2. SCREENING TECHNIQUES

2.1 X-ray techniques

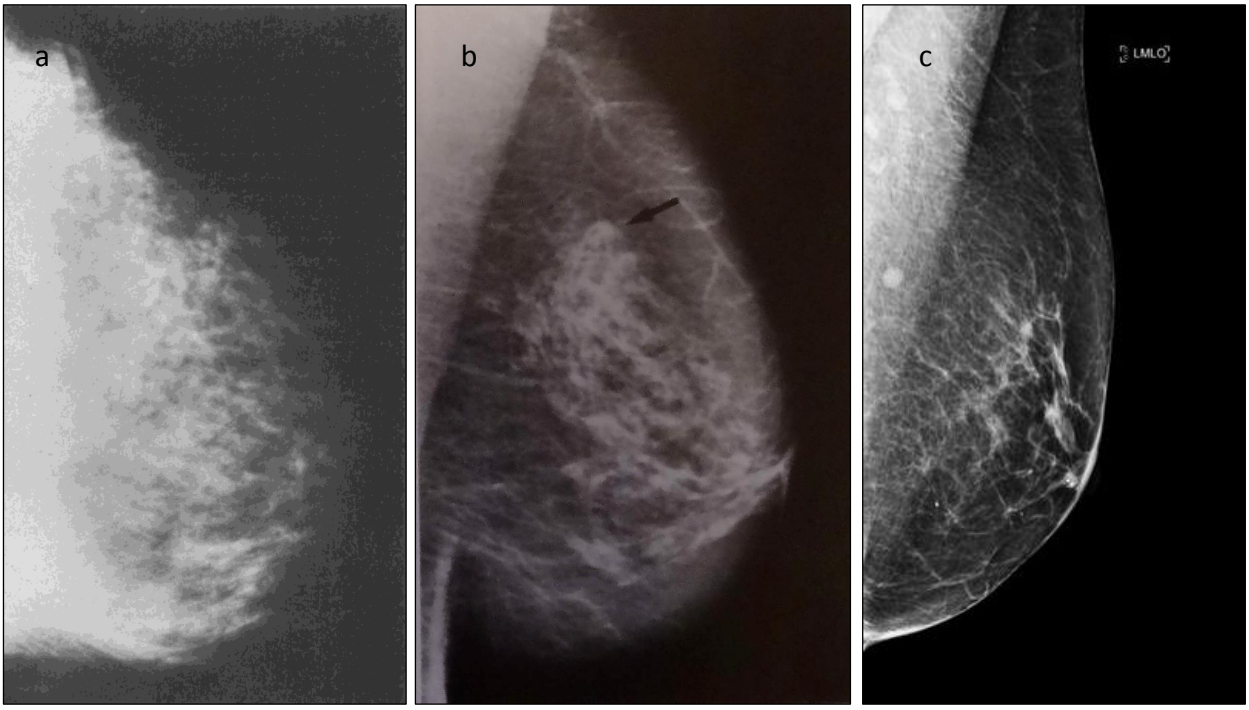
The original technique for mammography was introduced by Salomon in Germany in 1913, 18 years after the discovery of X-rays by Roentgen (Salomon, 1913). A mammogram is formed by recording the two-dimensional (2D) pattern of X-rays transmitted through the volume of the breast onto an image receptor. Breast cancer is detected radiographically on the basis of four major signs: a mass density with specific shape and border characteristics, microcalcifications, architectural distortions, and asymmetries between the radiological appearance of the left and right breast (Kopans, 2006). These signs are often very subtle, and in order for them to be detected accurately and when the cancer is at the smallest detectable size, the technical image quality of the mammograms must be excellent (Young et al., 1994; Taplin et al., 2002). At the same time, because ionizing radiation is carcinogenic, it is desirable that the radiation dose received by the patient is as low as is reasonably achievable consistent with the required image quality (Young et al., 1997). The trade-off between imaging performance and radiation doses inevitably involves compromises, and optimization of imaging is inextricably linked to technical design elements in the imaging system. Fig. 2.1 shows examples of mammograms obtained during different periods and with different equipment. Fig. 2.1a shows a mammogram from one of the randomized controlled trials (RCTs) in the early 1980s; the image is poorly exposed, and both the contrast and the spatial resolution are poor, making detection of small lesions difficult. The mammogram in Fig. 2.1b, from the same era, is of much higher quality and illustrates a cancer seen on the basis of an irregularly shaped mass (black arrow). Fig. 2.1c shows a digital mammogram, illustrating the enormous improvement that has occurred in both technology and technique. Breast positioning, penetration of the tissue, and contrast are excellent, allowing visualization of a small area of ductal carcinoma in situ (DCIS) seen on the basis of microcalcifications, and, more importantly, providing the opportunity to detect an immediately adjacent high-grade invasive cancer 1.7 mm in diameter.

Excellent image quality is an essential component but not, on its own, a sufficient component to ensure a high level of accuracy in cancer detection. Of equal or perhaps greater importance are the skill of the radiographer who conducts the examination and sets the equipment operating factors and the skill, experience, and judgement of the radiologist who interprets the images. This emphasizes the need for thorough training and ongoing maintenance of skills of these individuals.

2.1.1 X-ray equipment

Mammography was originally carried out using general-purpose X-ray imaging systems. Although the principles remain the same, it was gradually recognized that the specific imaging requirements for effective detection of breast

Fig. 2.1 Examples of mammograms of different quality



(a) Mammogram produced in the early 1980s. (b) Mammogram from the same era produced with better breast compression, exposure factors, and film processing, illustrating a tumour mass (arrow). (c) Mediolateral oblique digital screening mammogram of a woman aged 62 years, illustrating a cluster of microcalcifications near the nipple, later diagnosed as high-grade ductal carcinoma in situ (DCIS) 4 mm in diameter, and an adjacent area of invasive cancer 1.7 mm in diameter.
Unpublished clinical mammograms kindly provided by (a) Dr Roberta Jong, Toronto, Canada, (b) Dr László Tabár, Falun Central Hospital, Sweden, and (c) Dr Pavel Crystal, Mount Sinai Hospital, Toronto, Canada.

cancer would be better met if equipment were adapted specifically for the purpose of mammography (AAPM, 1990; NCRP, 2004). Between the mid-1960s and 1990, several important technical improvements were introduced, and these resulted in a highly specialized imaging system (Feig, 1987; Haus, 1987). A major technical change came about in 2000 when the first digital mammography systems became available.

Some of the specialized features of mammography systems are briefly described here.

Very high spatial resolution is required in mammography to allow discrimination of fine microcalcifications and morphological features of soft tissue structures such as masses. To support this resolution requirement, the effective size of the X-ray source for mammography (known as the focal spot or target) is much smaller than that used for most general radiography procedures. Modern mammography systems most frequently use a nominal focal spot size of 0.3 mm for regular mammography and of 0.1 mm for magnification procedures (IAEA, 2014).

The spectrum, or distribution of X-rays of different energies in the beam, is also specialized for mammography (Jennings et al., 1981; Beaman & Lillicrap, 1982). To maximize the contrast between soft tissues such as normal fibroglandular tissue and carcinoma, it is desirable to use an energy spectrum with much lower energies than are used for general radiography.

The X-ray spectrum is determined by three factors: the material used to form the X-ray target, the type and thickness of metallic filter placed in the X-ray beam, and the kilovoltage applied to the X-ray tube (IAEA, 2014). These factors affect both the spectral shape and the intensity of X-rays in the beam that is incident upon the breast for imaging. Two other variables directly influence the amount of X-rays incident on the breast, but not the contrast characteristics of the beam: the tube current, typically measured in milliamperes (referred to as "the mA") and the exposure time (the time during which this current flows from the cathode of the tube to the target to produce the exposure).

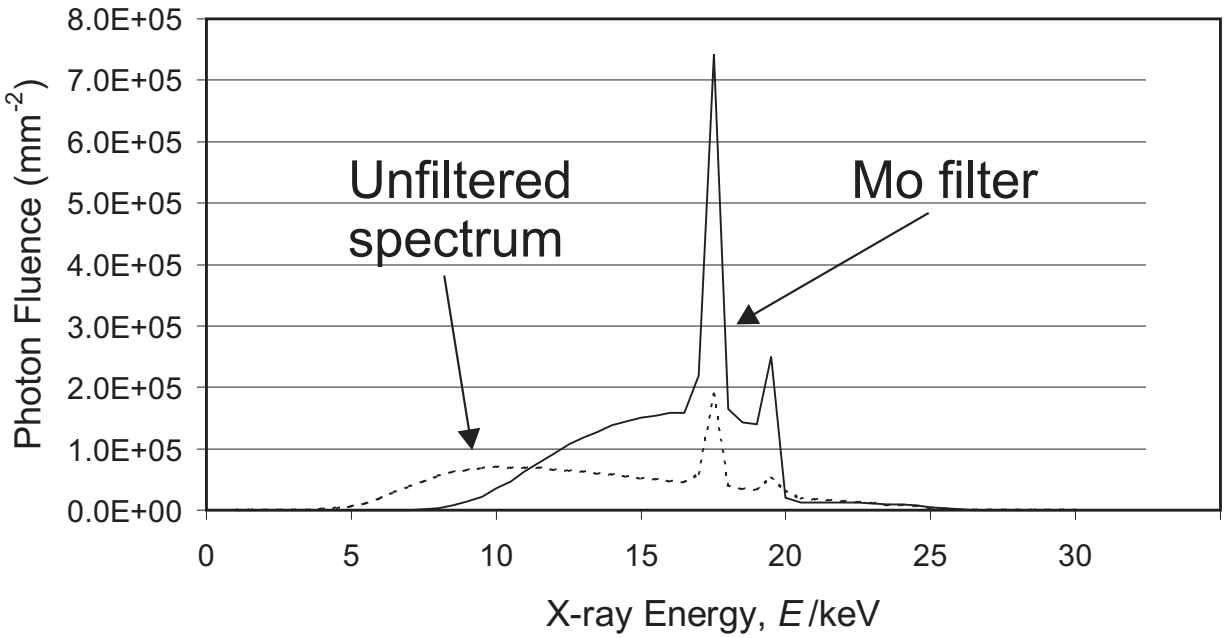
Decreasing the energy of the X-ray spectrum increases the differences in X-ray absorption between different tissue types, thereby increasing contrast. However, low-energy X-rays are more heavily absorbed in the breast, and therefore more need to be used to obtain an acceptable number of photons reaching the imaging system. This results in an increased radiation dose to the breast. As in any type of X-ray imaging, a compromise is required between maximizing contrast and controlling radiation dose.

In 1967, a specialized mammography tube was introduced by Gros in France (Gros, 1967). The tube was equipped with a molybdenum (Mo) target, rather than the tungsten used in general-purpose tubes. Mo emits characteristic X-rays at 17.5 keV and 19.5 keV in addition to a broader-energy bremsstrahlung spectrum (X-rays emitted when an electron suddenly slows down when impinging on a target material). Operated at a tube potential of 24–32 kV for imaging using a screen-film detector, the tube provides a more optimal compromise between low energy (with high contrast and the accompanying high dose) and a more-penetrating, high-energy spectrum that allows low-dose imaging but at the penalty of reduced image contrast.

The Mo target is typically used in conjunction with an external Mo beam filter. X-ray attenuation of the Mo filter increases sharply just above the characteristic energies emitted by the Mo target, creating a relatively transmissive energy "window" that allows the characteristic X-rays (emitted just below the K-edge energy of Mo) to pass through the filter and expose the image. The result is selective removal of both the low-energy and high-energy X-rays, leaving a fairly narrow spectrum (Fig. 2.2) with an effective energy suitable for imaging the breast.

In general radiography, it is customary to compensate for increased body-part thickness or attenuation properties by adjusting the kilovoltage applied to the tube (IAEA, 2014). However, when the spectrum is formed largely with characteristic X-rays, as is the case with many mammography systems, changing the kilovoltage has a limited effect on the energy spectrum, and this could make it difficult to adequately penetrate dense breast tissue to obtain the required image contrast in some parts of the breast. Inadequate contrast could result in cancers being missed. To alter the effective energy of the beam to a greater degree, most modern mammography systems provide a second, readily interchangeable filter, typically composed of rhodium (Rh). Together with a selection of increased kilovoltage, this Mo–Rh combination provides a more-penetrating spectrum than is possible with the Mo–Mo target–filter combination. A further increase in energy can be achieved by fitting the X-ray tube with dual target materials, for example with a Rh target in addition to the standard Mo target. The higher energy of the characteristic X-rays from Rh provides a more-penetrating beam, albeit with lower contrast. Depending on the breast thickness and fibroglandular content (often referred to as breast density), target–filter combinations of Mo–Mo, Mo–Rh, or Rh–Rh can today be selected and used in conjunction with a kilovoltage selection that optimizes imaging performance.

Fig. 2.2 Use of selected target materials and K-edge filters to define the energy spectrum for mammography



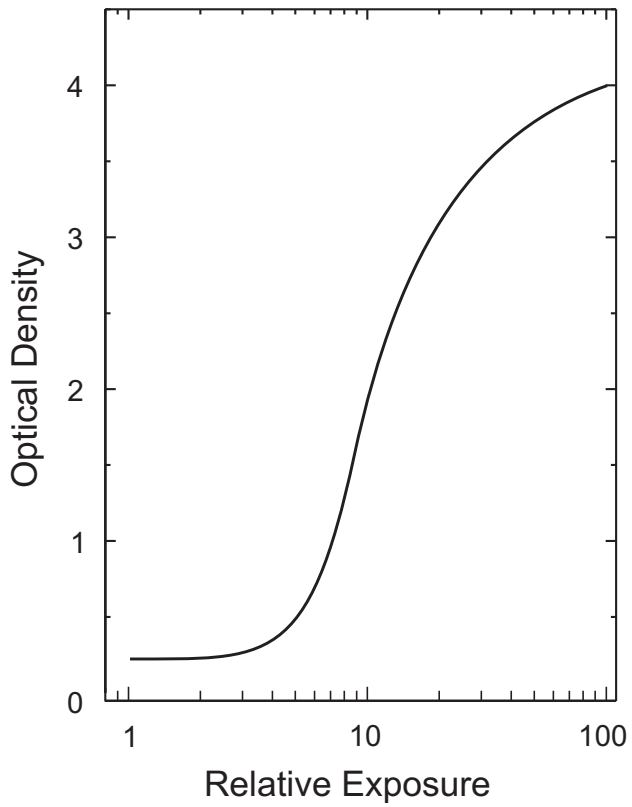
The filtered spectrum has been scaled upwards for clarity. Characteristic emission peaks from molybdenum (Mo) are seen at 17.5 keV and 19.5 keV.
Courtesy of Dr. M. Yaffe.

2.1.2 Screen-film mammography

To achieve high spatial resolution, the first mammograms were recorded on film exposed directly to X-rays (IAEA, 2014). The X-rays produce a latent image on the film, and this image is rendered visible by chemical processing of the film emulsion. This causes the silver bromide in the emulsion to be converted to metallic silver, which appears black upon trans-illumination of the processed film with white light. The degree of blackness, or optical density, increases with the amount of exposure of the film, which, in turn, is related to the transmission of X-rays through the breast. The optical density provides the visual signal, conveying information to the radiologist about the breast composition and the presence of suspicious lesions. Cancers and microcalcifications tend to be more absorbing of X-rays than fat or normal fibroglandular tissue; they therefore appear as areas of decreased optical density (white), whereas the fatty areas appear darker.

The characteristic curve of a mammography film is shown schematically in Fig. 2.3. The characteristic curve of the film transforms the X-ray fluence transmitted through the breast into the optical density of the processed film. Because the curve is sigmoidal in shape, the brightness of the image at each point will vary nonlinearly with X-ray exposure. The curve also transforms the contrast in the X-ray fluence transmitted through the breast into a difference in the optical density of the processed film (the displayed image contrast). Therefore, the displayed contrast is dependent on the gradient or slope of the characteristic curve at each point. Because the curve is nonlinear, the displayed contrast, which would ideally depend only on the tissue composition and the presence of lesions in the breast, also

Fig. 2.3 Characteristic curve of mammographic screen-film X-ray detector



This creates a compromise between the range of exposure that can be recorded and the contrast in different parts of the image. Courtesy of Dr. M. Yaffe.

depends on the degree of X-ray exposure to the film at each point.

In the earliest systems, the fraction of incident X-rays interacting with the film (referred to as the quantum efficiency) was very low, and so a relatively high exposure was required to achieve a useful working optical density, to provide adequate image brightness and contrast.

In the mid to late 1970s, non-screen film was largely replaced by dedicated mammographic screen-film image recording systems (Haus, 1987). Typically, these use a single thin screen to preserve spatial resolution and a film coated with emulsion on only one side. The system is used with a back screen, i.e. the X-rays pass through the film to strike and be absorbed by the phosphor of the screen, and the light emitted by the screen travels backwards towards the breast to be absorbed by the film emulsion. Intimate screen-film contact is essential for good resolution, and several different mechanisms have been used to maintain contact, including sealable plastic vacuum envelopes and cassettes containing a foam layer behind the screen to serve as a spring. These systems are considerably more sensitive to X-rays compared with non-screen film, and the peak gradient occurs at a much lower exposure. Further improvement in image quality came about, stimulated to a considerable extent by Logan-Young, a radiologist in Rochester, New York, USA, who brought together radiologists and scientists to promote scientific analysis of the performance of mammography systems and their technical advancement (Logan-Young & Muntz, 1979).

Rare-earth phosphor screens, which were introduced in the 1980s and improved progressively over the next decade (Brixner et al., 1985), provided a large increase in sensitivity. This occurred both through improved quantum efficiency of the screen compared with film alone and because of the amplification resulting when one X-ray, carrying say 20 keV, was absorbed and created thousands of light quanta, each carrying only 2–3 eV.

Logan-Young also advocated the use of firm compression of the breast during exposure. Compression serves several important purposes in improving image quality while reducing doses. It spreads out the tissues, reducing superposition, and thereby makes the boundaries of lesions easier to see. With a thinner breast, the transmission of primary radiation is higher, allowing a dose reduction while at the same time reducing the scatter-to-primary ratio of the X-ray beam exiting the breast and incident on the imaging system. More-uniform breasts represent less of a range of X-ray intensities and therefore require less exposure latitude or dynamic range from the film. This allows the use of higher-gradient films,

thereby offering greater contrast. When the breast is immobilized, there is less image blurring due to anatomical motion, and therefore improvement in spatial resolution. Compression also reduces the degree of geometric magnification of tissues within the breast, since all parts of the breast are closer to the imaging system. This last factor reduces the amount of blurring caused by the X-ray focal spot, again improving spatial resolution. Inadequate compression can contribute to poor image quality and reduce the detectability of small or subtle lesions.

Even at the relatively low energies used for mammography, X-rays scattered in the breast and recorded by the image receptor are still a major problem, degrading image quality by producing a haze over the image, reducing the contrast produced by the directly transmitted primary X-rays, and also adding random quantum noise without providing useful information (IAEA, 2014). The scatter-to-primary ratio at the image receptor can be as high as 0.6–1.0. When film is used to record the image, part of its limited range is "used up" in recording scattered radiation. In the 1980s, specially designed anti-scatter moving grids were introduced for mammography. These grids reduced the scatter-to-primary ratio to about 0.1, thereby markedly improving image contrast. However, a grid does not transmit all of the useful primary radiation; some is blocked by the septa of the grid, and some is absorbed in the interspace material that separates the septa. In addition, because some of the film-darkening energy of scattered X-rays is removed from the beam, it is necessary to increase the patient's exposure to maintain the chosen film optical density. The resulting Bucky factor (the factor by which patient dose must be increased) when a grid is used is about 2.5–3. Nevertheless, the improvement is considered so important that grids are now routinely used in mammography. For medium to large breasts of medium to high density, the gridless technique is now considered inadequate for film mammography, due to insufficient contrast and significantly decreased visibility of cancers in such breasts.

A major improvement in mammography technology was the introduction of automatic exposure control (IAEA, 2014). One of the limitations of radiographic film is that the gradient of the characteristic curve varies with exposure level. It is very small at low and high exposures and has a maximum value within a limited range of intermediate exposures. It is difficult for the technologist to determine the appropriate exposure factors to ensure that the most important part of the breast parenchyma is imaged with the highest gradient. The automatic exposure control incorporates a sensor located beyond the image receptor (so that the shadow of the sensor is not seen on the mammogram) that discontinues the exposure when a predetermined amount of radiation has fallen onto the sensor. The location of the sensor can be moved around the image plane to select the area of anatomy of greatest interest. The automatic exposure control played a very important role in improving the consistency of film optical density, contrast, and radiation exposure in mammography.

Modern mammography systems have advanced further in terms of automatic selection of exposure parameters (IAEA, 2014). The X-ray attenuation of the breast depends on both compressed thickness and composition. Whereas the automatic exposure control controls only the exposure time according to the overall attenuation of the breast, it is valuable to tune the X-ray spectrum according to compressed breast thickness and composition. This can be done by measuring both the compressed breast thickness, by means of a sensor attached to the compression device, and the rate of X-ray transmission through the breast. The rate can be determined via a short test exposure (lasting only a few milliseconds) conducted at the beginning of the imaging sequence using standard exposure conditions appropriate for the breast thickness. Based on the measured transmitted X-ray exposure rate, the

choice of X-ray target, filter, and kilovoltage can be adjusted automatically by the mammography equipment to optimize penetration and contrast in imaging, providing a better balance between image quality and radiation dose for each image produced.

2.1.3 Digital mammography

Despite the established value of film-based mammography for diagnosis and screening, screen-film mammography has several technological shortcomings that reduce its accuracy. Most of these stem from the fact that film is used both as part of the detector for image acquisition and as a display device. This necessitates certain compromises in performance for each of these roles. Because the gradient of the characteristic curve of the film depends on the exposure level (Fig. 2.3), the image contrast between tissues in the breast is reduced at both low and high exposures, corresponding to the most radiopaque and radiolucent parts of the breast. This loss of contrast can impair the visibility of structures within the breast in the image. Attempting to improve contrast by using a film emulsion with a higher gradient only reduces the exposure range over which the contrast is high (the exposure latitude or dynamic range), again causing parts of the breast to be imaged suboptimally.

Digital mammography attempts to overcome these limitations by decoupling image acquisition from display and archiving functions, and optimizing each separately. An electronic detector replaces the screen-film system for acquisition. Images are stored in digital form in computer memory and displayed on a high-resolution monitor. Additional advantages of digital mammography are the ability to make a detector that has increased quantum efficiency while maintaining spatial resolution, the elimination of the components of image noise due to film granularity and non-uniform sensitivity of the phosphor screen, the possibility of more-efficient approaches to reducing the effects of scattered radiation, and the ability to perform quantitative operations or analysis on the digital images.

Several different detector technologies have been developed and used for digital mammography. Further information on this topic is available (Pisano & Yaffe, 2005; Yaffe, 2010a).

Unlike screen-film technology, in which the elements of a phosphor X-ray absorber in contact with a film coated with photographic emulsion in a light-tight cassette are fairly common across all vendors, there is more diversity in the technology used for digital mammography, especially for the X-ray detectors used. This leads to differences in spatial resolution, signal-to-noise ratio, scatter-rejection characteristics, and radiation doses delivered to the breast. The photostimulable phosphor system, also often referred to as computed radiography, was introduced as a generic technology for use in digital mammography. In a series of physics measurements, computed radiography was found to have inferior performance characteristics, in terms of spatial resolution and signal-to-noise ratio at equivalent dose to the breast, to the other digital mammography technologies, which are typically collectively referred to as digital radiography systems (Young & Oduko, 2005; Yaffe et al., 2013).

These findings were later corroborated by observations of lower cancer detection rates and positive predictive values (PPVs) in screening programmes (Chiarelli et al., 2013) where computed radiography systems were used compared with those obtained with other types of digital mammography systems. Subsequently, the use of computed radiography systems was prohibited in the Ontario, Canada, screening programme. Similar observations were also made in the breast screening programme in France (INCa, 2010). Overall, among mammography systems, digital radiography systems appear to produce the highest and most consistent diagnostic image quality with a lower radiation dose.

Although digital mammography has considerably wider exposure latitude than screen-film mammography, it must still be optimized to provide excellent image quality at the lowest dose consistent with those quality requirements. The automatic exposure control need not be set to provide a target image optical density, as this can be adjusted on the computer monitor during image display, but instead a target image signal-to-noise ratio. There is also evidence that performance will be more optimal if digital systems are used with X-ray spectra of slightly higher beam quality than those used for screen-film mammography (Berns et al., 2003; Huda et al., 2003; Young et al., 2006).

(a) Image processing of digital mammograms

The digital mammogram is recorded on a numerical scale, where each pixel is given a value from 0 to 16 383 (where 16 383 represents the maximum transmitted X-ray intensity) (Yaffe, 2010b). This range exceeds the capability for optimal viewing by the human eye and also that of electronic display devices. Various types of image processing can be used to improve the conspicuity of relevant anatomical information before display by compressing or transforming this range and by correcting for certain imperfections in the imaging system. The first operation is commonly referred to as flat-fielding, gain correction, or uniformity correction. Detectors used to produce digital images frequently contain many (several million) elements, referred to as dels or pixels. These tend to vary slightly in sensitivity. In addition, the X-ray beam is not perfectly uniform in intensity. This causes variations across the image that would create fluctuations in the image unrelated to any features of the breast itself, a type of image granularity (referred to as structural or fixed-pattern noise). Fortunately, with digital technology these variations are generally temporally quite stable. The point-to-point fluctuations can be removed by recording an image of a uniform slab of X-ray absorbing material and using it to correct all subsequent images, thereby creating a very uniform image field.

It is also possible to improve the sharpness of display by various edge enhancement techniques, such as unsharp masking. Here, a blurred version of the original mammogram is made by filtering the image in the computer with a function that controls the degree of blurring. When this blurred mask is subtracted from the original image, the resulting difference image is composed mainly of the sharp features of the mammogram without the broad area structures. This edge map is then added to the original image to provide enhancement of the edges of microcalcifications, fine fibres, and blood vessels. The amount of edge enhancement is controlled by a weighting constant by which the edge image is multiplied before the addition takes place. Excessive enhancement also increases the intrinsic granularity of the image, and such noise can interfere with image interpretation. After flat-field correction and sharpening have been applied to the image, it is referred to as the "for processing" or "raw" digital mammogram.

A useful image processing feature applied to digital mammograms is referred to as peripheral equalization. The breast varies in thickness, and therefore in attenuation of X-rays, from the central region out towards its periphery. Such a variation in X-ray transmission is seldom relevant to the task of detecting suspicious compositional changes in the breast, and its recording would waste part of the limited display range of the viewing monitor. Therefore, it is common to implement a correction to the image that suppresses the overall change in image signal due to the changes in breast thickness, preserving the range to allow more-sensitive detection of lesions (Byng et al., 1997; Stefanoyiannis et al., 2000).

Another means of enhancing the display is through modification of the histogram of image display values. If the histogram is calculated, it is frequently found that certain display values are not used or are used infrequently. Histogram

equalization is a technique to remap the image display values so that all grey levels in the display are used with approximately equal frequency. This can help to make better use of the capability of the display (Pizer et al., 1987; Pisano et al., 1998; Goldstraw et al., 2010). The correction is applied in small subregions of the image to optimize the local contrast. Again, care must be taken to control the amplification of display contrast to avoid excessive appearance of noise. After these operations have been applied to the original "for processing" image, it is referred to as the "for presentation" image.

(b) Display of digital mammograms

Digital mammograms can be printed; however, the advantage of being able to manipulate the brightness, contrast, and sharpness of the images interactively while viewing them is then lost. High-resolution, 5-megapixel monitors are available for "soft copy" display, and this is now the preferred means of viewing and interpreting digital mammograms (IAEA, 2014).

The final, and perhaps most useful, image processing operations are look-up table modifications. Most digital mammography systems are configured such that this is done by the radiologist interactively while viewing the "for presentation" image. The range of values of a digital mammogram exceeds the sensitivity capability of the eye for contrast perception and also the capability of most electronic display devices. Typically, on a monitor it is considered feasible to display the image in terms of 10 bits or 1024 shades of brightness at any one time. A look-up table is used by the digital mammography computer to map the original range of image data at 16 384 levels to the 1024 levels available for display (Pisano, 2004).

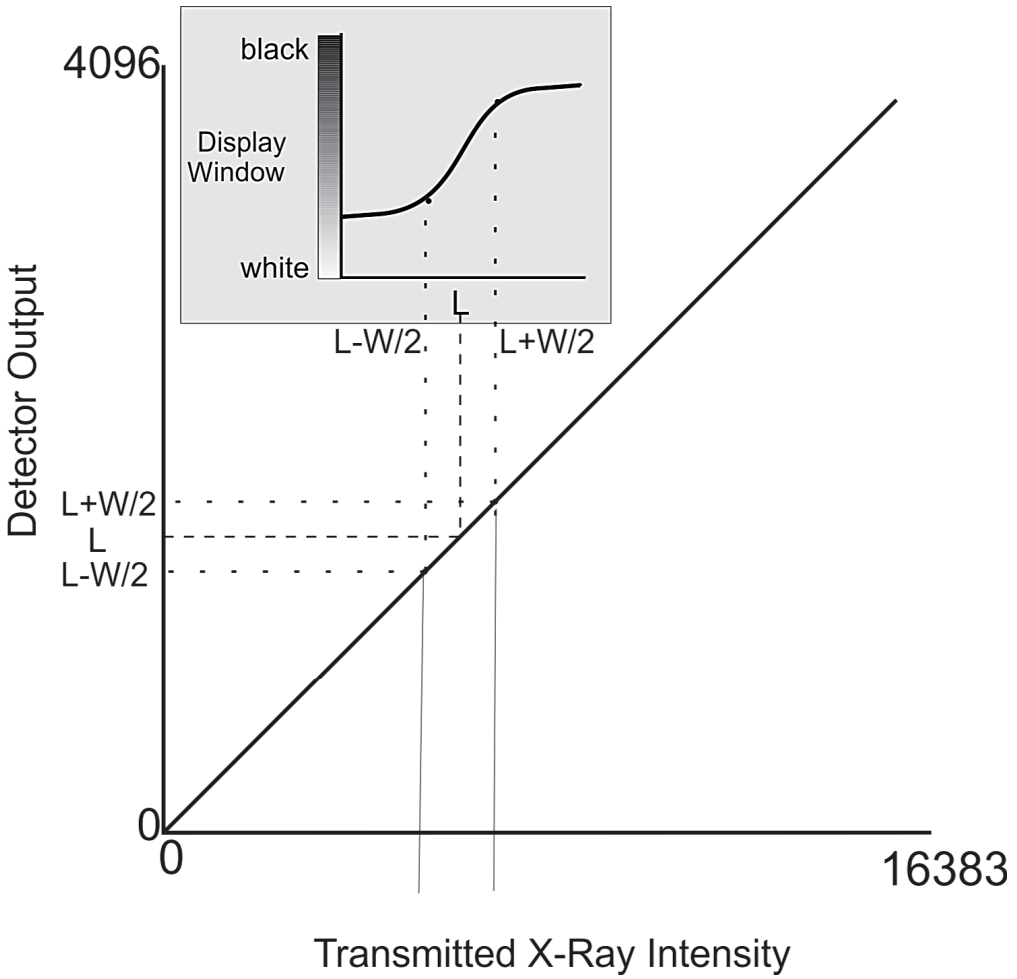
A simple use of look-up table modification, illustrated in Fig. 2.4, is called linear scaling and clipping. It is familiar to users of computed tomography systems, where a window level, L, is set, which describes the image value that will be displayed as the mid-value of display intensity, and a window, W, is chosen, which is the range of original image values to be displayed. Image values below L – W/2 are displayed as black, and those above L + W/2 are displayed at the maximum intensity of white. Intermediate values are displayed on a linear range of grey values between black and white, so that the entire range of display values is used. This allows the user to ensure that the anatomy of interest will be viewed in the optimal part of the display brightness as well as to adjust contrast as desired. By controlling WL, the display window can be used to inspect regions of the breast that vary greatly in density. The degree of contrast with which the image is displayed is increased (without the necessity to re-image the breast) by reducing W.

The value of W can be reduced until the appearance of noise in the displayed image becomes unacceptable. This is determined by the intrinsic noise of the image acquisition, which, in turn, can be controlled by the use of very-low-noise X-ray detection systems and by the dose to the breast. The dose can be chosen according to the required signal-to-noise ratio for a particular imaging situation, rather than by the need to produce an image of a given "brightness".

More generally, it may be found that other, nonlinear mappings from image intensity to display brightness may be more suitable. These may be found to better compensate for deficiencies in the display device or for the perceptual characteristics of the observer. An optimal look-up table modification remains to be determined.

One of the important advantages of digital imaging is that these image processing features can be turned on and off instantly to allow the radiologist to view the images under different enhancement conditions. This can facilitate decisions about whether suspicious structures are real or artefactual. Although very sophisticated image processing is possible, it is likely that the main benefit of image enhancement will derive from relatively simple operations that improve contrast in dense regions or sharpen subtle

Fig. 2.4 Interactive control of image brightness and contrast characteristics during viewing by look-up table adjustment



L, window level, digital pixel value set to mid-value of display intensity; W, window, range of original digital pixel values to be displayed between full black and full white.
Created by the Working Group.

structures. The optimal manner in which to display image contrast scales, the possible value of equalization, and the role of edge enhancement and other image sharpening techniques in digital mammography must be carefully investigated in terms of their efficacy.

Another important advantage of digital mammography is the immediate availability of current and previous examinations. Comparison with previous mammograms is extremely valuable for screening mammography, considering that each breast is individually different. Consideration of changes from a previous mammogram allows detection of subtle abnormalities, whereas a finding that is stable over time may not require a recall.

Digital mammography has been available since 2000. Due to the number of pixels available on high-resolution monitors (typically about 5 million), it is usually not possible to present even a single mammogram at full resolution on a monitor. In screening the radiologist is often required to work with eight images, four from the current examination and four from a

previous examination. This implies that multiple monitors be used in a digital mammography workstation and, even so, that it would be necessary to present images at reduced spatial resolution when viewing the entire mammogram and then to apply zooming or scrolling operations to inspect areas of interest at full spatial resolution. This requires that the image manipulation tools provided with the digital mammography workstation are fast and user-friendly and that the radiologist undergoes a learning process to develop a regimen for efficiently and thoroughly inspecting the mammograms.

2.1.4 Digital breast tomosynthesis

An important limitation in mammography is that it is a projection imaging technique, where shadows from structures throughout the thickness of the breast superpose to form the image. The conspicuity of a lesion is frequently reduced by the obscuring effect of normal fibroglandular tissue of similar X-ray attenuation properties located along the path of the X-ray beam, above and below the lesion. This is most pronounced for women with dense breasts (those in which there is a high proportion of fibroglandular tissue; see Section 2.1.9). Overlap of tissues from different planes in the breast creates structural complexity in projection images that can mask the presence of a cancer in the dense breast, reducing sensitivity, or can mimic the presence of a lesion that does not exist, resulting in reduced specificity. Reducing the effect of tissue superposition in images should improve both sensitivity and specificity.

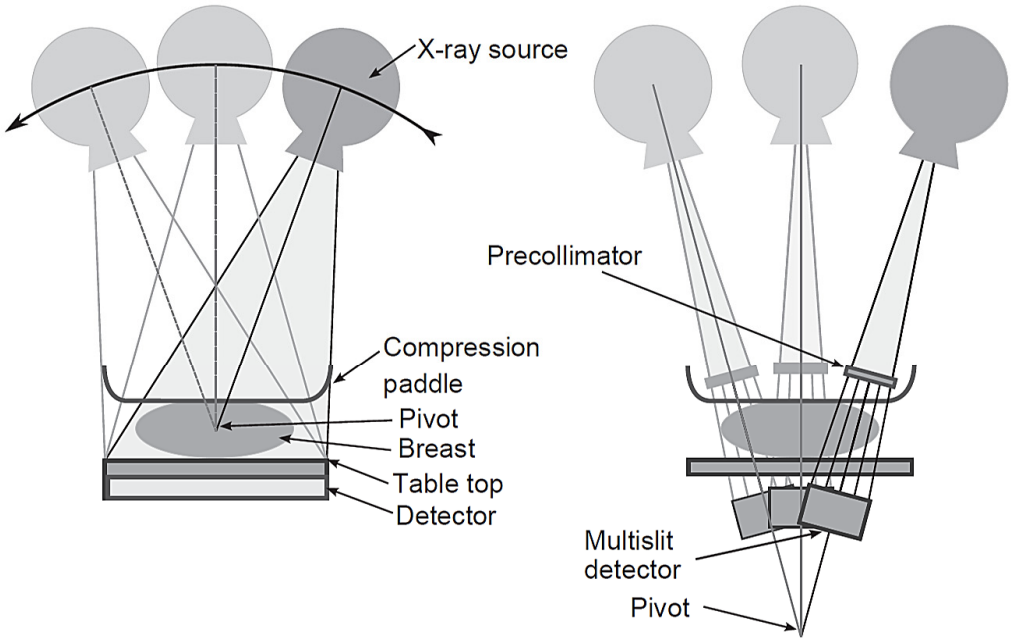
Digital breast tomosynthesis is a technique that produces quasi three-dimensional (3D) images of X-ray attenuation coefficients from a series of about 9–25 projection images (very-low-dose conventional mammograms) acquired over a limited range of angles around the breast (Fig. 2.5; Yaffe & Mainprize, 2014). The 3D image is created by mathematical reconstruction of the data in this set of 2D images. It is possible to make lesions more conspicuous by largely eliminating the effects of tissue superposition from the planar images that are presented. Furthermore, the morphology of lesions can be appreciated more easily, improving discrimination between malignant and benign lesions. This may simplify the diagnostic imaging algorithm by reducing the number of additional assessment procedures. Finally, using tomosynthesis, lesions can be localized in three dimensions, facilitating more accurate planning of surgery or radiation therapy.

Tomosynthesis can be performed on a modified digital mammography system that has a motorized gantry system (Niklason et al., 1997; Wu et al., 2003). This can be advantageous because conventional projection mammography could be performed on the same unit as the need arises (for screening, magnification viewing, characterization of microcalcification, etc.). Reconstruction is accomplished using algorithms similar to those used for computed tomography (Gordon et al., 1970; Mueller et al., 1998; Chidlow & Möller, 2003). Doses can be kept low while maintaining high-quality images; the dose for a tomosynthesis examination is of 3–5 mGy, comparable to that for a two-view digital mammography (Yaffe & Mainprize, 2014).

The reconstructed images are often viewed as a "movie loop" in which adjacent x–y planes (parallel to the X-ray detector) are displayed sequentially and resemble a series of 2D mammograms, each representing a "slice" of tissue in the breast (Yaffe & Mainprize, 2014). Within these 2D images, the spatial resolution (x–y plane) is the same as or similar to that of a conventional digital mammogram (0.05–0.14 mm), but the slice-to-slice resolution (z plane) is considerably coarser (0.5–1 mm). Also, because a complete range of angular data is not obtained, the data set is highly undersampled, giving rise to artefacts.

The quality of the reconstructed image and the dose to the breast are dependent on the

Fig. 2.5 Schematic of a digital breast tomosynthesis system



The X-ray source moves in an arc around a pivot axis, generally placed near the breast support.
Reprinted from Yaffe & Mainprize (2014). *Radiologic Clinics of North America*, Volume 52, issue 3, Digital tomosynthesis: technique, Pages 489–497, Copyright (2014), with permission from Elsevier.

angular range and number of projections, the dose used per projection, and the performance of the X-ray detector and electronics.

An examination that consists of the 3D mammogram plus the conventional 2D mammogram requires a higher total radiation dose to the breast than either mammogram alone. Once a 3D data set has been created, it is possible to synthesize 2D views by projecting through the data set onto traditional 2D planes, thereby simulating either the craniocaudal or mediolateral oblique views. This can be done without any additional radiation dose, and appears to provide acceptable image quality and adequate clinical performance (Skaane et al., 2014a; Zuley et al., 2014).

Studies on the performance of tomosynthesis are presented in Section 5.5. Radiation doses are discussed in Section 2.1.6.

2.1.5 Breast computed tomography

The availability of flat-panel digital radiography detectors has stimulated recent efforts to develop true 3D dedicated breast computed tomography systems. These consist of a table on which the patient lies in the prone position with the breast pendant into the centre of a digital X-ray system that rotates in a horizontal plane below the table (Boone et al., 2001). These systems produce tomographic images, with isotropic spatial resolution elements, although spatial resolution is generally designed to be coarser in the x–y plane compared with tomosynthesis to allow control of the required radiation doses to achieve adequate signal-to-noise ratio. Clinical evaluation of prototype breast computed tomography systems is currently under way (Chen & Ning, 2002, 2003; Lindfors et al., 2008).

2.1.6 Radiation dose

The majority of the X-ray dose received from mammography examinations is to the breast. With proper imaging technique, the thyroid is not exposed to direct radiation and receives only a very small dose scattered towards the thyroid from breast tissue. Similarly, if a woman is pregnant, the direct dose received by the embryo or fetus is close to zero. The small amount of radiation directed towards the pelvis is greatly reduced, first by attenuation by the breast and the breast support of the mammography unit, then by X-ray absorption by tissue overlying the conceptus, and finally due to the distance from the breast.

In the early use of mammography, the image was recorded on direct-exposure film without intensifying screens. It is estimated that the dose to each breast of average compressed thickness and composition from a two-view examination was on the order of 30 mGy (Conway et al., 1994). The xeroradiographic method, using a sheet of amorphous selenium as the X-ray detector, was introduced in the early 1970s and resulted in doses to the two breasts of about 8 mGy (Haus, 1983; Conway et al., 1994).

A series of technical developments introduced for mammography enabled a reduction of the radiation doses received by the breast (Feig, 1987; Haus, 1987; AAPM, 1990; Yaffe, 1990; NCRP, 2004). These included (i) the introduction in the late 1970s of intensifying screens, which provided improved quantum efficiency (absorption of the X-rays) compared with direct-exposure film, as well as a high degree of signal amplification; (ii) improved sensitivity of film emulsions to light; and (iii) technical advances in the chemistry and technique used to process the film. The original screen-film combinations for mammography were introduced in the late 1970s and were used without an X-ray anti-scatter grid. These required doses to the breast of about 1 mGy for the two views (Hammerstein et al., 1979; Haus, 1983).

Other technical developments or alterations in imaging technique had the effect of increasing radiation dose while improving image contrast or reducing noise. Factors that caused an increase in dose, accompanied by better image quality, included (i) use of a grid, which doubled or tripled doses but produced much better image contrast; (ii) the necessity to use thin phosphor screens, to preserve high spatial resolution; (iii) use of reduced kilovoltage, to improve contrast; (iv) use of increased optical density in images, to make use of the highest gradient available with the film; and (v) the choice of fine-grained films, to reduce the image-degrading effects of film granularity. More aggressive compression of the breast improved contrast while reducing dose.

The overall result of the many technical developments that occurred mainly in the 1980s and 1990s was a major decrease in dose from the levels used with non-screen film technology; doses to the breast for screen-film mammography in 2000 were considerably lower than those required with xeroradiography (8 mGy) but higher than those used with the earliest screen-film systems (1 mGy) (Suleiman et al., 1999).

Digital mammography with more-efficient X-ray detectors requires lower doses without loss of diagnostic accuracy. Digital radiography mammography systems operate at doses that are on average 22% lower than those used for screen-film mammography (Table 2.1). However, if a system uses an inefficient detector technology or is not operated optimally, the doses can be similar to or exceed those used for film (Young & Oduko, 2005).

The combined procedure of digital mammography plus tomosynthesis increases the total radiation dose. In their comparison of digital mammography versus combined digital breast tomosynthesis and digital mammography for screening, Skaane et al. (2013) estimated the dose as 3.2 mGy for two-view digital mammography

Table 2.1 Radiation dose to each breast (mGy) from a two-view examination with different mammographic techniques

Reference	Screen-film mammography	Digital mammography	Digital breast tomosynthesis	Digital breast tomosynthesis + digital mammography
Hendrick et al. (2010)	4.7	3.7		
Yaffe et al. (2013)	3.2	2.3		
Skaane et al. (2013)		3.2	3.9	~7

alone and approximately 7 mGy (3.2 mGy for digital mammography plus 3.9 mGy for digital breast tomosynthesis) for the combined procedure (Table 2.1). If the synthesized 2D projection image can be used to replace the standard digital mammography, then no further radiation is required than that needed for digital breast tomosynthesis alone.

The dose values discussed correspond to a standard screening examination with two views to each breast. Single-view protocols will result in doses that are about 50% lower but will increase the risk that some breast tissue will not be included in the examination. Those women who are recalled due to abnormal findings at screening will have additional imaging procedures performed. Ultrasonography and magnetic resonance imaging (MRI) are used for some purposes, but women may also receive additional X-ray views, for example magnification mammography. This will result in increased dose to those women. The actual increase will depend on the specifics of the procedure (e.g. whether the entire breast is imaged or only an area of concern), but is roughly one half of the two-view mammography dose (digital or screen-film, as appropriate) for each additional X-ray image acquired of the breast. Evaluation of the radiation risk is presented in Section 5.3.4.

2.1.7 Quality assurance and quality control in mammography

The ability of a breast cancer screening programme to achieve an impact is heavily dependent on two general categories of activities. Both fall under the overall umbrella of quality assurance (see also Section 1.5.3d).

The first aspect of quality is closely related to the operational standards of a screening facility or programme. This includes procedures for encouraging participation in screening and compliance with the recommended screening intervals, assessment of positive screening findings, and monitoring of performance and outcomes. There are many excellent references setting out these standards (BreastScreen Australia, 2001; Klabunde et al., 2001; NHSBSP, 2005; Perry et al., 2006a, 2013; CPAC, 2013).

The second category is more closely related to the activities of acquiring and interpreting the screening images. The ability to detect breast cancer with high sensitivity and specificity is closely linked to the technical quality of the mammograms and the skill of the radiologists. These aspects of quality begin with the establishment of appropriate standards for qualifications, the training requirements of personnel, the specifications for the purchase of equipment, and the definition of the exposure factors for imaging.

Once an initial high-quality environment is established for screening, quality control refers to the set of procedures and tests that will enable that high quality to be maintained over time.

Guidelines for quality control in mammography for both screening and diagnostic purposes have been developed by many countries and by several international organizations (see Hendrick et al., 2002), including by the International Atomic Energy Agency (IAEA, 2009, 2011) and the European Reference Organisation for Quality Assured Breast Screening and Diagnostic Services (EUREF) (Perry et al., 2006b), in Germany through mammography screening legislation (Kassenärztliche Bundesvereinigung, 2004), in the United Kingdom through the National Health Service (NHS) Breast Screening Programme (NHSBSP, 2013), in the USA through the United States Food and Drug Administration (FDA, 2013) Mammography Quality Standards Act (Fintor et al., 1995; Houn et al., 1995; Linver et al., 1995) and the American College of Radiology (ACR, 2013a), and in Canada (Health Canada, 2013) (see Section 3.2 for further information by country/region).

Many of the quality control programmes in different countries are quite similar in content, providing in-depth discussions of the necessary equipment for mammography imaging, the standards that the equipment must meet, the upkeep of that equipment, the duties and qualifications of the radiographers involved in performing the procedures, the standards for interpretation, recall rates, and the testing procedures performed by medical physicists necessary to confirm that mammography units are performing optimally and in accordance with applicable regulations. Frequently, ranges are defined for the results to define what is acceptable (if results fall outside the range, imaging should be discontinued until a problem is corrected) and achievable (a desirable range for facilities with modern equipment and experienced personnel to aim for).

The quality control testing programme recommended by the International Atomic Energy Agency for screen-film mammography is given in Table 2.2 and Table 2.3, which outline the responsibilities of the radiographers and medical physicists, respectively. The corresponding tests for digital mammography systems are given in Table 2.4 and Table 2.5, respectively.

In addition, several jurisdictions (economic regions, countries, states, and provinces) operate accreditation programmes for mammography. These include components to monitor that quality assurance and quality control practices and procedures are in place. For example, accreditation programmes have been implemented by the American College of Radiology in the USA (McLelland et al., 1991), the NHS Cancer Screening Programme in the United Kingdom (Wilson & Liston, 2011), and the Canadian Association of Radiologists (Canadian Association of Radiologists, 2012).

One critical point to be considered for quality assurance is the criterion for credentialing professionals involved in the mammography process. The team of health-care professionals involved in the mammography process includes radiologists, radiographers, and medical physicists. Also needed are equipment specifications, monitoring and maintenance schedules, standards for image quality, standardized image evaluation procedures, meticulous record-keeping, and periodic review of data for outcomes of mammography services. All of these requirements are of vital importance in ensuring the quality of the screening programme.

An opportunity provided by the introduction of digital mammography is the potential to perform automated quality control (Brooks et al., 1993; Karssemeijer et al., 1995; Jacobs et al., 2006). When specially designed phantoms and test objects are imaged, relevant information about the imaging system can be discerned, and quantitative, objective measurements can be produced either by manual measurement or by automated algorithms. This makes it possible to detect (and correct) problems before they become clinically significant. Several manufacturers provide test tools and algorithms that can be used to verify

Table 2.2 Radiographer's quality control tests for screen-film mammography

Test	Priority[a]	Suggested frequency	Tolerances
Visual inspection			
Visual inspection and evaluation of the mammography unit	E	Monthly	
Film storage			
Temperature Humidity	E	Monthly	15–21 °C 40–60%
Position of film boxes and cassettes	E	Monthly	
Film inventory	D	Monthly	Time period for inventory updating < 3 months
Darkroom and film processing			
Darkroom cleanliness	E	Daily	—
Temperature Humidity Ventilation conditions	E E D	Monthly Monthly Monthly	15–21 °C 30–70%
White light leakage	E	Annually	
Safe lights	E	Annually	Rating ≥ 15 W FSL < 0.05 OD in 2 minutes
Developer temperature	E	Daily	Achievable: ± 0.5 °C Acceptable: ± 1.0 °C of the manufacturer-recommended value
Sensitometry	E	Daily	
Development time, specific gravity, pH, and replenishment rate		Only when problems are detected	
Artefact detection during processing	E	Weekly	Acceptable: no clinically significant artefacts
Imaging system			
Screen cleanliness	E	Weekly	
Screen-film contact	E	Semi-annually	Acceptable: spots ≤ 5 mm
Light-tightness of cassettes	E	Semi-annually	Acceptable: blackening ≤ 2 mm chest wall edge, ≤ 5 mm other edges
Matching of cassette sensitivity[b]	E	Semi-annually	Achievable: maximum deviation ≤ 0.20 OD Acceptable: maximum deviation ≤ 0.30 OD
Cassettes uniformity	D	Semi-annually	Acceptable: maximum deviation ≤ 5% mAs
Artefacts from each cassette	E	Semi-annually	Acceptable: no clinically significant artefacts
AEC			
Test of system constancy	E	Daily	Achievable: OD = OD_{target} ± 0.15 Acceptable: OD = OD_{target} ± 0.20 Acceptable: mAs within ± 10% of mAs that produces OD_{target} Acceptable: no clinically significant artefacts
Compensation of the AEC for different thickness	E	Monthly	Achievable: OD = OD_{target} ± 0.15 Acceptable: OD = OD_{target} ± 0.20 Acceptable: ± 10% of baseline mAs
Image quality			
ACR phantom score	D	Weekly	Acceptable: fibres: ≥ 4; microcalcifications: ≥ 3; masses: ≥ 3
OD difference between disc and background	D	Weekly	Achievable: ≥ 0.55 OD Acceptable: ≥ 0.40 OD

Table 2.2 (continued)

Test	Priority[a]	Suggested frequency	Tolerances
Reject analysis			
Reject films analysis	E	Quarterly	Achievable: ≤ 3% Acceptable: ≤ 8%

ACR, American College of Radiology; AEC, automatic exposure control; FSL, fog due to the safety light; OD, optical density.

[a] D, desirable, recommended; E, essential, basic requirement.

[b] This includes speed of screens and cassette attenuation.

From IAEA (2009). Table reproduced with permission from IAEA. IAEA Human Health Series No. 2: Quality assurance programme for screen film mammography. IAEA, Vienna (2009).

optimal performance. Some vendors provide automated quality control and tracking.

2.1.8 Mammography screening performance

(a) Interpreter training, skills, and experience

The setting for screening mammography is different from that of diagnostic mammography, where the woman generally presents with symptoms and the probability of cancer may be 10% or higher. In screening, women are asymptomatic and the cancer detection rates are typically in the range of 2–8 per 1000 examinations (Breast Cancer Surveillance Consortium, 2009; CPAC, 2013). Detecting these cancers against a background that is overwhelmingly non-cancer, while avoiding an unacceptably high abnormal recall rate, is a challenging task for the radiologist and requires training and maintenance of skills in identifying subtle signs of small lesions with a reasonable likelihood of being cancer. This may present a challenge in screening facilities where examination volumes per interpreter are low, because a given individual may see only one or two screening cancers per year in their screening workload.

This challenge can be approached in several ways; which, if any, are practical will depend on the individual screening environment (availability of interpreters, population density, etc.). One study found that the annual volume of examinations interpreted did not predict accuracy but that recent training and working in a facility where diagnostic mammograms and breast intervention procedures were performed were predictive of accuracy (Beam et al., 2003). Another factor associated with high performance in that study was working in a comprehensive breast centre or specialized mammography facility. These may point to the value of being able to gain feedback from the downstream outcome of screening through assessment, follow-up results, and radiological–pathological correlation, and being able to share knowledge gained with colleagues. Other studies observed a correlation between examination volume and screening accuracy (Esserman et al., 2002, Moss et al., 2005; Smith-Bindman et al., 2005). In addition, Smith-Bindman et al. found that radiologists with more years of screening experience tended to have higher specificity compared with more junior radiologists.

Other measures that have been implemented in large organized screening programmes to support the quality of image interpretation are outcome audits (cancer detection rates, percentage of small invasive cancers, specificity or PPV for screening) and review of programme interval cancers. Feedback on performance is essential for radiologists to improve their skills. A well-annotated set of cases, including screen-detected cancers, benign findings, and normal breasts, that could be made available for self-education and testing, such as the one developed by the University of Washington, USA (Dee, 2002; UW Medicine, 2015), may also be valuable.

Table 2.3 Medical physicist's quality control tests for screen-film mammography

Test	Priority[a]	Suggested frequency	Tolerances
Unit assembly evaluation			
Unit assembly evaluation	E	Annually	
Sensitometry and darkroom			
Sensitometry and darkroom	E	At commissioning and annually	
Darkroom radiation level	D	As required	Acceptable: < 20 μGy/week
Radiological equipment			
Radiation leakage	D	At acceptance and after changes	Acceptable: ≤ 1 mGy/h at 1 m
Accuracy and repeatability of the tube kVp	E	Annually	Acceptable: accuracy: ± 5%; repeatability: COV ≤ 2%
Half-value layer	E	Annually	
Output: repeatability and linearity	E	Annually	Acceptable: repeatability: COV ≤ 5%; linearity: ± 10%
Normalized output value	D	Annually	Acceptable: > 30 μGy/mAs at 1 m, 28 kV, Mo/Mo
Compression			
Compression force and thickness	E	Annually	
AEC			
Repeatability of the AEC	E	Annually	Acceptable: COV in mAs: ≤ 5%
Constancy of OD with baseline value	E	Annually	Acceptable: $OD = OD_{target} \pm 0.20$
Exposure time for 45 mm slab	E	Annually	Contact mammography: Achievable: $t \leq 1.5$ s Acceptable: $t \leq 2$ s Magnification mammography: Achievable: $t \leq 2$ s Acceptable: $t \leq 3$ s
Compensation of the AEC for different thickness and beam quality	E	Annually	Achievable: $OD = OD_{target} \pm 0.15$ Acceptable: $OD = OD_{target} \pm 0.20$
Increase of OD for each step of the density control	E	Annually	Acceptable: ΔOD = 0.1–0.2
Collimation system			
Light field/radiation field coincidence	D	Annually	Achievable: ≤ 1% of FFD for all edges
Radiation field/image receptor coincidence	E	Annually	Achievable: completely irradiate the image receptor, but does not extend beyond the shielded breast support except at the chest wall, where it may extend by ≤ 5 mm Acceptable: as above for the chest wall and within the breast support by ≤ 2% of FFD for the other edges
Compression paddle/breast support alignment	E	Annually	Acceptable: paddle not visible in image and edge of paddle ≤ 1% of FFD beyond chest wall edge of image receptor
Image viewing conditions			
Luminance of the viewboxes	E	Annually	> 3000 cd/m² (nit)
Viewboxes homogeneity and colour	E	Annually	Acceptable: < 30% for each viewbox and < 15% between panels in a viewbox
Ambient interpretation room illumination	E	Annually	Achievable: ≤ 10 lux Acceptable: ≤ 50 lux

Table 2.3 (continued)

Test	Priority[a]	Suggested frequency	Tolerances
Image quality[b]			
Target background density	E	Annually	Acceptable: OD = OD_{target} ± 0.20
OD difference between disc and background	E	Annually	Achievable: ≥ 0.55 OD Acceptable: ≥ 0.40 OD
Phantom image quality evaluation (ACR)	E	Annually	Acceptable: fibre score: ≥ 4 ; speck score: ≥ 3; mass score: ≥ 3
System spatial resolution	E	Annually	Achievable: ≥ 15 lp/mm Acceptable: ≥ 11 lp/mm
Dosimetry[c]			
Mean glandular dose (D_G)	E	Annually	Achievable: D_G ≤ 2 mGy Acceptable: D_G ≤ 2.5 mGy

ACR, American College of Radiology; AEC, automatic exposure control; COV, coefficient of variation; Δ, change in parameter; FFD, focus film distance; Mo, molybdenum; OD, optical density.

[a] D, desirable, recommended; E, essential, basic requirement.

[b] The ACR phantom has been taken as an example because it is probably the one most commonly used.

[c] Values obtained with grid for a compressed breast of thickness 53 mm and composition of 71% fat and 29% fibroglandular tissue.

From IAEA (2009). Table reproduced with permission from IAEA. IAEA Human Health Series No. 2: Quality assurance programme for screen film mammography. IAEA, Vienna (2009).

(b) One versus two views

In mammography it is customary to acquire two views of each breast, typically the mediolateral oblique projection and the craniocaudal projection. This results in more complete imaging coverage of tissue than can usually be obtained from a single view, due to the curved shape of the chest (which makes it impossible to include all breast tissue on a single rectangular view) and varying individual anatomy. It also allows correlation between the views to estimate the 3D location of structures of interest and to rule out anomalous findings created by superposition of tissue shadows from different planes in the breast in the projection images. Some screening programmes used single-view mammography to reduce screening costs and the radiation dose received by the breast. However, in a study conducted in the United Kingdom, it was found that two-view mammography resulted in 24% higher breast cancer detection rate while simultaneously reducing the screening recall rate by 15%; i.e. increasing both sensitivity and specificity (Wald et al., 1995; Patnick, 2004).

Another study in the United Kingdom found that the rate of detection of invasive cancers less than 15 mm in diameter was 45% higher when two-view mammography was used (Blanks et al., 1997). A further study suggested that many of the cancers often missed on a single oblique view of the breast can be seen in retrospect when guided by information seen on the craniocaudal view (Hackshaw et al., 2000). These cancers tend to be smaller by about 4 mm and lack some of the more pathognomonic features of malignancies, suggesting that the availability of the second view provides supporting information and raises the confidence in the radiologist to assess the lesion as positive.

(c) Double reading

Human observers attain performance in mammography screening with sensitivities typically above 80% and specificities between 88% and 96% (Stout et al., 2014). As mentioned previously, both sensitivity and specificity tend to be reduced for the dense breast. The relationship between sensitivity and specificity is described

Table 2.4 Radiographer's quality control tests for digital mammography

Test	Priority[a]	Comments
Daily tests		
Monitor inspection, cleaning, and viewing conditions	D	Daily (D); weekly (E)
Digital mammography equipment daily checklist	E	
Daily flat-field phantom image	D	
Visual inspection for artefacts (CR systems only)	E	
Laser printer sensitometry	E	Wet processor: daily (D); on day of use (E) Dry processor: monthly
Image plate erasure (CR systems only)	E	Secondary erasure: daily Primary erasure: weekly or as per manufacturer's instructions
Weekly tests		
Monitor QC	E	
Viewbox cleanliness	E	
Weekly QC test object and full field artefacts	E	
Image quality with breast-mimicking phantom	D	
Monthly tests		
Safety and function checks of examination room and equipment	E	
Full field artefacts	E	
Laser printer artefacts	E	
Quarterly tests		
Printed image quality	E	
Repeat image analysis	E	
Spatial resolution test (CR and scanning systems only)	E	
Semi-annual tests		
CR plate sensitivity matching	E	
CR plate artefacts	E	

CR, computed radiography; QC, quality control.

[a] D, desirable; E, essential, basic requirement.

From IAEA (2011). Table reproduced with permission from IAEA. IAEA Human Health Series No. 17: Quality assurance programme for digital mammography. IAEA, Vienna (2011).

by the receiver operating characteristic curve (a graph that plots the sensitivity versus the false-positive fraction, which is also 1 – specificity), and unless the intrinsic performance of the observer or the imaging system is increased, any attempt to improve sensitivity in detecting cancer will be met by a corresponding decrease in specificity.

Double reading is practised in some screening programmes to increase screening performance. Double reading can be implemented in several possible ways: (i) two readers individually interpret the mammography examination, and the patient is referred for further assessment if either of them reports a suspicious finding; (ii) the readers interpret the examination independently and then create a consensus opinion, upon which assessment is based; or (iii) after independent interpretation, a third radiologist arbitrates only if the two findings are different.

In a population screening programme using screen-film mammography, Thurfjell et al. (1994) showed a 15% increase in cancer detection rate and Anderson et al. (1994) showed a 10% increase in cancer detection rate with double reading, but with a 1.8% decrease in specificity. In studying

Table 2.5 Medical physicist's quality control tests for digital mammography

Test	Priority[a]	Suggested frequency	Tolerances
Unit assembly			
Unit assembly evaluation	E	Annually (E) Semi-annually (D)	
Compression			
Compression force and thickness accuracy	E	Annually (E) Semi-annually (D)	Powered: 150 N to ≤ 200 N Manual: ≤ 300 N
AEC evaluation			
Technique chart and AEC evaluation	E	Annually or after changes to AEC software	
Site baseline settings for radiographer SDNR test	E	At commissioning and after changes to AEC software	Not applicable
Detector performance			
Baseline detector performance	E	At commissioning and after detector change	Not applicable
Detector response and noise	E	Annually and after detector service	
Spatial linearity and geometric distortion of detector	E	Annually and after detector change	
Detector ghosting	E	Annually and after detector change	Ghost image SDNR ≤ 2.0
Detector uniformity and artefact evaluation	E	Annually and after detector change	
Evaluation of system resolution			
Modulation transfer function	E	Annually and after detector change	
Limiting spatial resolution	E	Annually and after detector change	
X-ray equipment characteristics			
Half-value layer	E	Annually and after X-ray tube change	
Incident air kerma at the entrance surface of PMMA slabs	E	Annually and after X-ray tube change	Not applicable
Dosimetry			
Mean glandular dose (D_G)	E	Annually	
Collimation system			
Radiation field/image receptor coincidence	E	Annually and after X-ray tube service/ replacement	
Compression paddle/breast support alignment	E	Annually and after X-ray tube service/ replacement	Acceptable: paddle not visible in image and edge of paddle ≤ 5 mm beyond chest wall edge
Missing tissue at chest wall	E	Annually and after X-ray tube service/ replacement	Achievable: ≤ 5 mm Acceptable: ≤ 7 mm
Image display quality			
Artefacts and uniformity (soft copy)	E D	Annually Semi-annually	
Monitor luminance response and viewing conditions	E	Annually and after monitor service	
Viewbox luminance and viewing conditions	E	Annually	
Laser printer (where applicable)			
Artefacts and uniformity	E D	Annually Semi-annually	

Table 2.5 (continued)

Test	Priority[a]	Suggested frequency	Tolerances
Film densities	E	Annually	
Image quality			
Phantom image quality	E	Annually	

AEC, automatic exposure control; PMMA, polymethylmethacrylate; SDNR, signal-difference-to-noise ratio.

[a] D, desirable; E, essential, basic requirement.

From IAEA (2011). Table reproduced with permission from IAEA. IAEA Human Health Series No. 17: Quality assurance programme for digital mammography. IAEA, Vienna (2011).

several different double reading programmes, Blanks et al. found that double reading, especially when practised with arbitration, was better than single reading for the detection of small (which they defined as < 15 mm) invasive cancers, and the increase in detection rate was 32% for prevalent screens (two-view mammograms) and 73% for incident screens (single-view mammograms) (Blanks et al., 1998). These improvements were not observed for larger cancers. Unfortunately, much of the work on double reading was confounded by factors such as the number of radiographic views used.

If performed by radiologists, double reading is labour-intensive and therefore expensive, and in some locations the availability of radiologists is limited. In the NHS Breast Screening Programme in England, highly trained radiographers are used as second readers (Bennett et al., 2012). In some cases, two radiographers may perform double reading together without a radiologist.

(d) Computer-aided detection

Another approach to improving the accuracy of interpretation is through computer-aided detection (Nishikawa, 2010). Computer-aided detection consists of a set of computer image analysis operations applied to a digital mammogram or to a digitized film mammogram. Typically, the algorithm uses a set of segmentation operations to identify the area of the breast on the mammogram and to select areas, generally corresponding to increased X-ray attenuation, as candidates for lesions. Further operations, which can include image texture analysis and morphological analysis, can then be applied to assign "features" to the image. The features are used collectively, often with different weighting factors, to classify an area of the mammogram as normal or suspicious for cancer. Typically, computer-aided detection algorithms produce marks on an overlay image of the mammogram to indicate the possible presence of microcalcifications, potentially malignant masses, asymmetry, or architectural distortion, and the accuracy of computer-aided detection algorithms generally decreases in that order.

In any detection task there will be a trade-off between sensitivity and specificity; for example, if all mammograms were interpreted as positive, the sensitivity would be 1.0 but the specificity would be 0. The operating point of a computer-aided detection algorithm, i.e. its aggressiveness in discriminating between suspicious and normal areas, can be set by the manufacturer.

Computer-aided detection is most frequently used as a prompt to the radiologist, indicating by marks areas that should be given special consideration in interpreting the image. This has been demonstrated to contribute to improving sensitivity of mammography, although generally the number of false-positive marks on the image is considered to be excessively high. This is an annoyance to experienced radiologists, and it may lead to an excessively high recall rate for

inexperienced interpreters who rely heavily on the computer-aided detection marks (Fenton et al., 2007; Philpotts, 2009).

Another application of computer-aided detection is as a surrogate for the second reader in double reading. In the NHS Breast Screening Programme in England, it was found that, with such practice, a single reader with computer-aided detection was able to detect cancers with similar pathological characteristics, achieving almost identical sensitivity (87.2% vs 87.7%), with slightly reduced specificity (96.9% vs 97.4%), compared with double reading (Taylor et al., 2004; Gilbert et al., 2008). Another study showed a 9% increase in sensitivity for a single reader plus computer-aided detection compared with single reading only, and a 2.4% non-significant increase compared with double reading, with a small increase in recall rate (Gromet, 2008).

2.1.9 Host factors that affect performance

(a) Breast density

To detect breast cancer mammographically, there must be adequate contrast for the lesion to be distinguished from surrounding tissue, and the contrast must exceed the random fluctuation (noise) in the image by a sufficient factor (contrast-to-noise ratio) to ensure that statistically reliable information is conveyed to the viewer. There must also be adequate spatial resolution to delineate the characteristic features of a lesion. Finally, masking effects due to overlapping tissues or image artefacts must not be excessive.

Tumours tend to be somewhat more attenuating of X-rays than adipose tissue and slightly more attenuating than surrounding fibroglandular tissue, although there the difference may be extremely small (Hammerstein et al., 1979; Johns & Yaffe, 1987). Therefore, the challenge of accurately detecting a tumour is greatest in the dense (highly fibroglandular) breast, where the contrast and contrast-to-noise ratio for lesions are likely to be diminished and the potential for masking is elevated (see Section 1.3.3d). Both sensitivity and specificity tend to be lower in the dense breast compared with the fatty breast (Table 2.6 and Table 2.7). Digital mammography tends to provide improved lesion conspicuity in the dense breast compared with film mammography. The accuracy of digital mammography relative to screen-film mammography was evaluated in a large trial (Pisano et al., 2005) in which more than 40 000 women received both film and digital examinations. Digital mammography was found to have a better diagnostic accuracy (superior area under the receiver operating characteristic curve and superior relative sensitivity, without loss of specificity) in women with dense breasts, those younger than 50 years, and those who were premenopausal or perimenopausal (groups overlap). Similar results were reported in observational data from the Breast Cancer Surveillance Consortium in the USA (Stout et al., 2014).

(b) Size of lesion

Sensitivity also depends on the size of the lesion (generally it is much easier to detect large cancers because they provide greater contrast) and on whether microcalcifications are present.

Radiologists frequently consider changes between the current mammogram and previous examinations, especially densities that increase in size over time, suggestive of a cancer. Therefore, the presence of previous images for comparison is of great value. Table 2.6 and Table 2.7 provide data on sensitivity and specificity of mammography by age range, breast density, and whether the examination is an initial one or one of a sequence (where there is the possibility for comparisons to be made). In screening, sensitivity typically increases with the time since the previous screen because the cancer has had more time to grow. Conversely, to obtain optimal lead time in mammography, the system (equipment, technique, and radiologist) must achieve high sensitivity for small lesions.

Table 2.6 Sensitivity of mammography by age group, breast density, and screening interval

Screening interval	Breast density	Age at examination (years)							
		40–49		50–59		60–69		70–79	
		Film	Digital	Film	Digital	Film	Digital	Film	Digital
Initial screen	Extremely dense	0.75	0.81	0.79	0.89	0.82	0.91	0.86	0.92
	Heterogeneously dense	0.85	0.90	0.88	0.88	0.91	0.91	0.93	0.93
	Scattered density	0.89	0.92	0.91	0.93	0.93	0.95	0.94	0.96
	Mainly fatty	0.90	0.94	0.92	0.86	0.94	0.89	0.95	0.91
Recurring annual screen	Extremely dense	0.57	0.65	0.62	0.78	0.66	0.81	0.71	0.85
	Heterogeneously dense	0.73	0.79	0.77	0.78	0.80	0.81	0.84	0.85
	Scattered density	0.78	0.85	0.82	0.85	0.85	0.88	0.89	0.91
	Mainly fatty	0.80	0.85	0.83	0.73	0.86	0.77	0.89	0.81
Recurring biennial screen	Extremely dense	0.68	0.73	0.70	0.83	0.74	0.86	0.79	0.89
	Heterogeneously dense	0.79	0.84	0.82	0.83	0.85	0.86	0.88	0.89
	Scattered density	0.84	0.88	0.86	0.89	0.89	0.91	0.91	0.92
	Mainly fatty	0.85	0.89	0.87	0.80	0.90	0.83	0.92	0.87
Recurring triennial screen	Extremely dense	0.68	0.82	0.72	0.85	0.76	0.88	0.80	0.91
	Heterogeneously dense	0.81	0.81	0.84	0.84	0.87	0.87	0.90	0.90
	Scattered density	0.85	0.88	0.87	0.90	0.90	0.92	0.92	0.93
	Mainly fatty	0.86	0.78	0.88	0.81	0.91	0.84	0.93	0.87

Values interpolated by the Working Group using data from Stout et al. (2014) and British Columbia Cancer Agency (2011).

Table 2.7 Specificity of mammography by age group, breast density, and screening interval

Screening interval	Breast density	Age at examination (years)							
		40–49		50–59		60–69		70–79	
		Film	Digital	Film	Digital	Film	Digital	Film	Digital
Initial screen	Extremely dense	0.84	0.82	0.86	0.84	0.87	0.85	0.88	0.87
	Heterogeneously dense	0.82	0.78	0.84	0.80	0.85	0.82	0.87	0.83
	Scattered density	0.86	0.83	0.87	0.84	0.88	0.86	0.90	0.87
	Mainly fatty	0.92	0.90	0.93	0.91	0.94	0.92	0.94	0.93
Recurring annual screen	Extremely dense	0.91	0.90	0.92	0.91	0.93	0.92	0.94	0.93
	Heterogeneously dense	0.90	0.87	0.91	0.88	0.92	0.89	0.93	0.91
	Scattered density	0.92	0.90	0.93	0.91	0.94	0.92	0.94	0.93
	Mainly fatty	0.96	0.95	0.96	0.95	0.97	0.96	0.97	0.96
Recurring biennial screen	Extremely dense	0.90	0.88	0.91	0.90	0.92	0.91	0.93	0.92
	Heterogeneously dense	0.88	0.85	0.89	0.87	0.90	0.88	0.91	0.89
	Scattered density	0.91	0.89	0.92	0.90	0.93	0.91	0.93	0.92
	Mainly fatty	0.95	0.94	0.96	0.94	0.96	0.95	0.97	0.95
Recurring triennial screen	Extremely dense	0.89	0.88	0.90	0.89	0.91	0.90	0.92	0.91
	Heterogeneously dense	0.87	0.84	0.89	0.86	0.90	0.87	0.91	0.88
	Scattered density	0.90	0.88	0.91	0.89	0.92	0.90	0.93	0.91
	Mainly fatty	0.95	0.93	0.95	0.94	0.96	0.95	0.96	0.95

Values interpolated by the Working Group using data from Stout et al. (2014) and British Columbia Cancer Agency (2011).

2.2 Non-mammographic imaging techniques

Non-mammographic imaging methods might be considered as the only screening method or as adjunct (supplementary) to mammography. The evidence reviewed here, as far as available, includes (i) sensitivity and specificity in a defined consecutively examined screening population (at average, intermediate, or increased risk) and/or incremental detection rates when the technique is used as an adjunct, where specified; (ii) potential side-effects of the screening application that can be assessed immediately (e.g. false-positive recommendations of biopsy or of 6-month follow-up); (iii) potential side-effects inherent to the method (such as risks associated with radiation or the contrast agent); and (iv) any other data on test accuracy or biological background of the test. An overview of the results is presented in Table 2.8.

Proof of efficacy and effectiveness (reduction in mortality or more-aggressive treatment of late changes among screened vs non-screened women) and other outcomes (stage shifting, interval cancer rate) are discussed in Section 5.5 and Section 5.6. Information on potential overdiagnosis can only be expected after long-term follow-up and is not available for any of the non-mammographic imaging modalities.

2.2.1 Ultrasonography

(a) Equipment

Currently, breast ultrasonography can be performed using equipment for handheld ultrasonography (HHUS) or equipment for automated breast ultrasonography (ABUS), which has also been named 3D ultrasonography.

HHUS is performed manually, like ultrasonography of other organs. Adequately high resolution is needed. HHUS can also be used to screen the whole breast, but screening with HHUS is time-consuming and is known to be operator-dependent. So far, documentation has relied on imaging of representative slices, and the representative slices need to be selected by the operator.

Earlier ABUS systems, developed about 30 years ago, had low image quality and different types of artefacts. A new generation of ABUS equipment has now become commercially available, which allows all the breast tissue to be covered in a reproducible manner. Image acquisition is performed by trained health professionals and takes up to 10 minutes per breast. During ABUS, the transducer moves automatically over the breast; all images and their corresponding location in the breast are automatically recorded. Artefacts are significantly reduced compared with former systems. Reading requires adequate software and storage space (approximately 1 gigabyte per breast) and takes about 5–10 minutes per patient.

The anticipated advantage of ABUS systems is the decoupling of image acquisition and reading, which improves the possibilities for implementing breast ultrasonography in a screening setting and reduces the required time of an expert.

Sonoelastography is a new feature that is now offered by many manufacturers. Elastography calculates elasticity values based on the small shift of echoes, which occurs due to respiratory or cardiac motion, as a result of manual pressure or application of a shear wave. The type of elastography depends on the equipment and yields semiquantitative or quantitative measurements. The information from elastography is then provided by colour-coding of the B-mode image. Elastography provides additional diagnostic information to breast ultrasonography. It cannot be used as a stand-alone method but requires combination with B-mode ultrasound. So far, it has been used only for targeted analysis of lesions, not for screening of the whole breast (Wojcinski et al., 2010; Berg et al., 2012c;

Table 2.8 Non-mammographic imaging techniques – comparison of technologies

Technology	Diagnostic advantages for screening	Diagnostic drawbacks for screening	Reproducibility	Advantages inherent to technology	Disadvantages inherent to technology	Time needed for acquisition	Time needed for reading	Costs for screening[a]	Costs for assessment	Relevance to screening
HHUS ("2D")	Incremental detection of cancers in dense tissue	Low specificity, high biopsy rates, high rates of short-term follow-up	Depends strongly on diagnostic skills of operating health professional (crucial for teaching and for QA) Inter-reader variability (important for teaching and QA)	No radiation Absence of discomfort	None	20 min	10–20 min[b]	Equipment costs + Non-physician time ++ Physician/ expert +++	Many assessments, low costs	Limited data
ABUS ("3D")	Incremental detection of cancers in dense tissue (limited data available to date)	Low specificity, high biopsy rates, high rates of short-term follow-up (limited data available to date)	Usual QA for adequate image acquisition required	No radiation Absence of discomfort	None	10 min	5–10 min (independent of acquisition)	Equipment costs ++ Storage space ++ Non-physician time ++ Physician/ expert +++	Many assessments, low costs	Limited data
Non-contrast-enhanced MRI (including DWI and spectroscopy)	No data	No data	NA	No radiation No contrast agent	Side-effects of magnetic field Claustrophobia	> 20 min	Not tested	Equipment costs +++ Otherwise not tested	Very high	No data

Table 2.8 (continued)

Technology	Diagnostic advantages for screening	Diagnostic drawbacks for screening	Reproducibility	Advantages inherent to technology	Disadvantages inherent to technology	Time needed for acquisition	Time needed for reading	Costs for screening[a]	Costs for assessment	Relevance to screening
Contrast-enhanced MRI	High sensitivity	Low specificity, high biopsy rates, high rates of short-term follow-up	QA for image acquisition; see guidelines for contrast-enhanced breast MRI Inter-reader-variability No QA programme for screening available	No radiation	Side-effects of magnetic field Side-effects of contrast agent Claustrophobia	15 min	5–10 min (independent of acquisition)	Equipment costs +++ Cost for contrast agent ++ Non-physician time ++ Physician/ expert ++	Very high	Limited data
PET	No data	Low sensitivity for small cancers	No data		Very high radiation dose	20–40 min	5–10 min (independent of acquisition)	Equipment costs +++ Cost for tracer ++ Non-physician time ++ Physician/ expert ++	Not tested	No data for screening
PEM	No data for screening (high sensitivity in diagnostic studies)	No data for screening (specificity for diagnosis equal to that of MRI)	Not tested		Very high radiation dose	20–40 min	5–10 min (independent of acquisition)	Equipment costs +++ Cost for tracer ++ Non-physician time ++ Physician/ expert ++	Not tested	No data for screening
BSGI	One study with questionable applicability to screening (high sensitivity)	One study with questionable applicability to screening. (specificity similar to that of MRI)	Not tested		Very high radiation dose	20–30 min	5–10 min (independent of acquisition)	Equipment costs +++ Cost for tracer ++ Non-physician time ++ Physician/ expert ++	Not tested	Very limited data with questionable applicability to screening

Table 2.8 (continued)

Technology	Diagnostic advantages for screening	Diagnostic drawbacks for screening	Reproducibility	Advantages inherent to technology	Disadvantages inherent to technology	Time needed for acquisition	Time needed for reading	Costs for screening[a]	Costs for assessment	Relevance to screening
Electrical impedance imaging	NA	One study on screening; very low sensitivity	Not tested; high variation of results with equipment	No radiation	None	NA	NA	NA	NA	No data for screening
Thermography	NA	Low sensitivity and low accuracy for screening	Not tested; high variation of results with equipment	No radiation	None	NA	NA	NA	NA	Low accuracy
Near-infrared spectroscopy	NA	No data for screening; existing other data: low accuracy	Not tested; high variation of results with equipment	No radiation	None	NA	NA	NA	NA	No data for screening
Molecular imaging (other than MRI or BSGI)	NA	Not clinically applied	NA	Depend on vector	Depend on vector	NA	NA	NA	NA	Fundamental research

2D, two-dimensional; 3D, three-dimensional; ABUS, automated breast ultrasonography; BSGI, breast-specific gamma imaging; DWI, diffusion-weighted imaging; HHUS, handheld ultrasonography; min, minute or minutes; MRI, magnetic resonance imaging; NA, not available; PEM, positron emission mammography; PET, positron emission tomography; QA, quality assurance.

[a] +, low; ++, moderate; +++, high.

[b] Depending on the physician performing the examination.

Compiled by the Working Group.

Schäfer et al., 2013; Zhi et al., 2013; reviewed in Vreugdenburg et al., 2013).

(b) Technique

The technique of HHUS is described in national and international guidelines (Mainiero et al., 2013). Scanning, reading, and image documentation of HHUS are observer-dependent.

The technique of ABUS scanning depends on the equipment and is taught by the manufacturers. There still appears to be significant interobserver variability for the interpretation of ABUS as well; however, this might be improved by adequate training and by reading of ABUS together with mammography (Shin et al., 2011; Golatta et al., 2013; Kim et al., 2013; Skaane et al., 2014b; Wojcinski et al., 2013).

There exist few studies comparing the diagnostic accuracy of ABUS and HHUS. The latest studies have reported approximately comparable performance (Lin et al., 2012; Wang et al., 2012; Zhang et al., 2012; Chen et al., 2013). Whereas an experienced ultrasonographer might obtain more information from evaluating the elasticity and mobility of tissues when applying the ultrasound probe manually (Chang et al., 2011), automated ultrasonography avoids missing any areas of the breast tissue, a known problem of ultrasonography due to the mobility of breast tissue.

The technique of sonoelastography varies with the equipment and the manufacturer.

(c) Quality control

Some quality control for diagnostic HHUS of the breast is established in most national health systems. Currently, no recommendations or guidelines exist to assure high quality of ultrasonography screening examinations.

If HHUS screening is performed by health professionals, whereas reading is performed by a breast physician, then excellent training of the health professional is crucial since the operator has to select which images will be recorded and thus read by the physician. Any error of recording risks a miss. Thus, the health professional must have a high level of diagnostic skills and quality assurance.

To date, quality assurance of ABUS has been taught by the manufacturer. Overall quality assurance of ABUS image acquisition is far less demanding than for HHUS since the health professional only needs to warrant complete coverage of the breast tissue and adequate coupling. Thus, ABUS may aid in reducing the operator-dependence of the image acquisition.

Currently, no recommendations or guidelines exist to assure high quality of ultrasonography screening examinations.

(d) Screening performance

Based on existing data, ultrasonography is not envisaged as a stand-alone screening modality in most countries where it is in use (Albert et al., 2009). Instead, with rare exceptions with limited data (Hou et al., 2002; Honjo et al., 2007), it has been investigated almost exclusively as a supplementary test for screening women with dense breast tissue. This selective application is based on the suggested increased breast cancer risk with increased mammographic density (McCormack & dos Santos Silva, 2006; Price et al., 2013; see Section 1.3.3d) and the decreased sensitivity of mammography in dense breasts caused by the masking effect of dense tissue (Blanch et al., 2014; Boyd et al., 2014; see Section 2.1.9). Furthermore, use of ultrasonography in large and fatty breasts has limitations.

Recently, prospective studies from China have become available, where ultrasonography was used consecutively in women at average risk, alone or together with other modalities.

A recent study in China (Kang et al., 2014) reported the exclusive prospective use of ultrasonography in 2471 asymptomatic women at average risk, and achieved a sensitivity, specificity, and PPV in this population of 78.6%, 99.7%, and 11.4%, respectively.

Another study in China (Xu et al., 2010) reported the prospective use of ultrasonography, mammography, and clinical breast examination in 118 273 women. Cancer was detected in 0.66% of the population, and 34.8% at an early stage. In women younger than 44 years, the detection rate of early disease was better with ultrasonography, and in women older than 44 years, it was better with mammography.

A large study in China (Xu et al., 2014) reported on the use of ultrasonography, mammography, and clinical breast examination in 23 910 consecutive women at increased risk. The overall detection rate was 1.3 per 1000 women. With respect to sensitivity, specificity, and area under the receiver operating characteristic curve, the combination of all methods performed best (90.3%, 94.6%, and 0.95, respectively). Mammography alone (74.2%, 91.7%, and 0.85, respectively) and ultrasonography alone (71.0%, 90.3%, and 0.81, respectively) were comparable but inferior to the combination of all methods. CBE proved inferior to the other methods (41.9%, 82.7%, and 0.68, respectively).

Further studies (Huang et al., 2012; Wang et al., 2013) comparing the sensitivities of different screening modalities in a Chinese population, including very young women (< 25 years), confirm the increased screening performance of ultrasonography in dense breasts and in younger women (< 55 years). [The authors pointed out an earlier onset of breast cancer and the generally higher tissue density in the Chinese population.]

Incremental cancer detection rates by adjunct ultrasonography reported in several prospective and retrospective studies range from about 2 per 1000 to about 5 per 1000 (reviewed in Nothacker et al., 2009).

This incremental detection is achieved at the cost of high biopsy rates (1.8–5.3%) and mostly high rates of incremental short-term follow-up recommendations, ranging from 1.2% to 7.5%.

For further details and implications concerning prognostic impact, see Section 5.5 for the screening of women at average risk and Section 5.6 for the screening of women at an increased risk.

Recent studies comparing the use of ABUS and HHUS in asymptomatic women with dense tissue and normal mammograms reported comparable results (Kelly et al., 2010; Giuliano & Giuliano, 2013; Brem et al., 2014).

Currently, elastography is used for diagnosis only. The first multicentre studies and a meta-analysis indicate that sonoelastography promises improved diagnostic accuracy of imaging assessment (Wojcinski et al., 2010; Barr et al., 2012; Berg et al., 2012c; Schäfer et al., 2013; Vreugdenburg et al., 2013; Zhi et al., 2013). With further technical development, elastographic information might become applicable to ABUS as well. However, so far no data exist on the use and the diagnostic accuracy that could be achieved if sonoelastography were used for screening.

(e) Host factors that affect performance

Decreased accuracy may be expected for large breasts. The reasons include limited penetration and the risk of missing part of the breast tissue (with HHUS). Since most breast cancers are hypoechoic, sensitivity may decrease in breasts with hypoechoic breast tissue (largely fatty breast tissue) and in breasts with heterogeneous echogenicity (due to hypoechoic mastopathic regions or many interposed fat lobules).

2.2.2 Magnetic resonance imaging

(a) Equipment

Breast MRI is performed on state-of-the-art MRI scanners. National and international updated guidelines recommend scanners of 1.5 T or more, special breast coils, and imaging protocols that allow dynamic contrast studies at high spatial and temporal resolution. Pulse sequences and evaluation software are provided by manufacturers.

Since contrast-enhanced MRI can detect small lesions not detected at mammography, MRI-guided biopsy and/or marking may be performed simultaneously. For such interventions, dedicated software, an MRI-compatible biopsy vacuum pump, and appropriate one-way MRI-compatible biopsy needles are indispensable. Solutions are expensive.

Diffusion-weighted imaging (DWI) is a new option on state-of-the-art MRI scanners of 1.5 T or 3 T. It is performed without contrast agent and allows calculation of the apparent diffusion coefficients of the imaged tissues. Apparent diffusion coefficient values provide a measure of the motion of water molecules in tissue, which appears restricted in many malignancies.

MRI spectroscopy also yields information on molecular binding of the imaged protons. It thus allows the identification of certain groups of molecules contained in the imaged voxel. The most promising results concern imaging of phosphocholines, which are also increased in many malignancies. This method is technologically demanding, is less promising on scanners of less than 3 T, and is not widely available.

Thus, both above-mentioned methods promise additional potentially valuable pathophysiological information. Their imaging resolution is restricted, and their accuracy is predicted to decrease with small lesion size and in cancers with a diffuse growth pattern (dispersed malignant cells). Their value for diagnosis is currently being investigated.

(b) Technique

When MRI is used (for diagnostic applications or for screening of women at an increased risk), dynamic contrast-enhanced breast MRI (CE-MRI) is currently considered state-of-the-art for reliable detection or exclusion of malignancy. With CE-MRI, the complete breast is imaged before and several times after intravenous administration of the MRI contrast agent (a gadolinium chelate). Standard procedures have been published in national and international guidelines (Sardanelli et al., 2010; Mainiero et al., 2013; Breast Imaging Working Group of the German Radiological Society, 2014).

To improve performance and feasibility, modified pulse sequences have been suggested, which might enable the specificity to be improved further (Mann et al., 2014) and/or the imaging time to be shortened (Kuhl et al., 2014). So far very limited experience concerning their diagnostic performance and reproducibility is available.

Even though gadolinium chelates are generally well tolerated and risks are much lower than for X-ray contrast agents, patients must be informed about potential side-effects. These include allergic reactions and nephrogenic fibrosing dermopathy/nephrogenic systemic fibrosis. Slight allergic reactions occur in up to 2.4% of applications; however, severe allergic reactions are rare (1–10 per 100 000 applications) (ACR, 2013b). Nephrogenic systemic fibrosis has been described in up to 3 per 100 000 applications (ACR, 2010). Among other risk factors, end-stage chronic kidney disease is associated with the highest risk of nephrogenic systemic fibrosis (up to 7%). Therefore, blood tests are officially recommended in patients who are older than 60 years or have pre-existing renal problems (Widmark, 2007; ACR, 2013b; Matsumura et al., 2013). Finally, the absence of cardiac pacemakers, certain metallic implants, or pumps must be ensured before MRI can be performed, to avoid severe injury to the patient (Expert Panel on MRI Safety, 2013).

Methods for MRI-guided marking and percutaneous breast biopsy have been developed and tested and are widely available (Perlet et al., 2006; Siegmann-Luz et al., 2014).

(c) Quality control

National and international guidelines concerning quality assurance of breast MRI have been published (Sardanelli et al., 2010; Mainiero

et al., 2013; Breast Imaging Working Group of the German Radiological Society, 2014). No dedicated protocol for quality assurance of MRI screening has so far been developed or tested. Consensus recommendations for the use of MRI-guided vacuum-assisted breast biopsy have been issued, to assure adequate assessment of MRI-detected lesions (Heywang-Köbrunner et al., 2009).

(d) Screening performance

To date, no RCTs or observational prospective studies exist in which MRI has been applied consecutively for screening of **asymptomatic women at average risk**. Considering the high costs of MRI, the costs for further assessment of MRI-detected benign changes, the very large number of women at average risk, and the potential side-effects of the contrast agent or the magnetic field, MRI screening does not appear to be a sensible option for women at average risk.

"**Intermediate risk**" defines a broad range between average risk (< 15% lifetime risk) and increased risk (> 30% lifetime risk according to the definition in Europe, or > 20% lifetime risk according to the definition in the USA). This group of women at intermediate risk is heterogeneous and consists of different subgroups, such as women with a personal history of breast cancer or DCIS, women with a moderate family risk of breast cancer, or women with histologically proven high-risk lesions, such as atypical ductal hyperplasia (ADH) or lobular carcinoma in situ (LCIS).

Data for the use of MRI for screening of women at intermediate risk are limited. The largest body of data probably exists for MRI screening of the contralateral breast to the tumoural breast. A large prospective multicentre study (Lehman et al., 2007) in 969 women showed a significant incremental detection rate (compared with mammography) of 3.1%. The corresponding sensitivity was 91% and the specificity 88%. A meta-analysis (Brennan et al., 2009) that included this prospective study and a further 21 small and heterogeneous prospective and retrospective studies yielded an incremental detection rate of 4.1%. A retrospective single-centre study (Gweon et al., 2014) reported an incremental detection rate of only 1.8% in 607 patients. These incremental detections were at the cost of an increased rate of indicated percutaneous biopsies of 13.9% (Lehman et al., 2007), 9.3% (Brennan et al., 2009), and 9.4% (Gweon et al., 2014). PPVs varied from 21% (Lehman et al., 2007) to 43.5% (Gweon et al., 2014).

One recent study (Kuhl et al., 2014) assessed the use of MRI for "screening" women at "mildly to moderately increased risk". However, it included a mixture of variable indications (diagnostic problems, personal history of breast cancer) and thus cannot contribute significant evidence to this question.

In women with increased risk due to a history of LCIS, retrospective studies of MRI examinations on limited numbers of patients showed low incremental detection rates (of DCIS or invasive carcinoma), high rates of biopsy recommendations, and high rates of short-term follow-up (Friedlander et al., 2011; Sung et al., 2011). Similar results were also reported from studies of women with mixed intermediate risks (Kuhl et al., 2010; Berg et al., 2011, 2012b).

For **women at an increased risk** (with or without *BRCA1* or *BRCA2* mutation), there is ample evidence of significant incremental detection by MRI. It is based on at least 16 single-armed large cohort studies and three systematic reviews (Lord et al., 2007; Warner et al., 2008; Phi et al., 2015).

A recent meta-analysis showed an average sensitivity and specificity both of 84% for the diagnostic use of DWI (Chen et al., 2010). A first attempt at an MRI protocol that included plain MRI and DWI achieved a sensitivity of 76–78% and a specificity of 90% (Trimboli et al., 2014). Thus, to date DWI does not appear to be applicable for screening. The same is true for MRI

spectroscopy, for which sensitivities and specificities of about 80% have been reported (Baltzer & Dietzel, 2013).

For further details and implications concerning prognostic impact, see Section 5.5.

(e) Host factors that affect performance

Contrast-enhanced MRI may not be possible for claustrophobic patients. It is not indicated in women with a known allergy to the MRI contrast agent or with a severe other disease that increases the risk of the contrast agent. It is contraindicated in women with pacemakers or other metallic devices (Expert Panel on MRI Safety, 2013).

Accuracy may be heavily degraded by motion artefacts. This must be considered in particular for women who – due to neurological disorders, lack of compliance, or other reasons – cannot lie still during the procedure.

Finally, high levels of progesterone may cause strong background enhancement and may interfere with the diagnostic accuracy. Therefore, whenever possible, MRI should be scheduled with respect to the menstrual cycle and progesterone treatment should be stopped for about 4 weeks before the MRI is performed (Sardanelli et al., 2010).

2.2.3 Positron emission tomography/ mammography

Positron emission tomography (PET) monitors the uptake of a radiotracer, and thus measures the activity of a metabolic pathway without interfering with it. Most PET studies have been performed using [^{18}F]-fluorodeoxyglucose (FDG), which represents glucose metabolism. Glucose metabolism is assumed to be increased in tumours. Other agents, such as [^{18}F]-fluorothymidine as a proliferation marker or [^{18}F]-labelled annexin V as an apoptosis marker, are under investigation (Surti, 2013).

(a) Equipment

Whole-body PET scanners allow imaging not only of the primary cancer but also of the lymph nodes and of distant metastases. However, due to insufficient resolution and signal-to-noise ratio, whole-body PET has low sensitivity for small tumours, and it is thus considered inappropriate for imaging of early breast cancer (Avril et al., 2000). Therefore, dedicated breast PET scanners have been developed. These dedicated scanners are called positron emission mammography (PEM) scanners. Their resolution, which is about 2–3 mm, is much higher than that of PET scanners.

(b) Technique

Most PEM scanners resemble mammography units. Imaging with these scanners is performed on the moderately compressed breast. Compression is applied to improve signal-to-noise ratio. Other PEM systems under development examine the breast in the prone position or may function as an add-on to whole-body PET scanners (Surti, 2013). The radiotracer (usually 370 MBq or 10 mCi FDG) is injected intravenously, and imaging can be performed after about 60 minutes. The time reported for a complete scan of both breasts is about 20–40 minutes. Toxic or allergic side-effects of the tracer are extremely rare and are negligible. However, the radiation dose, which is applied to the whole body, is high (~7 mSv). Due to the intravenous administration and its clearance time from the body, the lifetime attributable risk of one PEM scan has been calculated to be about 23 times that of a digital mammogram (~0.4 mSv) for a woman aged 40 years and more than 75 times that of a digital mammogram for a woman aged 60 years (Hendrick, 2010).

(c) Quality control

Standard doses of the tracer have been established. No protocol has yet been developed for PEM or for screening by PEM. Studies assessing interobserver variability and reproducibility of PEM diagnoses showed different results (Narayanan et al., 2011; Berg et al., 2012a). Thus, special training and quality assurance of PEM remain issues to be solved.

(d) Screening performance

No studies on the use of PEM (or PET) for screening asymptomatic women have been published. Data on accuracy are available from the use of PEM for diagnosis in patients with suspicious lesions or for preoperative staging (Berg et al., 2011; Schilling et al., 2011; Kalles et al., 2013). These studies show sensitivities of 85–90%, which are comparable to that of MRI.

(e) Host factors that affect performance

Limited sensitivity of PEM is expected in patients with uncontrolled diabetes mellitus since high blood levels of glucose interfere with FDG uptake in tumour tissue. In fertile women, physiological breast uptake of FDG may interfere with interpretation since FDG uptake is increased during all phases of the menstrual cycle except the proliferative phase (Rabkin et al., 2010; Park et al., 2013). Individual anatomical problems that prevent proper positioning are as crucial for PEM as they are for mammography.

2.2.4 Scintimammography

Breast-specific gamma imaging (BSGI), or scintimammography, is considered another method of molecular imaging. ^{99}Tc-sestamibi or ^{99}Tc-tetrofosmin binds to mitochondria (Sun et al., 2013). The density of mitochondria is assumed to be increased within cancer cells.

(a) Equipment

Dedicated scintimammography systems (BSGI systems) have been developed and are commercially available. The dedicated systems allow imaging of small breast lesions with sufficient reliability. Based on positive results in diagnostic examinations, the method has already been tested as a complementary tool for early detection and imaging of the mammographically dense breast. The initial BSGI systems required intravenous administration of a dose of 750–1100 MBq or 20–30 mCi ^{99}Tc-sestamibi. The most recent systems have improved detector technology (cadmium zinc telluride detectors and dual detector heads), leading to improved sensitivity and/or a reduction of the required applied radiation dose.

(b) Technique

Imaging with BSGI scanners is performed on the moderately compressed breast to increase signal-to-noise ratio. Individual anatomical problems that prevent proper positioning are as crucial for BSGI as they are for mammography.

The radiotracer (usually 750–1100 MBq or 20–30 mCi ^{99}Tc-sestamibi) is injected, and imaging can be performed after about 10 minutes. The time reported for a complete scan of both breasts is about 20–30 minutes. The radiation dose, which is applied by intravenous injection to the whole body with single-head systems, is even higher than that for PEM. Compared with a mean calculated radiation dose of mammography of 0.44 mSv to the breast, the dose for ^{99}Tc-sestamibi has been calculated to be about 9 mSv. The associated lifetime attributable cancer risk of one ^{99}Tc-sestamibi scan has been calculated to be about 20–30 times that of a digital mammogram for a woman aged 40 years (Hendrick, 2010). New technologies are expected to reduce the radiation dose to about 4 mSv.

(c) Quality control

So far, no official guidelines beyond the usual quality assurance of nuclear medicine exist for scintimammography. However, correct positioning is a prerequisite to allow imaging and thus detection of at least part of the lesion. Dose optimization studies for this technology are in progress. No quality assurance protocol exists for BSGI screening.

(d) Screening performance

No data exist on screening performance in women at average risk.

In one study (Rhodes et al., 2011), BSGI and mammography were performed in 936 women with mammographically dense tissue (ACR categories 3 and 4) and with additional risk factors (including family history, *BRCA* mutation, personal history, and other risks). The authors reported a sensitivity of 82% and a specificity of 93% for BSGI, and an astonishingly low sensitivity of 27% and a specificity of 91% for mammography. [The low sensitivity of mammography is explained by the diversity of patients. The study included women at an increased risk, who may develop tumour types that are particularly difficult to diagnose mammographically, and women with a personal history of breast cancer, where scarring impairs mammographic evaluation. The correct comparison would have been with MRI. Overall selection bias is probable (see Section 5.5 and BlueCross BlueShield Association, 2013).]

For the diagnostic use of BSGI, a sensitivity of 95% and a specificity of 80% were reported (Sun et al., 2013), which approximate those of MRI. No publications were available on BSGI-guided biopsy.

(e) Host factors that affect performance

Individual anatomical problems that prevent proper positioning are as crucial for PEM as they are for mammography.

2.2.5 Electrical impedance imaging

(a) Equipment

Electrical impedance, which derives from electrical conductivity and permittivity, is measured at different frequencies. Conductivity and permittivity vary with frequency in the different breast tissues (Hope & Iles, 2004). Electrical impedance imaging relies on the assumption that cancer cells have increased conductivity and thus decreased impedance (Vreugdenburg et al., 2013).

Different types of equipment have been developed for non-invasive measurement of the electrical properties of breast tissue (Ng et al., 2008). Electrical impedance tomography yields 2D and 3D tomographic images of the impedance (conductivity and permittivity). Electrical impedance mapping yields surface images of the distribution of conductivity and permittivity. One system did not yield images but solely allowed a classification as probably benign or malignant based on measurements from one selected location. (That system can, of course, not be used for screening.) The systems allow either areas of low impedance ("white spot") to be detected or a grading of suspicion or a classification as benign or malignant to be assigned based on selected algorithms (Zou & Guo, 2003; Ng et al., 2008).

The most commonly described devices in clinical studies were the electrical impedance scanner TransScan TS2000 system and the multiprobe resonance-frequency-based electrical impedance spectroscopy system (Malich et al., 2001; Martín et al., 2002; Wersebe et al., 2002; Diebold et al., 2005; Fuchsjaeger et al., 2005; Zheng et al., 2008, 2011; Wang et al., 2010; Lederman et al., 2011). Some of the electrical impedance technologies only detect asymmetry between breasts but do not localize the abnormality, and therefore may require another imaging technique, such as ultrasonography,

to localize the abnormality (Zheng et al., 2008, 2011; Wang et al., 2010; Lederman et al., 2011).

(b) Technique

The technique varies with the equipment and is taught by the manufacturer (Ng et al., 2008).

(c) Quality control

Given the different types of equipment and techniques, no standard procedures exist that would be valid for all equipment types.

(d) Screening performance

Only one study applied electrical impedance scanning in asymptomatic women (Stojadinovic et al., 2008). It yielded a sensitivity of 26.4%.

A recent systematic review identified 10 studies that reported results concerning the diagnostic use of electrical impedance scanning. Most of these assessed initial testing with or without blinding to the standard. Due to significant heterogeneity between the studies, pooled estimates of the diagnostic accuracy could not be calculated. Most studies reported sensitivities that ranged from 62.0% to 97.5% (median, 83%) and specificities that ranged from 42.0% to 80.9% (median, 68%). The large range of sensitivities and specificities and their median values do not support the diagnostic use of this method (Vreugdenburg et al., 2013).

This technology has not been validated for screening women.

(e) Host factors that affect performance

Lesions close to the chest wall or close to the nipple may not show adequately (Ng et al., 2008). Also, the results appear to vary with hormone levels (Sardanelli et al., 2010).

2.2.6 Other techniques

Thermography measures temperature distribution on the breast surface, assuming a higher temperature in malignant tumours. The method has been tested in several studies. In two systematic reviews of diagnostic studies, sensitivities ranged from 25% to 97% and specificities from 12% to 85% (Gohagan et al., 1980; Fitzgerald & Berentson-Shaw, 2012; Vreugdenburg et al., 2013). Given these limitations, the available data cannot justify the application of thermography for screening.

Near-infrared spectroscopy evaluates spectral differences of the examined tissue. Without the use of contrast agent, mainly tissue concentrations of haemoglobin and deoxyhaemoglobin can be measured. Higher proportions of deoxyhaemoglobin than haemoglobin are assumed to be present in malignant tumours. Initial results have not been encouraging. However, such a technology might become useful in the future if fluorescent probes can be developed for molecular imaging that can be administered intravenously and that attach to malignant cells and thus allow the identification of malignant tumours by this fluorescent marking.

2.3 Clinical breast examination

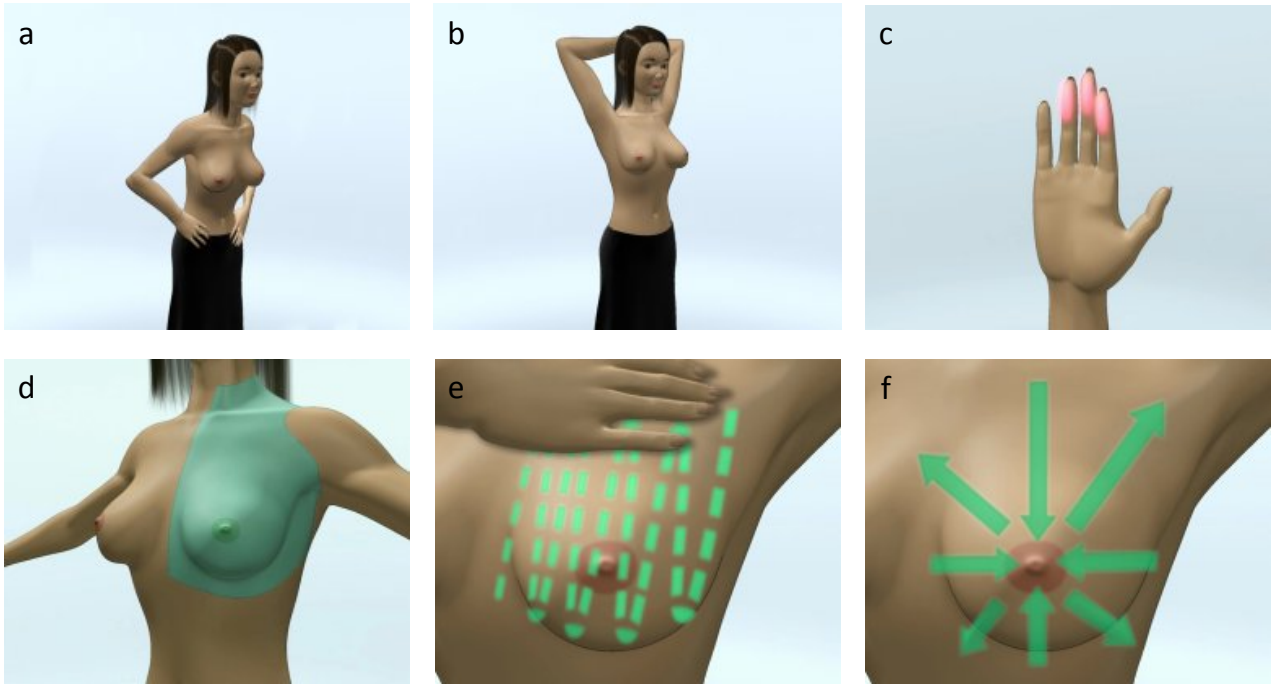
Clinical breast examination (CBE), also called physical breast examination, is part of the clinical examination for early detection of breast cancer and is practised routinely by health-care providers, i.e. nurses, physicians, and surgeons, in high-income countries. CBE for primary breast screening takes on importance in low- and middle-income countries (LMICs) where mammography screening is not feasible and/or affordable.

2.3.1 Technique

Fig. 2.6 gives a description and illustrations of CBE.

The CBE screening technique involves visual inspection and palpation of both breasts by a health-care provider. During visual inspection, the provider looks for subtle changes in breast

Fig. 2.6 Clinical breast examination



A visual examination should be performed with the woman in three different standing positions: with her arms relaxed at her sides, with her hands pressed firmly on her waist and leaning forward (a), and with her arms above her head (b). The examiner should seek subtle asymmetries in the appearance of the breasts. Three levels of pressure – superficial, medium, and deep – should be applied at each palpation site. Palpation is done with the finger pads of the middle three fingers (c), and pressure is applied with circular motions at each site. Palpation of the supraclavicular and axillary nodes is done with the woman seated, and re-palpation of the axillary nodes is done with the woman supine. Palpation of the breasts is performed over an area extending from the mid-axillary line to the mid-sternum and from above the subcostal margin (fifth rib) to the clavicle (d), including palpation of the nipple and areola. Palpation should be done systematically, either in vertical strips (e) or in circular motions from the centre to the periphery or vice versa (f). For the lateral half of the breast, the woman should be asked to rotate her body slightly in the opposite direction (right side for left breast, and left side for right breast); for the medial half of the breast, the body should be rotated laterally in order to spread out the breast tissue. When an abnormality in shape or contour is detected, the corresponding area of the other breast should be examined. If the finding is not bilateral, further investigation is required.

contour and skin and nipple changes that appear asymmetrically (i.e. not seen in both breasts), while the woman stands and clasps her waist tightly with both hands (Coleman & Heard, 2001). During palpation, the provider uses the soft pads of the middle three fingers to examine all areas of both breasts and axillae for the presence of lumps and thickening of breast tissue and lymph nodes. Palpation is performed with the woman in sitting and supine positions (Coleman & Heard, 2001). Several techniques for CBE have been described by researchers. Bassett (1985) described a "spoke and wheel" technique (f) for CBE as part of the Canadian National Breast Screening Study (CNBSS), whereas Saunders et al. (1986) described a vertical strip pattern (e). The most widely disseminated technique is probably that described by Pennypacker & Pilgrim (1993). Pennypacker et al. (1999) also suggested a minimum of 5 minutes of examination per breast. Fletcher et al. (1989) found that variations in CBE technique were responsible for 27–29% of variance in sensitivity and 14–33% of variance in specificity of lump detection. They also observed that increased duration of search time of the examination was correlated with higher sensitivity and lower specificity. However, there are no studies that have conclusively proven the superiority of any one technique over the others.

2.3.2 Training

Most training programmes use silicone models that simulate normal and abnormal human breast tissue (McDermott et al., 1996; Pennypacker et al., 1999). The effect of training on the improvement of providers' skills has been assessed (Costanza et al., 1995, 1999). Studies of medical students have shown low performance scores in many CBE components and also low sensitivity and specificity using silicone models (Sloan et al., 1994; Chalabian et al., 1996), whereas other studies have shown that CBE training on silicone breast models enhances the performance of examiners (Hall et al., 1980; Pilgrim et al., 1993).

Saslow et al. (2004) suggested that CBE training should be flexible and accommodate diverse settings and trainee needs. Miller et al. (1991) used the services of nurses who were trained by surgeons to provide CBE in the CNBSS. Pisani et al. (2006) trained nurses and midwives to perform CBE in an RCT in Manila, Philippines. Women in Mumbai, India, with a 10th grade education and good communication skills who were trained for 4 weeks to perform CBE per a modified version of the CNBSS protocol were able to perform CBE as well as trained surgeons ($\kappa = 0.849$) (Mittra et al., 2010). Sankaranarayanan et al. (2011) trained graduate female health workers for 3 weeks using silicone breast models to perform CBE in an RCT in Trivandrum, India (see Section 4.3).

2.3.3 Quality control

A general lack of quality control and standardization of technique is seen across CBE screening studies and programmes. Studies had reported that graduating primary care physicians were lacking adequate CBE skills and that healthcare providers expressed a need for CBE training (Chalabian & Dunnington, 1998; Pennypacker et al., 1999). In the CNBSS, the providers were trained per a designed CBE protocol, and the CBE skills of the providers were monitored (Baines et al., 1989; Baines, 1992a). The RCT in Mumbai, India, used a modified version of the CNBSS protocol and maintained quality control by comparing a 5% sample of the results of CBE examinations by the study providers with those of surgeons (Mittra et al., 2010). The RCTs in the Philippines and in Trivandrum, India, described structured CBE training of the providers, but there was no mention of quality monitoring of the process during the intervention (Pisani et al., 2006; Sankaranarayanan et al., 2011).

2.3.4 Screening performance

Morimoto et al. (1993) reported a sensitivity of 61% and a specificity of 94.5% for CBE in Zentsūji, Kagawa Prefecture, Japan. Ohuchi et al. (1995) reported a sensitivity of 85% and a specificity of 96% for CBE in Miyagi Prefecture, Japan. In these studies, sensitivity and specificity were calculated by observing all screening participants for a period of 2 years after screening. Barton et al. (1999) analysed the screening performance of CBE by pooling data from six studies: the Health Insurance Plan of Greater New York study, the United Kingdom Trial, the Breast Cancer Detection Demonstration Project of the United States National Cancer Institute, the West London Study, the CNBSS 1, and the CNBSS 2 (see Section 4.3 for descriptions of the studies). For the purpose of analysis, sensitivity was defined as the proportion of cancers detected by CBE, among all breast cancers detected/diagnosed within 12 months of screening; specificity was defined as the proportion of CBE-negative women who did not develop breast cancer within 12 months after screening, among all women who did not develop breast cancer within 12 months after screening. The authors reported a pooled sensitivity of 54.1% and a pooled specificity of 94.0%. Bobo et al. (2000) reported CBE sensitivity, specificity, and PPV of 58.8%, 93.4%, and

4%, respectively, from the United States Centers for Disease Control and Prevention's National Breast and Cervical Cancer Early Detection Program. Pisani et al. (2006) reported a sensitivity of 53.2% and a PPV of recall of 1.2%. Sankaranarayanan et al. (2011) reported CBE sensitivity, specificity, false-positive rate, and PPV of 51.7%, 94.3%, 5.7%, and 1.0%, respectively. Variances in screening performance by technique and duration of screening are discussed in Section 2.3.1.

2.3.5 Host factors that affect performance

Age, menopausal status, body weight, breast density, nodularity (lumpiness), ethnicity, and use of hormone replacement therapy are known to affect the performance of CBE. With respect to age and menopausal status, van Dam et al. (1988) observed that CBE sensitivity was significantly lower in premenopausal and perimenopausal women compared with postmenopausal women. Oestreicher et al. (2002) observed a bell-shaped pattern, with CBE sensitivity low in women aged 40–49 years, higher in women aged 50–59 years, and decreasing gradually in women aged 60 years and older. In contrast, Bobo & Lee (2000) found that CBE sensitivity was higher among women younger than 50 years than among those aged 50 years and older. Also, CBE sensitivity was reported to decrease with increasing body weight (Oestreicher et al., 2002). van Dam et al. (1988) observed that higher nodularity of breasts resulted in lower CBE specificity. The test characteristics of CBE reported from regions that are geographically separated and ethnically and demographically diverse are almost the same, although higher sensitivity values have been reported from one study in Japan (Ohuchi et al., 1995) and among Asian women in a study in the USA (Oestreicher et al., 2002).

2.4 Breast self-examination

Breast self-examination (BSE) is an examination of a woman's breasts by the woman herself, purportedly for early detection of breast cancer.

2.4.1 Technique

The essential components of BSE are visual inspection in front of a mirror and palpation of the breasts and nipples with the soft pads of the middle three fingers. Many techniques have been described for practising BSE (Mamon & Zapka, 1983; Carter et al., 1985; Baines, 1992b). Mamon & Zapka described a BSE technique with 34 systematic steps: 4 steps for visual inspection of both breasts in front of a mirror, 7 steps for each breast in an upright position, and 8 steps for each breast in a supine position. Carter et al. suggested a 21-step procedure, omitting the examinations in the supine position. It is unlikely that women would go through the rigours of such elaborate procedures. Therefore, Baines proposed a simpler technique. It is important to understand that a large proportion of women in LMICs cannot afford the privacy needed to perform BSE with such time-consuming procedures. Therefore, BSE has to be very simple for it to become a popular practice in LMICs.

2.4.2 Training

Clarke & Savage (1999) conducted a literature review of BSE training studies and found that BSE training improves compliance, confidence, and proficiency. Structured individual training in BSE improved the thoroughness of examination in terms of the depth of palpation and the duration of search time (Bragg Leight et al., 2000). Also, periodic reassessment and retraining are required to prevent deterioration of BSE skills (Pinto & Fuqua, 1991). In a study in Denmark, women showed a preference for individual instruction versus group instruction in BSE (Bech et al., 2005). Also, it has been reported

Fig. 2.7 Indicators appropriate for an evaluation of breast self-examination

- Is any visual examination done?
- Is most of the breast examined?
- Are the armpits examined?
- Is there a systematic search pattern?
- Are three fingers used?
- Are finger pads used?
- Is a rotary palpation applied?
- Is breast self-examination performed 12 times a year?

Photo from the United States National Cancer Institute Visuals Online, available from visualsonline.cancer.gov.

that individual instruction improved the proficiency and frequency of BSE performance compared with group instruction (Dorsay et al., 1988; Coleman & Pennypacker, 1991). Systematic training of women to perform BSE has been found to significantly increase the practice of BSE in several studies in Turkey (Hacihasanoğlu & Gözüm, 2008; Oezaras et al., 2010; Donmez et al., 2012).

2.4.3 Quality control

Very few studies have assessed quality control in BSE performance. Mamon & Zapka (1983) described a set of indicators for BSE quality (Fig. 2.7). The weakness is that they are equally weighted. Coleman & Pennypacker developed a weighted scoring system comprising: percentage of total breast area actually palpated, duration of examination, type of pressure, pattern and number of motions, and number and part of fingers used (Coleman & Pennypacker, 1991).

2.4.4 Screening performance

The sensitivity, specificity, and PPV of BSE to detect breast cancer have been reported as 58.3%, 87.4%, and 29.2%, respectively (Wilke et al., 2009). [The study was conducted in a single institution and among women at an increased risk.] In Shanghai, China, an RCT found that women in the BSE instruction group had greater specificity in lump finding in the silicone models compared with women in the control group (Thomas et al., 2002). A nested case–control study within the CNBSS compared the frequency and proficiency of BSE performance between the cases and controls at 1, 2, and 3 years before the diagnosis of the case (Harvey et al., 1997). No difference in BSE frequency was found between cases and controls. However, visual inspection, use of finger pads, and use of the middle three fingers were found to have a significant association with breast cancer diagnosis when performed 2 years before the diagnosis, with an odds ratio for death or distant metastases from breast cancer of 2.2 among women who omitted one, two, or three of these BSE components.

2.4.5 Host factors that affect performance

Because BSE might be of some value in the early detection of breast cancers in LMICs, it is most relevant to examine the host factors likely to affect BSE practice in such countries. A study among Iranian women identified lack of privacy as the principal barrier to BSE practice (Tavafian et al., 2009). In a study in Taiwan, China, personal and social factors were reported to affect the motivation of women attending BSE training (Yang et al., 2010). A study looking for predictors of BSE practice among Malaysian teachers found that higher level of knowledge about breast cancer, greater confidence in performing BSE, and regular visits to a physician were significant predictors for practising BSE (Parsa et al., 2011). Socioeconomic status, level of education, knowledge about breast cancer, and knowledge about BSE performance was found to affect BSE practice in Iranian women (Haji-Mahmoodi et al., 2002). Many studies in LMICs have identified the absence of breast symptoms, lack of breast cancer awareness, and lack of knowledge about BSE performance as the main host factors that affect BSE practice (Choi, 2005; Satitvipawee et al., 2009; Azage et al., 2013). A study in a mixed population of Caucasians and African-Americans in the USA found that high school education, employment status, and marital status were significant variables influencing BSE practice (Madan et al., 2000), whereas ethnicity did not affect compliance.

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