Breast cancer screening in women taking hormone replacement therapy needs updating.

Running title: Breast Cancer Screening and HRT

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Abstract

Breast cancer screening by mammography is widely used. The diagnostic accuracy is limited, with a positive predictive value of 16%. Therefore, a stepwise investigation, with repeat mammography and confirmation by pathology, is usually proposed. Although this stepwise investigation intends to avoid overtreatment, the many false positives result in unnecessary fear and diagnostic surgery in many women. The false negatives are not known since these women have not been investigated. Given the estimated low risk of missing breast cancer and the slow growth, repeating a screening mammography every two years is sufficient.

The false positive screening results increase with breast density, and breast density increases when hormone replacement therapy (HRT) is given. It, therefore, is suggested to use clinical judgment and stop HRT for 3 to 6 months before repeating the mammography instead of starting immediately a stepwise investigation in all women.

Introduction

Mammography is widely used for breast cancer screening. The risk of overdiagnosis, overtreatment, and the many factors involved (Ryser et al., 2022), and the benefits measured by the estimated lifetime gained (Bretthauer et al., 2023) have been widely discussed. Less emphasised is that the reported sensitivities and specificities, varying between 73% and 88% (Schünemann et al., 2020) to 80% and 98% (Mushlin et al., 1998), result, at best, in positive predictive values of less than 5% to 18% for prevalences of 0.5% in the screened population (Fig 1). This is also illustrated by the Belgian breast cancer screening program with biannual mammography in women between 50 and 69 years old, following The European quality assurance program (Schünemann et al., 2020) Data from 2017 to 2020 illustrate that 5% of women screened, had a second mammography, and 2% had more exams, such as MRI or biopsies, to detect between 0.5% and 0.6% breast cancers. Thus, out of 200 women screened, 10 are selected for a second mammography and 4 for more invasive exams to find 1 cancer (Belgium, 2021).

This stepwise procedure compensates for the low predictive values of mammography with sensitivities and specificities of 67 % and 98% when prevalences are low (Koninckx et al., 2023). Sensitivities and specificities are test characteristics, while clinically, it is important to know the risk of having breast cancer if the test is positive and the risk of missing cancer when the test is negative. These are the predictive values, which decrease sharply when prevalences are less than 10%, the PPV being the sensitivty*prevalence / (sensitivity*prevalence + (1-specificity)(1-prevalence)) (Lesaffre and Lawson, 2012). Therefore, excellent sensitivities and specificities around 80% and 98% result in poor predictive values when prevalences are 0.5%.

Although the interpretation of mammographies and the definition of abnormal findings or suspicious lesions seem to be established (Gøtzsche and Jørgensen,

2013), there is little consensus about screening ages and intervals between screening (Schünemann et al., 2020). Without discussing ductal carcinoma in situ, the clinical benefits of screening or contrast mammography, we must realise the difficulties of performing randomised controlled trials for breast cancer screening and of translating the findings into guidelines. False and true negatives are poorly known since these women are not investigated. Evidence-based medicine and guidelines rely heavily on double-blind randomised controlled trials. However, RCTs are poorly suited to investigate multivariate events because of randomisation problems. A 2 or 3 Y/N factorial design already requires 4 or 8 groups. An RCT is not suited for rare events, and breast cancer trials require huge numbers taking time to perform with the risk of being outdated before being finished. This explains the lack of data on newer techniques in ultrasound, digital imaging, deep learning (Arun Kumar and Sasikala, 2023) and artificial intelligence (Gao et al., 2023). The translation of predictive values or Bayesian probabilities, into guidelines, results from estimating truth or clinical importance, decided by consensus or voting by a group of experts (Kubota et al., 2023), thus introducing subjectivity based on previous experiences. Therefore, guidelines may vary, although based on the same RCTs (Jhangiani et al., 2023). More fundamental is that accuracies and predictive values of abnormal or suspicious findings are crude estimates and should be stratified for factors such as breast densities, increasing the difficulty of interpretation and the risk of abnormal findings (Freer, 2015, Schünemann et al., 2020). Finally, although beyond this discussion, it should be realised that the accuracy of the diagnosis by pathology cannot be established since it is the gold standard, which cannot be compared with a better test. In addition, it is unclear whether histopathological parameters reflet the expression profile or molecular genetic features (Simpson et al., 2005).

These poor predictive values of mammography and the stepwise clinical approach result in more lumpectomies and mastectomies(Gøtzsche and Jørgensen, 2013, Schünemann et al., 2020) with an estimated 30% overdiagnosis out of prudence. Without discussing whether screening results in a reduction in breast cancer mortality, we should realise that a reduction of breast cancer mortality by 15% and an overdiagnosis and overtreatment of 30% results in preventing one mortality for every 2000 women screened for ten years, but at the cost of 10 women being treated unnecessarily, and 200 women having experienced psychological distress and anxiety. Although the exact figures can be discussed, the conclusion of overdiagnosis and little effect on mortality seems repetitively confirmed (Bretthauer et al., 2023)

Breast cancer screening, clinical medicine and Bayesian statistics

Clinical medicine is multivariate, and in the individual woman (Koninckx et al., 2023), the probability of having breast cancer varies not only with the image of mammography (or MRI) but also with the clinical exam, age, heredity, obesity, breast density, race and many other factors. The estimation of the probability in the individual woman that an abnormal or suspicious lesion is a cancer should include all these factors besides the mammography. This requires multivariate Bayesian statistics, but these results are unfortunately not available.For example, since multivariate RCTs are difficult to perform, the added value of mammography following a negative clinical exam, with a reported sensitivity of 54% and specificity of 94% (Jatoi, 2003), is still unknown. Therefore, the translation of an abnormal or suspicious lesion into the management of the individual woman remains a clinical judgment. This explains that recommendations for the diagnostic workup of abnormal or suspicious breast lesions vary.

Breast cancer screening and hormone replacement therapy

Hormone replacement therapy (HRT) increases breast density and thus the risk of finding abnormal and suspicious lesions (Rutter et al., 2001, Freer, 2015, Azam et al., 2018). Therefore, it was suggested that HRT be stopped for a few months before screening mammography is performed (Beckmann et al., 2013). Unfortunately stopping HRT for several months is clinically poorly accepted. Since breast cancer screening by mammography is recommended to be performed only every two years, the risk of delaying the workup and eventual treatment of abnormal or suspicious lesions for 3 to 6 months must be very low. Therefore, managing women on HRT and abnormal or suspicious lesions on screening mammography must be clinically individualised. Considering all risk factors, the increase of abnormal or suspicious images in women taking HRT and the low risk of delaying therapy for a few months, it may be considered to stop HRT for 3 to 6 months before repeating mammography. The women whose repeat mammography returns to normal will have avoided unnecessary cancer workups and surgery, and the continuation of HRT can be discussed.

Conclusion and discussion

The limitations of performing multivariate RCTs and the frequentist statistical analysis hamper the interpretation of breast cancer screening by mammography. It is still not fully appreciated that the predictive value of any test is strongly affected by the prevalence of the disease (Lesaffre and Lawson, 2012). For breast cancer with a prevalence of 0.5%, the positive predictive value is only 16% for sensitivities of 67% and specificities of 98%. Unfortunately, negative predictive values cannot be estimated since the women in whom breast cancer is missed (false negatives) are unknown since they have not been further explored. Also, although estimated as high as 40% (Ryser et al., 2022), the true incidence of false positives is not clear since expectant management of suspicious lesions is considered unethical. Clinically important is that frequentist statistical analysis

calculates the positive predictive values of breast cancer screening but not the added value besides age, heredity and breast density. This would require a Bayesian statistical approach, which has not been performed yet to the best of our knowledge.

The diagnostic workup of abnormal and suspicious lesions follows a clinical logic of repeat exams and, eventually, biopsies, with the dogma (without data) that delaying the workup and treatment can only be harmful. Overtreatment and unnecessary fear have been discussed, but the hypothesis that some lesions could disappear spontaneously, especially in women stopping HRT, has not been tested.

It is beyond this manuscript to discuss the limitations of frequentist statistics or the need to individualise therapy and to consider all predictive factors or medical and corporate pressures, as we recently did for endometriosis (Koninckx et al., 2022). However, individualising follow-up and postponing exams for three months in women with abnormal or suspicious lesions and dense breasts while HRT is stopped has the potential to decrease overtreatment. Although it would be an easy trial to demonstrate that some abnormal images become normal after stopping HRT for three months, it is close to impossible to demonstrate that a delay of 3 months does not increase the risk since proving the absence of an effect requires huge numbers. Therefore, an adequately performed RCT to demonstrate a decreased risk of unnecessary treatments without increasing risks is unlikely to be performed. In conclusion, individualising follow-up and letting the woman decide whether to stop HRT for three or more months before repeating mammography has the potential to decrease overtreatment.

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Fig 1 Positive predictive values (PPV= sensitivty*prevalence / (sensitivity*prevalence + (1-specificity)(1-prevalence)) of a mammography if sensitivities and specificities are 73% and 88% or 80% and 98%. This illustrates the crucial importance of the specificity and of the prevalence of the disease (0.5 and 1% indicated).

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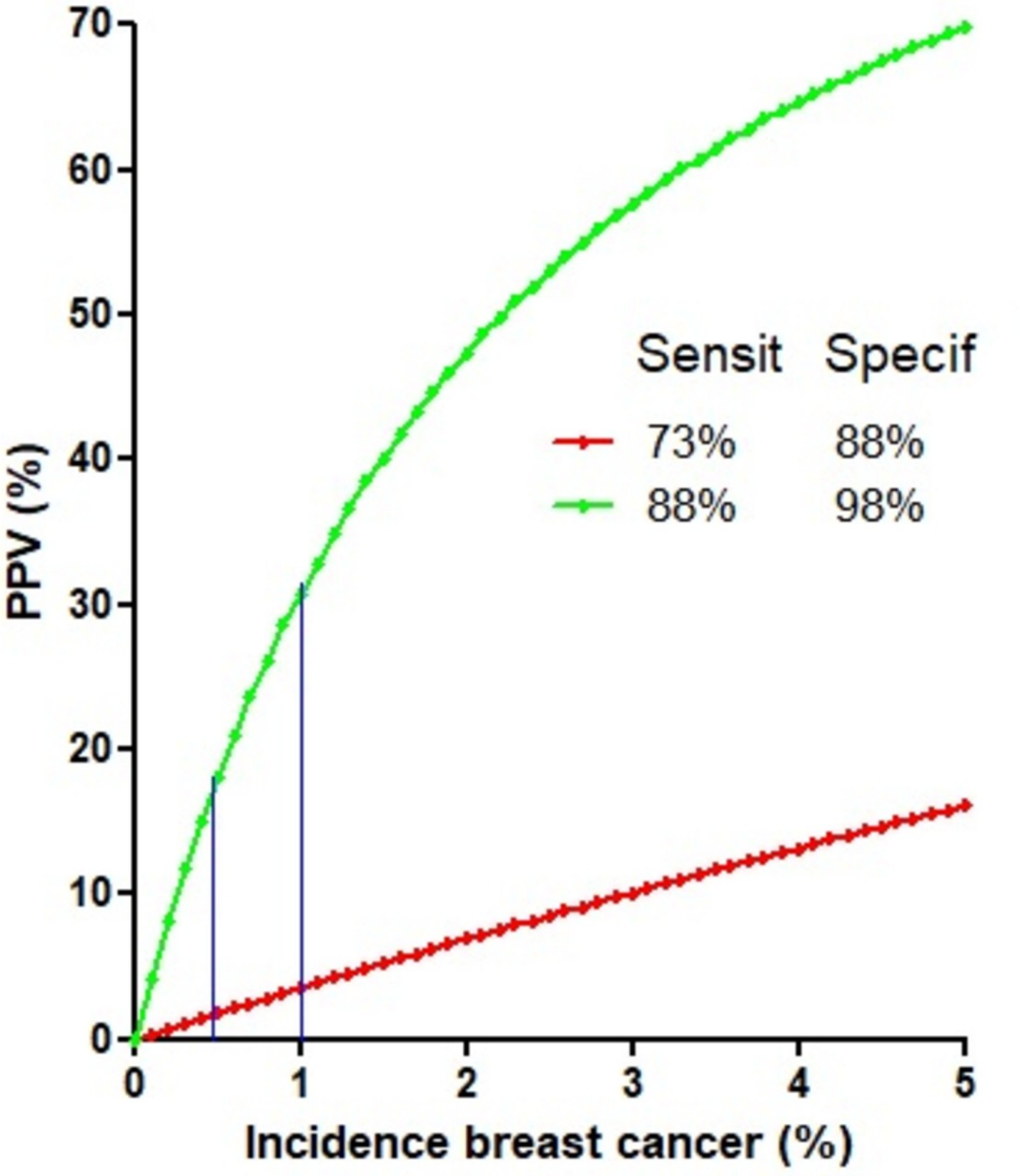
70
60
50
40
30
20
10
0
PPV (%)
Sensit
Specif
73%
88%
88%
98%
0
1
2
3
4
5
Incidence breast cancer (%)

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Abstract

Breast cancer screening by mammography is widely used. The diagnostic accuracy is limited, with ~~only~~ a positive predictive value of 16%. Therefore, a stepwise investigation, with repeat mammography and confirmation by pathology, is usually proposed. Although this stepwise investigation intends to avoid overtreatment, the many false positives result in unnecessary fear and diagnostic surgery in many women. ~~-~~ The false negatives are not known since these women have not been investigated. Given~~However, considering~~ the estimated low risk of missing breast cancer and the slow growth, repeating a screening mammography every two years is ~~considered~~ sufficient.

The false positive screening results increase with breast density, and breast density increases when hormone replacement therapy (HRT) is given. It, therefore, is suggested to use clinical judgment and~~to~~ stop HRT for 3 to 6 months before repeating the mammography instead of starting immediately a stepwise investigation in all women.

Introduction

Mammography is widely used for breast cancer screening. , ~~, and t~~The risk of overdiagnosis, ~~and~~ overtreatment, and ~~-~~the many factors involved (Ryser et al., 2022), ~~-~~and the benefits measured by the estimated lifetime gained (Bretthauer et al., 2023) have been widely discussed. Less ~~emphasised~~ emphasised is that the reported sensitivities and specificities, ~~-~~varying~~ing~~ between 73% and 88% ~~(Abdullah et al., 2021)~~(Schünemann et al., 2020) to 80% and 98% (Mushlin et al., 1998), ~~, -~~result~~ing~~, at best, in ~~less than 5% to 18%~~ positive predictive values of less than 5% to 18% for prevalences of 0.5% in the screened population (Fig 1). This is also illustrated by the Belgian breast cancer screening program with biannual mammography in women between 50 and 69 years old, following The European quality assurance program (Schünemann et al., 2020) ~~(Schünemann et al., 2020b)(Von Karsa and Arrossi, 2013)(Von Karsa and Arrossi, 2013)~~ Data ~~f~~from 2017 to 2020 illustrate that ~~in women between 50 and 69 years old, with~~ 5% of women screened, had~~undergoing~~ a second mammography, ~~evaluation~~ and 2% had more exams, ~~,~~ such as MRI or biopsies, to detect~~find~~ between 0.5% and 0.6% breast cancers. ~~The Belgian stepwise screening program,~~ Thus, out of 200 women screened, 10 are selected for a second mammography and 4 for more invasive exams to find 1 cancer (Belgium, 2021).

This stepwise procedure compensates for the low predictive values of mammography with sensitivities and specificities of 67 % and 98% when prevalences are low (Koninckx et al., 2023)~~with a sensitivity of 67% and a specificity of 98% (Belgium, 2021), thus has at best (prevalence 0.6%) a positive predictive value of 16% and 29%, following a first or second positive screening, respectively~~. Sensitivities and specificities are test characteristics, while clinically, it is important to know the risk of having breast cancer if the test is positive and the risk of missing cancer when the test is negative. These are the predictive values, which decrease sharply when prevalences are less than 10%,

the PPV being the sensitivty*prevalence /(sensitivity*prevalence + (1-specificity)(1-prevalence)) (Lesaffre and Lawson, 2012). Therefore, excellent sensitivities and specificities around 80% and 98% result in poor predictive values when prevalences are 0.5%.

Although the interpretation of mammographies and the definition of abnormal findings or suspicious lesions seems to be established (Gøtzsche and Jørgensen, 2013), there is little consensus about screening ages and intervals between screening (Schünemann et al., 2020). Without discussing ductal carcinoma in situ, the clinical benefits of screening ~~(Gøtzsche, 2015, Bretthauer et al., 2023) or the recent advances in reading mammography using artificial intelligence (Gao et al., 2023)~~ or contrast mammography, we must ~~realise~~ realise the difficulties of performing randomised controlled trials for breast cancer screening and of ~~uncertainty of~~ translating the findings ~~mammography as a screening test into sensitivity and specificity~~into guidelines. ~~First, f~~False and true negatives are poorly known since these women are not investigated. Evidence-based medicine and guidelines rely heavily on double-blind randomised controlled trials. However, RCTs are poorly suited to investigate multivariate events because of randomisation problems. A 2 or 3 Y/N factorial design already requires 4 or 8 groups. An RCT is not suited for rare events, and breast cancer trials require huge numbers taking time to perform with the risk of being outdated before being finished. This explains the lack of data on newer techniques in ultrasound, digital imaging, deep learning (Arun Kumar and Sasikala, 2023) and artificial intelligence (Gao et al., 2023). The translation of predictive values or Bayesian probabilities, into guidelines, results from estimating truth or clinical importance, decided by consensus or voting by a group of experts (Kubota et al., 2023), thus introducing subjectivity based on previous experiences. Therefore, guidelines may vary, although based on the same RCTs (Jhangiani et al., 2023). ~~Secondly,~~

~~sensitivities and specificities are test characteristics, while clinically, it is important to know the risk of having breast cancer if the test is positive and the risk of missing cancer when the test is negative. These are the predictive values, which decrease sharply when prevalences are less than 10%, the PPV being the sensitivty*prevalence /(sensitivity*prevalence + (1-specificity)(1-prevalence)) (Lesaffre and Lawson, 2012). Therefore, excellent sensitivities and specificities around 80% and 98% result in a poor predictive value of 16% when prevalences are 0.5%. This explains the sequential approach of retesting abnormal or suspicious lesions once or twice before pathology makes the final diagnosis. Thirdly, although beyond this discussion, it should be realised that the accuracy of the diagnosis by pathology cannot be established since it is the gold standard and thus cannot be compared with a better test.~~ More fundamental is that ~~Fourthly,~~ accuracies and predictive values of abnormal or suspicious findings are crude estimates and should ~~need to~~ be stratified for factors such as ~~for~~ breast densities, ~~which~~ increas~~inges~~ the difficulty of interpretation and the risk of abnormal findings (Freer, 2015, Schünemann et al., 2020). Finally, although beyond this discussion, it should be realised that the accuracy of the diagnosis by pathology cannot be established since it is the gold standard, which cannot be compared with a better test. In addition, it is unclear whether histopathological parameters reflet the expression profile or molecular genetic features (Simpson et al., 2005)~~.(Kubota et al., 2023)~~

These poor predictive values of mammography and the stepwise clinical approach result in more lumpectomies and mastectomies ~~(RR 1.31, 95% CI 1.22 to 1.42)~~(Gøtzsche and Jørgensen, 2013, Schünemann et al., 2020) with an estimated 30% overdiagnosis out of prudence. Without discussing whether screening results in a reduction in breast cancer mortality, we should ~~realise~~ realise that a reduction of breast cancer mortality by 15% and an overdiagnosis

and overtreatment of 30% results in preventing one mortality for every 2000 women screened for ten years, but at the cost of 10 women being treated unnecessarily, and 200 women having experienced psychological distress and anxiety. Although the exact figures can be discussed, the conclusion of overdiagnosis and little effect on mortality seems repetitively confirmed (Bretthauer et al., 2023)

Breast cancer screening, clinical medicine and Bayesian statistics

Clinical medicine is multivariate, and in the individual woman (Koninckx et al., 2023), the probability of having breast cancer varies not only with the image of mammography (or MRI) but also with the clinical exam, ~~AND~~ age, ~~AND~~ heredity, ~~AND~~ obesity, ~~AND~~ breast density, ~~AND~~ race and many other factors. The estimation of the probability in the individual woman that ~~prediction of the risk of an~~ an abnormal or suspicious lesion is a cancer ~~in the individual woman~~ should include ~~interpret the mammography findings considering~~ all these ~~other risk~~ factors besides the mammography. ~~.~~ This requires multivariate Bayesian statistics, but these results are unfortunately not ~~yet~~ available. For example, since multivariate RCTs are difficult to perform, ~~For example,~~ the added value of mammography following a negative clinical exam, with ~~having~~ a reported sensitivity of 54% and specificity of 94% (Jatoi, 2003), is still unknown. ~~, could not be demonstrated. (Arun Kumar and Sasikala, 2023)~~ Therefore, the translation of an abnormal or suspicious lesion into the management of the individual woman remains a clinical judgment. For example, the added value of mammography following a negative clinical exam, having a sensitivity of 54% and specificity of 94% (Jatoi, 2003), could not be demonstrated. This explains that recommendations for the diagnostic workup of abnormal or suspicious breast lesions vary. ~~vary from no recommendation to triple diagnosis by imaging, physical examination, and biopsy. (Jhangiani et al., 2023)~~

Breast cancer screening and hormone replacement therapy

Hormone replacement therapy (HRT) increases breast density and thus the risk of finding abnormal and suspicious lesions (Rutter et al., 2001, Freer, 2015, Azam et al., 2018). Therefore, it was suggested that HRT be stopped for a few months before screening mammography is performed **(Beckmann et al., 2013)**. ~~.~~ Unfortunately stopping HRT for several months is clinically poorly accepted.

Since breast cancer screening by mammography is recommended to be performed only every two years, the risk of delaying the workup and eventual treatment of abnormal or suspicious ~~suspected~~ lesions for 3 to 6 months must be very low. Therefore, managing women on HRT and abnormal or suspicious lesions on screening mammography must be clinically ~~individualised~~individualised.

Considering all risk factors, the increase of abnormal or suspicious images in women taking HRT and the low risk of delaying therapy for a few months, it may~~can~~ be considered to stop HRT for 3 to 6 months before repeating mammography. The women whose repeat mammography returns to normal will have avoided unnecessary cancer workups and surgery, and the continuation of HRT can be discussed. ~~With GN-RH antagonists becoming widely available, this therapy might even be considered for a few months in women with dense breasts before menopause.~~

Conclusion and discussion

The limitations of performing multivariate RCTs ~~The low prevalence of breast cancer~~ and the frequentist statistical ~~data~~ analysis hamper the interpretation of breast cancer screening by mammography. It is still not fully appreciated that the predictive value of any test is strongly affected by the prevalence of the disease (Lesaffre and Lawson, 2012). For breast cancer with a prevalence of 0.5%, the positive predictive value is only 16% for sensitivities of 67% and specificities of 98%. Unfortunately, negative predictive values cannot be estimated since the women in whom breast cancer is missed (false negatives) are unknown since

they have not been further explored. ; aAlso, although estimated as high as 40% (Ryser et al., 2022), the true incidence of false positives is not clear since expectant management of suspicious lesions is considered unethical. Clinically important is that frequentist statistical analysis calculates the positive predictive values of breast cancer screening but not the added value besides age, heredity and breast density. This would require a Bayesian statistical approach, which has not been performed yet to the best of our knowledge.

The diagnostic workup of abnormal and suspicious lesions follows a clinical logic o, withf repeat exams and, eventually, biopsies, with the dogma (but without data) that delaying the workup and treatment can only be harmful. Overtreatment and unnecessary fear have been discussed, but the hypothesis that some lesions could disappear spontaneously, especially in women stopping HRT, has not been tested.

It is beyond this manuscript to discuss the limitations of frequentist statistics or the need to ~~individualise~~ individualise therapy and to consider all predictive factors or medical and corporate pressures, as we recently did for endometriosis (Koninckx et al., 2022). However, ~~individualising~~ individualising follow-up and postponing exams for three months in women with abnormal or suspicious lesions and dense breasts while HRT is stopped has the potential to decrease overtreatment. Although it would be an easy trial to demonstrate that some abnormal images become normal after stopping HRT for three months, it is close to impossible to demonstrate that a delay of 3 months does not increase the risk since proving the absence of an effect requires huge numbers. Therefore, an adequately performed RCT to demonstrate a decreased risk of unnecessary treatments without increasing risks is unlikely to be performed. In conclusion, individualising follow-up and letting the woman decide whether to stop HRT for three or more months before repeating mammography has the potential to

decrease overtreatment. ~~This is an important message for clinicians involved in the long-term follow-up of women after surgery for other indications such as endometriosis.~~

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Authors role. All authors discussed the manuscript and agreed with the final manuscript.

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