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REVIEW ARTICLE

Is the false-positive rate in mammography in North America too high?

MICHELLE T LE, BMRSc, CARMEL E MOTHERSILL, PhD, BSc, COLIN B SEYMOUR, PhD, MA, BL, FIONA E MCNEILL, PhD, BSc

Medical Physics & Applied Radiation Sciences Department, McMaster University, Hamilton, ON, Canada

Address correspondence to: Miss Michelle T Le
E-mail: *lem8@mcmaster.ca*

ABSTRACT

The practice of investigating pathological abnormalities in the breasts of females who are asymptomatic is primarily employed using X-ray mammography. The importance of breast screening is reflected in the mortality-based benefits observed among females who are found to possess invasive breast carcinoma prior to the manifestation of clinical symptoms. It is estimated that population-based screening constitutes a 17% reduction in the breast cancer mortality rate among females affected by invasive breast carcinoma. In spite of the significant utility that screening confers in those affected by invasive cancer, limitations associated with screening manifest as potential harms affecting individuals who are free of invasive disease. Disease-free and benign tumour-bearing individuals who are subjected to diagnostic work-up following a screening examination constitute a population of cases referred to as false positives (FPs). This article discusses factors contributing to the FP rate in mammography and extends the discussion to an assessment of the consequences associated with FP reporting. We conclude that the mammography FP rate in North America is in excess based upon the observation of overtreatment of *in situ* lesions and the disproportionate distribution of detriment and benefit among the population of individuals recalled for diagnostic work-up subsequent to screening. To address the excessive incidence of FPs in mammography, we investigate solutions that may be employed to remediate the current status of the FP rate. Subsequently, it can be suggested that improvements in the breast-screening protocol, medical litigation risk, image interpretation software and the implementation of image acquisition modalities that overcome superimposition effects are promising solutions.

INTRODUCTION

Background

Breast carcinoma is currently the most common cancer among the female population constituting 25.9% of all cancers in Canada (25,000 new breast cancer cases of 96,400 total cancer cases diagnosed in 2014[1]), 29.6% in the UK (50,750 breast cases of 171,727 total cancers in 2012[2]) and 28.7% in the USA (232,670 of 810,320 total cancer cases in 2014[3]). The breast cancer incidences exceed even those of lung cancer and colorectal cancer, which possess overall incidence rates of approximately 14% and 12%, respectively.[4] The most common breast cancer subtype is invasive ductal carcinoma, accounting for approximately 75% of all malignant cases.[5] It has recently been reclassified as invasive carcinoma of no special type by the World Health Organization owing to its presentation of characteristics non-specific to a given histological origin.[6]

The first breast-screening programme was introduced in New York, USA, in the 1960s and in Canada beginning in the 1980s to address the high mortality rates attributed to invasive breast cancer. The objective of breast screening, most often employed by means of X-ray mammography, is to detect invasive carcinomas at an early stage such that the prognosis for survival can be significantly improved.[7] The breast cancer mortality incidence in Canada was approximately 12,000 cases per year prior to the advent of screening.[1] Over two decades later, breast cancer mortality has been reduced by over 35%.[8] It is estimated that screening contributes to approximately 50% of this reduction,[8,9] while the remaining proportion is attributed to improvements in cancer treatment methodologies.[9]

While it can be seen that breast screening is beneficial in improving survival for individuals diagnosed with invasive carcinoma, it is also associated with the risk of false-positive (FP) reporting and overdiagnosis. An FP occurs when a benign lesion or completely normal tissue is interpreted as abnormal, indeterminate or is recommended for additional work-up during screening[10] and is assessed

further by diagnostic tools such as a biopsy, fine needle aspiration or additional imaging.[11] Overdiagnosis is the identification and diagnosis of a disease which will not manifest to become symptomatic over a patient's lifetime. Reporting of breast images is standardized by the breast imaging reporting and data system (BI-RADS) developed by the American College of Radiology.[12] The appearance of a BI-RADS score of 0, 4 or 5 on a report for a benign lesion would be considered an FP.[13] On a population-based level, the FP rate is traditionally defined as the probability of receiving a positive result, given an absence of the disease. In this review, the FP rate will be defined as the number of FPs as a proportion of the total number of screening examinations conducted (*i.e.* accounting for cases of both the presence and absence of malignant disease). The definition has been modified from the true technical definition as a result of an observed trend, whereby the FP rate is reported in the latter manner by most of the publications concerning mammographic screening. It is speculated that the latter method of reporting is preferred, as it provides a more meaningful mechanism by which to convey the risk of conferring an FP result among the entire screened population. The lesions relevant to FP diagnoses are those which are benign that may mimic malignancy on a screening image. Furthermore, ductal carcinoma *in situ* (DCIS) is one *in situ* disease that is popularly discussed in the context of over-diagnosis. DCIS arises in the epithelium of the terminal and subsegmental mammary ducts.[14] Regardless of the cellular grade, DCIS is considered a Stage 0 cancer because it has not infiltrated structures outside of the epithelial lining. In DCIS, the ductal basement membrane remains intact and retains normal cellular characteristics.[14] Although DCIS is considered non-invasive, it has been widely documented as a non-obligatory precursor lesion for invasive breast carcinoma.[5,14–17] Furthermore, much debate surrounds the suitability of classifying DCIS as a precursor lesion, when DCIS itself has been observed to affect mortality.[18] For this reason, its classification as a precursor disease has been questioned.[19] This controversy will be addressed in the present review in concert with the justification for treating DCIS using invasive methodologies.

FP reporting is considered a consequence of breast screening, since it can lead to detriment for those females who are recalled for further testing and ultimately are not diagnosed with invasive cancer. Concerns are raised regarding the harms associated with invasive diagnostic work-up, the anxiety of undergoing diagnostic testing and the risks associated with the treatment of benign lesions. This report will assess factors that have contributed to the mammography-related FP rate in North America and the risks faced by females following prescription for additional diagnostic work-up. The extent and proportion of detriment experienced by the population affected by FP reporting will be the measure that will determine whether the FP incidence is truly too high. In a further analysis of the literature, the breast-screening protocol will be assessed to determine whether the current schedule is optimal for conferring mortality-based benefits while limiting the FP rate as much as reasonably possible. The ultimate objective was to identify potentially detrimental aspects of breast screening and subsequently propose feasible solutions for addressing such harms.

Scope of review

PubMed, Google Scholar and Web of Science were searched up to March 2016 to find studies encompassing the topics of FPs in mammography, consequences of FP reporting and protocols/technologies used in mammography. While it is necessary to consider the benefits of breast screening in order to provide the reader with adequate context, the scope of this review was predominantly focused upon the harms of mammographic screening. The sources and implications of these harms are discussed in order to propose solutions which have the greatest potential for addressing and reducing the discussed harms. Studies published during and after 2005 were considered for the review. Of those considered, 7 meta-analyses, 10 systematic reviews, 9 randomized controlled trials, 29 retrospective studies, 21 prospective cohort studies and 5 modelling studies were included. Studies included in the review but published prior to 2005 were used as general references or used to refer to prior trends in the field of screening mammography. This review acknowledged that different practices are carried out in different jurisdictions such that the variability in practice accounts for unique FP rates. Much of the perspectives discussed in this review are North American, while UK and other European research are used in an illustrative manner to supplement the discussions.

FACTORS AFFECTING INCIDENCE

False-positive incidence and prevalence

FP incidence rates associated with screening programmes in North America have proven to be variable, ranging from 10.2%[11] to 14.4%[20] of the screened population upon first screen and dropping to observed rates as low as 5.2%[21] for subsequent screening rounds.[21] FP incidence drops substantially upon subsequent screening rounds as a result of the availability of prior images to which radiologists may refer for comparison upon encountering a suspicious radiographic appearance.[21] The overall FP prevalence, taking into account the rates for first and subsequent screens, reported by the Ontario Breast Screening Program in Canada is 6.9%.[22] This figure is closely representative of the overall FP rates that result from screening in other Canadian provinces such as British Columbia and Nova Scotia, whereby first and subsequent FP incidence rates are 14.1% and 5.23%[21] and 10.2% and 5.2%,[11] leading to prevalence rates of 6.84%[21] and 6.8%,[11] respectively. In the USA, the FP incidence rates are slightly higher than those reported in Canada such that data from the Breast Cancer Surveillance Consortium (BCSC) registries and the National Breast and Cervical Cancer Early Detection Program produced FP rates of 14.4% (first screen) and 8.7% (subsequent screens) and 12.5% (first screen) and 8.0% (subsequent screens), respectively.[20] From these data, it can be seen that the average FP rate associated with screening mammography in North America can be estimated to fall between approximately 6% and 10%. The North American rates contrast greatly with those observed in Europe, whereby the average FP rate among the first and subsequent screens in the Netherlands and the UK are only 2%[23] and 4.9%,[24] respectively. In accordance with European regulations, these jurisdictions are in compliance with the mandate for limiting the mammography FP rate to below 5%.[25]

The magnitude of effect that FP reporting presents to populations undergoing screening can be put into perspective upon assessing FP prevalence among the females screened. Among those females who participated in US breast screening programmes monitored by the BCSC, 43.7% of the total population received at least one FP result over a 4-year study period.[20] This prevalence was similar for US females studied under the National Breast and Cervical Cancer Early Detection Program, whereby 40.5% of females received an FP, again, over a 4-year duration.[20] These US prevalence rates contrast significantly with those observed in the population of females participating in the UK National Health Service (NHS) breast-screening programme, where only 15.4% of participants received an FP report between the years of 1996 and 1999.[20] Keeping these incidence and prevalence rates in mind, it is a goal of this report to elucidate factors contributing to the occurrence of FPs subsequent to mammography screening in North America. The investigation of such contributing factors will be crucial to determining the remedial actions that could be taken towards achieving an FP rate which is as low as reasonably achievable.

Screening protocol

On an individual level, various factors affect the probability of receiving an FP report. The frequency of screening, the number of views and radiologist reporting are all considered influential. Higher screening frequency is associated with a higher cumulative FP risk for the patient. Two prospective cohort studies and two retrospective studies all concluded that annual screening increased the 10-year cumulative FP probability over biennial screening.[26–29] The highest risks were reported by Kerlikowske,[29] where annual, biennial and triennial screening conferred FP risks of 56.7%, 35.9% and 25.5%, respectively, among US females from the BCSC registries. While a number of studies concluded that annual screening frequency significantly increased the cumulative FP risk compared with biennial screening,[26,27,30,31] and triennial screening,[32] the triennial acquisition of mammograms did not significantly exacerbate the FP rate above that observed subsequent to biennial screening.[32] The rationale put forth by the US Preventive Services Task Force for conducting annual screening is based upon the idea that frequent screening will be more effective in detecting invasive cancers and thus can reduce the incidence of interval cancers.[33] While this recommendation for more frequent screening is made with good intentions, the net benefit conferred by annual screening over biennial or triennial screening must also be assessed against the harms to determine the validity of this rationale; this issue will be discussed further below.

For mammographic screening applications, some protocols only require the acquisition of a single view (mediolateral oblique)[34] in an effort to limit the radiation dose received by the patient, limit image archiving costs and optimize throughput in the clinical setting.[35] However, it has been shown that the acquisition of two views (craniocaudal and mediolateral oblique) decreases the FP rate significantly[34,36] owing to the availability of additional information to the radiologist, thus facilitating greater confidence in ruling out a given lesion as benign. In a UK randomized controlled trial, the transition from one-view to two-view acquisition resulted in an overall reduction in the recall rate by 11%, concurrent with a 20% increase in the cancer detection rate.[37] Beyond the benefit accrued in terms of a lower FP rate, the more important benefit conferred as a result of two-view screening mammography compared with single view manifests as a significant increase in the cancer detection rate for both screen-detected cancers and interval cancers.[35]

It is important to assess the benefits of early cancer detection and reduced recall risk against the radiation risks and acquisition costs associated with a two-view examination to determine the appropriate acquisition protocol. In regard to the excess radiation dose delivered as a result of acquisition of the second view, risk modelling indicates that a doubling of the radiation dose could increase the number of excess cancers induced by two times than that observed with single view.[38] Studies which have modelled the number of excess cancers induced by radiation during two-view mammographic screening report figures ranging from 10 to 26.6 cases per 100,000 females.[38–40] However, the transition to two views from a single view would also be expected to increase the number of detected cancers. Based upon the results reported by Blanks et al,[37] the transition to two-view mammography would increase the overall number of detected cancers by 20% and thus would be expressed as an additional 117 cancers detected per 100,000 females. The assessment of detriment relative to the benefit manifesting as a greater number of detected cancers relative to induced cancers demonstrates a balance in favour of two-view acquisition.

In regard to acquisition costs, the addition of a supplementary view to the mammography protocol resulted in a 1.9% increase in cost per screening examination as observed in a Dutch breast-screening programme,[35] the bulk of which was attributed to costs associated with digital image archiving. As far as acquisition time is concerned, the time to complete a single examination is lengthened by approximately 1–2 min when performing a two-view examination as opposed to a single-view examination, whereby the mean acquisition time for a single-view examination is approximately 118 s.[41] This increase in acquisition time has been proven to reduce the number of females who are screened within 1 h.[42] However, it seems that this change in clinical throughput had no influence upon the rate at which radiologists were able to report the images.[42] Furthermore, the length of two-view examinations could be expected to improve over time as radiographers become more accustomed to acquiring the second view. It can be suggested that the slight elevations in cost and throughput time associated with the transition from single-view to two-view screening mammography are justified in order to confer a greater cancer detection rate.

In response to these findings, the NHS breast-screening programme introduced a transition to two-view screening in 2003.[43] Since the 1980s, standard practice in both the USA and Canada sees that screening mammography is conducted using two views at first and successive screening rounds.[33,44] From this observation, it can be suggested that the long-practised acquisition of two views during mammography screening in North America has not contributed to the FP rates observed; rather this practice is expected to have assuaged the incidence of FPs. It is

therefore apparent that other factors, and not the number of views taken during mammographic screening in North America, contribute to the FP incidence that currently exists.

Double reading (*i.e.* two radiologists reading each mammogram) can change the FP rate depending on the manner in which it is conducted. Independent radiologist reporting has shown an increase in the probability for FPs because patients are recalled if either one of the radiologists considers the mammogram to be abnormal.[45] On the other hand, arbitration and consensus between the two readers has resulted in a significant decrease in the FP rate.[34,46] It has also been reported that blinded double reading, whereby the second reader was not aware of the first reader's suggestions, significantly increased the FP rates compared with a situation where double reading was not blinded.[47] The advantage of blind double reading, however, is the significant improvement in cancer detection sensitivity associated.[47] From these studies, it is clear that the policies which are implemented are important in affecting the probability for FP results. Assessment of the scientific evidence and implementing policies which reflect the risks and benefits clarified in the literature will be crucial for limiting the FP rate.

Practice policies and radiologist perception

Radiologist reporting may also be dependent upon guidelines for FP tolerance. US guidelines specify an acceptance rate of $\leq$10%,[48] whereas the European acceptable FP rate is $<$5%.[25] In turn, the difference in threshold for the acceptance rate values in different jurisdictions may be attributed to the culture unique to each respective jurisdiction. For example, the perceived risk of severe litigation consequences associated with medical malpractice in the USA has been identified as a possible contributor to the relatively high recall rates that exist in the USA.[20,49] In this respect, guidelines in the USA may have been set with the perception of a heightened risk for litigation in mind. Survey-based studies conducted among US radiologists demonstrated that radiologists estimated a substantially higher risk of future malpractice than the actual risk noted upon follow-up[50] or upon comparison with historical malpractice risk.[7] It is evident that radiologists' concern regarding malpractice is a pressure that is strong among US radiologists to such an extent that it has contributed to considerations of opting out of mammography reporting by a large proportion of practising radiologists (50.4%).[7] Concern of malpractice liability is also a presence among Canadian radiologists, as 72% of a population of surveyed radiology residents expressed a strong concern of mammography-specific malpractice risk when compared with other imaging examinations.[51]

Elmore et al[7] surveyed 124 US radiologists in an effort to assess the relationship between radiologists experience with diagnosis-specific malpractice in the mammography setting and their recall rates subsequent to those experiences. Prior involvement in a mammography-related medical malpractice case did not increase the recall rate or FP rate above that observed in those who were not involved in prior litigation claims. Further evidence suggesting that radiologist perception is not always predictive of his/her reporting patterns can be observed in the results published by a study investigating the effect of introducing new breast density reporting laws upon radiologist reporting. The introduction of breast density-reporting laws in Pennsylvania led to an increase in the volume of reporting cases as BI-RADS 2 (scattered fibroglandular density) as opposed to BI-RADS 3 (heterogeneously dense),[52] indicating a shift towards less conservative reporting rather than the expected shift towards more conservative reporting that would be expected with the pressures of possible litigation. Most importantly, the changes in radiologist reporting were compared with the radiologists' estimations of their own behaviour to find that the performance of 44% of the radiologists differed from their estimations.[52] Thus, although concern of litigation is a large concern among North American radiologists, their perceived risk has not influenced their reporting as strongly as they predict it has.

Despite these results, litigation risk should not be discounted as a potential contributing factor to the heightened recall rates observed in North America when compared with other jurisdictions, since the volume of malpractice claims put forth in the USA is actually substantially greater than that in European countries such as Italy and the Netherlands. The 5-year malpractice risk associated with mammography among a surveyed population of US radiologists was found to be 10%.[50] In contrast, the risk of mammography-related malpractice claims among radiologists belonging to the Italian Society of Medical Radiology is 10.5 per 1000 cases or 1.05% over a 10-year period,[53] while the observed rate of malpractice claims filed in a Dutch breast cancer screening programme was 3 cases out of $>$300,000 screening examinations or 0.001% over a 15-year period.[41] Because a greater risk of litigation is a reality in the USA, it is possible that it has led to an overall greater awareness of litigation risk among all North American radiologists. This in turn could contribute to an overall greater recall and FP rate compared with other jurisdictions where this pressure does not weigh upon practice as heavily.

An alternative factor which may contribute to high recall rates is the difference in reporting experience required of radiologists interpreting mammograms in the USA and Canada compared with other jurisdictions such as the UK. While the US Mammography Quality Standards Act considers the reporting of only 480 mammograms per annum to be adequate,[54] the UK mandates that practising radiologists must read a minimum of 5000 mammograms per year to continue practising in mammography specialization.[55] The drastic contrast between these requirements suggests a clear difference in the experience that UK radiologists acquire early on in their careers over US radiologists and thus potentiates a propensity to generate reports with greater certainty and accordingly fewer recalls. Similar to the US regulations, the Canadian Mammography Quality Guidelines also only require that radiologists report at least 480 mammograms per year to maintain their qualification.[56] It can be suggested that this more lax requirement contributes to the relatively high FP and recall rates that can be observed in North America, as reading volume has been shown to have a significant impact upon the sensitivity and specificity of mammographic reporting.[57]

Shift from film to digital mammography

Mammographic screening employing digital technology as opposed to screen-film technology has become a prevalent practice in recent years. For instance, digital mammography units constituted 23% of all mammography units used clinically in the province of Ontario (Canada) in 2010.[58] This proportion of clinically employed digital mammography units has since climbed to 84.4% as of 2015.[59] Studies assessing the transition from screen-film mammography (SFM) to digital mammography in females older than 50 years have reported an increased sensitivity for detecting invasive carcinomas by digital technology.[60,61] However, the US/Canadian Digital Mammographic Imaging Screening Trial extended their study population to include females under 50 years of age (40–49 years) and subsequently reported that digital mammography did not confer significantly better diagnostic accuracy than SFM among the entire study population (40–69 years old).[13] However, the study did conclude that females in the 40–49-year age group, particularly those who were pre-menopausal or perimenopausal, were conferred significant benefits in terms of diagnostic accuracy from digital mammography compared with SFM. In this under 50 age group, a reduction in the FP rate at a given diagnostic sensitivity level was also observed as a result of the shift from SFM to digital.[13] The observed diagnostic advantage presented by digital mammography among the under 50 age group may be attributed to the post-acquisition image manipulation capabilities that digital technology can afford. The capability of manipulating the displayed image contrast would likely aid in identifying lesions existing among dense fibroglandular breasts that are often characteristic in young pre-menopausal females.

In contrast to the previously described study, other studies exist which have reported an associated increase in the FP rate following a transition to digital mammography compared with the rates previously observed during the clinical employment of SFM.[60–62] Based upon modelling of a transition from film to all-digital screening in the USA, Stout et al[63] estimate that digital screening contributes an additional 220 FPs per 1000 females above the FP incidence seen with the current mixed use of film and digital. It can be suggested that the rise in the FP rate following the transition to digital technology is actually associated with the use of computer-aided detection (CAD) image interpretation software rather than being attributed to factors inherent to the acquisition of images by digital mammographic units themselves.

Higher detection of benign lesions by digital mammography has contributed to the observed rise in the FP rate. A large number of studies have reported the superior detection of DCIS with digital than SFM.[60,64–68] Among 200,000 females screened over a 6-year period, DCIS was accurately found in 0.09% of the females screened by digital means compared with 0.05% by SFM ($p = 0.010$).[23] The most common radiographic appearance of DCIS is microcalcification.[60,66,69] A study demonstrating CAD's ability to identify 100% of cases presenting with microcalcifications provides a plausible explanation for the superior detection of benign and *in situ* lesions in the digital setting.[70]

A meta-analysis assessing the use of CAD against the interpretation of soft-copy digital mammograms alone showed that CAD significantly elevated the FP rate by an additional 1.19% over the rate observed with unassisted reporting (11%).[71] The contribution of CAD to the FP rate is attributed to its relatively low ability to distinguish between malignant and benign masses, its low sensitivity for detecting architectural distortions (50–72%) and its tendency to prompt inconsequential regions as suspicious.[72] CAD relies on global and local thresholding to identify the pixels on an image which possess signal intensities above a given value.[73] While it can often discriminate between calcification and noise by means of morphological erosion,[73] CAD can occasionally be at fault for incorrectly identifying a feature present upon an image which resembles a microcalcification.[74] Incorrect identification by CAD has also been demonstrated in the case of benign masses being prompted as malignant.[72] Ultimately, it is at the discretion of the radiologist to consider or rule out the suggested abnormality. However, it has been shown that less experienced readers are more susceptible to heeding advice from CAD rather than to scrutinize a suggestion.[75]

Patient characteristics

FPs are more probable in females who have undergone breast biopsies or have endured trauma to the breast, in general.[36,76] Tissue damage caused by surgical trauma, radiotherapy, biopsy or tissue puncture can lead to fat necrosis, the radiographic appearance for which can commonly resemble malignancy.[77] While the incidence of fat necrosis in the breast is only 0.6% and represents 2.75% of all breast lesions,[78] its presence warrants due consideration, since it may affect a proportion (regardless of how small the proportion) of females adversely if mistaken for a malignant lesion upon screening.

The age-related FP rate demonstrates a higher frequency at a younger age and declines with increasing age at the time of screening.[11,76,79,80] Younger females are at greater risk for an FP result because greater breast density and complexity are often associated with a lower diagnostic certainty.[29,81,82] Breast density is therefore also explanatory of the greater risk for FP results in pre-menopausal females than in post-menopausal females.[36,83]

Inherent limitations of conventional mammography

Poor discrimination between malignant and benign pathologies can be linked to limitations inherent to the method by which a mammogram is acquired. The two-dimensional (2D) projection of an X-ray beam through a three-dimensional volume of soft tissue results in the unavoidable superimposition of various structures upon an intricate network of the glandular tissue.

The summation of many layers of the overlying glandular tissue can easily mimic a stellate lesion and subsequently raise suspicion of malignancy.[84] A true stellate lesion can be clarified from a superimposition effect with the acquisition of extra images (magnified view, spot compression). However, these extra views are not performed often during a screening mammogram unless malignancy is highly suspected by the X-ray technologist. Consequently, these superimposition effects that mimic stellate

lesions frequently result in the recommendation for further investigation and diagnostic work-up.

Superimposition of the glandular tissue upon a benign soft-tissue mass can mimic the malignant appearance of spiculations extending from a mass.[84] Visualizing the mass on the perpendicular view can aid in distinguishing true malignancy from a superimposition phenomenon; however, this information is not always available, as some screening protocols only mandate the acquisition of a single projection.

Overall, the results presented in this section indicate a great dependence of the FP rate upon screening practices and radiologist perception. A need is evident for optimization of the screening schedule and for solutions which will facilitate superior discrimination of malignant from benign and normal glandular tissue in order to reduce the incidence of FPs.

RISK–BENEFIT ANALYSIS

Diagnostic follow-up

An FP result is perceived as a negative consequence of screening owing to the various harms associated with it. Patients affected by an FP have been observed to experience depression,[85] short-term anxiety[79,86,87] and lack of sleep[87] persisting for a short period of time up to 6 months following the initial recall examination.[87] Furthermore, concern regarding breast cancer development has been reported to persist in some individuals even 12 months following the receipt of a benign clinical diagnosis.[79,86] Beyond psychological effects, invasive diagnostic procedures such as biopsies can result in post-procedural pain lasting up to 2 weeks in approximately 30% of patients[88] and less often, patients may experience minor haemorrhage[89] and infection,[90] although these complications are very rare. From a financial perspective, diagnostic follow-ups are estimated to cost anywhere from $134.80 USD for additional imaging to $1374.69 USD for invasive diagnostic testing per FP.[63]

Although these harms are predominantly short term and are justified for patients in which progressive invasive cancer is detected, they are considered unjustified for those patients possessing true benign cases. Benign cases are defined as cases which do not require any intervention, nor are they any cause for concern. For this group of individuals, the emotional, financial and physical burdens associated with these tests impart detriment with no offer of benefit.

Of the patients recalled for additional diagnostic testing from the Nova Scotia Breast Screening Program (Canada), approximately 83% patients will undergo additional imaging, 15% patients will require stereotactic core biopsy and 2% patients will undergo surgical biopsy.[11] That is to say that 5.6%, 1.02% and 0.14% of all the females screened in the Nova Scotia screening programme received diagnostic imaging, core biopsy and surgical biopsy, respectively. It is noted that the rate of surgical biopsy in both the USA and the UK are similar to that in Canada such that 0.14% of females screened by US radiologists qualified under the Mammography Quality Standards Act[91] and just over 0.1% of females screened in the NHS breast-screening programme underwent surgical biopsy.[92] Subsequent to breast biopsy in patients aged 40–79 years from the US BCSC registries, 55–85% of pathology results were returned as truly benign (*i.e.* cases that do not include invasive cancer, DCIS or other atypical cellular growth characteristics).[93] These rates are again consistent with the rate observed among UK NHS breast-screening programme participants, whereby 70% of diagnostic biopsies resulted in benign diagnoses.[94] The proportion of benign diagnoses is even greater when taking into account diagnostic work-ups carried out by means of additional imaging and clinical examination. Data from the BCSC registries demonstrated that of 4082 patients prescribed to diagnostic follow-up by means of imaging, clinical follow-up or biopsy following mammographic screening, only 316 cases were diagnosed as invasive cancer or DCIS.[95] In this respect, the FP rate among the population of females sent for follow-up testing is 92.3%. When considering the FP rate among the entire population of screened females, a rate of approximately 8–10% does not appear to be excessive. However, when the rate is assessed within the population of females who are actually subjected to diagnostic follow-ups, it is evident that the FP rate is too high. This conclusion is justified based on the opinion that an acceptable FP rate would be characterized by an equal proportion of harm and benefit in the recalled population, at the least. However, it is evident that the proportion of females who currently experience detriment far outnumber those who confer benefit. To achieve an ideal 50/50 distribution of harm and benefit in the recalled population, the FP rate among the screened population would have to be reduced to 0.83% (Calculation A1). While it is noted that achieving an FP rate of 0.83% may be difficult without compromising the level of early-stage detection thus leading to late treatment and poor prognostic outcomes, the feasibility of achieving low FP rates such as that formerly stated is not unreasonable, as European randomized controlled trials have been able to lower rates to those approaching the ideal suggested here.[96,97]

Treatment of *in situ* lesions

The increasing detection and subsequent treatment of *in situ* breast tumours, particularly DCIS, has been debated in the scientific community in recent years. The implementation of population-based breast screening in the USA during the late 1970s was met with a concomitant increase in the number of DCIS cases detected.[98,99] In the 30-year span from 1974 to 2004, the DCIS incidence has increased from 1.87 to 32.5 cases per 100,000 females.[100] The increased detection of DCIS by screening mammography has led to extensive assessments involving the magnitude of overdiagnosis owing to breast screening;[101] that is, the detection of DCIS cases which would not have become clinically apparent owing to either the non-progression of disease or the manifestation of a different ailment before the consequences of DCIS could become threatening. Although overdiagnosis is often considered the primary harm of screening based on the assumption that overdiagnosis leads to overtreatment,[101] this review takes an alternative position, agreeing with the opinion of Michell,[102] in believing that overtreatment should be the primary focus rather than its predecessor overdiagnosis. While the two terms are often used interchangeably as a result of the assumption that almost all overdiagnosed cases will lead to overtreatment, efforts should be made to deviate away from this paradigm of thinking, as predictive information regarding pathological

progression becomes elucidated and thus treatment decisions following diagnosis become more informed. Although follow-up data collection is still ongoing, the Sloane project has gathered pathology, imaging and treatment data on thousands of DCIS cases to generate an archive of *in situ* breast cases with the goal of improving the management of patients diagnosed with DCIS.[103] The utility of this database may prove to reduce the incidence of invasive treatment administration following DCIS diagnosis and thus validates the distinction between overdiagnosis and overtreatment. The focus of this report will therefore be skewed towards the discussion of the consequences associated with overtreatment.

Up until recently, the relative uncertainty regarding the prognostic factors for carcinogenic progression of DCIS has led to a conservative recommendation of surgical treatment for almost all cases by clinicians. Data extracted from the Surveillance, Epidemiology and End Results registries indicate that over 97% of DCIS cases are treated by surgical intervention, while fewer than 3% of cases are treated non-surgically.[104,105] Treatment of DCIS by means of breast-conserving surgery (alternatively, lumpectomy) with adjuvant radiotherapy is the most frequently prescribed contemporary intervention.[104] Radiotherapy following lumpectomy has been proven effective in significantly reducing the local recurrence rate by approximately 50% when compared with lumpectomy alone (Table 1). Accordingly, radiotherapy also reduces the risk of breast cancer-related mortality compared with lumpectomy alone [odds ratio = 0.94, 95% confidence interval (CI) 0.88–1.00; $p = 0.03$][106] (Table 1). Despite these benefits, treatment of the breast with radiotherapy is also associated with perceived risks.

Whole-breast irradiation, as is carried out as an adjunct in DCIS treatment, has been associated with a risk of disease development in adjacent structures such as the cardiovascular system.[107] Radiotherapy of early-stage breast cancer in females treated from 1973 to 2001 conferred a significantly greater risk of mortality from cardiovascular disease when compared with non-irradiated females [relative risk (RR) = 1.58, 95% CI 1.29–1.95; 15-year follow-up].[107] Radiotherapy has been linked to cardiovascular disease because significant doses can be imparted to the heart and the coronary arteries during irradiation. The use of traditional radiotherapy technologies such as orthovoltage radiotherapy beams have resulted in the delivery of mean and maximum doses of 4.7 and 48.1 Gy to the heart, respectively.[108] The irradiation of a left breast tumour is especially detrimental owing to the delivery of a dose four times greater than that of a right breast irradiation.[108] Left-sided irradiation also imparts significant doses to the left anterior descending coronary artery (21.8 Gy in the left side *vs* 0.9 Gy in the right side[108]). To determine the extent of radiation-induced coronary arterial damage, myocardial perfusion imaging has been conducted. The results demonstrated marked deficiencies in cardiac perfusion in areas which received high doses.[109] Furthermore, atherosclerotic changes in coronary vessels and cardiac fibrosis are generally observed to be isolated to within regions subjected to the irradiation field.[110] These findings thus strongly indicate a role for radiation in contributing to cardiovascular morbidity.

In light of the cardiovascular detriment induced by radiation in the past, recent research suggests that the risk of cardiovascular mortality has decreased over the past decades to the extent

Table 1. Studies comparing local recurrence in ductal carcinoma *in situ* cases treated by breast-conserving surgery (BCS) with and without radiotherapy (RT) treatment

Characteristic	McCormick 2015[18]		Wapnir 2011[111]		Bijker 2006[112]		Rakovitch 2013[113]	
Study type	Prospective randomized control trial		Prospective randomized control trial		Prospective randomized control trial		Retrospective cohort (Ontario Cancer Registry)	
Study period	1998–2006		1985–1990		1986–1996		1994–2003	
Follow-up (median)	11 years		17.25 years		10 years		10 years	
Location	Canada, USA		USA		Europe		Canada	
Total (*n*)	636		818		1010		5752	
BCS only (*n*, %)	298, 47		405, 49.5		503, 49.8		3762, 65.4	
BCS + RT (*n*, %)	287, 45.1		413, 51.1		507, 50.2		1895, 32.9	
RT prescribed	50.4 Gy/25 frac/5 weeks		50 Gy/5 weeks		50 Gy/25 frac		50 Gy/25 frac/5 weeks	
Boost	–		10 Gy to surgical bed		–		–	
Local recurrence	BCS	BCS+RT	BCS	BCS+RT	BCS	BCS+RT	BCS	BCS+RT
Total (%)	6.7	0.9	35.0	19.8	26.2	14.8	19.5	12.3
Invasive (%)	2.8	0.45	19.6	10.7	13.0	8.0	10.0	7.0
In situ (%)	3.9	0.45	15.4	9.0	14.0	7.0	10.8	6.1
Contralateral recurrence (%)	4.8	3.9	7.9	9.3	5.8	7.7	4.8	5.1
Breast cancer mortality (%)	4.9	1.1	8.2	8.0	1.6	1.1	2.5	3.3

Frac, fraction.

where the risk in the irradiated population is the same as that in the general population.[107,114,115] The reductions in mortality risk have been attributed to modern radiotherapy techniques, leading to reduction in dose delivery to the heart and coronary arteries. The transition to megavoltage radiotherapy systems has reduced the mean dose to the heart by approximately 50% (4.7–2.3 Gy),[116] while other contributors to dose reduction include breath-hold techniques, respiratory gating and prone positioning.[117] While promising, the observed reduction in radiation-induced cardiovascular mortality must be followed for a longer period of time to validate its long-term resilience. Radiation-induced cardiovascular diseases typically have latent periods between 10 and 20 years.[107] Furthermore, cardiovascular morbidity remains to be a risk associated with radiotherapy, since cardiac doses of 2.3 Gy are still estimated to pose a risk of developing a long-term coronary event (*i.e.* myocardial infarction, ischaemic heart disease) at an excess incidence of 17.0% over an unexposed individual.[118,119]

Complications associated with lumpectomy itself must also be considered in the analysis of treatment risks. Bacterial skin infection manifesting subsequent to breast-conserving surgery presents as cellulitis or as a breast abscess.[120] Cellulitis is characterized by pain, erythema and swelling of the affected breast, whereas a breast abscess presents as a palpable mass. The most common cause for infection is microtrauma of the lymphatic vessels, leading to the stasis of fluid within the breast.[120] Oral antibiotic treatment is often sufficient; however, cases of persistent abscess will require incision and drainage.[120] Chronic pain persisting for over 5 years has also been reported to affect 31% of patients with lumpectomy.[121] Although the reported degree of pain is tolerable (2.5 on a 10-point visual analogue scale), the persistent discomfort is considered inconvenient for most patients.[120]

Considering the risks associated with radiotherapy treatment and surgical intervention, it is questioned whether invasive intervention for some DCIS cases is required at all. Presently, over 97% of DCIS cases are treated surgically; however, there is evidence suggesting that surgery and radiation treatment are unnecessary for a crop of lower risk cases that will never lead to clinical detection. Evidence supporting the existence of this undetected reservoir is present in the autopsy results for females over 40 years old who died of non-breast cancer-related causes. By means of histopathological analysis, Welch et al[122] identified 76 clinically occult cases of DCIS among 852 females who were autopsied between 1966 and 1997. The authors suggest that this 8.9% of undetected cases is significant enough to expect a favourable prognosis from at least a proportion of DCIS cases.

To further investigate this query, Sagara et al[105] analyzed the survival benefit of surgery ($n = 56{,}053$) compared with no surgery ($n = 1169$) for DCIS cases by means of a retrospective longitudinal cohort study. The authors found that breast cancer-specific survival was significantly different ($p < 0.001$) for patients who received surgery (98.5%) compared with those who did not (93.4%). However, for low-grade DCIS (15.8% of all cases), analysis showed that there was no significant difference in the breast cancer-specific survival rates (98.6% for surgery and 98.8% for non-surgery; $p = 0.95$). From this, we observe that radical interventions are not necessary to achieve a favourable prognosis for low-grade DCIS cases. Alternative treatment in the form of active surveillance (by means of endocrine therapy and biennial breast monitoring) has proven effective for low-risk cases such as these.[123] Further work investigating the feasibility of active surveillance is currently ongoing in a randomized control trial entitled the Low Risk DCIS (LORIS) trial, which will employ surgical and active surveillance arms among a cohort of females recruited between 2014 and 2020.[124] The UK-based LORIS trial is a positive step towards elucidating the comparability of treatment efficacy for surgical interventions and active monitoring of low-risk DCIS cases. The outcomes of this study will help clarify the risks and probable outcomes associated with a given treatment and will thus facilitate a more informed decision-making process for both the physician and the patient. Apart from the initiation of the LORIS study, there is an evident lack of randomized controlled trials being conducted to address the question of appropriate treatment actions for DCIS. It is surprising that the necessity for additional trials has not been widely addressed, considering the significant consumption of healthcare resources by DCIS treatment and the debate that the topic has generated among the scientific community. The implementation of trials in other jurisdictions throughout North America and Europe would be of utmost importance to determine the potential influence that legislation-specific lifestyle and screening practices have upon the outcome of conservatively managed low-grade DCIS. Results conferred by LORIS and additional trials will be valuable in establishing future treatment guidelines.

The evidence discussed here validates the claim that overtreatment of diseases classified as *in situ* is indeed taking place. For those cases which are Stage 0 high-grade cases or those which will progress to invasive cancer, surgery and radiotherapy are justified to reduce the risk of breast cancer-related death. Considering that the current risk of radiotherapy-related cardiovascular mortality is equivalent to the cardiovascular mortality risk observed in non-irradiated individuals, the benefit in terms of gained survival prevails and treatment for high-risk DCIS cases is considered justified. However, for those cases which are at a lower risk for carcinogenic progression, there are substantial risks of developing radiation-induced cardiovascular morbidities and experiencing complications associated with the surgical procedure itself, such that it can be suggested that the complications far outweigh the lack of survival benefit conferred from surgical and radiation-based treatments. A further consequence of overtreatment in DCIS extends to the consumption of resources in the form of consumable goods and staff from a number of departments throughout the healthcare setting. It cannot be stressed enough that the first crucial step in preventing overtreatment will be physician education regarding DCIS treatment outcomes, the information for which can be reliably gained only by following trials such as LORIS.

Based upon an assessment of DCIS treatment decisions, the FP rate is considered too high because it is contributing to the incidence of overtreatment, such that we are acting beyond the extent of necessity and benefit to the point where detriment is

becoming an issue among those overtreated. Furthermore, based upon the observation that DCIS itself can lead to breast cancer-related mortality and upon the fact that the increasing incidence of DCIS detection *via* breast screening has not resulted in a reduction in the rate of screen-detected invasive cancers,[124] it is reasonable to suggest that DCIS cannot always be classified as a precursor lesion to invasive breast carcinoma. This report therefore agrees with claims in the literature which state that DCIS should be considered a *de facto* breast cancer.[19] In this respect, DCIS should not contribute to the FP incidence, effectively resulting in a slight drop in the FP rate by 0.09%.[23]

REMEDIATING THE FALSE-POSITIVE RATE

In response to the excessive incidence of FPs, predominantly contributed by unnecessary diagnostic recall, this section will assess screening schedules to determine whether the FP rate may be reduced by a change in protocol. Furthermore, discussion will extend to the employment of alternative image acquisition and analysis techniques to address the limitations faced in discriminating between benign and malignant diseases.

Breast screening

The ideal screening protocol would limit the frequency of screening in order to limit the harms associated with FPs and those directly associated with the practice of screening, while still detecting malignancy at a treatable stage. Furthermore, the screened population should be limited to those individuals whose prognoses would confer significant benefit from screening. Although the FP rate in mammography is comparable with the rates of other screening methods [*i.e.* prostate-specific antigen: 13.3%[125] and Papanicolaou (Pap) test: 11.1%[126]] indicating comparable technical competence, the risks associated with mammography can be considered much greater than the aforementioned screening tests, given the additional harm of radiation carcinogenesis posed directly by mammographic image acquisition. In this respect, detriment conferred as a result of FPs and that conferred as a direct result of the screening practice (namely, the risk of radiation carcinogenesis) are not mutually exclusive events; rather, they compound with each other to produce a net harm. Therefore, when setting out to optimize a mammographic screening protocol, the harms associated with FPs cannot be assessed independent of the risk for radiation carcinogensis.

One single mammographic view will result in a mean glandular dose of 1.5–2 mGy.[127] A typical mammogram will deliver a total of approximately 3–4 mGy to the glandular tissue of each breast. Although this is considered a relatively low dose, the negligibility of low-energy mammography X-rays is questioned owing to the potential for these low doses to induce double-strand breaks (DSB) beyond the levels of unirradiated controls.[128] Mills et al[129] exposed the human breast cell line, MCF 10A, to 3, 9 and 30-mGy mammography X-rays (29 kVp) and found that 9 and 30-mGy irradiations yielded significantly elevated levels of radiation-induced phosphorylated H2AX foci. Phosphorylated H2AX foci yield was used as the end point to assess DNA DSB induction. Colin et al[130] further observed persistence of DSBs at 24 h post-irradiation. The abundance of persistent DSB lesions confers the cell vulnerable to aberrant DNA rejoining and thus formation of chromosomal aberrations. Consequently, non-lethal chromosomal anomalies are capable of promoting the development of breast cancer *via* activation of oncogenes such as human epidermal growth factor 2[131] and inactivation of tumour suppressor genes such as p53 and breast cancer-associated genes 1 and 2.[132]

Radiation-induced breast cancer related to mammography is not an end point that can be measured directly in a screened population owing to the inability to distinguish a radiation-induced cancer from a cancer induced by an alternative aetiology. However, risk models can be used to predict the number of breasts cancers attributed to screening radiation. In three publications, the risk of radiation-induced cancer from screening was estimated using the Biological Effects on Ionizing Radiation excess absolute risk model.[38–40] Among these estimates, the total lifetime risk of developing breast cancer as a result of biennial screening fell between 10[40] and 14[38] cancers induced per 100,000 females, where 1[40]–4[39] of those would result in mortality. The rates of radiation-induced cancer are negligible compared with the number of deaths prevented by screening (242–1302 prevented deaths).[38,39] However, it is important to note that a study of eight cohorts of females receiving breast irradiation (including the female Japanese atomic bomb survivors from the Life Span Study) demonstrated a greater excess risk of developing breast cancer when exposed at a younger age.[133] That being said, radiation exposure from screening would have a greater impact upon an individual who started participating in screening at age 40 years as opposed to age 50 years, for example. Among these 3 studies, 1 study compared the effect of annual screening with biennial screening upon radiation-induced cancer incidence to find that annual screening (27 cancers) results in 2 times more cancers than biennial screening (14 cancers).[38] These results indicate a need for minimizing the screening frequency while still achieving cancer detection at a relatively early stage in order to maintain a good prognosis.

In an observational study by White et al,[28] biennial screening for 40–74-year-old females was found to be associated with a higher but non-significant probability of late-stage cancer detection above annual screening. Furthermore, a UK randomized control trial found a statistically significant difference in the proportion of tumours >20 mm in the triennially screened group (28%) compared with those screened annually (21%).[134] However, a difference in the grade and node status was not found. This pool of data is further diversified by a report of no difference in tumour size or stage for annual *vs* biennial screening in the 50–74-year age group.[29] However, triennial screening did prove to increase the incidence of late-stage cancers discovered. The pooling of these results leads to the conclusion that a biennial schedule is sensible to prevent cancer progression to a late stage.

Breast cancer mortality in relation to screening has also been assessed. A meta-analysis combined relative ratios for breast cancer mortality to find a magnitude of benefit that was similar between annual (RR = 0.77, CI 0.61–0.96) and biennial (RR = 0.77, CI 0.59–1.0) screening frequencies when compared with no screening in females 50–74 years old.[135] In contrast, screening of females 40–49 years old at any interval was not effective in significantly reducing the risk of breast cancer

mortality (RR = 0.99 annual, RR = 0.88 biennial). Similarly, the Canadian National Breast Screening Study 1 also saw no reductions in breast cancer mortality upon screening females 40–49 years old, over a 25-year follow-up period. The RR of breast cancer mortality in the Canadian National Breast Screening Study 1 was found to be 1.36 (95% CI 0.84–2.21) at 8.5 years,[136] 1.14 (95% CI 0.83–1.56) at 13 years,[137] 1.06 (95% CI 0.80–1.40) at 16 years[138] and 0.99 (95% CI 0.88–1.12) at 25 years[44] compared with a control group which did not undergo screening. It is therefore suggested that screening of females under 50 years does not confer greater utility over routine self examination and care. In females 50–74 years, screening was effective in reducing the rate of breast cancer mortality. The interval with which screening was carried out (1 or 2 years) was not influential; thus, a 2-year screening interval is considered adequate to reduce breast cancer mortality.

Regarding females over 70 years of age, past study has estimated the provision of little to no benefit by screening in this age group owing to the perceived manifestation of diagnosis and treatment of cancers that never would have become clinically apparent otherwise.[33] However, a longer life expectancy for individuals in today's modern society[139] is justification for the required assessment of this age group. Vacek et al[140] performed a prospective study upon a population of 20,697 females over 70 years of age with no history of breast cancer. Upon following the cohort, they observed a 9% decline in screening participation each year after 70 years of age, while reporting a concurrent increase in the number of clinically detected invasive breast cancers. These findings themselves indicate that at least a proportion of screen-detected cancers will progress to the extent of clinical detection within the lifetimes of older females. Furthermore, clinically detected cancers are generally found at a later stage than screen-detected cancers[140,141] and the stage at which invasive cancer is detected in patients older than 70 years proved to be greatly influential upon mortality risk.[140] Simon et al[141] determined that the breast cancer mortality risk related to advancement of cancer in this age group can be limited by screening at an interval protracted over a period no longer than every 2 years. These results collectively indicate continued utility for screening on a biennial schedule for females over 70 years.

Taken together, the screening of females between 40 and 49 years old would not confer utility, since breast cancer mortality rates are comparable for both screen-detected and clinically detected cancers. The exclusion of these younger females also reduces their risk for radiation-induced carcinogenesis. In females 50–74 years, annual screening was proven unnecessary, while triennial screening demonstrated harm manifesting as an increase in late-stage cancers. An optimal screening protocol would therefore be represented by the biennial screening of females over 50 years old. Considering that the current screening recommendations in Canada match this proposed schedule, it would not be reasonable to make modifications to these screening protocols to reduce the FP rate, since they are already optimized to prevent detriment.

It can be suggested, however, that US females may benefit from the protraction of breast screening to a biennial frequency from the current annual schedule. Furthermore, the screening of US females encompassing the ages of 40–49 years may be omitted in an effort to limit the occurrence of FPs attributed to the greater glandular tissue density often associated with younger breasts. This action may be justified by the observed lack of mortality-based benefit associated with the screening of this younger age group.

Strategies to address the issues surrounding litigation risk

Litigation risk is a prominent contributor to the volume of recall examinations prescribed subsequent to a screening mammogram. One way of reducing the recall and FP rate in mammography is to reduce the actual incidence of litigation cases enacted towards radiologists such that a marked decline in the rate of medical malpractice claims may lead to a relief in the pressure that is felt by radiologists reporting on mammograms. A large proportion of mammography-related malpractice claims in the USA is related to misinterpretation of radiographs, leading to delayed diagnosis of invasive cancer.[142] Available literature states that one prominent reason for the high volume of malpractice claims in the USA is an apparent lack of education or even perhaps the provision of misinformation to the general public by organizations seeking to promote the benefits of breast screening in an endeavour to encourage participation in screening programmes.[143,144] The perception of the public is based largely upon the information that is provided to them, which places emphasis upon the benefits of screening but rarely focuses upon the limitations that are associated with the practice. These limitations include factors which are inherent to the screening modality itself (*i.e.* superimposition of structures obscuring visibility of the clinically relevant lesion) and can extend to radiologist error. Kopans[144] notes that no matter the skill level and experience of a given radiologist, it is a probabilistic certainty that a radiologist will occasionally make an unintentional error in failing to see a visible pathological abnormality. This is not to say that we should allow a radiologist to occasionally practice intentional negligence; rather, there is always a probability of committing honest errors in reporting. It is therefore the responsibility of the healthcare providers and the associations advocating for participation in mammographic breast-screening programmes to also inform the general public of the real limitations of the screening procedure such that participants are not coming in with false perceptions of the screening tool's detection power. The first step towards reducing the volume of medical malpractice claims therefore manifests as the need to address public education and disseminate information regarding the risks or limitations of the screening process.[143] A policy which has been proven effective in a Dutch mammography screening trial is the provision of a written invitation to participate in screening accompanied by a written disclaimer regarding the potential for an incorrect occult diagnosis upon screening.[41] The invitation letter further encouraged participants to seek further consult in the case of persistent breast abnormality or complaints following the receipt of a negative diagnosis upon screening. The authors suggested that providing participants with this information likely contributed to the relatively low volume of litigation claims set forth by the participants in their screening study.[41]

While public education is a positive first step towards reducing the volume of mammography-related malpractice claims, studies have also demonstrated an importance of personal communication between the affected patient and the radiologist in affecting the outcomes of a possible legal situation. A survey conducted by Gallagher[145] indicated that patients prefer to be informed regarding harmful errors that were committed during the course of their care and that communication of information cultivates trust between themselves and the healthcare provider. Furthermore, in a study by van Breest Smallenburg et al,[41] open communication between the interpreting radiologists and females who either had interval cancer or were diagnosed with invasive cancer during a subsequent screening round proved effective in preventing the enactment of legal action regarding medical malpractice. Also noted in this study was the observation that in all three cases of females who filed malpractice claims, further information and communication was not sought out prior to the claim being made. Based upon the results of this study, it was suggested that open discussion with the patient regarding the errors that were made by the radiologist during reporting likely enhanced the patients' satisfaction and trust in the healthcare providers such that the motivation to file a malpractice claim was mitigated. Other studies involving medical practice outside of the field of mammography have similarly suggested a possible reduction in litigation risk following the communication of errors by the radiologist with the patient.[146,147] These study results therefore suggest the utility of a paradigm shift in radiologist perception regarding the disclosure of errors to patients. The current outlook on this issue reflects a reluctance of radiologists to communicate the occurrence of medical errors to patients, the hesitation for which is, ironically, motivated by a fear of litigation.[148,149]

While the litigation rate may be addressed, in part, by alluding to the perception of the public regarding mammography screening, emphasis must also be placed upon the perceptions of the radiologists themselves, to effectively address the issue of excessive diagnostic recall. With this in mind, it is reasonable to consider modifying current practices along the lines of implementing adverse consequences in response to excessive ordering of unnecessary diagnostic tests. A previous example from which future action may be modelled is the restriction of payment for diagnostic testing to only medically justified cases of chronic low back pain by the Ontario Government in Canada.[150] In 2012, the Ontario Government announced that the Ontario Health Insurance Plan would only cover diagnostic testing services which were justified by a strong suspicion of or a known presence of pathology in the lumbar spine region. In cases where a physician orders a test which is deemed unnecessary by the Health Insurance Act section 18.2(1) and 18.2(2), the physician will be responsible for payment of the testing fees.[150] In the context of recommending further diagnostic work-up following screening mammography, the rationale for adopting similar regulations is to motivate the radiologist to increase his/her awareness regarding the risks associated with the acquisition of unnecessary recall examinations. In this respect, the decision to recommend a patient for follow-up diagnostic testing is motivated not only by a perceived litigation risk, but also counteracted by his/her duty to limit the patient from experiencing unnecessary harm, whether that is in the form of physical injury or emotional distress. It is noted, however, that the implementation of such disciplinary actions places further stress upon the radiologists and may result in the deferral of new and existing radiologists from entering or continuing in the field of mammographic image interpretation. This consequence is postulated based upon the previous observation of physician outmigration from the province of Ontario following the imposition of coverage cuts across a broad range of medical services.[151] Therefore, while the suggestion of implementing regulations to prevent the skew towards ordering excessive volumes of diagnostic examinations is entertained, the consequences of these disciplinary actions must be assessed further to determine their feasibility. A comprehensive discussion regarding these consequences, however, is beyond the scope of this review.

Developments in computer-aided detection

Because a change in the screening schedule is not a feasible route to limit the FP rate in the case of Canadian and European mammographic screening, a focus should also be placed upon implementing measures which will aid in accurately characterizing malignant lesions from benign lesions.

One of the contributors to the high FP rate is the implementation of digital technology and more specifically the use of CAD. Since the introduction of CAD into the clinical setting, many developments have been made in an effort to improve its sensitivity in detecting malignant disease. An early improvement was the reduction of false cueing of noise as microcalcifications by means of adjusting the pixel threshold and the configuration of morphological erosion kernels.[73] Another step towards improving lesion classification manifested as the integration of artificial neural networks (ANN) into the CAD design. For mammographic CAD, developers trained ANN using sets of 100–10,000 images containing numerous biopsy-proven malignant and benign cases.[152,153] The function of ANN is to take input data such as border continuity, spiculation and contrast measures to produce an output which estimates the degree of malignancy associated with a given case.[154] As a result of this development, CAD does not simply identify all incidences of abnormality on a radiograph; rather its scope now extends to interpreting the classification of a lesion. It is expected that the association of a malignancy suspicion score with each CAD cue will aid in limiting the FP reporting rate by helping radiologists to differentiate between benign and malignant lesions.[154]

A further effort to limit the FP rate manifests as a shift in the manner in which CAD cues are presented to the end-user. Hupse et al[153] hypothesized that an interactive decision support system would be more effective than the traditional prompt system that is currently used in clinical practice. The interactive approach is based on the premise that a CAD cue will not be presented to the reader unless a region of suspicion is queried by a mouse click. Query of a suspected region by the reader will subsequently reveal the contour identified by CAD and its associated suspicion score. The intention of an interactive system is to aid in the interpretation of regions deemed suspicious by the reader, while limiting the FP incidence. The authors presume that the hiding of cues will be effective in minimizing reading

disruptions and biases that are normally brought on by the numerous prompts that are readily displayed.[153] Initial testing of interactive CAD has demonstrated a statistically significant improvement in detection sensitivity concurrent with a reduction in the FP rate when compared with prompt-based CAD (receiver-operating characteristic area under curve: 0.62 for interactive CAD and 0.57 for prompt-based CAD; $p = 0.009$ with a 95% confidence level).[153]

Overcoming tissue superimposition

The 2D depiction of a three-dimensional breast is one of the major limitations inherent to mammography. As previously discussed, this can lead to the false representation of a benign mass as having malignant characteristics. An alternative imaging modality which can be employed to overcome tissue superimposition is digital breast tomosynthesis (DBT). DBT takes advantage of the basic principles associated with conventional digital mammography, while acquiring images in a modified manner. In DBT, multiple low-dose projection exposures are acquired by an X-ray source moving in a limited-range arc relative to a stationary compressed breast.[155] The projections are used to reconstruct cross-sectional images of the breast that are representative of sections spaced 1–10-mm apart.[155,156]

The inspection of the breast tissue on DBT planar sections has been shown to be very useful in ruling out suspicious regions which manifest as a result of tissue superimposition.[157,158] Studies comparing the use of DBT and digital mammography for screening showed that combining both modalities results in the greatest reduction in the FP rate (15[159]–50% reduction[160]) with a concurrent improvement in the cancer detection rate (27[159]–34% increase in detection[160]). The caveat associated with acquiring both sets of images is that the patient sees a twofold increase in the dose, since acquisition of a single DBT view can impart a mean glandular dose of up to 2.28 mGy.[161] However, one study which assessed radiologist reporting of 2D mammograms synthesized from DBT data compared with digital mammograms acquired by conventional means found that the use of either mammogram resulted in similar rates of true-positive and FP reporting.[162] The comparable magnitudes of detection sensitivity and FP reporting among digital mammograms and DBT-synthesized mammograms thus show promise for the employment of DBT-synthesized mammograms as an alternative to the acquisition of a conventional digital mammogram. In this respect, radiation dose can be limited to the contribution by DBT image acquisition only, while diagnostic sensitivity and specificity may be maintained with the employment of the synthesized 2D mammogram as an adjunct to the volumetric set of cross-sectional DBT slices through the breast.

The evidence presented here suggests the utility of DBT as a means by which superimposition in conventional mammography can be overcome. However, the limitations associated with DBT, including the potential delivery of doses to out-of-field anatomical structures and the cost of clinical implementation, must be assessed further to determine its feasibility as a stand-alone screening modality.

CONCLUSION

A review of the literature has indicated a contribution by screening procedures, litigation risk, technological limitations and radiologist perception to the incidence of FP reporting in mammography. These contributions have subsequently led to an excessive volume of unnecessary diagnostic work-ups and to the unwarranted treatment of patients possessing low-risk pathologies. These actions can be considered unwarranted, since the degree of clinical action has extended considerably far beyond the confines of benefit and necessity. Based upon this observation, the FP rate associated with mammography in North America can be considered too high and thus, there is presently an evident need for a reduction in the FP rate. In response to this finding, the present report has focused upon addressing factors which are considered major contributors to the overall FP incidence. Modification of the US screening protocol from an annual to a biennial schedule may be implemented to reduce the FP rate while maintaining a beneficial outcome in terms of early-stage cancer detection and breast cancer mortality. Improvements in radiographic interpretation software and the implementation of imaging methodologies which overcome breast tissue superimposition also demonstrate great promise for remediating the FP incidence. In regard to litigation concerns, educating the public regarding the limitations of screening may prove to decrease the overall incidence of mammography-related litigation and subsequently ameliorate radiologists' concern over medical malpractice litigation. Accordingly, a decrease in the recall and FP rates would also be expected, given the suggested link between litigation concern by radiologists and propensity to order further diagnostic testing following a screening mammogram. Upon taking the appropriate actions to remediate and improve upon the excessive FP rate associated with mammography, the harms associated with breast screening may be reduced to the extent whereby the magnitude of benefit offered by breast screening may be more clearly quantified.

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APPENDIX A

Sample calculation 1: required reduction in the overall FP rate among the screened population to achieve an acceptable FP rate (equal proportion of harm *vs* benefit in the recalled population).

Population of Canadian female aged 45–74 years in 2010: 3.171×10^6.[A1]

Assumption: 3.0×10^6 female participate in screening

Assumed FP rate in screened population: 10%[A2] − 0.09%[A3] = 9.91% (in this estimate, DCIS is excluded from the benign disease classification owing to reasons discussed in "Treatment of benign lesions" section).

Total number of screened female receiving FP result:

$$\begin{aligned} \mathrm{NFP} &= (3 \times 10^6)(0.0991) \\ &= 2.973 \times 10^5 \end{aligned} \quad (1)$$

Total number of females who get recalled subsequent to screening (including both benign and malignant results):

$$\begin{aligned} N_{\mathrm{recall}} &= \frac{(2.973 \times 10^5)}{(0.923)} \\ &= 3.22102 \times 10^5 \end{aligned} \quad (2)$$

From N_{recall}, we can deduce that $(3.22102 \times 10^5 - 2.973 \times 10^5) = 24{,}802$ females were diagnosed with invasive cancer or DCIS. Thus, to achieve an acceptable FP rate, the other half of the recalled population can be made up by benign results.

Acceptable FP rate for the screened population:

$$\begin{aligned} \mathrm{FP} &= \frac{(24,802)}{3 \times 10^6} \\ &= 0.00827 \\ &= 0.83\% \end{aligned} \quad (3)$$

Strategies to decrease the FP rate to this extent will have to be employed carefully so as not to decrease the number of invasive cancers detected while targeting the limitation of recall for benign cases.

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