Cancer surveillance based on imaging techniques in carriers of BRCA1/2 gene mutations: a systematic review
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CRD summary
This review appropriately concluded that it was not possible to determine with the available data whether intensive surveillance was a viable alternative to other preventative measures (such as prophylactic surgery) offered to women with BRCA1/2 mutations.

Authors' objectives
To determine the diagnostic performance of surveillance techniques and programmes for the early detection of breast and ovarian cancers in carriers of the BRCA1 or BRCA2 mutations.

Searching
MEDLINE, EMBASE, The Cochrane Library, ClinicalTrials.gov, National Research Register of the NHS, DARE, NHS EED and HTA databases were searched from 1996 to 2005 without language restrictions; search terms were reported. Websites related to the topic and bibliographies of included studies were searched for additional articles.

Study selection
Studies of any imaging technique conducted in the context of surveillance or of any surveillance programme intended to provide early diagnosis of breast or gynaecological cancers in women carrying the BRCA1/2 mutations were eligible for inclusion; included studies were required to report diagnostic performance outcomes. No inclusion criteria were specified for the reference standard or method of confirming diagnosis; reference standards used included pathology in some, but not all patients in studies of surveillance techniques and histology and yearly examinations in studies of surveillance programmes. Studies with a sample size of less than 10 or where BRCA mutations were a subgroup population for which separate data could not be derived were excluded.

The mean age of participants was under 46 years in all studies. The imaging techniques assessed were ultrasound, mammography and magnetic resonance imaging (MRI). The duration of follow-up of surveillance programmes ranged form 1.4 to 7 years (most were three years or less).

The authors stated neither how studies were selected for the review nor how many reviewers performed the selection.

Assessment of study quality
Two reviewers independently assessed the methodological quality of included studies using the QUADAS tool. Disagreements were resolved by consultation with a third reviewer.

Data extraction
Data were extracted on the diagnostic test(s) and threshold used, number of cancers detected, number of cancers detected in the interval between testing (performance of surveillance programmes only), frequency of testing (performance of surveillance programmes only), follow-up time (performance of surveillance programmes only) and sensitivity and specificity of the test(s) (sensitivity only for performance of surveillance programmes). Interval cancers were treated as failures of the screening programme (false negatives) in the calculation of sensitivity.

All data were extracted by the same reviewer.

Methods of synthesis
Studies were combined in a narrative synthesis, grouped by study type (studies of surveillance techniques and studies of surveillance programmes) and further stratified by target cancer (gynaecological or breast).
Results of the review
Thirteen studies were included in the review: 11 reported data for breast cancers, one for gynaecological cancers and one for both. Most included studies (11 out of 13) were prospective. The main methodological flaws related to the reference standard used and its application: in studies of surveillance techniques the reference standard (biopsy) was frequently performed only in women with a positive test (screening) result, (partial verification bias); in studies of surveillance programmes the reference standard used tended to vary according to which test(s) had been used for screening, (differential verification bias); no study reported blinding of the pathologists who conducted the reference standard to the results of screening.

Surveillance techniques: Ultrasound and mammography had low sensitivity for the detection of breast cancers: 20% to 33% (three studies) for ultrasound and 0 to 50% (eight studies) for mammography. Corresponding specificities, where reported, were high: 91% to 96% (two studies) for ultrasound and 97% to 100% (two studies) for mammography. By contrast, sensitivity of MRI ranged from 77% to 100% (eight studies) and specificity, where reported, ranged from 81% to 98% (three studies). No studies assessed the diagnostic accuracy of surveillance techniques for gynaecological cancers.

Surveillance programmes: Three out of the seven studies (n=714) assessing breast cancer surveillance programmes used yearly MRI and mammography. In the remaining four studies (n=369), screening was based on mammography, with MRI/ultrasound used only in suspected cases. The sensitivity of screening programmes that included MRI for all women ranged from 85% to 95% and the sensitivity of mammography-based programmes ranged from 40% to 56%.

Two studies (n=147) assessed gynaecological cancer surveillance programmes, both used trans vaginal ultrasound and serum CA-125 measurement: a study that used twice-yearly testing reported a sensitivity of 100%, which dropped to 71% when cancers detected at prophylactic salpingo-oophorectomy and missed by screening were included; the second study used yearly testing and reported a sensitivity of 83% and one interval cancer.

Authors’ conclusions
MRI and surveillance programmes that included MRI appeared to have the highest sensitivity for the detection of breast cancer in women with BRCA1/2 mutations. However, all studies had methodological flaws. MRI was an expensive technique that was poor at ruling in disease, and had not been proven to reduce mortality rates in women who carried BRCA1/2 mutations. The lack of data meant that no conclusions could be drawn on the performance of ovarian cancer surveillance in women who carried BRCA1/2 mutations.

CRD commentary
The review addressed a clearly stated research question generally defined by appropriate inclusion criteria, although the reference standard was unspecified. The search strategy was wide ranging and likely to have retrieved a high proportion of the available data, but may have been susceptible to publication bias as only published studies were included and no assessment of publication bias was reported. The review methods lacked measures to limit error and bias and the included studies (as noted by the authors) were methodologically flawed and subject to a number of significant sources of bias. Given the poor quality heterogeneous data available, the authors' use of a narrative synthesis was appropriate and this synthesis was constructed clearly. The authors' conclusions were appropriately cautious given the limitations of the available data.

Implications of the review for practice and research
Research: The authors suggested further research into the ideal interval between imaging tests to maximise the benefits of screening for the smallest possible number of tests over a lifetime, as well as research into the effects of surveillance strategies on mortality.

Practice: The authors stated that it was not possible to determine with the available data whether intensive surveillance was a viable alternative to other preventative measures (such as prophylactic surgery) offered to women with BRCA1/2 mutations.

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