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| **Author, year Quality** | **Sub-category** | **Study design** | **Country/ population/setting** | **Inclusion/exclusion criteria** |
| **Breast cancer screening** | |  |  |  |
| ***2013 Review*** |  |  |  |  |
| Kriege et al., 2004201  NA  Dutch MRISC study | Physical harms of increased screening | Prospective cohort (breast cancer characteristics compared to registry data and women with breast cancer from another prospective cohort study) | The Netherlands  Women with increased familial or genetic predisposition for breast cancer attending academic and/or cancer centers at 6 sites | Inclusion: Cumulative lifetime risk of breast cancer >15% due to genetic or familial predisposition according to modified Claus tables; age at entry between 25 to 70 years (could be tested at age younger than 25 if family member diagnosed before age of 30 years)  Exclusion: Women with symptoms suggestive of breast cancer or who had a personal history of breast cancer; women proven not to have a mutation in a family with a proven mutation |
| Kriege et al., 2006202  NA  Dutch MRISC study | Physical harms of increased screening | Prospective cohort (breast cancer characteristics compared to registry data and women with breast cancer from another prospective cohort study) | The Netherlands  Women with increased familial or genetic predisposition for breast cancer attending academic and/or cancer centers at 6 sites | Inclusion: Cumulative lifetime risk of breast cancer >15% due to genetic or familial predisposition according to modified Claus tables, age at entry between 25 to 70 years (could be tested at age younger than 25 if family member diagnosed before age of 30 years), no previous breast cancer or symptoms suspicious for breast cancer  Exclusion: Women with symptoms suggestive of breast cancer or who had a personal history of breast cancer; women proven not to have a mutation in a family with a proven mutation |

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| **Author, year**  **Quality** | **Risk level definition** | **N** | **Demographics** | **Duration/followup** |
| **Breast cancer screening** | |  |  |  |
| ***2013 Review*** |  |  |  |  |
| Kriege et al., 2004201  NA  Dutch MRISC study | Cumulative lifetime risk of breast cancer >15% due to genetic or familial predisposition according to modified Claus tables | Enrolled: 1952  Analyzed: 1909  n=358 mutation carriers (276 *BRCA1* , 77 *BRCA2* , 1 both *BRCA1* and *BRCA2* , 2 PTEN and 2 TP53), n=1052 high-risk, n=499 moderate-risk | Mean age at entry, years: 40 (range 19 to 72) | 1999 to 2003  Median 2.9 years (mean 2.7, range 0.1 to 3.9 years) |
| Kriege et al., 2006202  NA  Dutch MRISC study | Cumulative lifetime risk of breast cancer >15% due to genetic or familial predisposition according to modified Claus tables | Analyzed: 1909  n=358 mutation carriers (276 *BRCA1* , 77 *BRCA2* , 1 both *BRCA1* and *BRCA2* , 2 PTEN and 2 TP53), n=1052 high-risk, n=499 moderate-risk | Mean age at entry, years: 40 (range 19 to 72) | 1999 to 2003  Median 2.9 years (mean 2.7, range 0.1 to 3.9 years) |

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| **Author, year**  **Quality** | **Surgical procedure or screening method and interval** | **Results** | **Funding source** |
| **Breast cancer screening** | |  |  |
| ***2013 Review*** |  |  |  |
| Kriege et al., 2004201  NA  Dutch MRISC study | 1. Bi-annual CBE 2. Annual mammography 3. Annual contrast enhanced MRI   Note: When one of the examinations reported as "probably benign finding" or "need additional imaging evaluation" (BI-RADS 3 or 0), further investigation undertaken by ultrasonography +/- fine needle aspiration, or mammography or MRI repeated; When one of the examinations reported as "suspicious abnormality" or "highly suggestive of malignancy" (BI-RADS 4 or 5), cytologic or histologic evaluation of biopsy specimen performed; When results of imaging was negative but clinical breast exam was uncertain or suspicious, additional investigations performed. | **Based on 45 cancers, B vs. C**  Additional investigations  -Ultrasound, 889 times/627 women  - Fine needle aspiration, 312 times (267 times plus ultrasound, 45 times plus palpation)  -Biopsy, used 85 times/82 women (malignancy in 50 cases, lobular carcinoma in situ in 1 case; rate of positive histologic findings 60.0%)  -Benign additional exams\*: 207 vs. 420 Benign biopsies: 28% (7/25\*) vs. 43% (24/56†) | Grant from Dutch Health Insurance Council |
| Kriege et al., 2006202  NA  Dutch MRISC study | 1. Bi-annual CBE 2. Annual mammography 3. Annual contrast enhanced MRI   Note: When one of the examinations reported as "probably benign finding" or "need additional imaging evaluation" (BI-RADS 3 or 0), further investigation undertaken by ultrasonography +/- fine needle aspiration, or mammography or MRI repeated; When one of the examinations reported as "suspicious abnormality" or "highly suggestive of malignancy" (BI-RADS 4 or 5), cytologic or histologic evaluation of biopsy specimen performed; When results of imaging was negative but clinical breast exam was uncertain or suspicious, additional investigations performed. | **Imaging rounds of 39 evaluable invasive breast cancers, B vs. C**  First imaging round, with prior mammography  False positive rate (%): 5.5 vs. 14.0, P<0.001  False negatives (n): 12 vs. 1  Subsequent imaging rounds  False positive rate (%): 4.6 vs. 8.2, p<.001  False negatives (n): 12 vs. 4 | Grant from Dutch Health Insurance Council |

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| **Author, year**  **Quality** | **Sub-category** | **Study design** | **Country/ population/ setting** | **Inclusion/exclusion criteria** |
| **Breast cancer screening** | |  |  |  |
| ***2013 Review*** |  |  |  |  |
| Leach, 2005203  NA  MARIBS study | Physical harms of increased screening | Prospective cohort, one-arm | U.K.  Women attending one of 22 participating centers in the U.K. with increased breast cancer risk | Inclusion: Asymptomatic women aged 35 to 49 years fulfilling one of the following: known carrier of a deleterious *BRCA1* , *BRCA2* , or TP53 mutation; they were a FDR of someone with one of these deleterious mutations; they had a strong family history of breast or ovarian cancer, or both; or they had a family history consistent with classic Li-Fraumeni syndrome  Aim was to include women whose affected FDRs had ≥60% chance of being a *BRCA1* or *BRCA2* mutation carrier or women with an annual risk of ≥0.9%.  Exclusion: Women with previous breast cancer, those with any cancer such that prognosis was <5 years, participants who underwent predictive genetic testing during study and whose results were negative, women who developed cancer during study period |

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| **Author, year Quality** | **Risk level definition** | **N** | **Demographics** | **Duration/followup** |
| **Breast cancer screening** | |  |  |  |
| ***2013 Review*** |  |  |  |  |
| Leach, 2005203  NA  MARIBS study | Known carrier of a deleterious *BRCA1* , *BRCA2* , or *TP53* mutation; they were a FDR of someone with one of these deleterious mutations; they had a strong family history of breast or ovarian cancer, or both; or they had a family history consistent with classic Li-Fraumeni syndrome | 649  13% (82/649) with known *BRCA1* mutation  6% (38/649) with known *BRCA2* mutation | Median age at entry, years: 40 (range 31 to 55; only 1 woman aged >50 years) | Study recruitment 1997 to 2003  Variable screening episodes per individual but screening continued until each women had ≥2 annual scans (in 2004) |

| **Author, year**  **Quality** | **Surgical procedure or screening method and interval** | **Results** | **Funding source** |
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| **Breast cancer screening** | |  |  |
| ***2013 Review*** |  |  |  |
| Leach, 2005203  NA  MARIBS study | 1. Annual mammography from age 35 years (or younger if FDR developed cancer at age <35 years) 2. Annual CE MRI   Note: In women with equivocal results, high specificity MRI exam done 2 to 6 weeks later (followed by ultrasound, fine needle aspiration, localization and tissue sampling by conventional methods as appropriate). | **Recall rates, A vs. B (based on 33 screen detected cancers)**  279 exams led to recall (40 based purely on reader's judgment, not score)  3.9% vs. 11% per woman year A plus B: 13% per woman year 245 recalls for benign findings  73% diagnosed cancer-free using non-invasive tests  **Additional diagnostic procedures in 245 women without cancer**  Ultrasound, n=93  Core biopsy, n=32  Fine needle aspiration, n=47  Surgery, n=7 (3% of recalled women without cancer, 27% of recalled women with cancer)  8.5 recalls per cancer detected  0.21 benign surgical biopsies per cancer detected  Number of women per 1000 screening episodes needing diagnostic surgical biopsy was 0.4% (7/1881) for benign lesions, 0.5% (9/1881) for malignant lesions  PPV of diagnostic surgical biopsy: 56%  62% (172/279) of suspicious findings on MRI resolved without invasive procedure, n=16 women had diagnostic surgery to complete diagnosis, n=91 had some form of percutaneous biopsy procedure  Pre-op diagnosis of cancer made in 73% (24/33) of screen detected cancers | Grant from U.K. Medical Research Council; MRI cost paid from subvention funding for research from U.K. National Health Service |

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| **Author, year**  **Quality** | **Sub-category** | **Study design** | **Country/ population/ setting** | **Inclusion/exclusion criteria** |
| **Breast cancer screening** | |  |  |  |
| ***2013 Review*** |  |  |  |  |
| Le-Petross et al., 2011204  NA | Physical harms of increased screening | Retrospective analysis of prospective cohort study, one-arm | U.S.  Women at increased genetic risk of breast cancer at single-institution | Inclusion: Women aged ≥18 years, having undergone alternating screening mammography and breast MRI every 6 months at study institution, either confirmed *BRCA1/2* carriers or FDR of confirmed *BRCA1/2* carrier  Exclusion: Women with history of breast cancer, who had calculated lifetime risk of breast cancer >20%, or who did not undergo a screening MRI, women who used chemoprevention or underwent bilateral prophylactic mastectomy, those with metastatic disease, undergoing treatment, or high BMI preventing MRI, women lost to followup, or died during original trial |

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| **Author, year Quality** | **Risk level definition** | **N** | **Demographics** | **Duration/followup** |
| **Breast cancer screening** | |  |  |  |
| ***2013 Review*** |  |  |  |  |
| Le-Petross et al., 2011204  NA | Based on BRCA status or FDR of BRCA mutation carrier | Screened: 321  Analyzed: 73 (51% *BRCA1*, 49% *BRCA2* ) | Median age at entry, years: 44 (range 23 to 75) | Records from 1997 to 2009  Median followup, years: 2 (range 1 to 6)  Mean followup from suspicious finding to diagnosis, years: 1.7 (range 1 to 3) |

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| **Author, year**  **Quality** | **Surgical procedure or screening method and interval** | **Results** | **Funding source** |
| **Breast cancer screening** | |  |  |
| ***2013 Review*** |  |  |  |
| Le-Petross et al., 2011204  NA | All women underwent:   1. Mammography every 6 months 2. MRI every 6 months   Note: imaging was performed on an alternating basis, women had clinical breast exam every 6 months, ultrasound used to evaluate abnormal mammographic or MRI findings, biopsy as required. | 13 cancers in 11 women (12 on screen, 1 on prophylactic mastectomy)  20/73 women underwent biopsy, 11 cancers diagnosed by biopsy in 10 women  Overall biopsy yield for MRI was 50% (10/20)  **False positive, A vs. B**  Overall: 15% (11/73) vs. 11% (8/73)  Required further imaging: 8 vs. 4  Required biopsy: 3 vs. 2  Required imaging plus biopsy: 0 vs. 2 | Not reported |

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| **Author, year**  **Quality** | **Sub-category** | **Study design** | **Country/ population/ setting** | **Inclusion/exclusion criteria** |
| **Ovarian cancer screening** | |  |  |  |
| ***2013 Review*** |  |  |  |  |
| Bourne et al., 1993188  NA | Physical harms of increased screening | Prospective cohort, one-arm | United Kingdom  Self-referred asymptomatic women with a close relative diagnosed with ovarian cancer | Inclusion: Women ≥25 of age with ≥1 close relative who had developed ovarian cancer; symptomless |
| Hermsen et al., 2007198  NA | Physical harms of increased screening | Prospective cohort, one-arm  (Staging compared to 2 external comparison groups; unscreened family members with cancer, combined data from multiple studies) | The Netherlands  Women with BRCA mutation screened at 6 University Family Cancer Clinics | Inclusion: Women with *BRCA1/2* mutation screened at one of participating centers  Exclusion: Women with symptoms at first visit, who had only one visit, or who were found to have cancer at first screening visit |

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| **Author, year**  **Quality** | **Risk level definition** | **N** | **Demographics** | **Duration/followup** |
| **Ovarian cancer screening** | |  |  |  |
| ***2013 Review*** |  |  |  |  |
| Bourne et al., 1993188  NA | Based on pedigree/pattern of inheritance | 1601 | Mean age, years: 47 (range 17 to 79) | Unclear duration  4 years |
| Hermsen et al., 2007198  NA | Based on BRCA status | 883  n=683 *BRCA1* , 200 *BRCA2*  459 for analysis of screening/compliance (data available for all screening visits) | **Median age, years**  *BRCA1* : 40 (range 21 to 76)  *BRCA2* : 44 (range 25 to 77) | 1993 to 2005  1473 person-years |

| **Author, year**  **Quality** | **Surgical procedure or screening method and interval** | **Results** | **Funding source** |
| --- | --- | --- | --- |
| **Ovarian cancer screening** | |  |  |
| ***2013 Review*** |  |  |  |
| Bourne et al., 1993188  NA | TVUS +/ color flow imaging‡ (screening interval NR) | 11 cancers diagnosed (6 screen-detected, 5 interval) 3.8% (61/1601) with positive screening result, referral to surgery  False-positive cases: 55/61 referred cases (cancer detected in 6/61 referred cases)  False-positive rate: 3.4% (95% CI 2.6 to 4.5%; 55/1595)  **Addition of color flow imaging and criterion of morphological score ≥5 or pulsatility index <1**  Retrospective addition (applied to positive ultrasound results): 15 false-positive cases  Prospective addition (applied at the time of ultrasound exam): 6 false-positive cases  Note: 43% of women had only one TVUS (prevalent screen). | Not reported |
| Hermsen et al., 2007198  NA | 1. Annual serum CA-125 measurement 2. Annual TVUS   Starting at age 35 years or 5 years earlier than youngest diagnosed ovarian cancer in the family  Note: Biannual screens were done in some centers during the study period, but this was not systematically adopted. | 15 cancers diagnosed in cohort  10 cancers diagnosed during followup 5 screen-detected  **Based on 459 women with data on each visit**  7 cancers diagnosed (2 prevalent, 2 interval, 3 incident) Abnormalities were found by one or both screening modalities in 3% (38/1116) of screening visits.  Overall, abnormalities were found in 9% (40/459) of women (some due to physical complaints), resulting in 26 diagnostic operations.  **Benign§ diagnostic surgery, A vs. B**  67% (4/6) vs. 100% (9/9)  A+B: 55% (6/11)  Note: not all benign diagnostic surgeries were done due to abnormal screen findings; some surgeries were undertaken to followup on abnormal findings from CA-125 measurement +/- TVUS done to assess symptomatic complaints. | NIHR Biomedical Research Centre at Central Manchester Foundation Trust |

\*Additional investigation included ultrasound +/- fine needle biopsy, or repeat mammography, or repeat MRI

†Women with BIRAD score => 3 on mammography or MRI

‡Color flow imaging applied prospectively to 600 ultrasound exams; retrospectively after a positive ultrasound result to the remainder

§Surgery for final benign diagnosis

**Abbreviations:** BIRADS=Breast Imaging Reporting and Data System; BMI=body mass index; BRCA=breast cancer susceptibility gene; CA-125=cancer antigen-125; CBE=clinical breast exam; CI=confidence interval; CE=contrast enhanced; FDR=first degree relative; MARIBS=Magnetic Resonance Imaging Breast Screening; MRI=magnetic resonance imaging; MRISC=Magnetic Resonance Imaging Screening Study; NA=not applicable; NIHR= National Institute for Health Research; NR=not reported; PPV=positive predictive value; PTEN=phosphatase and tensin homolog; TP53=tumor protein 53; TVUS=transvaginal ultrasound; U.K.=United Kingdom; U.S.=United States