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ROUTINE SCREENING RECOMMENDATIONS FOR WOMEN

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Abstract:

Introduction: *Breast cancer incidence in the US is known to increase dramatically at the age of forty and elevates steadily with higher age since then. In the year 2015, there were about forty-eight years,160 females aged between forty years to forty-nine years who were diagnosed with breast cancer in the US, that is responsible for about seventeen percent or one in six, of all breast cancer diagnoses. in addition, an estimated forty percent of the years of life that were lost due to breast cancer can be attributed to females diagnosed while in their forties. therefore, breast cancer burden among females aged forty to forty-nine is very important. In this review, we will discuss routine screening in women.*

Methodology: *We conducted this review using a comprehensive search of MEDLINE, PubMed, and EMBASE, January 1985, through February 2017. The following search terms were used: Routine screening, breast cancer, women, prevention, preventive medicine, family medicine women health*

Conclusions: *There is a large body of evidence demonstrating a thirty percent to fifty percent mortality benefit of screening mammography for females aged between forty years and forty-nine years. The magnitude of the mortality benefit is equal to that for females over fifty years. Because of more rapid cancer growth rates in younger females and shorter average lead-times, annual screening has been shown to be more effective than biennial screening. Critics of mammography have over-emphasized the potential harms of screening relative to the life-saving benefits. Research has shown that a vast majority of females are highly tolerant of false-positive results, which in most instances merely consist of additional imaging. The best available evidence indicates that fewer than ten percent of breast cancers are over-diagnosed. If implemented, the recent USPSTF breast cancer screening guidelines, which recommend against routine screening of females in their forties, can result in thousands of preventable breast cancer deaths per year.*

Key words: *Routine screening, breast cancer, women, prevention.*

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INTRODUCTION:

Breast cancer incidence in the US is known to increase dramatically at the age of forty and elevates steadily with higher age since then. According to data between the years 2009 and 2013 that was obtained from the Surveillance, Epidemiology, and End Results database of the US National Institutes of Health, the annual incidence increases from about 0.3 to 0.6 per 1000 females between ages of 30 years to 39 years to 1.2 to 1.9 per 1000 between the ages of forty years and forty-nine years, consequently raising to 2.2 to 2.6 for females aged fifty years to 59 and 3.4 to 4.2 for females aged 60 years to 69 years. [1] In the year 2015, there were about forty-eight years,160 females aged between forty years to forty-nine years who were diagnosed with breast cancer in the US, that is responsible for about seventeen percent or one in six, of all breast cancer diagnoses. [2] in addition, an estimated forty percent of the years of life that were lost due to breast cancer can be attributed to females diagnosed while in their forties. [3] therefore, breast cancer burden among females aged forty to forty-nine is very important. in this review, we will discuss the most recent evidence regarding Breast cancer routine screening in females.

METHODOLOGY:

• Data Sources and Search terms

We conducted this review using a comprehensive search of MEDLINE, PubMed, and EMBASE, January 1985, through February 2017. The following search terms were used: Routine screening, breast cancer, women, prevention, preventive medicine, family medicine women health

• Data Extraction

Two reviewers have independently reviewed the studies, abstracted data, and disagreements were resolved by consensus. Studies were evaluated for quality and a review protocol was followed throughout.

The study was approved by the ethical board of King Abdulaziz University Hospital

Efficacy and effectiveness of screening mammography in females aged forty to forty-nine years

Multiple research studies are present to evaluate the effects of a screening. The most rigorous and informative studies, randomized trials (RCTs) and observational studies, need specific attention. The underlying premise of screening is that achieving early detection of the disease followed with treatment could stop the natural progression of a pathology and prevent the occurrence of death. Early diagnosis, however, does not always achieve a benefit. In fact, detecting a cancer earlier might not change its long-term prognosis. A screened individual might look to have a longer survival when compared to an unscreened individual, but this might be a reflection of the earlier diagnosis with the absence of a corresponding delay in the actual time of death. Such an example is usually called the 'lead-time bias'. additionally, screening might preferentially find some indolent pathologies, which is usually called 'length-biased sampling'.

Due to the presence of these possible biases, the single way to prove impact of a screening test is to assess mortality as an endpoint in the setting of an RCT. [4] population-based RCTs of screening with mammography alone or in combination with clinical examination were done in the US and Europe between the 1960s and the 1980s, with including females aged between forty years and forty-nine years years at time of trial entry. Additionally, a single non–population-based RCT, known as the Canadian National Breast Screening Study-1, where females volunteered to participate, was done in the 1980s. Meta-analyses at ten-year to eighteen-year follow-up have detected statistically significant mortality decreases for females aged between forty years to forty-nine years years at invitation of twenty-four percent in the seven population-based RCTs, twenty-nine percent in the five Swedish RCTs, and fifteen percent to eighteen percent in all eight RCTs. At subsequent twelve-year to thirteen-year follow-up of two Swedish trials, statistically significant mortality decreases of forty-five percent and thirty-six percent, respectively, were detected in females aged between 39 years and forty-nine years years at randomization in the Gothenburg breast screening trial and for females aged between 45 years to forty-nine years years at entry in the Malmo¨ mammographic screening program trial. [5]

Randomized Controlled Trial Controversy

Controversy initially started over screening of females in their forties when a retrospective analysis was performed for the first RCT study, the Health Insurance Plan (HIP) trial of New York, which was done in the 1960s. Using age fifty as a surrogate for menopause, the investigators assessed mortality benefit separately for females aged between forty years and forty-nine years and between fifty years and 64 years. primary results at four-year follow up (which is considered to be a very short follow-up interval) was not able to detect statistically significant benefits for females aged between forty years to forty-nine years as there was for females aged between fifty years to sixty-four years. [10] At eighteen years of follow-up, a twenty-three percent mortality decline was observed for the forty to forty-

nine age group, the same relative benefit as for females aged between fifty years and sixty-four years; but the efficacy for females aged between forty years and forty-nine years remained to be statistically insignificant. [10]

The absence of a statistically significant benefits for females aged between forty to forty-nine years was due to the fact that there were not enough females in this age group enrolled in the study to provide the statistical power to detect a benefit. [6] A larger study population was needed given the lower incidence of breast cancer in this age group. Unfortunately, the lack of a statistically significant benefit was erroneously interpreted by many as proof that there was no benefit. [7]

None of the RCTs was designed to evaluate the effectiveness of screening for females aged forty to forty-nine years. thus, early subset analyses for this age group did not detect statistically significant efficacy. Longer-term follow-up finally made up for the absence of statistical power. In the year 1997, after ten-year to eighteen-year follow-up, meta-analysis of five Swedish RCTs detected a statistically significant twenty-nine percent mortality reduction for females aged forty to forty-nine years, which was the same relative benefit as for older females.6 multiple individual trials also found a statistically significant mortality decline for the forty to forty-nine years age group, ranging from twenty-three percent in a reanalysis of the HIP trial at eighteen years of follow-up to thirty-six percent to forty-five percent for the Swedish Malmo¨ and Gothenburg trials at twelve years to thirteen years of follow-up.

The Canadian National Breast Screening Study requires specific attention and review. After the HIP trial, CNBSS-1 was started in the year 1980, particularly conducted to study the efficacy of screening mammography for females in their forties. The CNBSS-1 allocated about fifty years,430 female volunteers aged forty to forty-nine years to undergo annual mammography, physical breast examination, and breast self-examination; or usual care. After eleven to sixteen years of follow-up, the investigators detected no significant decline in breast cancer mortality. [8]

Statistical analysis of the CNBSS-1 trial showed significant flaws and deviations from sound scientific methodology. First, despite claiming to be an RCT, rather than undergoing blinded randomization, the study subjects underwent clinical breast examinations done by the trial staff. Study organizers were not blinded to the results of clinical examination when they assigned females to either the study group or the control group. There are indications that allocation was likely to be biased by this information based on the fact that there were more females with advanced-stage, node-positive cancers in the screening group than in the control group at trial entry. As a result, there were in fact more cancer mortality in the screened group when compared to the control group. [9]

Another major concern regarding the CNBSS-1 is that the mammographic technique was poor. No professional training had been provided for the technologists or radiologists involved in the study, and external expert reviewers deemed the examinations technically insufficient. [10] The study's own reference physicist stated that the examinations were "far below state of the art, even for that time (early 1980s)." [11] The combination of these concerns severely compromised the CNBSS-1 and help explain why the CNBSS-1 study is an outlier being the only RCT that was not able to detect any benefits following screening for any age group. therefore, including CNBSS-1 results in RCT analyses diminishes the real potential benefits of screening.

Age Trial

In the year 1991, the UK Age trial was conducted to re-assess the effects of screening females in their forties. A total of 160,921 females aged between 39 years to 41 years were randomized to the treatment group, which consisted of an invitation to undergo annual mammography until the age of forty-eight years or the control group with no invitation to screening.

Both the intervention group and the control group then started tri-annual screening at the age of fifty years in accordance with national policy. In contrast to the preceding RCTs, screening in the treatment group was stopped before the age of fifty years so as not to confound the results with benefits accrued from screening after age fifty years. After a median follow-up of 17.7 years, there was a non-significant twelve percent decline in mortality. [12]

Although the UK Age trial concluded a mortality improvement, the investigators stated that these benefits could likely have been higher if specific conditions had been achieved.19 Specifically, single-view mammography was done in the trial after the first screen, despite knowledge that two-view mammography could raise the rate of early cancer detection. Literature from the UK suggests single-view mammography results in twenty percent to

twenty-five percent of cancers being not detected.[13] in addition, a lower threshold for biopsy of microcalcifications could have led to a raise in cancer detection. An analysis of the false-negative interval cancers during the trial found calcifications to be the most common imaging feature. The rate of ductal carcinoma in situ detection was three times lower than for the current UK national screening program.

Limitations of those Randomized Controlled studies have continuously showed an eighteen percent to twenty-nine percent mortality declines associated with screening females aged between forty years and forty-nine years. These types of trials, on the other hand, continue to underestimate the mortality effects of screening for multiple reasons. Not all females who are invited to be screened in fact participate (noncompliance). If any of the invited females who were not screened die due to breast cancer, their deaths are counted against the screened group, even though the female never actually received the intervention. Additionally, some females who are randomized to the control group in fact pursue screening outside of the trial (contamination). These females have potentially better survival because they were screened but are counted in the control group. These effects are crucial; in the screening RCTs, there was a ten percent to thirty-none percent non-compliance rate and thirteen percent to twenty-five percent contamination rate. [14] To prevent the occurrence of selection bias, adjustments could not be made for non-compliance or contamination.

Evidence from Observational Studies

RCTs are considered to be the gold standard for detecting the benefits of screening using mammography. Due to the limitations, discussed earlier, on the other hand, RCTs can potentially underestimate the real benefits of screening. thus, observational studies are another possible approach to detect the real effectiveness of screening. Service screening, in which all eligible females receive invitation letters to undergo screening, was started in Europe and Canada after the RCTs and provide this type of population data on outcomes of screening in females aged between forty years and forty-nine years.

In Sweden, Tabar and colleagues, [15] compared breast cancer mortality rates in two counties among females aged between forty years and forty-nine years in the twenty years before (1958– 1977) and twenty years after (1978–1997) the introduction of screening. There were mortality declines of forty-eight percent for females aged between forty years and forty-nine years and forty-four percent for all females aged between forty years and sixty-nine years. In British Columbia, Coldman and colleagues [16] published a large observational study stating the outcomes of seven Canadian screening programs, which encompassed eighty-five percent of the Canadian population of more than 2.7 million females. From the year 1990 to the year 2009, there was a thirty-none percent mortality decline among females aged forty to forty-nine years when compared to forty percent for all females aged between forty years and seventy-nine years.

Taken together, those observational studies of screening mammography predicted greater mortality declines for females aged between forty years and forty-nine years than the RCTs with similar screening intervals and have concluded a similar magnitude of mortality decline for females aged between forty years and forty-nine years as for those over the age fifty years.

2016 update to the us preventive services task force guidelines

In February 2016, the USPSTF released an update to their screening mammography guidelines, but gave a C rating for screening of females aged between forty years and forty-nine years, stating that the net efficacy to this cohort was still found to be small. They continued to state that the decision to undergo screening mammography before the age of fifty years must be made on an individual basis and must be based on whether a patient places greater importance on the benefits or harms. [17]

In the 2016 guidelines, the USPSTF also considered DBT to be an investigational technique and thus it was not recommended for use in routine screening. The American College of Radiology disputed this evaluation, citing the numerous large-scale studies of DBT involving more than 200,000 females that have consistently detected improvements in recall rates and cancer detection rates when DBT is used in association with full-field digital mammography when compared to full-field digital mammography alone. Kopans has detected the “inconsistency” of the USPSTF position on DBT, given that they could propose to withhold screening mammography from younger females in large part because of false-positive results and yet they do not support the use of DBT, which has been proven to decrease the recall rate in every study to date.

Update of american cancer society guidelines

In October 2015, the American Cancer Society (ACS) released their guidelines on breast cancer screening for females at average risk. The previous

2003 ACS guidelines had recommended annual screening mammography for all females beginning at the age of forty years. In the year 2015, however, the ACS modified their recommendations for younger females to allow for individualized decision making that considers both benefits and possible harms of screening. For females aged between forty years and forty-four years, the ACS issued a "qualified recommendation" to provide the opportunity for annual screening mammography, stating that most females would choose this option. They also issued a "strong recommendation" for females to undergo regular screening mammography beginning at age of forty-five years. Contrary to the USPSTF guidelines, the ACS cited evidence from the RCTs as well as observational studies showing similar relative benefits of screening mammography among females in their forties and fifty years. They stated, on the other hand, that the absolute benefit varied due to the fact that incidence of disease varies according to specific age groups. For example, the ACS stated that the five-year risk estimates among females aged between forty-five years and forty-nine years and females aged between fifty years and fifty-four years are similar (0.9 percent vs 1.1 percent) but exceed that for females aged between forty years and forty-five years (0.6 percent). The proportions of person-years of life lost were similar for females aged between forty-five years and forty-nine years and between fifty years and fifty-four years at diagnosis (both approximately fifteen percent). Thus , the ACS concluded that the burden of disease was very similar among females aged forty-five years to forty-nine years and those aged fifty years to fifty-four years, which could justify similar screening regimens for both of these age groups. Because disease incidence was slightly lower for females aged forty to forty-five years, on the other hand, they concluded that a minority of females in this age group may reasonably elect to forego screening due to concerns about harms. The ACS stated, on the other hand, that the evidence suggested that a majority of females will still elect to begin screening at the age of forty years. For example, Schwartz and colleagues reported that nearly all (ninety-six percent) of American females who experienced a false-positive mammogram were glad they underwent the test and remained supportive of screening. additionally, females involved in the Digital Mammographic Imaging Screening Trial demonstrated only transient, limited anxiety increases after a false-positive mammogram when compared with those with a negative mammogram, and there was no difference between the groups' intentions to undergo mammography in the subsequent two years.

Cost analysis

With the adoption of the Affordable Care Act in the year 2010, there has been raising interests in reducing national health care expenditures. Analyses of the costs of screening mammography have assessed the possible savings due to more limited screening strategies. For example, O'Donoghue and colleagues68 estimated the costs associated with three different screening strategies: annual (ages forty to eighty-four years), biennial (ages fifty years to sixty-nine years), and USPSTF (high-risk ages forty to forty-nine years, biennial ages fifty years to seventy-four years). The annual cost for each of these plans was estimated to be about 10.1 billion dollars, 2.6 billion dollars, and 3.5 billion dollars, respectively. The investigators were not successful in acknowledging that screening costs are offset by savings due to down-staging of disease and a concomitant decrease in the need for aggressive treatments, such as extensive surgery and chemotherapy. [18] A more recent analysis by Blumen and colleagues assessed the stage-dependent cost of breast cancer treatment of a commercially insured population of females with newly diagnosed breast cancer. The average cost per patient in the year following the diagnosis was fifty-eight percent higher for stage III ($129,387) than for stage I/II ($82,121) disease, and this cost differential was primarily caused by chemotherapy costs.

In a 1994 study, Rosenquist and Lindfors estimated a cost per life year gained of $26,000 for females aged between forty years and forty-nine years when compared with $20,000 for females aged between sixty years and sixty-nine years, assuming a thirty percent mortality decline through annual screening mammography. Although the primary costs of screening are higher for younger females, these costs are counterbalanced by the greater life expectancy of younger females when compared with their older counterparts. Even when the analysis of Rosenquist and Lindfors is adjusted for the current costs of mammography, the estimates still fall well below the $ 100,000 per year of life threshold that is commonly accepted for preventive tests. [19]

CONCLUSIONS:

There is a large body of evidence demonstrating a thirty percent to fifty percent mortality benefit of screening mammography for females aged between forty years and forty-nine years. The magnitude of the mortality benefit is equal to that for females over fifty years. Because of more rapid cancer growth rates in younger females and shorter average lead-times, annual screening has been shown to be more effective than biennial screening. Critics of

mammography have over-emphasized the potential harms of screening relative to the life-saving benefits. Research has shown that a vast majority of females are highly tolerant of false-positive results, which in most instances merely consist of additional imaging. The best available evidence indicates that fewer than ten percent of breast cancers are over-diagnosed. Meanwhile, ample studies indicate that selective screening of females based on risk factors to decrease the harms could miss the majority of breast cancers. Most females find the modest risks of screening acceptable tradeoffs for the far greater benefit of early detection, which means a lesser chance of dying from breast cancer and a reduced need for aggressive and toxic treatments. If implemented, the recent USPSTF breast cancer screening guidelines, which recommend against routine screening of females in their forties, can result in thousands of preventable breast cancer deaths per year.

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