Maximizing the benefits of screening mammography for women 40-49 years old

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Summary

Background: While women aged 50 and older are broadly considered to benefit from screening mammograms, the evidence of any similar advantages for younger women are still considered insufficient to form any substantial conclusions on the matter. The primary goal of this study was to examine whether or not the mortality rate of younger women is benefited by mammography, and if so, how can this beneficial effect be maximized. *Methods*: The authors have taken into account all available randomized control trials (RCTs) and have conducted a meta-analysis based on those RCTs to study the effect of mammography on the mortality rate of women younger than age 50. Further interpretation on various aspects of the results has also led to separate meta-analyses, with the RCTs included grouped in accordance to the mean time interval between screening mammograms employed by each study. The findings and conclusions of the comparison were used to calculate the number of mammograms necessary to reduce the absolute death risk, depending on the time interval between screening mammograms. *Results:* The meta-analysis indicated a reduction in breast-cancer mortality in the intervention group, which reached statistical significance (relative risk (RR) 0.81 [95% CI 0.71-0.93] $p < 0.01$). Furthermore, when the RCTs included were grouped according to their mean time interval between mammograms, there was a definite increase of statistical significance in favor of those RCTs with shorter interval times (RR 0.76 [95% CI 0.64-0.89] $p < 0.01$). *Conclusions:* The significant mortality rate reduction demonstrated by the meta-analytical results is a key indicator of the beneficial effect of mammography on the age group of women younger than 50. Additionally, the increase in the aforesaid significance when combining RCTs with short time intervals between mammograms, as opposed to those RCTs with longer intervals, suggests that the optimal use of mammographic screening lies with the former. This is better demonstrated when taking in account our approach to answering the practical question of "how many screening mammograms will take to save one life?" in correlation with the mean time interval involved.

Key words: Mammography before 50 years old; Screening mammography; Mammography in young women.

Introduction

The unequivocal belief in mammography as a beneficial factor when applied to women aged 50 years and older is the result of several randomized controlled trials which indicate a mortality risk reduction of about 25% [1] in those women who underwent screening procedures. What has been less certain, is whether or not screening mammography is of a similarly advantageous nature on younger age groups, namely on women aged 40-49 years of age. Several randomized controlled trials (RCTs) [1-8] have been conducted to elucidate on the matter, beginning with the HIP trial of Greater New York [4] up to the NBSS Canadian study [7] and the greatly anticipated British Age Trial [8].

The results of most of the trials were consistent with the approach of conducting screening mammography on younger women, albeit, statistically those results did not reach significance – with two possible reasons being either that indeed mammography does not constitute an effective screening method on those specific age groups, or simply because the RCTs themselves were of a limited statistical power to detect any actual difference between the control and study groups. This latter possibility stands as such, primarily because the number of participants was indeed small in relation to the issue at hand, which also poses an issue in accordance with the relatively low incidence of breast cancer in that age group when compared to older age groups [9-11].

The answer to the statistical weakness of several separate studies came in the form of meta-analyses which combined different RCTs, adjusting their different model approach in accordance to the studies' heterogeneity. At least seven meta-analyses [1, 12-17] have been conducted so far, at least three of which [1, 2, 5, 18, 19] have been revised and updated some years after the initial publication. Only three of those meta-analyses [11, 15, 16] reached a statistical significance regarding the relative mortality risk reduction.

With the majority of studies showing a non-significant trend towards the effectiveness of screening mammograms in younger women, and only a handful demonstrating statistical significance, the question arose: why was mammographic sensitivity in younger age groups lagging behind that of older women? Certain studies [20, 21] indicated that mammographic sensitivity was greatly

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affected by the density of breast tissue, which is greater in younger women, whereas rapid tumor growth shared an equally important role in decreased sensitivity when the time-interval between mammograms was lengthened.

With the aforementioned issues in mind, we facilitated the first data of the ten-year follow-up results made available by the British Age Trial. We used these data to conduct our own meta-analysis combining the majority of previous RCTs and we furthermore explored and interpreted different meta-analytical plots in an attempt to shed some light on the importance of interval times between mammograms and the level on which they influence the ultimate effectiveness of mammography on younger women.

Materials & Methods

The results of the analyses of all available RCTs [1, 3-8] were gathered in order to form the statistical pool needed to conduct the meta-analysis. The relative risks (RRs) and confidence intervals (CIs) were used as presented without re-conducting separate analyses of individual data for each RCT and re-evaluated data were used in cases where that approach was applicable [1, 2, 5, 18, 19]. The data were analyzed using MIX v1. 7 [22, 23]. All meta-analyses conducted utilized the inverse variance method with a fixed-effects model, although a random-effects model and homogeneity check were also used for cross-check purposes. All RCTs mentioned in this paper were used for the final meta-analysis, excluding the Canadian NBSS Trial. An all inclusive meta-analysis has nevertheless been conducted to study whether the exclusion of this study significantly altered the outcome, and a sensitivity analysis was also used to study the same matter.

Once the results of the meta-analysis were obtained, the studies included were sorted by the mean interval time they used between screening mammograms. The statistical trend was examined and two new meta-analyses, consisting of those studies with a mean interval time shorter than 24 months and those consisting of studies with a mean interval time longer than 24 months, respectively, were conducted. The relative risk reduction (RRR) was calculated for all groups of studies that were used to examine if and when that reduction was more significant and to draw a comparison where applicable.

Finally, we calculated the absolute death risk reduction for the two groups consisting of studies using different time intervals to answer the practical question of "how many screening mammograms are needed in order to save a life?" and explicate its correlation to the time interval between screening mammograms.

Results

The meta-analysis resulted in statistical significance (RR 0.81 [95% CI 0.71 - 0.93] $p = 0.0025$) (Figure 1). Although homogeneity among the included samples justified the use of a fixed-effects model ($Q = 8.0431$, p value = 0.4293), we also conducted a meta-analysis using a random-effects model and the results of each approach were shown to be identical. All studies were included, with the exception of the Canadian NBSS Trial and to ascertain that this study's exclusion did not affect the statistical significance of the results, we used as reference both a sensitivity analysis plot (Figure 2) as well as another meta-analysis (Figure 3), this time including the NBSS Trial. The results of this all-including meta-analysis were also significant (RR 0.84 [95% CI 0.74 - 0.95] $p = 0.0049$).

Once statistical significance was ascertained, we moved on to examine possible trends in our results and their respective interpretations. During that procedure, we examined the cumulative forest plot of our meta-analysis with the RCTs arranged by decreasing mean time interval between mammograms. A cumulative plot graphically exhibits the meta-analytical outcome resulting by adding studies up to that point and it was thus demonstrated that with each addition of a study of a shorter mean interval time, the overall RR decreased while the RRR increased (Figure 4). To better examine the importance of time interval between mammograms, we divided the included RCTs in two groups, one consisting of RCTs with a mean time interval between mammograms over 24 months and a second group with studies of a mean time interval less than 24 months. We then conducted a separate meta-analysis for each group (Figure 5) and calculated the relative risk reduction (= 1 - RR) for both of these groups to present a viable comparison of the effect of time intervals between screening mammograms. For the group of studies with a mean time interval shorter than 24 months, the RRR was shown to be 24% (RR 0.76 [95% CI 0.64 - 0.89] $p = 0.0007$) while for the group of studies with mean interval times longer than 24 months, the results were not significant (RR 0.96 [95% CI 0.74-1.25] $p = 0.7856$).

We then moved on to calculate the RRR for all RCTs included in the meta-analysis and it was found to be 19% (RR 0.81 [95% CI 0.71-0.93] $p = 0.0025$). We compared this result with that of the meta-analysis consisting only of RCTs with interval times shorter than 24 months and although in both cases the p value was well below 0.01, the significance of the results when considering only the short interval time RCTs, increases 3-fold.

With that in mind, we went ahead to calculate the reduction of absolute death risk (RADR) for both cases. The RADR is equal to the RRR, multiplied by the absolute death risk (ADR). Keen & Keen [24] have estimated that the ADR at age 40 is 0.475% and that risk more than doubles between the starting ages of 45 and 55. We have chosen the modest approach of using the lowest percentage, that of 0.475%. Using the aforementioned formula (RADR = RRR * ADR) we calculated the RADR to be 0.0906% and 0.1155% for all RCTs of the meta-analysis and for the shorter mean time interval RCTs, respectively. Because the ADR acts as a constant, the 22% difference between the two results remains fixed, regardless of the actual value of the ADR.

Discussion

Our aim was to attempt a conclusive analysis of the previous RCTs, facilitated by the relatively new results from the British Age Trial to statistically ascertain

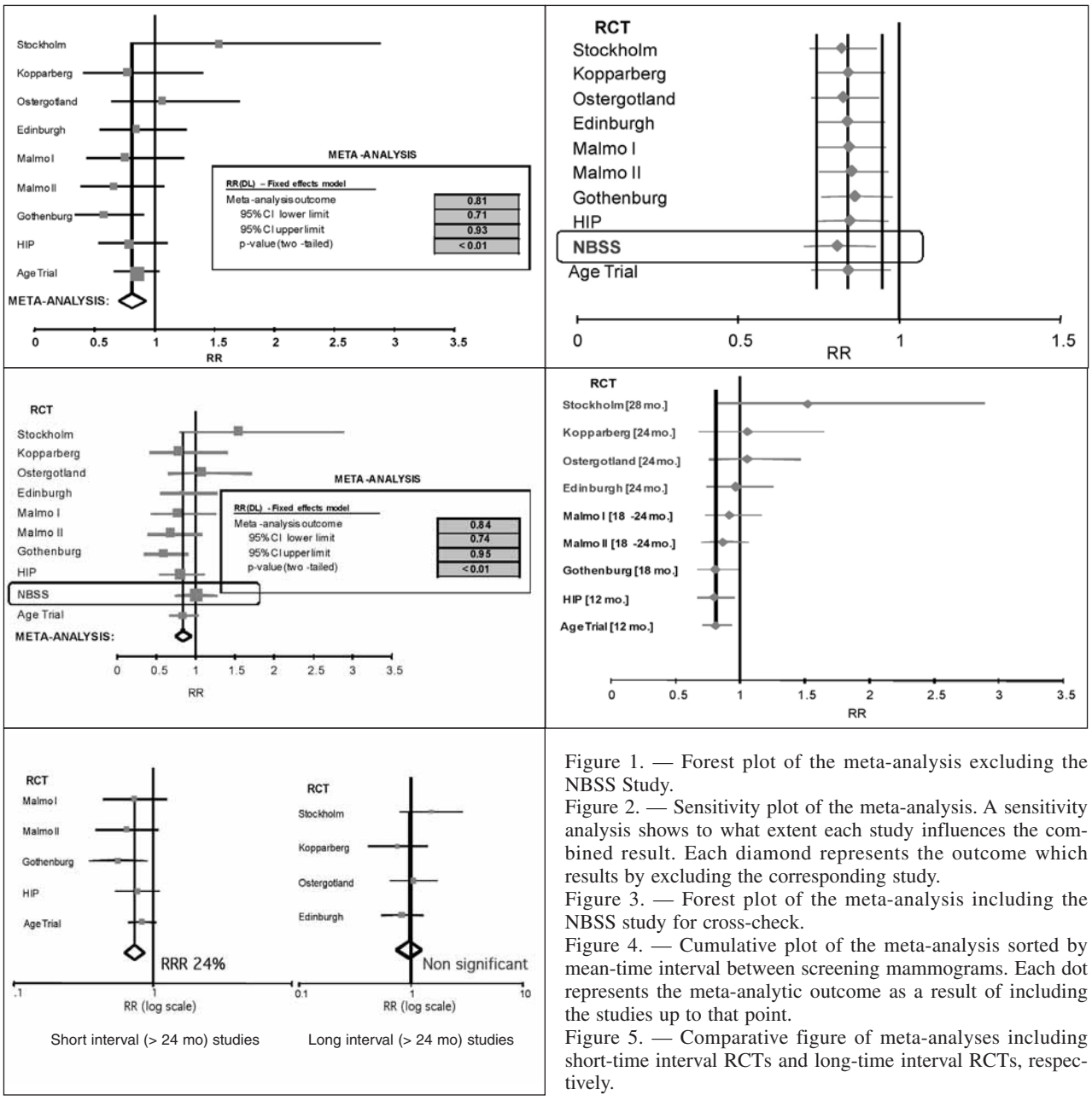

Figure 1. — Forest plot of the meta-analysis excluding the NBSS Study.
Figure 2. — Sensitivity plot of the meta-analysis. A sensitivity analysis shows to what extent each study influences the combined result. Each diamond represents the outcome which results by excluding the corresponding study.
Figure 3. — Forest plot of the meta-analysis including the NBSS study for cross-check.
Figure 4. — Cumulative plot of the meta-analysis sorted by mean-time interval between screening mammograms. Each dot represents the meta-analytic outcome as a result of including the studies up to that point.
Figure 5. — Comparative figure of meta-analyses including short-time interval RCTs and long-time interval RCTs, respectively.

whether or not, screening mammography's beneficial effects transcends the 50-year-old limit and positively affects younger women as well.

The study selection was based on the up to standard methodology from a statistical and academic point of view. As such, all studies were included with the exception of the NBSS trial which was found lacking the necessary credibility for adding to the statistical conclusions facilitated by the rest of the RCTs. The reasons for this lack of credibility, as have been explicitly described by a number of publications [25-27], include the nature of the selection of the participants for this specific trial, as the NBSS study invited volunteers which were afterwards randomized in study or control groups and thus, a selection bias may have been generated. Additionally, the NBSS study prescreened all participants with a clinical breast examination, something which could have weakened the findings of the trial by distributing women with clinical findings to the control and study groups. This prescreening procedure also leaves room for selection bias within the study, a possibility all the more striking when considering the noteworthy difference of advanced cancer occurrences between the control and the study group: the rate of advanced cancers of the latter was 3.8 times higher compared to that of the control group, a difference that would constitute reason enough to exclude this study from a meta-analysis regardless of the reasons that caused it. Furthermore, a rough 26% of the control

group underwent mammography screening during the study. Criticism has also been addressed towards the quality of the mammography conducted, which may have resulted in false-negative results and unfounded encouragement to the study group as well as to the short-follow up period of the study. For those reasons, we chose not to include the findings of this study in our meta-analysis.

Although the NBSS study was not included, we wanted to make sure that the significant results of our meta-analysis did not occur due to the exclusion of this trial alone. We thus conducted a separate, all-including meta-analysis and a sensitivity analysis. The all-inclusive meta-analysis turned out significant results while the exclusion of the study was adequately supported by the sensitivity analysis as well.

During examination of the cumulative plot of the meta-analysis, it was observed that a tendency of increasing significance occurred simultaneously with a decrease of the mean interval time between screening mammograms. Further examination using two separate meta-analyses, one for short-interval time mammograms and one for long-interval time ones, provided us with statistical evidence that more frequent screening mammograms provide more significant results in terms of mortality reduction. This statistically apparent indication is consistent with previous suggestions [28-33] that due to the differences of mastic density between younger and older women as well as to the more aggressive nature of tumors affecting the former, a more frequent approach of mammographic screening should be implemented.

In particular, while the RRR for the short-interval time mammograms was a promising 24%, the respective result for long-interval time mammograms was not significant statistically. When the RR of the short-interval time mammograms was compared to the RR of all studies included (short and long interval time alike) the significance factor was found to increase 3-fold in favor of the former. This pointed us in a direction of turning numbers to more practical functions, and we attempted to seek an answer to the question of "how many mammograms does it take to save a life?".

The results were naturally in favor of the short-time interval approach when compared to all time intervals included, with 865 mammograms with a short-time interval between them, as opposed to 1,103 mammograms with a longer intervening time-span. What is noteworthy is that although the actual numbers may vary, the difference between them remains a fixed 22% in favor of the short-interval time mammograms. The idea that fewer mammograms are needed to save a life while at the same time they should be more frequent, may seem hard to grasp initially, but considering a fixed time-span of screening might ease the concept: in a 4-year period of screening, four lives will be respectively saved if an adequate number (in our case, 865) of women attend each year. If the screening examination was biannual, only two lives would have been saved if an adequate number of women (1,103 in our case) did attend every two years. In our simplified example, this means that out of 3,460 women, four will be saved in four years if annual screening is implemented, while out of 4,412 women, only two will be saved in the same period of time, if implementing biannual screening.

Conclusions

The statistical significance of the meta-analysis, is an explicit indicator of the beneficial results of screening mammography in women younger than 50 years. The RRR of 19% can be considered as a designating factor in the approach of screening mammography where the minimum age for regular screening mammograms is above the 50-year-old "barrier".

Moreover, the considerable difference between the RRR of those studies comprising short-interval times between mammograms and their long-interval time counterparts, represents the rather obvious advantage of the former in terms of mortality reduction. In a more practical aspect of the results, the obtained values from the meta-analyses of the above-mentioned groups of long-interval and short-interval studies can be used to calculate the number of screening mammograms needed to avert an event of RADR, or, put simply, to save a life. Having the RADR calculated, the number of mammograms needed to save a life when taking into account all studies, long-time and short-time intervals alike, is 1/0.0906% = 1103 while when using the short-interval studies alone, the number of necessary screening mammograms drops to 1/0, 1.155% = 865.

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