Radiological Screening Programs for Women at High Risk of Developing Breast Cancer

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Abstract: The aim of this review is to identify the evidence for the surveillance of women at high risk of breast cancer with the different modalities. The definition of high risk refers to the subpopulation of women with a family history of breast cancer, including both those with and without identified genetic mutations. The following topic has been evaluated: clinical breast examination (CBE), mammography, ultrasound and MRI accuracy of detecting breast cancer among women at high risk. The search was limited to full reports published in English and published between 1996 and March, 2010. We found consistent evidence that adding MRI provides a highly sensitive screening strategy (sensitivity range: 93-100%) compared to mammography alone (32-86%) or mammography plus ultrasound +/- CBE (26-93%). Three studies that compared MRI plus mammography versus mammography alone showed the sensitivity of MRI plus mammography as 93% (95% CI 86-100%) and the incremental sensitivity of MRI as 60%. Incremental sensitivity of MRI was lower when added to mammography plus ultrasound (43%) or to the combination of mammography, ultrasound plus CBE. Estimates of screening specificity with MRI were less consistent but suggested a 3-5-fold higher risk of patient recall for investigation of false positive results. No studies assessed whether adding MRI reduces patient mortality, interval or advanced breast cancer rates, even if we found strong evidence that MRI leads to the detection of earlier stage disease. This review suggests that a surveillance strategy would be accurate and effective in improving health outcomes for women at high risk of breast cancer, but randomized studies should be considered for a better evaluation of these topics.

Keywords: Breast MRI, high risk women, mammography, surveillance, ultrasound.

INTRODUCTION

Women at high risk of breast cancer are considered as having a family history of breast cancer, including women with and without known genetic mutations that predispose to breast cancer. All age groups are included and some studies include women with individual risk factors, such as a personal history of breast cancer. To assess women for a family history of breast cancer it is recommended to obtain a three or more generation family history [1]. The major features of an inherited predisposition are: early-age of onset of breast cancer in the index case and in relatives; multiple affected family members; bilateral cancers in paired organs; multiple primary tumours in an individual; specific cancer constellations, e.g. breast and ovary; and an autosomal pattern of inheritance [2]. It has been estimated that up to 27 per cent of women with family history may have an inherited predisposition to breast cancer [3]. However, only some of the genes responsible have been identified. Known genetic mutations, which confer a very substantial increased risk of developing breast cancer, are thought to be carried in 5-10 per cent of patients [4]. *BRCA1* and *BRCA2* are two such genetic mutations, and are implicated in both breast and ovarian cancer. Carriers of these mutations reportedly have a lifetime cumulative risk of 50 [5] to 84 [6] per cent of developing breast cancer. The prevalence of these genetic mutations varies between ethnic groups and is especially high in women of Ashkenazi Jewish descent. A statistical computer program called BRCAPro has recently been validated as an accurate tool for determining the probability of carrying *BRCA1* or *BRCA2* genetic mutations [7, 8]. Some rarer mutations associated with breast cancer are *TP53* and *PTEN*. Several uncommon genetic syndromes also confer an increased risk of breast cancer, including Li Fraumeni syndrome, Muir Torre syndrome, Peutz Jeghers syndrome, Cowden's disease and ataxia telangectasia. Women with a clear family history of breast cancer, in whom an underlying genetic mutation has not yet been identified, are also at increased risk of neoplasia. The inability to detect a mutation may be due to there being no living family member affected with breast cancer to test, or because the family's mutation is, as yet, undiscovered. Therefore, a negative genetic test result does not rule out increased risk of breast cancer unless it is negative for a specific mutation which has been identified to run in the family. Several empirical and statistical models have been designed to estimate the magnitude of the risk of breast cancer in individuals with a family history for breast cancer but no known mutation. Some of these focus on aspects of family history alone and others also incorporate individual risk factors. A review of these models [9] suggests that two of the former type, developed by Claus *et al.* [4, 10] and Gail *et al.* [11] are likely to underestimate the lifetime risk for developing breast cancer as their baseline risk for women is too low. These calculations primarily consider the age of the women

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1875-6581/12 $58.00+.00

in question, the number of first-degree and second-degree relatives affected, and the age of onset of breast cancer in any affected first-degree and second-degree relatives. A threshold is then set, usually a lifetime risk greater than 20 per cent [12], over which women are considered to be at significantly increased risk compared with the general age-matched population. Both are likely to underestimate the lifetime risk for developing breast cancer as their baseline risk for women is too low. The Tyrer-Cuzick algorithm [13] was developed to model breast cancer risk in unaffected women by taking into account: their probability of carrying genetic risk factors, namely a rare, high penetrance mutation in *BRCA1* or *BRCA2* and a notional common, low-penetrance dominant susceptibility allele that stood for all other genetic risk factors; and a range of other individual clinical and epidemiological factors known to influence risk, such as menarche and parity. The genetic risk component of the calculations derives from a Bayesian segregation analysis that takes into account known *BRCA1/2* genotyping data and family history of breast cancer in first- and second-degree relatives. Antoniou *et al*. [14] developed a model using complex segregation analysis of breast and ovarian cancer occurrence in a combined data set of a population-based series of 1484 breast cancer cases and 156 multiple-case families. Briefly, the model allows for evaluate the simultaneous effects of *BRCA1*, *BRCA2*, with disease allele frequencies of 0.051% and 0.065%, respectively, and the effect of low-penetrance genes with multiplicative effects on the breast cancer risk. The Tyrer-Cuzick model and the BOADICEA model seem good choice for current clinical practice in predicting breast cancer in women for whom there is no known mutation. It is unknown how many women in Italy comprise this sub-population at high risk of breast cancer. It has been estimated that for a total population of 1 million, there would be 20-40 families whose family history of breast cancer would indicate that members had a high risk of developing breast cancer [3]. Estimates of population carrier frequency have been reported as 0.32 per cent for *BRCA1* and 0.69 per cent for *BRCA2* mutations [15]. This would translate to approximately 72000 women being carriers of either *BRCA1* or *BRCA2* mutations in Italy census population of women. For women at high risk of breast cancer, there are three options for managing their risk. These are:

1. Chemoprevention;
2. Surgical – bilateral mastectomy or bilateral salpingo-oophorectomy (BSO);
3. Surveillance.

The focus of this review is on surveillance.

MODALITIES FOR SURVEILLANCE

Surveillance, as opposed to screening, refers to monitoring individuals known to have a disease or to be at increased risk of disease. Similar issues need to be considered for any proposed surveillance program. However, the benefit–to-risk ratio of surveillance as opposed to population screening is more favourable. This is because a greater proportion of a surveillance population is likely to benefit from monitoring due to the high prevalence of disease in this population. This population is also more willing to accept the risks associated with surveillance than would healthy, average-risk individuals. A discussion of some issues that need to be addressed in considering surveillance for women at high risk of breast cancer follows. The population of women at high risk of breast cancer may be relatively small but the likelihood of disease in these women is extremely high. Due to the early onset of disease, it results in considerable loss of quality-adjusted life years. The burden of this disease affects both the individuals at high risk and the greater community, and this renders it a suitable candidate for surveillance. The primary objective of screening is to detect disease at an early stage, before it causes symptoms. The individual can then be treated to ameliorate or cure the disease [16]. This is also the primary objective of surveillance and depends on the natural history of the disease allowing early detection, as well as treatment at an early stage improving the prognosis. It is possible to detect *in situ* breast cancer, i.e. ductal carcinoma *in situ* (DCIS) and preneoplastic lesions, such as lobular neoplasia or atypical hyperplasia, with surveillance. Without this surveillance, these early-stage lesions would not be detectable as they are not palpable and would not present symptomatically. Therefore surveillance has the potential to improve breast cancer survival through early detection. The mainstay of screening and surveillance for breast cancer has been clinical breast examination (CBE) and mammography. Breast self-examination (BSE) was at times advised, but has been found by randomized controlled trial (RCT) not to reduce breast cancer mortality and to increase unnecessary biopsies [17]. Latterly, other imaging modalities have been considered, particularly for women at high risk of breast cancer. Characteristics of these tests are described briefly below, along with the issues surrounding each test's use for surveillance in women at high risk of breast cancer.

Current recommendations for the management of high-risk women include semi-annual CBE and annual mammography beginning between the ages of 25 and 35 [18]. Despite widespread endorsement of mammographic screening for high-risk women, no evidence to date has shown that routine mammography reduces cancer mortality in *BRCA1* or *BRCA2* carriers. Most hereditary breast cancers occur in premenopausal women, and the value of risk reduction of death by screening mammography is significantly lower for women below age 50, with a 22% in women over the age of 50 years, and 15% in women between the ages of 40 and 49 years [19].

Clinical Breast Examination

The effectiveness of BSE has not been formally evaluated in women with a hereditary risk for breast cancer. A meta-analysis of studies performed in women at average risk showed no significant reduction in breast-cancer mortality with BSE but did show an increase in the number of biopsies performed [20]. CBE is a systematic examination by a clinician of the four quadrants of each breast and the axillary areas. The value of clinician-performed breast examination as an adjunct to radiographic screening is also unclear. In three large studies of women at average risk, 3 to

8% of cancers were detected solely by clinical examination [21, 22]. In smaller studies of women with a hereditary risk, the proportion of cancers that were identified solely by clinical screening was 0 to 4% [23, 24]. However, CBE is usually carried out in conjunction with radiological imaging and in some cases does detect tumours that were not identified by other means.

Mammography

Mammography is an imaging modality that utilizes low dose ionizing radiation to examine the breasts. The results of eight RCTs have established the ability of mammographic screening to improve outcome in breast cancer [25]. A decrease in mortality of up to 30 per cent has been shown through mammographic screening of women over the age of 50-69 years [26]. The evidence for women aged less than 50 years is less clear. A RCT of mammographic screening of women from age 40 was carried out in the UK. Moss [27] suggested that a reduction in breast cancer mortality may be observed in the trial, even if the reduction is not significant. Women at high risk require surveillance from an early age, often from 30 years or five years before the youngest affected relative if they were diagnosed under the age of 30. There is no RCT evidence for mammographic surveillance of women at high risk, and from such a young age. It is unlikely that such evidence could be obtained. It would no longer be considered ethical to conduct an RCT as this would mean one arm of the study receiving no surveillance. Women at high risk are usually offered mammographic surveillance based on the evidence of its use as a screening tool in older women. However, it is known that mammography is less accurate in younger women due to the higher density of their breasts [28, 29] with much higher interval cancer rate [30] and also perhaps due to the phenotype of their tumours which have a smoother, more benign appearance on mammography [31, 32]. Further, dense breast tissue is itself a marker of increased risk of breast cancer on the order of 4 to 6 fold [33]. In dense breasts, digital mammography has improved performance, with sensitivity increasing from 55% with screen film to 70% with digital in one large series using mammographic and clinical follow-up as a gold standard [34]. Digital mammography does not, however, eliminate the fundamental limitation that non calcified breast cancers are often obscured by surrounding and overlying dense parenchyma. Using a screening interval of 12 months, rather than 24 months, should improve results with rapidly growing malignancies [35], though dense tissue remains a major limitation to improving outcomes.

Women at high risk of breast cancer also require more frequent mammography as they are prone to more rapidly developing, biologically aggressive tumours [36]. A disadvantage of mammography in women at high risk is its use of radiation. If surveillance commences at a young age and is repeated frequently they will be exposed to a high cumulative dose of radiation. This is increased by the need for recall mammography when breast density makes the images difficult to interpret. *BRCA1* and *BRCA2* mutation carriers are of particular concern. These mutations have been implicated in cell cycle regulation and DNA repair [37, 38] which means that carriers may be more susceptible to the mutagenic effects of low-dose radiation [39, 40]. As suggested by Berrington de Gonzalez [41] the estimated lifetime risk of radiation induced breast cancer mortality per 10 000 women resulting from annual mammography was 26 for screening at age 25-29 years, 20 for screening at age 30-34 years, and 13 for screening at age 35-39 years. To weigh these risks, screening would have to reduce breast cancer mortality by 51% at age 25-29 years, by 12% at age 30-34 years, and by 4% at age 35-39 years; estimates were similar for *BRCA2* mutation carriers. If we assume that the mortality reduction from mammography is 15%-25% or less for young women, these results suggest that there would be no net benefit from annual mammographic screening of *BRCA* mutation carriers at age 25-29 years; the net benefit would be zero or small at age 30-34 years, but there should be some net benefit at age 35 or older. These disadvantages suggest that it may be preferable to utilize other modalities of surveillance in women at high risk of breast cancer either in addition to, or instead of mammography. A good choice might be to avoid mammography and to use MRI and ultrasonography in high-risk women, at least up to the age of 35 years [42]. Methods to address improving detection despite dense breast tissue are needed.

Ultrasonography

Ultrasound (US) imaging, also called ultrasonography, obtains images through the use of high-frequency sound waves. The reflected sound wave echoes are recorded and displayed as real-time visual images. US has traditionally been used as a diagnostic tool for breast imaging rather than for screening or surveillance. An advantage of US, particularly for women at high risk, is that it does not use ionizing radiation. It is also the simplest way to guide biopsies and is therefore a unique problem-solving tool [43]. The disadvantages of US are that storing images for review is not as simple as other imaging modalities and its accuracy is extremely operator dependent, causing poor inter-observer reliability. The addition of ultrasonography to screening mammography in asymptomatic women with nonfatty breasts yielded a rate of breast-cancer detection of 0.35 percentage point [44]. The benefit in women with a familial risk has not been established. In two studies of women with a hereditary risk who underwent screening with mammography, ultrasonography, and MRI, only 2 of 83 cancers were detected solely by annual ultrasonography [24, 45]. Two additional nonpalpable cancers were detected by screening ultrasonography performed at 6-month intervals in one study. Ultrasonography did identify a significant number of mammographically occult tumors. Of the 83 cancers in these series, only 32 (39%) would have been identified by mammography alone, whereas 45 (54%) would have been detected by a combination of mammography and ultrasonography. In a study performed on different risk categories, included *BRCA1/2* carriers, ultrasonography was useful for bridging the relatively long time interval between the annual surveillance rounds [46], as in other series [47]. Adding US to mammography improved the

sensitivity of screening from 78% to 97%. In *BRCA1/2* carriers, US showed a very high sensitivity in addition to mammography yielding the sensitivity from 50% with only mammogram to 75% with both modalities. As expected, the major advantage of US was seen in women aged less than 50 years where the sensitivity was up to 64% such as mammography and the combination sensitivity reached the 100%. In a recent study adding a single screening with US to mammography will yield an additional 1.1 to 7.2 cancers per 1000 high-risk women, but will also substantially increase the number of false positives [48]. As in prior studies, the vast majority of cancers seen only on US were invasive, as DCIS is difficult to see on US. Invasive cancers not seen on mammography can be expected to present as interval cancers with worse prognosis: detection of asymptomatic, mammographically-occult, node-negative invasive carcinomas with US should reduce mortality from breast cancer. In an elevated-risk study population, enriched in women with dense breasts, mammographic sensitivity was only 50% and the sensitivity of US+mamography was 77.5%. From a detection standpoint, it may be reasonable to offer supplemental screening US to women with similar risk criteria. US is well tolerated, the technology is widely available, and it does not require intravenous contrast material. If, however, screening US is to be widely implemented, several major issues remain. The time to perform bilateral screening US is problematic, at a median of 19 minutes. Nineteen minutes is considerably longer than the average 4 minutes 39 seconds reported by Kolb *et al*. [29] for physicians scanning, or the average 10 minutes reported by Kaplan *et al*. [49] for technologists. The final barrier to implementing screening US is the risk of false positives. In the Berg study [48] of 2637 participants, (with 136 participants having suspicious findings on US but not with mammography) 235 (8.9%) were recommended for biopsy based on US. Only 21/235 (8.9%) of participants biopsied based on US proved to have cancer. The 8.8% to 8.9% positive predictive value (PPV) of US-prompted biopsy in this study is similar to the 11% rate seen across prior series [50]. Diagnostic uncertainty for complicated cysts remains a major source of false positives. This finding suggests that ultrasonography may add benefit beyond mammography alone in women with a hereditary risk but provides little incremental benefit in women undergoing screening with MRI.

MRI

MRI uses the signal produced by hydrogen ions or protons placed in a powerful magnetic field stimulated by radio waves to produce images. Initially it was thought that MRI would not be a useful tool for imaging breast disease as the signal from breast cancer was very similar to that of normal fibroglandular tissue. However, in 1986 a first report on 20 patients undergone breast examinations by MRI without and with Gd-DTPA as contrast medium indicated that MRI of breast using Gd-DTPA may be helpful for the evaluation of dense breasts and the differentiation of dysplasia and scar tissue from carcinoma [51].

The same author reported that the use of intravenous contrast agent caused breast cancers to become rapidly enhanced and conspicuous against the normal background tissue [52]. Subsequently, MRI has been used for locating occult primary breast tumours, pre-surgical and post-surgical assessment of breast tumours, and assessment of treatment response to systemic therapy. Furthermore the recommendation of annual breast MRI to women who underwent mantle chest radiation therapy for Hodgkin disease was proposed because of the high risk of secondary breast cancer in this group [12]. It has also been trialed in the surveillance of women at high risk of breast cancer [53]. The advantage of MRI is that, like US, it does not use ionizing radiation. The absolute contraindications for its use are pacemakers or defibrillator, endocranial ferromagnetic metallic clips on aneurysms, metallic foreign bodies in particular sites (e.g., intraocular). The absolute contraindication for pacemaker is debatable since a 77 years old woman with dual chamber demand pacemaker underwent a 1.5 T breast MRI without complications, allowing to identifying a bifocal cancer in the right breast [54]. Relative contraindications are orthopedic implants, artificial heart valves, implanted port, or infusion catheter and frequently do not contraindicate breast MRI. Moreover acute renal failure and chronic kidney disease with eGFR <30 ml/min/1.73m2 have to be considered contraindications to gadolinium-based contrast agents since they have been suggested to trigger the development of nephrogenic systemic fibrosis. Gadobenate dimeglumine and gadopentetate dimeglumine would be used in patients with eGFR less than 30 mL/min/1.73m2 in whom the contrast administration was deemed medically necessary [55, 56]. A large body mass index (BMI) and claustrophobia may also cause difficulties. Disadvantages of MRI are that it is expensive and not readily available in all facilities. This is especially because breast MRI requires specialized equipment, such as breast coils and facilities, to allow MRI-guided biopsy. These are all required in order to perform adequate surveillance, as is a radiologist with significant experience in breast MRI. As with any modality of surveillance, the accuracy depends heavily on the experience of the interpreting radiologist. The total number of breast MRI studies read each year in the USA is estimated to be 0.02 per cent of the screening mammography which are read. This may well account for the lower measures of accuracy (PPVs) of MRI in some studies, and should improve over time as experience is gained [57]. Several single-center and multicenter studies have evaluated screening MRI in women with a hereditary risk for breast cancer. Prospective studies involving 3991 high-risk patients, including 913 with *BRCA* mutations, showed that MRI detects more than twice as many cancers as does simultaneously performed mammography or ultrasonography [23, 24, 45, 58]. In the studies, MRI detected 64 to 100% of cancers, whereas mammography and ultrasonography each detected 16 to 40%. Of all cancers identified, 78% were detected by MRI, 38% by mammography, and 42% by ultrasonography (when performed). Rates of interval cancer were less than 10% when MRI was performed. In the EVA trial [59] prospective multicenter screening trial on women at elevated familial risk, with measures for quality assurance established not only for mammography and US, but also for MRI, screening was successful in that the stage of breast cancers at the time of diagnosis was low, and the rate of interval cancers

was 0%. The absence of interval cancers could be explained by the small number of *BRCA1/2* carriers (9.5% of all enrolled women) which are more likely to developing fast growing tumours compared to women at relatively lower risk.

Although stage distribution is only a surrogate end point, and although a downward shift of stage does not prove a survival benefit, the detection of high-grade DCIS or of small, node-negative breast cancers is closely correlated with a reduction in breast cancer mortality. In good agreement with previous trial [60] MRI proved to be the most important contributor to this success. The cancer yield achieved with MRI alone was significantly higher than that achieved with mammography or US or both, and it did not increase significantly if MRI was read in conjunction with mammography or US. This means that the outcome of this multimodality screening program was solely determined by the use of MRI, whereas the use of other imaging methods, including mammography, had no significant influence on cancer yield.

Systematic annual screening mammography is currently recommended for all women at increased familial risk– despite the superior diagnostic performance of MRI compared to mammography that was consistently found across all, including the very early, published screening trials [32, 61-63]. If further studies confirm the high sensitivity of MRI for invasive cancers and for DCIS that was found in the EVA trial, then it is conceivable to discontinue mammographic screening in young women who have access to quality assured screening breast MRI. Even existing evidence suggests that this may be an option for young women under 40, especially if they carry a *BRCA1* mutation or a high risk of heterozygosity. Another important finding of the EVA trial was that MRI was not only superior to mammography for diagnosing invasive breast cancers, but also for DCIS. In the EVA cohort, not only half of the invasive cancers (eight of 16), but also more than half of the DCIS (six of 11) were only MRI detected. This result contradicts earlier studies that suggested MRI to be substantially less sensitive than mammography specifically with regards to DCIS [23, 62]. The discrepancy is probably best explained by the advances that have been made in the field of breast MRI since the first screening studies were conducted. The MRI diagnosis of DCIS requires the use of diagnostic criteria that have only recently been described [64, 65] and is improved by observing standards for interpretation and reporting that have only recently been introduced. The rate of DCIS in the EVA trial was 53% which is more than twice as high as the DCIS rate expected for mammographic screening [66]. It is the highest rate of preinvasive cancers stages ever reported for breast cancer screening. Although this finding could be considered a particularly successful example of secondary prevention, the high rate of DCIS also raises concerns regarding a possible overdiagnosis. The mammographic hallmarks of cancer (i.e., architectural distortions and calcifications) are caused by regressive changes (i.e., fibrosis, necrosis), one reason for the fact that mammographic screening preferably identifies slowly-growing cancers [67], an effect referred to as length time bias, of which overdiagnosis is an extreme form. In Italy a model based on the statistical adjustment for lead time of the observed incidence rate in the Florentine screening programme found a risk of overdiagnosis of 5% for DCIS [68]. As opposed to this, a cancer's detectability in MRI is determined by its angiogenic activity (i.e., by tissue alterations that have been implicated in carcinogenesis, cancer proliferation, and metastatic growth) [69-73]. MRI characteristics can therefore serve as biomarkers for cancer vitality. MRI-only cancers tend to exhibit histopathologic evidence of biologic aggressiveness [74, 75]. This was also true for the DCIS identified in the EVA trial: all MRI-only detected DCIS exhibited intermediate or high nuclear grading, whereas the only DCIS missed by MRI (picked up by mammography) was the only low-grade DCIS in the cohort. US appears to be complementary to mammography, but not to MRI, and is no equivalent replacement for MRI.

RESULTS

1. The first aim is to demonstrate that surveillance with mammography has a higher cancer detection rate and is more accurate than CBE alone. Summaries of these results are presented in Tables **1** and **2**.

Overall, a higher cancer detection rate and sensitivity with mammography surveillance compared to CBE was seen. This is logical as tumours are only detectable by CBE once they have reached approximately 10 mm in size [76]. CBE surveillance performed better than mammography in two studies [77, 78]. The second comparison made was between the cancer detection rates in the studies and in established breast screening programs for women over 50 years of age. The assumption was that if there were similar rates of detection then surveillance for women at high risk should be acceptable. However, this does not take into account the potential harms, for example radiation exposure, for high-risk women undergoing surveillance from an early age and over a longer time period. Cancer detection rates would be expected to be higher in women with a high risk of breast cancer due to the higher prevalence among this group. However, it is also postulated that cancer detection with mammography is reduced in women at high risk. This is because they require screening from a younger age when their breasts are denser, and also due to the histopathological characteristics of their tumours, which appear more benign. The results suggest equivalence of cancer detection rates to those of the breast screening programs.

In conclusion, surveillance with mammography in women at high risk of breast cancer appears to be more effective and accurate in detecting early breast cancer than surveillance with CBE alone. The cancer detection rates appear to be equivalent or higher than those in established breast screening programs for women over 50 years of age. A high level of interval tumours remained in these studies of mammography and CBE surveillance. This suggests that to improve detection of early breast cancer in this population of high risk women and especially those at highest risk, i.e. mutation carriers, more intensive surveillance strategies or the addition of other modalities of surveillance is required.

Table 1. Summary of Cancer Detection Rates from the Studies of Surveillance by Mammography and CBE

Study	Cancer Detection Rate Per 1000 Women	Cancer Detection Rate by Modality of Screening
Chart *et al*. (1997) [82]	18.0 per 1000 w/s	CBE 1.9 per 1000 w/s mammography 3.8 per 1000 w/s
Lalloo *et al*. (1998) [83]	11.0 per 1000 w/s	CBE 4.7 per 1000 w/s mammography N/R
Kollias *et al*. (1998) [84]	14.0 per 1000 w/s	CBE N/R mammography 12.0 per 1000 w/s
Federico *et al*. (1999) [85]	39.0 per 1000 w/s	CBE N/R mammography 39.0 per 1000 w/s
Kerlikowske *et al*. (2000) [86]	6.0 per 1000 w/s	CBE 0 mammography 6.0 per 1000 w/s
Gui *et al*. (2001) [77]	17.6 per 1000 w/s (includes interval tumours)	CBE 14.8 per 1000 w/s mammography 8.3 per 1000 w/s (includes interval tumours)
Hou *et al*. (2002) [80]	22.0 per 1000 w/s (includes US)	CBE 7.0 per 1000 w/s mammography 12.0 per 1000 w/s
Scheuer *et al*. (2002) [87]	42.4 per 1000 w/s	CBE N/R mammography 30.0 per 1000 w/s
Trecate *et al*. (2003) [78]	170 per 1000 w/s (includes US and MRI)	CBE 130.0 per 1000 w/s mammography 0
Kriege *et al*. (2004) [23]	23.0 per 1000 w/s (includes MRI)	CBE 1.6 per 1000 w/s mammography: 6 per 1000 w/s BIRADS >4 9 per 1000 w/s BIRADS >3
Warner *et al*. (2004) [24]	93.0 per 1000 w/s (includes US and MRI)	CBE 8.0 per 1000 w/s mammography 34.0 per 1000 w/s
Murday *et al*. (2004) [88]	31.0 per 1000 w/s	CBE 15.6 per 1000 w/s mammography 31.0 per 1000 w/s
Kuhl *et al*. (2005) [45]	76.0 per 1000 w/s	CBE 2.0 per 1000 w/s mammography N/R
Gui *et al*. (2006) [89]	6.2 per 1000 w/s	CBE 5.3 per 1000 w/s mammography 6.2 per 1000 w/s
Cortesi *et al*. (2006) [46]	33.2 per 1000 w/s (includes US and MRI)	CBE 6 per 1000 w/s mammography 27.1 per 1000 w/s (includes interval tumours)
Sardanelli *et al*. (2007) [58]	64.7 per 1000 w/s (includes US and MRI)	CBE 32.3 per 1000 w/s mammography 64.7 per 1000 w/s
Weinstein *et al*. (2009) [79]	29.4 per 1000 w/s (includes US and MRI)	CBE N/R mammography 21.2 per 1000 w/s
Bennet *et al*. (2010) [81]	21.7 per 1000 w/s	CBE 14 per 1000 w/s mammography 16 per 1000 w/s

N/R = not reported.

The following chapters will review the evidence for the accuracy and efficacy of surveillance with additional modalities in women at high risk of breast cancer.

2. The second aim is to demonstrate that surveillance with US has a higher cancer detection rate and is more accurate than CBE alone. Summaries of these results are presented in Tables **3** and **4**.

These results show that the cancer detection rate for US is on the whole greater than that from CBE alone. The results of all studies but one [79] show US to be more sensitive than

Table 2. Sensitivity of Surveillance for Women at High Risk of Breast Cancer by Mammography and CBE

Study	Measure of Accuracy	CBE (95% CI)	Mammography (95% CI)
Brekelmans *et al*. (2001) [90]	Sensitivity	40% (24% to 58%)	60% (42% to 76%)
Gui *et al*. (2001) [77]	Sensitivity	84% (60% to 97%)	47% (24% to 71%)
Hou *et al*. (2002) [80]	Sensitivity Specificity	31.8% (14% to 55%) 99.4% (98.7% to 99.8%)	50% (28% to 72%) 99.6% (98.9% to 99.9%)
Scheuer *et al*. (2002) [87]	Sensitivity	50% (21% to 79%)	42% (15% to 72%)
Warner *et al*. (2004) [24]	Sensitivity Specificity PPV NPV	9.0% (1% to 29%) N/R N/R N/R	36.3% (17.1% to 59.3%) 99.8% (98.7% to 99.9%) 88.9% (51.7% to 99.7%) 96.9% (94.8% to 98.3%)
Murday *et al*. (2004) [88]	Sensitivity	33% (7% to 70%)	67% (30% to 92%)
Halapy *et al*. (2005) [91]	Sensitivity Specificity	40.5% (25% to 56%) 94% (93% to 95%)	76.3% (63 % to 90%) 94.6% (94 to 95%)
Kuhl *et al*. (2005) [45]	Sensitivity Specificity PPV NPV	2.3% (0.1 to 12%) N/R N/R N/R	32.5% (19% to 48.5%) 96.8% (95.7% to 97.7%) 23.7% (14 to 37%) 97.9% (97% to 98.6%)
Gui *et al*. (2006) [89]	Sensitivity	14% (0.3% to 58%)	85.7% (42.5 to 99.6%)
Cortesi *et al*. (2006) [46]	Sensitivity	18.1% (0.3% to 60%)	65.9% (30% to 90%)
Sardanelli *et al*. (2007) [58]	Sensitivity	50% (29% to 71%)	58.8% (36% to 78.4%)
Weinstein *et al*. (2009) [79]	Sensitivity Specificity	N/R N/R	36% (22% to 50%) 92.5% (92 to 94%)

PPV= Positive predictive value
NPV=Negative predictive value
N/R = not reported

Table 3. Cancer Detection Rates in Surveillance of Women at High Risk of Breast Cancer with CBE and US

Study	Cancer Detection Rate	CBE	US
Hou *et al*. (2002) [80]	22 per 1000 w/s	7 per 1000 w/s	20 per 1000 w/s
Warner *et al*. (2004) [24]	93 per 1000 w/s	8 per 1000 w/s	30 per 1000 w/s
Kuhl *et al*. (2005) [45]	76 per 1000 w/s	2 per 1000 w/s	32 per 1000 w/s
Cortesi *et al*. (2006) [46]	33 per 1000 w/s	6 per 1000 w/s	17 per 1000 w/s
Sardanelli *et al*. (2007) [58]	65 per 1000 w/s	32 per 1000 w/s	39.5 per 1000 w/s
Berg *et al*. (2008) [48]	15 per 1000 w/s	3 per 1000 w/s	8 per 1000 w/s
Weinstein *et al*. (2009) [79]	29 per 1000 w/s	N/R	5 per 1000 w/s
Kelly *et al*. (2009) [92]	7 per 1000 w/s	2 per 1000 w/s	5 per 1000 w/s
Bennett *et al*. (2010) [81]	22 per 1000 w/s	14 per 1000 w/s	17 per 1000 w/s

N/R = not reported

CBE in the surveillance of women at high risk of breast cancer. Kuhl *et al*. [45] shows that the sensitivity of US decreases as the risk status of women increases, being especially low for mutation carriers while Cortesi *et al*. [46] shows an increasing US sensitivity from low risk to *BRCA* carriers. It is noted that the PPV of US is low, 29.2 per cent in Warner *et al*. [24], 11.2 per cent in Kuhl *et al*. [45] and 64.2 per cent in Sardanelli *et al*. [58]. This is due to the high number of false - positives generated by US examination. This is of importance due to the anxiety and potential harm related to further invasive investigation of abnormal surveillance results.

Table 4. Measures of Accuracy in Surveillance of Women at High Risk of Breast Cancer with CBE and US

Study	Accuracy	CBE% (95% CI)	US% (95% CI)
Hou *et al*. (2002) [80]	Sensitivity Specificity	31.8 (13.9-54.9) 99.4 (98.7-99.8)	86.4 (65.1-97.1) 99.4 (98.7-99.8)
Warner *et al*. (2004) [24]	Sensitivity Specificity	9.1 (1-29) N/R	33.3 (14.6-56.9 96 (93.7-97.7)
Kuhl *et al*. (2005) [45]	Sensitivity Specificity	2.3 (0.1-12.3) N/R	39.5 (25-55.6) 90.5 (88.8-92)
Cortesi *et al*. (2006) [46]	Sensitivity Specificity	18.1 (0.3-60) N/R	47.7 (30-61.2) N/R
Sardanelli *et al*. (2007) [58]	Sensitivity Specificity	50 (29-71) N/R	64.7 (41.3-82.7) NR
Berg *et al*. (2008) [48]	Sensitivity Specificity	19.5 (1-61) N/R	50 (33.8-66.2) 91.8 (90.7-92.8)
Weinstein *et al*. (2009) [79]	Sensitivity Specificity	N/R N/R	17 (0.2-55.8) 88 (86.6-91.4)
Kelly *et al*. (2009) [92]	Sensitivity Specificity	19.2 (0.9-60.2) N/R	40.3 (27.5-54) 89.9 (89.1-90.6)
Bennett *et al*. (2010) [81]	Sensitivity Specificity	64.1 (41-81.1) N/R	79.2 (70.3-88.2) N/R

N/R = not reported

In conclusion, it appears that surveillance with US is more sensitive than surveillance with CBE alone in women at high risk of breast cancer. However, the sensitivity is still relatively low except for in the study by Hou *et al*. [80] and Bennett [81].

This would suggest that CBE and US alone are not adequate for the surveillance of women at high risk of breast cancer and that other modalities of screening are required in addition or instead of this strategy. The following result reviews the evidence for surveillance with US and mammography for women at high risk of breast cancer.

3. The third result is that cancer detection rates are similar between mammography and US surveillance and the combination of mammography and US appears to offer a slightly higher cancer detection rate. The results of the cancer detection rates and measures of accuracy are summarised in Tables **5** and **6** for surveillance with US,

Table 5. Cancer Detection Rates in Surveillance of Women at High Risk of Breast Cancer with Mammography and US

Study	Cancer Detection Rate	Mammography	US	Mammography + US
Hou *et al*. (2002) [80]	22 per 1000 w/s	12 per 1000 w/s	20 per 1000 w/s	N/R
Podo *et al*. (2002) [93]	76 per 1000 w/s (includes MRI)	9 per 1000 w/s	9 per 1000 w/s	N/R
Warner *et al*. (2004) [24]	93 per 1000 w/s (includes MRI)	34 per 1000 w/s	30 per 1000 w/s	N/R
Kuhl *et al*. (2005) [45]	76 per 1000 w/s	26 per 1000 w/s	32 per 1000 w/s	40 per 1000 w/s
Cortesi *et al*. (2006) [46]	33 per 1000 w/s	27 per 1000 w/s	17 per 1000 w/s	27 per 1000 w/s
Sardanelli *et al*. (2007) [58]	65 per 1000 w/s	65 per 1000 w/s	39.5 per 1000 w/s	N/R
Berg *et al*. (2008) [48]	15 per 1000 w/s	8 per 1000 w/s	8 per 1000 w/s	12 per 1000 w/s
Weinstein *et al*. (2009) [79]	29 per 1000 w/s	21 per 1000 w/s	5 per 1000 w/s	N/R
Kelly *et al*. (2009) [92]	7 per 1000 w/s	2 per 1000 w/s	5 per 1000 w/s	3 per 1000 w/s
Bennett *et al*. (2010) [81]	22 per 1000 w/s	16 per 1000 w/s	14 per 1000 w/s	N/R

N/R = not reported

Table 6. Measures of Accuracy in Surveillance of Women at High Risk of Breast Cancer with Mammography and US

Study	Accuracy	Mammography	US	Mammography + US
Hou *et al*. (2002) [80]	Sensitivity Specificity	50% (28.2-71.8%) 99.5% (98.9-99.95)	86% (65.1- 97.1%) 99.4% (98.7 -99.8%)	N/R N/R
Sim *et al*. (2004) [47]	Sensitivity Specificity	53.3% 85.7%	83.3% 65.5%	92.9% 62.5%
Warner *et al*.(2004) [24]	Sensitivity Specificity	36.3% (17.1%- 59.3%) 99.8% (98.7% -99.9%)	33.3(14.6-56.9) 96 (93.7-97.7)	64% N/R
Kuhl *et al*. (2005) [45]	Sensitivity Specificity	32.6% (19.0-48.5%) 96.8% (95.7-97.7%)	39.5% (25.0-55.6%) 90.5% (88.8-92.0%)	48.8% (33.3-64.5%) 89.0% (87.2-90.6%)
Cortesi *et al*. (2006) [46]	Sensitivity Specificity	65.9% (30-90%) N/R	47.7(30-61.2) N/R	81.8% (75.2-86.8%) N/R
Sardanelli *et al*. (2007) [58]	Sensitivity Specificity	58.8% (36- 78.4%) N/R	64.7 (41.3-82.7) N/R	N/R N/R
Berg *et al*.(2008) [48]	Sensitivity Specificity	50% (33.8-66.2%) 95.5% (94.6-96.3%)	50 (33.8-66.2) 91.8 (90.7-92.8)	77.5% (61.5-89.1%) 89.4% (88.1-90.5%)
Weinstein *et al*. (2009) [79]	Sensitivity Specificity	36% (22 - 50%) 92.5% (92 - 94%)	17 (0.2-55.8) 88 (86.6-91.4)	N/R N/R
Kelly *et al*. (2009) [92]	Sensitivity Specificity	14% (7.2-34.2%) 95.1% (94.6-95.7%)	40.3(27.5-54%) 89.9 (89.1-90.6%)	26.3% (21.2-48.2%) 98.7% (98.3-98.9%)
Bennett *et al*. (2010) [81]	Sensitivity Specificity	73.6% (59.2-86.8%) N/R	79.2 (70.3-88.2) N/R	92.5% (89.2-94.3) N/R

N/R = not reported

mammography and the combination of mammography and US.

The principal studies which give measures of accuracy and have the raw data to calculate statistical significance [24, 45, 48, 58, 92] demonstrate that there is no significant difference between the sensitivity of mammography and US surveillance in women at high risk of breast cancer. There is a significant difference in the specificity with lower values for US than mammography due to the number of false positive examinations created by US surveillance.

In conclusion, surveillance in women at high risk of breast cancer with mammography or US has equivalent sensitivity, but US has a lower specificity. The combination of mammography and US has a better sensitivity than either modality alone, yet retains the poorer specificity of US. This is due to the number of false positives generated by US. US has the advantage of not using ionising radiation for surveillance and being a functional tool for biopsy. However, the number of false positives generated is a disadvantage as it would lead to anxiety and a higher rate of invasive investigations. Due to this, US should be used in combination with mammography to increase his sensitivity in detecting cancer in women at high risk. The following result examine the role of MRI in this surveillance.

4. The fourth result is that MRI is more sensitive than CBE in detecting cancerous lesions in women at high risk of breast cancer as reported in Table **7**.

The specificities for MRI in four studies [23, 24, 45, 59] are relatively high. However, in the study by Kriege *et al*. [23], a slightly lower specificity score for MRI (89.8% compared to 98.1% for CBE) is suggestive of a higher rate of false positive results for MRI surveillance. This is an important consideration, given the higher levels of anxiety faced by women who are referred for biopsy because of a suspicious surveillance test result, in particular because their family history makes it highly likely they have witnessed family members be diagnosed and treated for breast cancer. In the study by Kuhl *et al*. [45], the specificity for MRI was 97.2 per cent compared to a 99.4 per cent in Kuhl *et al*. [59]. This is potentially suggestive of a learning effect whereby those reading the MRI scans become more skilled as a result of increased experience and the availability of previous films for comparison, and this may result in fewer false-positive results over the course of the study.

5. The fifth result is that surveillance with MRI appears to be associated with substantially higher sensitivity than for mammography in terms of detecting cancers in women at high risk of breast cancer owing to familial or genetic history as reported in Table **8**.

In conclusion, MRI appears to be more sensitive than mammography for the detection of breast cancers in women at high risk of breast cancer owing to genetic or family history. The increase in sensitivity is particularly noticeable in women who carry mutations in *BRCA1*. However, the specificity of MRI is generally lower than that of mammography, which has implications for resource use and anxiety of those undergoing surveillance.

Table 7. Summary of Results for MRI Surveillance Compared to CBE

Study	Screening Modality	N°cancers Detected/N°total Cancers	Sensitivity (95%CI)	Specificity (95%CI)
Trecate *et al*. (2003) [78]	MRI CBE	4/4 3/4	100% 75%	N/R N/R
Kriege *et al*. (2004) [23]	MRI CBE	32/45 8/45	71.1% (56 to 84%) 17.8% (8 to 32%)	89.8%-99.9% 98.1%-99.9%†
Warner *et al*. (2004) [24]	MRI CBE	17/22 2/22	77% (55 to 92%) 9.1% (1 to 29%)	95.4% (92.9 to 97.2%) N/R
Kuhl *et al*. (2005) [45]	MRI CBE	39/43 1/43	90.7% (78 to 97%) 2.3% (0 to 12%)	97.2% (96.2 to 98%) N/R
Cortesi *et al*. (2006) [46]	MRI CBE	4/4* 8/44	100% 18.1% (0.3 to 60%)	N/R N/R
Sardanelli *et al*. (2007) [58]	MRI CBE	15/16** 9/18	93.8% (71.7 to 98.9%) 50% (29 to 71%)	N/R N/R
Kuhl *et al*. (2010) [59]	MRI CBE	25/27 1/27	92.6% (84.2 to 99.7%) 3.7% (1.2 to 15.1%)	99.4% (95.9 to 99.9%) N/R

N/R = not reported
*MRI was performed only in *BRCA1/2* carriers
**In two cases MRI was not performed

Table 8. Summary of Results for MRI Surveillance Compared to Mammography Surveillance

Study	Screening Modality	N°Cancers Detected/N°Total Cancers	Sensitivity (95%CI)	Specificity (95%CI)
Kriege *et al*. (2004) [23]	MRI Mammography	32/45 18/45	71.1% (56 to 84%) 40% (26 to 56%)	89.8%-99.9% 98.1%-99.9%†
Warner *et al*. (2004) [24]	MRI Mammography	17/22 8/22	77% (55 to 92%) 36% (17 to 59%)	95.4% (92.9-97.2) 99.8% (98.7-99.9)
Kuhl *et al*. (2005) [45]	MRI Mammography	39/43 14/43	90.7% (78 to 97%) 32.6% (19 to 48%)	97.2 % (96.2-98.0) 96.8% (95.7-97.7)
Leach *et al*. (2005) [62]	MRI Mammography	27/35 14/35	77% (70 to 90%) 40% (24 to 58%)	81% (80-83) 93% (92-95)
Cortesi *et al*. (2006) [46]	MRI Mammography	4/4* 29/44	100% 65.9% (30 to 90%)	N/R N/R
Sardanelli *et al.* (2007) [58]	MRI Mammography	15/16** 10/17***	93.8% (71.7 to 98.9%) 58.8% (36 to 78.4%)	N/R N/R
Weinstein *et al*. (2009) [78]	MRI Mammography	12/20 13/20	71% 33.5%	79% 92.5%
Kuhl *et al*. (2010) [59]	MRI Mammography	25/27 9/27	92.6% (84.2 to 99.7%) 33% (17.2 to 53.9%)	99.4% (95.9-99.9) 99.1% (99.5-99.5)

*MRI was performed only in *BRCA1/2* carriers
**In two cases MRI was not performed
*** In one case mammography was not performed
N/R = not reported

Considering the combination surveillance protocol utilizing both MRI and mammography compared to MRI used alone, only three studies evaluated the sensitivity and specificity and results are summarized in Table **9**.

In conclusion the sensitivities were high with both modalities, suggesting that each surveillance regimen is efficacious for detecting tumours in women at high risk of breast cancer owing to family or genetic predisposition. However, it is not clear whether combination surveillance offers any additional benefit over screening with MRI alone. There was little difference in the specificity in each of the trials between MRI alone and MRI plus mammography.

Table 9. Summary of Results for MRI Plus Mammography Surveillance Compared to MRI Surveillance

Study	Screening Modality	N°Cancers Detected/N°Total Cancers	Sensitivity (95%CI)	Specificity (95%CI)
Kuhl *et al*. (2005) [45]	MRI MRI+ Mammography	39/43 40/43	90.7% (78 to 97%) 93% (80.9 to 98.5%)	97.2 % (96.2-98.0) 96.1% (94.9-97)
Leach *et al*. (2005) [62]	MRI MRI+ Mammography	27/35 14/35	77% (70 to 90%) 94% (81 to 99%)	81% (80-83) 95% (75-99)
Kuhl *et al*. (2010) [59]	MRI MRI+ Mammography	25/27 27/27	92.6% (84.2 to 99.7%) 100% (95.8 to 100%)	99.4% (95.9-99.9) 97.6% (96.7-98.2)

Table 10. Measures of Accuracy for Combination Screening Strategies in Women at High Risk of Breast Cancer

Study	Mammography	US	Mammography +US	MRI	MRI+ Mammography	Overall
Warner (2004) [24] Sensitivity Specificity	36.3% (17.1-59.3%) 99.8% (98.7-99.9%)	33 % (14.6-66.9%) 96 % (93.7-97.7%)	64% (with CBE) N/R	77.3% (54.6-92.2%) 95.4 % (92.9-97.2%)	86% (with CBE) N/R	95% N/R
Kuhl (2005) [45] Sensitivity Specificity	32.6% (19.0-48.5%) 96.8% (95.7-97.7%)	39.5% (25.0-55.6%) 90.5% (88.8-92.0%)	48.8% (33.3-64.5%) 89.0% (87.2-90.6%)	90.7% (77.9-97.4%) 97.2% (96.2-98.0%)	93.0% (80.9-98.5%) 96.1% (94.9-97.0%)	93% N/R
Kuhl (2010) [59] Sensitivity Specificity	33.3 % (17.2 -53.9%) 99.1% (98.5 -99.5%)	37.0% (20.0-57.5%) 98.0 % (98.2 -99.3%)	48.1% (29.1-67.6%) 98.3% (97.5 -98.8%)	92.6% (84.2 -98.7%) 98.4% (95.9 -98.9%)	100.0% (85.8-100.0%) 97.6 % (96.7-98.2%)	100% 97.6%

N/R=not reported

6. The sixth result was that MRI appears to be significantly more sensitive than mammography, US or the combination of mammography and US in the surveillance of women at high risk of breast cancer.

It may also be especially effective for women at highest risk, i.e. mutation carriers, as its sensitivity does not decrease as the risk status increases. However, the specificity of MRI may be lower than mammography [24]. This is due to false-positive examinations and as discussed previously has implications for resource use and anxiety in women involved in the surveillance programme. Surveillance with MRI and mammography appears to offer little advantage over MRI alone, although the MARIBS study, in the previous chapter, did suggest an advantage of this combined strategy [62]. The measures of accuracy of the individual and combined surveillance strategies are summarised in Table **10**.

The measures of accuracy in the study by Warner *et al*. [24] show that MRI is significantly more sensitive than either mammography (p=0.01) or US (p=0.009) alone. The specificity is not significantly different between MRI and US, but the specificity and PPV are significantly lower for MRI than mammography (p<0.01 and 0.02 respectively). The results from Kuhl *et al*. [45] estimate that the sensitivity of MRI is significantly better than mammography (p<0.001) or US alone (p<0.001) and the combination of mammography and US (p<0.01). There is no apparent difference between the sensitivity of MRI and the combination of MRI and mammography. In the EVA trial, Kuhl *et al*. [59] show that the cancer yield achieved with MRI alone was significantly higher than that achieved with mammography or US or both, and it did not increase significantly if MRI was read in conjunction with mammography or US. In close agreement with the Berg study adding US to mammography increased the cancer yield by almost 50%. However, the direct comparison with MRI in the same patients reveals that even if US is added to mammography, only about half of the breast cancers are detected. Accordingly, US appears to be complementary to mammography, but not to MRI, and is no equivalent replacement for MRI. The use of MRI, and even more so the use of US, led to additional short-term follow-up examinations and additional core biopsies. This may cause harm and unnecessary anxieties. However, there is evidence to suggest that women at elevated risk perceive the additional work-up of false-positive diagnoses as an acceptable part of intensified surveillance.

CONCLUSIONS

In conclusion, MRI alone or in combination with other surveillance modalities appears to be promising for the surveillance of women at high risk of breast cancer. However, improved cancer detection does not necessarily translate to a decrease in mortality. More research with larger numbers of participants and longer follow-up is required to truly assess the performance of MRI, and

combination strategies, for the surveillance of women at high risk of breast cancer. In addition to its accuracy, MRI has the advantage of not using ionising radiation. The drawbacks of MRI are primarily related to the potential harm of false-positive diagnoses, cost and availability. If the introduction of a surveillance strategy for women at high risk of breast cancer with MRI was to be contemplated, a more complete assessment would need to be carried out. This should include the potential benefit from surveillance versus the potential physical and psychological harm caused by the test, diagnostic procedures and treatment; the health care system being capable of supporting all the necessary elements of the surveillance pathway, including diagnosis, follow-up and evaluation; consideration of social and ethical issues and consideration of cost-benefit issues.

CONFLICT OF INTEREST

None declared.

ACKNOWLEDGEMENTS

This work was supported by grants from the Italian Minister of University and Research, PRIN 2008 (20088RFCMH) and by grants from Associazione Angela Serra per la Ricerca sul Cancro.

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Received: September 12, 2010 Revised: July 26, 2011 Accepted: July 30, 2011