis from Wong et al. The ICER reduces to 31874 Euro per QALY if I use the data from Groot et al. In both cases, the ICER is below the threshold value, thus cost effective.

To sum up, expanding the Norwegian breast cancer screening program to invite averaged risked women aged between 40 and 69 for biennial mammography
screening appears to be cost effective in Norway. Given the high attention and increasing prevalence of breast cancer in Norway, it is highly recommended for the Norwegian government to start looking into the possibility of expanding the national breast cancer screening program.

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