Effects of early breast cancer screening through film-screen mammography on mortality reduction of breast cancer

Introduction

Breast cancer claims the highest number of female lives among cancer-related deaths and a significant number of male lives globally. In 2017, it was the third highest incident cancer among females (Lin et al., 2019). Currently, in both developed as well as developing countries, the incidence and mortality of breast cancer are steadily increasing. Several factors impact its survival rate such as screening at a later age, lack of suitable diagnostic techniques, and lack of inexpensive therapy. The mortality rate due to breast cancer is especially high in Latin America, Europe, Arab countries, and India (Li et al., 2019).

Two of the most important reasons for substantial increase in mortality due to breast cancer include population growth and longevity. Alcohol consumption is heavily linked to breast cancer as it has been shown to induce genetic as well as epigenetic modifications due to continuous consumption. Other important risk factors include obesity and diabetes, which are both chronic and serious health issues in most countries around the world (Li et al., 2019).

This paper aims to describe the incidence, pathophysiology, and risk factors of breast cancer in detail and discuss the available mammographic screening techniques for early diagnosis and better prognosis. Following this, it will describe the design, implementation, and results of two randomized controlled trials that studied the effect of early mammographic screening on mortality reduction of breast cancer. Finally, it will connect the results of these two trials to a cohort study conducted in New Zealand, compare the results of the studies, and make informed recommendations for breast cancer screening.

Breast Cancer

One of the most common cancers that occur in women globally is breast cancer, which affects about 1.5 million women annually and accounts for 25% of all cancers in

women (Stewart and Wild, 2014). It is a metastatic cancer which can easily spread to other distant organs such as liver, bones, brain, and lungs, making its control and treatment challenging. As a result, early diagnosis of breast cancer is considered to be useful for its good prognosis and higher chance of survival (Sun et al., 2017).

Breast cancer usually starts with ductal hyperproliferation following which it develops into a benign tumour or a metastatic carcinoma depending on the presence of carcinogenic factors in the body and the environment. The initiation and progression of breast cancer is heavily dependent on the tumour microenvironment such as macrophages or stromal influences in the body. Macrophages have the capability of creating an inflammatory microenvironment in the body that can promote angiogenesis and lead to the failure of cancer cell detection in the body (Dumars et al., 2016). Epigenetic modifications may also be involved in the progression of breast cancer as observed by DNA methylation patterns in patients (Basse and Arock, 2015).

An important class of cells that have been increasingly linked to breast cancer is cancer stem cells (CSC) which is associated with the initiation and recurrence of breast cancer. This may either develop from progenitor cells or stem cells in the body, are capable of self-renewal, and are resistant to radiotherapy and chemotherapy. It has been shown that as few as even 100 CSC in the body can lead to the initiation of new cancers (Al-Hajj et al., 2003). According to the CSC theory, all the subtypes of tumours are derived from stem cells or progenitor cells, and the type of tumour depends on the genetic and epigenetic mutations that have taken place in these cells. In contrast to the CSC theory, the stochastic theory of cancer states that a single cell type that may be a stem cell or a differentiated cell gives rise to the tumour subtypes. Once enough random mutations have accumulated in the breast tissues, formation of a tumour is initiated (Polyak, 2007).

The risk factors of breast cancer are a mix of genetic and environmental factors. Age is an important factor and over 70% of breast cancer cases occur in women aged between 40 and 60 years. Reproductive predisposing factors include early menarche, late age during first pregnancy, late menopause, and low parity. High estrogen levels, both exogeneous as well as endogeneous, increase the risk of breast cancer in women.

Exogeneous estrogen is usually supplied by oral contraceptive pills and hormone replacement therapy (HRT), and women who use these interventions for prolonged periods have a higher risk of breast cancer. Finally, lifestyle factors include excessive consumption of alcohol, high fat intake, and smoking (Sun et al., 2017).

Mammography

Breast cancer is considered to be the second leading cause of death, the first one being cardiovascular disease (Wang, 2018). Early diagnosis of breast cancer has been shown to improve the survival rate of patients by at least 5 years. The primary diagnostic tool currently used is manual examination which looks for signs and symptoms such as swelling of breast tissue, fixed masses, thickening and discolouration of skin, nipple pain, and nipple discharge. However, most countries actively implement several prevention and screening programs to diagnose breast cancer at the very initial stages in order to improve its prognosis in patients (Iranmakani et al., 2020).

Mammography is a screening technique for breast cancer that aims at diagnosing it at an early and curable stage. It is estimated that one out of every 235 breast cancer deaths is prevented by regular screening with mammography (Marmot et al., 2013). This technique uses low energy X-rays of 20 – 30 keV power to detect abnormalities in the breast tissue. The sensitivity of this technique is 75%; however, for higher breast mass densities, the sensitivity is reduced to 50%. This makes it difficult to differentiate between benign and malignant tumours. The result of a mammogram is in the form of a two-dimensional image which identifies and reports deformation in the breast, asymmetric calcifications, and masses (Iranmakani et al., 2020).

The technique of mammography involves pressing the breast tissue with a plate, passing X-rays through the breast tissue, and generation of 2D radiographic images. These images are obtained in the oblique and craniocaudal planes; however, other views may be obtained if a tumour is suspected. Several enhancements over the standard mammography have been introduced over the years in order to improve its sensitivity and diagnostic capabilities. Film-screening mammography is used for

improving the sensitivity of lesion detection in highly dense breast tissues. However, the risk of false positives is high because dense breast tissues have less adipose tissue and more fibroglandular tissue, and this may give the appearance of abnormalities in a mammogram. In contrast, digital mammography is considered to have more sensitivity for dense breast tissues, apart from other advantages such as easy storage, transfer, and retrieval of images. Further enhancements of digital mammography have given rise to newer techniques such as digital breast tomosynthesis (DBT) and contrast-enhanced digital mammography (CEDM). DBT provides 3-dimensional information about the breast tissue thereby attributing high sensitivity to the technique. CEDM has a much higher sensitivity as it provides angiogenic patterns of lesions; however, its disadvantages are high cost, difficult operation, and lack of knowledge of the technician (Iranmakani et al., 2020).

Study Presentations

Duffy et al. (2020) conducted a randomized controlled trial known as the UK Age Trial with women aged between 39 and 41 years. Participants were selected from patient lists of general practitioners' (GPs) who held the information about the randomization of participants and were given the authority to remove participants from either group if they considered them unsuitable for the study. The selected participants were randomly assigned to annual screening until they reached the age of 48 years (intervention group) or no screening until the age of 50 years when they underwent the National Health Service Breast Screening Programme (NHSBSP) (control group). Participants in the intervention group were invited by post to attend the annual screening and participants in the control group were not aware of their inclusion in the trial. The screening took place at 23 units across Scotland, Wales, and England. A total of 107,000 participants were in the control group and 53,000 were in the intervention group, and the follow-up period was 14 years.

The technique used for screening was two-view film mammography for the first screen followed by single view in subsequent screens. The primary endpoint that was measured was mortality due to breast cancer that occurred before the first NHSBSP invitation for both groups. The secondary endpoint was measured as a diagnosis of

breast cancer and mortality due to reasons other than breast cancer. All data was analyzed using Poisson regression, calculation of relative rates (RR), Nelson-Aalen estimates, and Cuzick's method of self-selection bias.

The results of the trial showed that after 10 years of follow-up, the mortality of breast cancer was lower in the intervention group (83 deaths) as compared to the control group (219 deaths) with RR 0.75 [95% CI (0.58 – 0.97); p = 0.029]. After 10 years of follow-up, there was no significant change in mortality between the two groups with RR 0.98 (0.79 – 1.22) and p = 0.86. Overall, by the end of the follow-up period, the difference in mortality between the 2 groups was shown by RR 0.88 (0.74 – 1.03) and p = 0.13. Therefore, a significant reduction in mortality of breast cancer at around 25% is associated with early annual screening by mammography between the ages of 40 to 49 years. A summary of the methods and results of this trial is given in Table 1.

Table 1: Summary of the UK Age Trial

Study	Sample Size	Objective	Intervention	Follow-up Period	Results
Duffy et al., 2020	Intervention group – 53,000 Control group – 107,000	To evaluate the effects of early mammographic screening from the age of 40 years on breast cancer mortality in women aged 40 to 49	Intervention group - Two-view film mammography for the first screen followed by single view in subsequent screens annually Control group – usual care	23 years	Within 10 years of follow-up: RR 0.75 [95% CI (0.58 – 0.97); p = 0.029] After 10 years of follow-up: RR 0.98 (0.79 – 1.22) and p = 0.86 Overall, after 23 years of follow-up: RR 0.88 (0.74 – 1.03) and p = 0.13

Tabar et al. (2011) conducted a randomized controlled trial known as Swedish Two-County Study using participants from two counties in Sweden namely, Dalarna and Ostergotland, with ages of women varying between 40 and 74 years. The participants were randomly assigned to the intervention group which underwent screening

mammography and the control group which was given usual care. The total number of participants in the intervention group was 77,080 women and the total number in the control group was 55,985 women. Participants who were aged between 40 to 49 years were invited for screening every 2 years and participants who were aged between 50 to 74 years were invited for screening every 33 months. The screening method used in the study was one-view film-screen mammography with a single reading and no additional manual examination.

The initial results of the trial were published in 1985 and represented a 30% reduction in breast cancer mortality in the intervention group as compared to the control group (Tabar et al., 1985). The results of this trial were published after following the participants for 29 years and were analyzed by the original trial's end-point committee as well as another overview committee appointed by the Swedish Cancer Society. The data was analyzed using significance testing and negative binomial regression, and RRs for breast cancer were calculated in both groups.

The results from the local end-point committee showed that there was a significant reduction in breast cancer mortality in the intervention group with RR 0.69 [0.56 – 0.84; 95% CI, P < 0.0001]. The Swedish committee results showed a lesser but still a significant mortality reduction with RR 0.73 [0.59 – 0.89; 95% CI, P = 0.002]. A summary of the methods and results of this trial is given in Table 2.

Table 2: Summary of the Swedish Two-County Trial

Study	Sample Size	Objective	Intervention	Follow-up Period	Results
Tabar et al., 2011	Intervention group – 77,080 Control group – 55,985	To evaluate the effects of early mammographic screening from the age of 40 years on breast cancer mortality in women aged 40 - 74	Intervention group - One-view film-screen mammography with a single reading and no additional manual examination	29 years	Within 10 years of follow-up: 30% mortality reduction [result not a part of this study] Results from local committee: RR 0.69 [0.56 – 0.84; 95% CI, P < 0.0001]

			annually Control group – usual care		Results from appointed committee: RR 0.73 [0.59 – 0.89; 95% CI, P = 0.002]

Discussion

Until now, a total of eight randomized controlled trials (RCT) have been performed worldwide to assess the affect of early mammography screening on the mortality of breast cancer, out of which four have been conducted in Sweden (Nystrom et al., 2017). This paper has compared the results of two RCTs, one conducted in UK titled the UK Age Trial and the other conducted in Sweden titled the Swedish Two-County Trial. Other RCTs have been conducted in New York, Edinburgh, and Canada (Nystrom et al., 2017).

The UK Age Trial began in 1991 and its objective was to identify the usefulness of mammography screening for women between the ages 39 to 41 on the mortality reduction of breast cancer. The Swedish trial was older which began in 1977, and it studied the effect of regular mammography screening on women between the ages 40 to 74 years. The follow-up period for the UK trial was 22 years and for the Swedish trial, it was 29 years. Therefore, both were long-term studies and both trials reported results after 10 years as well as upon completion of the trial. The method of screening for both studies was film screen mammography, possibly because they were started before the year 2000 when newer mammography technologies had not been introduced.

While both studies proved that mammography screening successfully reduced mortality in breast cancer patients, there were significant differences in the results. The UK trial found the maximum benefit in the early stages of the trial where the mortality reduction was 25% within the first 10 years of follow-up. However, the study reported that after 10 years of follow-up, the reduction in mortality was not significant. In contrast, the Swedish study reported a 30% reduction in mortality within 10 years of follow-up, and a 27 – 31% reduction in mortality after 29 years of follow-up. As per the results of

both studies, the mortality of breast cancer can be reduced by decreasing the age of routine mammography from 50 to 40 years.

Based on the results of the RCTs on breast cancer mortality worldwide, a cohort study was conducted in New Zealand by Morrell et al. (2017) in order to understand the mortality of breast cancer in this population. It was conducted between the period of 1999 to 2011 and found that the breast cancer mortality in the screened population was found to be 62% lower than the never screened population. Additionally, it was seen that women who underwent regular screening through mammography had better prognosis as compared to women who never underwent routine screening. As a result, based on the results of the RCTs as well as studies in New Zealand, it is evident that early screening through mammography is helpful in reducing mortality due to breast cancer as compared to late or never screening.

Both the trials discussed here had a large sample size, used randomization for participant allocation, and used the conventional technique of film screen mammography. In contrast to the Canadian trial which had a lot of controversial issues regarding its implementation, both these trials were sound and their results were considered to be reliable. The objective in both cases was to assess if it would be beneficial to reduce the age of routine screening for breast cancer in women from 50 to 40 years and it was found, in both studies, that early screening has the potential to reduce mortality due to breast cancer.

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