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| **Author, year** **Quality** | **Design** | **Purpose** | **Population/setting** | **Inclusion/exclusion criteria** |
| **Breast Cancer** |  |  |  |  |
| ***Current Review*** |  |  |  |  |
| Vreeman et al., 2018215NA | Retrospective cohort | To evaluate the performance of a breast cancer screening program with multiple followup rounds for women with different categories of increased breast cancer risk | The NetherlandsAcademic hospitalWomen with increased risk of breast cancer | Inclusion: Women at increased risk of breat cancer undergoing screening breast MR or mammogramExclusion: NR |
| ***2013 Review*** |  |  |  |  |
| Cortesi et al., 2006218NAModena Study Group for Familial Breast and Ovarian Cancer participants | Prospective cohort (Expected incidence ratio derived from registry data) | To describe the results of an intensive surveillance program and document effectiveness of the program in selecting individuals at risk of breast cancer. | ItalyWomen with increased risk of breast cancer | Inclusion: Women ages >18 years with *BRCA1* or *BRCA2* mutations discovered through genetic testing or increased risk for breast cancer relative to the general population based on Gail model, Claus tables and modified BRCAPRO model (adapted to the Italian population) and study defined criteria: ≥3 relatives diagnosed with breast cancer or ovarian cancer in 2 different generations; ≥1 of these 3 relatives must be FDR of one of the other 2, in case of male interposition, a relationship of different degree is allowed; ≥1 breast cancer diagnosed at <35 years of age regardless of family history; ≥1 breast cancer and 1 ovarian cancer in the same woman, regardless of family history; ≥1 male breast cancer, regardless of family history; 1 sporadic breast cancer or ovarian cancerExclusion: Women with symptoms suggestive of breast cancer; women with a personal history of breast cancer |

| **Author, year** **Quality** | **Risk level definitions** | **N** | **Baseline demographics** |
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| ***Breast Cancer*** |  |  |  |
| ***Current Review*** |  |  |  |
| Vreeman et al., 2018215NA | *BRCA1*, *BRCA2*, family history of breast cancer, personal breast cancer history, other (e.g. history of chest wall radiation or of high-risk lesions like atypical ductal hyperplasia or lobular carcinoma in situ) | 2773 women included8818 breast MRIs6245 mammograms471 *BRCA1*299 *BRCA2* | **Mean age at start of screening (range), years***BRCA1*: 39 (23 to 75)*BRCA2*: 41 (23 to 73) |
| ***2013 Review*** |  |  |  |
| Cortesi et al., 2006218NAModena Study Group for Familial Breast and Ovarian Cancer participants | Risk level was defined by Gail model, Claus tables, modified BCAPRO model, and study defined criteria (see inclusion)Carrier (Gail model lifetime risk of 50 to 85%): presence of mutant BRCA genesHigh-risk (Gail model lifetime risk of 30 to 50%): ≥3 relatives with breast cancer (or ovarian cancer) in 2 different generations; 1 breast cancer/ovarian cancer case is a FDR of the other 2; ≥1 case has been diagnosed at age <40 years or with bilateral breast cancer; breast cancer diagnosed <35 years, regardless of family history; breast and ovarian cancer in same woman, regardless of family historyIntermediate risk (Gail model lifetime risk of 18 to 29%): male breast cancer, regardless of family historySlightly increased risk (Gail model lifetime risk of 6 to 18%): breast/ovarian cancer without any of the described criteria | 1325 enrolled48 mutation carriers (37 *BRCA1* and 11 *BRCA2* )674 high-risk257 intermediate-risk346 slightly increased- risk | **Mean age at surveillance (range), years**Carrier: 42 (20 to 75)High-risk: 42 (15 to 75)Intermediate-risk: 43 (19 to 67)Slightly increased-risk: 40 (18 to 75) |

| **Author, year** **Quality** | **Screening method and interval** | **Scoring criteria** | **Duration/followup** |
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| **Breast Cancer** |  |  |  |
| ***Current Review*** |  |  |  |
| Vreeman et al., 2018215NA | A) Mammography: annual from age 30 years in BRCA carriersB) MRI: annual from age 25 years in BRCA carriers | Screen-positive for cancer: BIRADS 0, 3, 4, or 5 (biopsy conducted for BIRADS 4, 5, and some BIRADS 3) | 2003 to 2014Followup not reported (retrospective study) |
| ***2013 Review*** |  |  |  |
| Cortesi et al., 2006218NAModena Study Group for Familial Breast and Ovarian Cancer participants | From 1994 to September 2000 all women underwent:1. Mammography
2. Ultrasonography
3. CBE
4. Transvaginal ultrasound and serum CA-125 levels Testing interval varied by assessed risk (see below)

From October 2000 mutation carrier surveillance modified to include:1. CE MRI

BRCA risk: Started at age 25 with annual mammography and MRI, bi-annual CBE and ultrasound plus transvaginal ultrasound and serum CA-125 levelsHigh-risk: started at age 30 with mammography every 2 years until age 36 and then annually, bi-annual CBE and ultrasound plus annual transvaginal ultrasound and serum CA-125 levels Intermediate risk: Started at age 30 with mammography every 2 years until age 40 and then annually, bi-annual CBE and ultrasound plus annual transvaginal ultrasound and serum CA- 125 levelsSlightly increased risk: Started at age 30 with one mammogram before 40 years then every 18 to 24 months, and annual CBE and ultrasoundNote: if possible, all exams performed on the same day during the second week of the menstrual cycle in premenopausal women; additional investigation using fine needle aspiration or core biopsy performed as required. | Not reported | 1992 to 2005Median 55 months (range 1 to 151 months) |

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| **Author, year** **Quality** | **Outcome: test characteristics** | **Cancer incidence** |
| **Breast Cancer** |  |  |
| ***Current Review*** |  |  |
| Vreeman et al., 2018215NA | **Sensitivity (95% CI), A vs. B vs. A+B***BRCA1*, all cancers: 45% (32 to 59) vs. 63% (50 to 74) vs. 66% (53 to 77)*BRCA1*, excluding occult: 51% (37 to 65) vs. 77% (64 to 87) vs. 81% (68 to 90)*BRCA2*, all cancers: 36% (21 to 53) vs. 67% (50 to 80) vs. 70% (53 to 83)*BRCA2*, excluding occult: 44% (27 to 63) vs. 88% (70 to 96) vs. 92% (75 to 98)**Specificity (95% CI), A vs. B vs. A+B***BRCA1*: 98% (98 to 99) vs. 95% (94 to 96) vs. 94% (93 to 95)*BRCA2*: 98% (97 to 98) vs. 94% (93 to 96) vs. 94% (92 to 95)**PPV of recall (95% CI), A vs. B vs. A+B***BRCA1*: 0.49 (0.35 to 0.63) vs. 0.32 (0.25 to 0.42) vs. 0.30 (0.23 to 0.38)*BRCA2*: 0.32 (0.19 to 0.49) vs. 0.26 (0.18 to 0.36) vs. 0.24 (0.17 to 0.34) | **Breast cancers (invasive + DCIS) in study population (screen-detected, interval with symptoms, and occult found at prophylactic mastectomy)***BRCA1* (n=471): 39, 9, 11*BRCA2* (n=299): 23, 2, 8All patients (n=2463): 129, 16, 25All patients, invasive cancers only: 104, 16, 7 |
| **2013 Review** |  |  |
| Cortesi et al., 2006218NAModena Study Group for Familial Breast and Ovarian Cancer participants | 44 breast cancers detected; 64% (n=28) invasive, 36% (n=16) DCIS36 screen-detectedCarriers: n=5 cancers (4 invasive, 1 DCIS) High-risk: n=23 (14 invasive, 9 DCIS)Intermediate-risk: n=11 (8 invasive, 3 DCIS) Slightly increased-risk: n=5 (2 invasive, 3 DCIS)**Sensitivity, A vs. B vs. A+B vs. E**All: 78% (28/36) vs. 50% (18/36) vs. 97% (35/36) vs. 100% (4/4)Carriers: 50% (2/4) vs. 75% (3/4) vs. 75% (3/4) vs. 100% (4/4)High-risk: 90% (19/21) vs. 52% (11/21) vs. 100% (21/21)Intermediate-risk: 50% (4/8) vs. 450% (4/8) vs. 100% (8/8) Slightly increased-risk: 100% (3/3) vs. 0% (0/3) vs. 100% (3/3) | **Breast cancer incidence in study population vs. expected incidence**All: SIR 4.9, 95% CI 1.6 to 7.6, p<0.001 Carriers: SIR 20.3, 95% CI 3.1 to 83.9, p<0.001High-risk: SIR 4.5, 95% CI 1.5 to 8.3, p<0.001Intermediate-risk: SIR 7.0, 95% CI 2.0 to 17.1, p=0.0018 Slightly increased-risk: SIR not significantly increasedNote: SIR = ratio of observed to expected number of cancers; expected number of cancers based on Modena Cancer Registry rates from 1998 to 2002 in 5 year age groups from age 25 to >85 years old; observed women years at risk were multiplied by expected cancer incidence to estimate total number of cancers expected |

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| **Author, year Quality** | **Outcome: cancer characteristics Interval cancers** | **Outcome: disease-free survival Mortality** | **Conclusions** | **Funding source** |
| **Breast Cancer** |  |  |  |  |
| ***Current Review*** |  |  |  |  |
| Vreeman et al., 2018215NA | Characteristics of 16 interval cancers (all patients):Invasive: 100% (16/16)Mean size: 15.5 mm (range 5 to 26)Nodal status: 31% (5/16) node-positive | Survival not reported | Screening performance depended on risk category. Sensitivity was lowest in *BRCA1* carriers. Specificity improved at followup rounds. | Netherlands Organisation for Health Research and Development and European Union’s 7th Framework Programme |
| ***2013 Review*** |  |  |  |  |
| Cortesi et al., 2006218NAModena Study Group for Familial Breast and Ovarian Cancer participants | Staging: 61% (n=17) stage I; 25% (n=7) stage II; 7% (n=2) stage III; 7% (n=2) stage IVSize: 29% (n=8) <10 mm in diameter; 36% (n=10) were 10-15 mm in diameter; 32% (n=9) >15 mm in diameter; one was inflammatory breast cancerNodal status: 36% (n=10) node positiveInterval cancers: n=8; all identified with CBE; interval cancer rate 1.3 per 1000; diagnosed with CBE only (n=4); CBE plus ultrasound (n=3); CBE plus ultrasound plus mammography (n=1); time interval from last negative screen to diagnosis ranged from 1-14 months DCIS: Screening sensitivity for DCIS increased with age; low rate (65%) in women <50 years; high rate (93%) in oldest age group | Posttreatment, 4 recurrences and 3 deaths (2 for disease progression, 1 from heart failure). Actuarial 5 year survival rate was 93% | Rate of cancers detected in women at high-risk for breast cancer was significantly higher than expected in an age-matched general population. Results support increased screening surveillance program to identify and monitor high-risk individuals. | Italian consortium for Hereditary Breast and Ovarian Cancer; COFIN- MURST 2003 to 2005; Fondazione Cassa di Risparmio di Modena; Associazione Angela Serra per la ricerca sul Cancro |

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| **Author, year** **Quality** | **Design** | **Purpose** | **Population/setting** | **Inclusion/exclusion criteria** |
| **Breast Cancer** |  |  |  |  |
| ***2013 Review*** |  |  |  |  |
| Leach, 2005203NAMARIBS study | Prospective cohort, one-arm | To compare contrast enhanced MRI with mammography for breast cancer screening in women genetically predisposed to breast cancer. | U.K.Women attending one of 22 participating centers in theU.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 syndromeAim 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 at least 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 definitions** | **N** | **Baseline demographics** |
| **Breast Cancer** |  |  |  |
| ***2013 Review*** |  |  |  |
| Leach, 2005203NAMARIBS 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 analyzed  -13% (82) with known *BRCA1* mutation -6% (38) with known *BRCA2* mutation | Median age at entry, years: 40 (range: 31 to 55; only one woman aged >50 years) |

| **Author, year** **Quality** | **Screening method and interval** | **Scoring criteria** | **Duration/followup** |
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| **Breast Cancer** |  |  |  |
| ***2013 Review*** |  |  |  |
| Leach, 2005203NAMARIBS study | All women underwent:1. Annual mammography from age 35 years (or younger if FDR developed cancer at age <35 years)
2. Annual CE MRI

Note: if possible, exams done on same day, between days 6-16 of menstrual cycleNote: In women with equivocal results, high specificity MRI exam or repeat screening MRI done 2-6 weeks later followed by ultrasound, fine needle aspiration, localization and tissue sampling by conventional methods as appropriateNote: 93% of mammographic examinations were 2-view, 7% 1- view | Scoring system based on morphological and dynamic contrast uptake characteristics validated against histology (area under receiver operating characteristic curve =0.88, 95% CI 0.83 to 0.94) and diagnostic accuracy tested using subset of present study and 100 symptomatic cases (sensitivity=91%, 95% CI 83 to 96; specificity=81%, 95% CI 79 to 83)Note: All scoring was double reported; in statistical analysis, scoring system was paired to BIRADS as follows: for MRI; score of B, suspicious = BIRADS 0,3, or 4 and score of A, malignant = BIRADS 5; for mammography; score M3, indeterminate = BIRADS 0 to 3, M4, suspicious = BIRADS 4, and M5, malignant = 5 | Study recruitment 1997 to 2003 Variable screening episodes per individual but screening continued until each women had at least 2 annual scans (in 2004) |

| **Author, year** **Quality** | **Outcome: test characteristics** | **Cancer incidence** |
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| **Breast Cancer** |  |  |
| ***2013 Review*** |  |  |
| Leach, 2005203NAMARIBS study | **All cancers (n=35)**Sensitivity (95% CI), A vs. B: 40% (24 to 58) vs. 77% (60 to 90), p=0.01Sensitivity (95% CI), A + B: 94% (81 to 99)Specificity (95% CI), A vs. B: 93% (92 to 95) vs. 81% (80 to 83), p<0.0001Specificity (95% CI), A plus B: 77% (75 to 79)PPV (95% CI), A vs. B: 10% (5.8 to 17) vs. 7.3% (4.9 to 10)NPV (95% CI), A vs. B: 99% (98 to 99) vs. 99% (99 to 100)AUC (95% CI), A vs. B: 0.70 (0.68 to 0.72) vs. 0.85 (0.84 to 0.87), p=0.035**Excluding DCIS (n=6)**Sensitivity (95% CI), A vs. B: 31% (15 to 51) vs. 86% (68 to 96), p=0.0009Sensitivity (95% CI), A plus B: 97% (82 to 100)***BRCA1* carriers or relative with *BRCA1* mutation (n=139)**Sensitivity (95% CI), A vs. B: 23% (5 to 54) vs. 92% (64 to100), p=0.004Sensitivity (95% CI), A plus B: 92% (64 to 100)Excluding 1 DCIS case: 25% (5.5 to 57) vs. 100% (74 to 100)Specificity (95% CI), A vs. B: 92% (88 to 94) vs. 79% (75 to 83), p<0.0001Specificity (95% CI), A plus B: 74% (69 to 78)PPV (95% CI), A vs. B: 9.1% (1.9 to 24) vs. 14% (7.2 to 23)***BRCA2* carriers or relative with *BRCA2* mutation (n=86)**Sensitivity (95% CI), A vs. B: 50% (21 to 79) vs. 58% (28 to 84), p=1.0Sensitivity (95% CI), A plus B: 92% (62 to 100)Sensitivity (95% CI), excluding 3 DCIS cases: 33% (7.5 to 70) vs. 67% (30 to 93), p=0.45Specificity (95% CI), A vs. B: 94% (91 to 97) vs. 82% (77 to 87), p=0.0001Specificity (95% CI), A plus B: 78% (72 to 83)PPV (95% CI), A vs. B: 9.1% (1.9 to 24) vs. 14% (7.2 to 23)Note: Anonymous testing was restricted to women with breast cancer so that women with BRCA positive relatives but no breast cancers themselves, were not tested; Sensitivities refer only to tested mutation carriers, specificities are only preliminary estimates**Incident screens (n=15 cancers, n=1217 non-cancers)****Observed incidence rate: 1.9% per year****Sensitivity (95% CI), A vs. B**Any cancer: 40% (16 to 68) vs. 80% (52 to 96), p=0.11Excluding 6 DCIS cases: 31% (15 to 51) vs. 86% (68 to 96), p=0.0009A plus B: 97% (82 to 100)Any cancer, excluding *BRCA1* carriers/relatives: 50% (28 to 72) vs. 68% (45 to 86), p=0.45Any cancer, excluding *BRCA2* carriers/relatives: 35% (16 to 57) vs. 87% (66 to 97); A plus B: 96% (78 to 100)**Specificity (95% CI), A vs. B**All cancers: 94% (92 to 95) vs. 81% (79 to 83), p<0.0001 | 15 incident cancers, observed incidence rate was 1.9% per year |

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| **Author, year** **Quality** | **Outcome: cancer characteristics Interval cancers** | **Outcome: disease-free survival Mortality** | **Conclusions** | **Funding source** |
| **Breast Cancer** |  |  |  |  |
| ***2013 Review*** |  |  |  |  |
| Leach, 2005203NAMARIBS study | Grade: 10% (3/29) grade1; 24% (7/29) grade 2; 66% (19/29) grade 3 Size: 38% (11/29) were <10 mm in greatest dimension; 14% (4/29) were 10 to 14 mm in greatest dimension; 17% (5/29) were 15 to 19 mm; 31% (9/29) were ≥20 mm in greatest dimension; average tumor size = 15 mmNodal status: 81% (21/26) cancers node-negativeInterval cancers: n=2 (one considered benign on MRI and one considered benign on mammography; method of detection NR) | Not reported | Contrast enhanced MRI is more sensitive than mammography for breast cancer detection in women with familial risk for breast cancer. Specificity was acceptable for both. Detected tumors were small, and mostly node negative, suggesting that annual screening with mammography and contrast enhanced MRI would detect most tumors in this risk group. | 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** | **Design** | **Purpose** | **Population/setting** | **Inclusion/exclusion criteria** |
| **Breast Cancer** |  |  |  |  |
| ***2013 Review*** |  |  |  |  |
| Le-Petross et al., 2011204NA | Retrospective analysis of prospective cohort, one-arm | To investigate the efficacy of alternating screening mammography and breast MRI every 6 months in women with a genetically high risk of developing breast cancer for breast cancer detection | United StatesWomen 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* carrierExclusion: 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 definitions** | **N** | **Baseline demographics** |
| **Breast Cancer** |  |  |  |
| ***2013 Review*** |  |  |  |
| Le-Petross et al., 2011204NA | Based on BRCA status | 321 screened73 analyzed (51% (37) *BRCA1;* 49% (36) *BRCA2* ) | Median age at entry, years: 44 (range 23 to 75)Mean age at diagnosis, years: 51 (range 43 to 64) |

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| **Author, year** **Quality** | **Screening method and interval** | **Scoring criteria** | **Duration/followup** |
| **Breast Cancer** |  |  |  |
| ***2013 Review*** |  |  |  |
| Le-Petross et al., 2011204NA | All women underwent CBE every 6 months plus:1. Mammography every 6 months alternating with,
2. MRI every 6 months

Note: Ultrasound used to evaluate abnormal screen findings, biopsy as required | BIRADS | Records from 1997 to 2009 Median followup 2 years (range 1 to 6 years)Median number of screening cycles was 2 (range 1 to 6 cycles); 29% completed 1 cycle, 31% completed 2 cycles, 25% completed 3 cycles, 15% completed 4, 5 or 6 cycles |

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| **Author, year** **Quality** | **Outcome: test characteristics** | **Cancer incidence** |
| **Breast Cancer** |  |  |
| ***2013 Review*** |  |  |
| Le-Petross et al., 2011204NA | **Sensitivity, (95% CI), A vs. B**Not able to report vs. 92% (0.76 to 1.00) **Specificity, (95% CI), A vs. B**82% (0.72 to 0.92) vs. 87% (0.79 to 0.95)12/13 cancers identified on MRI (1/13 on prophylactic mastectomy), but not mammography 6 months prior; no cancer detected by mammography alone; no cancer palpable by CBE 5/13 cancers detected on targeted US post MRI detection | 13 cancers detected (10 invasive, 3 DCIS) in 11 patients 5/13 cancers detected on first screening cycle (likely prevalent), 8/13 incident cancers**No. of cancers detected by cycle in 11 patients**Post cycle 1: 5 cancersPost cycle 2: 2 cancers Post cycle 3: 3 cancers Post cycle 4: 1 cancer |

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| **Author, year Quality** | **Outcome: cancer characteristics Interval cancers** | **Outcome: disease-free survival Mortality** | **Conclusions** | **Funding source** |
| **Breast Cancer** |  |  |  |  |
| ***2013 Review*** |  |  |  |  |
| Le-Petross et al., 2011204NA | Size on MRI: Mean 14 mm (range 1 to 30 mm)Nodal status: 9% (1/11) women node- positiveInterval cancers: n=0 | Not reported | Screening women at increased genetic risk of breast cancer by alternating mammography with MRI every 6 months has a higher cancer yield than studies that screened using both modalities at the same time point. | Not reported |

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| **Author, year Quality** | **Design** | **Purpose** | **Population/setting** | **Inclusion/exclusion criteria** |
| **Breast Cancer** |  |  |  |  |
| ***2013 Review*** |  |  |  |  |
| Rijnsburger et al.,2010219See also Kriege et al., 2004201NADutch MRISC study | Prospective cohort (Registry data/data from another prospective study used for cancer characteristics comparison) | To evaluate the long term results of the Dutch MRI screening (MRISC) study, including separate analyses of *BRCA1/2* mutation carriers and survival results | The NetherlandsWomen with increased familial or genetic predisposition for breast cancer attending academic and/or cancer centers at 6 sites | Inclusion: Women aged 25 to 75 years with cumulative lifetime risk of breast cancer ≥15% due to genetic or familial predisposition (women 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 |

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| **Author, year** **Quality** | **Risk level definitions** | **N** | **Baseline demographics** |
| **Breast Cancer** |  |  |  |
| ***2013 Review*** |  |  |  |
| Rijnsburger et al.,2010219See also Kriege et al., 2004201NADutch MRISC study | Based on cumulative lifetime risk determined using modified Claus tables:*BRCA1/2* carriers, or other mutations: 50 to 85% riskHigh-risk: 30 to 50% riskModerate-risk (no documented gene mutation): 1 to -30% risk | Enrolled: 2275Analyzed: 2157 (422 *BRCA1* , 172 *BRCA2* , 5 other mutation, 1069 high-risk, 489 moderate-risk) | Mean age at entry, years:Cohort: 40.1 (range 19 to 75)*BRCA1* : 38.7*BRCA2* : 40.0High-risk: 40.8Moderate-risk: 40.0 |

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| **Author, year** **Quality** | **Screening method and interval** | **Scoring criteria** | **Duration/followup** |
| **Breast Cancer** |  |  |  |
| ***2013 Review*** |  |  |  |
| Rijnsburger et al.,2010219See also Kriege et al., 2004201NADutch MRISC study | All women underwent:A) Biannual CBEB) Annual mammographyC) Annual contrast enhanced MRINote: Both imaging investigations performed on same day or time period when possible, between day 5 and day 15 of menstrual cycleNote: When one of the examinations reported "probably benign finding" or "need additional imaging evaluation" (BIRADS 3 or 0), further investigation undertaken by ultrasonographyMalignancy diagnosis based on histological findings | BIRADS | 1999 to 2006Median 4.9 years, mean 4.0 years (range 0.1 to 6.3 years), followup post diagnosis for mortalityRelapse: Median 5.0 years (range 1.7 to 8.4 years) |

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| **Author, year** **Quality** | **Outcome: test characteristics** | **Cancer incidence** |
| **Breast Cancer** |  |  |
| ***2013 Review*** |  |  |
| Rijnsburger et al.,2010219See also Kriege et al., 2004201NADutch MRISC study | **Number of screen detected breast cancers; total, invasive, DCIS***BRCA1*: 21/35, 19/31, 2/4*BRCA2*: 15/18, 12/13, 3/5Other mutation: 1/5, 0/0, 1/1High-risk: 26/27, 22/23, 4/4 Moderate-risk: 15/16, 11/11, 4/5Total: 78/97, 64/78, 14/19***Screening method comparisons based on 75 breast cancers with data that included results for both imaging methods*****Sensitivity (95% CI), A vs. B vs. C**Any breast cancer: 21% (12 to 32) vs. 41% (30 to 53) vs. 71% (59 to 81), p=0.0016 for B vs. CInvasive: 22% (11.8 to 32) vs. 36% (24 to 49) vs. 77% (65 to 87), p<.00005 for B vs. CDCIS: 15% (1.9 to 45) vs. 69% (39 to 91) vs. 39% (14 to 68), p=0.388 for B vs. CMutation (any breast cancer)*BRCA1*: 13% (2.8 to 34) vs. 25% (9.8 to 47) vs. 67% (45 to 84), p=0.0129 for B vs. C*BRCA2*: 7.7% (0.2 to 36) vs. 62% (33 to 86) vs. 69% (39 to 91), p=1.0 for B vs. CRisk group (any breast cancer)High: 32% (13 to 56) vs. 46% (24 to 68) vs. 77% (55 to 92)Moderate: 33% (9.9 to 65) vs. 47% (21 to 73) vs. 67% (38 to 88)*BRCA1* vs. *BRCA2* sensitivity of methods comparedMammography, p=.04; all other comparisons between groups and screening methods were nonsignificant. Specificity of methods did not differ between groups.**Specificity (95% CI), A vs. B vs. C**Any breast cancer: 98% (97.5 to 98.2) vs. 95% (94.0 to 95.1) vs. 90% (88.9 to 90.4)Mutation (any breast cancer)*BRCA1*: 97% (95.7 to 97.9) vs. 95% (93.0 to 95.9) vs. 91% (89.1 to 92.6)*BRCA2*: 98% (96.4 to 99.4) vs. 94% (90.9 to 96.0) vs. 92% (88.7 to 94.5)Risk group (any breast cancer)High: 98% (97.7 to 98.7) vs. 95% (93.8 to 95.3) vs. 89% (87.9 to 90.1)Moderate: 98% (96.9 to 98.6) vs. 95% (93.5 to 95.9) vs. 90% (87.8 to 91.0)**PPV (95% CI), A vs. B vs. C**Any breast cancer: 10% (5.7 to 17) vs. 8.5% (5.8 to 12) vs. 7.7% (5.8 to 9.9)Mutation (any breast cancer)*BRCA1*: 8.8% (1.8 to 24) vs. 9.5% (3.6 to 20) vs. 14% (8.5 to 22)*BRCA2*: 14% (0.4 to 58) vs. 26% (12 to 45) vs. 23% (11 to 39)Risk group (any breast cancer)High: 9.8% (3.7 to 20) vs. 5.3% (2.6 to 9.5) vs. 4.5% (2.6 to 7.1)Moderate: 12% (3.4 to 28) vs. 8.5% (3.5 to 17) vs. 6.2% (3.0 to 11) | **Incidence of cancer per population group; total, invasive, DCIS** *BRCA1*: 35, 31, 4*BRCA2*: 18, 13, 5Other mutation: 5, 0, 1High-risk: 27, 23, 4Moderate-risk: 16, 11, 5Total: 97, 78, 19 |

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| **Author, year** **Quality** | **Outcome: cancer characteristics Interval cancers** | **Outcome: disease-free survival Mortality** | **Conclusions** | **Funding source** |
| **Breast Cancer** |  |  |  |  |
| ***2013 Review*** |  |  |  |  |
| Rijnsburger et al.,2010219See also Kriege et al., 2004201NADutch MRISC study | **Characteristics of detected breast cancers, includes 78 screen detected cancers and 11 interval cancers**Tumor size, cm: 40% (30/76) <1, 39% (29/76) 1 to 2, 20% (15/76) >2, p1=0.003, p2=0.0045Nodal status negative: 69% (50/72), p1=0.42, p2=1Histology: 29% (21/72) grade 1, 32% (23/72) grade 2, 39% (28/72) grade 3, p1<0.001, p2=0.15p1=overall comparison between subgroupsp2=comparison between *BRCA1* and *BRCA2*Note: Age at diagnosis, number of interval cancers, estrogen and progesterone receptor status significantly different between subgroups**Number of interval cancers; total, invasive, DCIS***BRCA1*: 10/35, 10/31, 0/4*BRCA2*: 1/18, 1/18, 0/5Other mutation: 0/0, 0/0, 0/0High-risk: 1/27, 1/23, 0/4Moderate-risk: 1/16, 0/11, 1/5Total: 13/97, 12/78, 1/19Note: denominator includes 6 breast cancers detected at prophylactic mastectomyKriege, 2004: Breast cancer characteristics, study group vs. control1 vs. control2 (based on 50 screen-detected cancers in study group, 1500 in control group 1, 45 in control group 2)No. of DCIS: 6 vs. 120 vs. 0 Invasive tumor size <1 cm: 19/44 vs. 193/1380 vs. 5/45, p<0.001 vs. control 1, p<0.04 vs. control 2 Nodal status negative: 28/44 vs. 657/1380 vs. 17/45, p<0.001 vs. control 1, p=0.001 vs. control 2 Histological grade 1: 19/44 vs. 99/1380 vs. 4/45, p<0.001 vs. control 1, p=0.01 vs. control 2Note: Control 1 = National Cancer Registry data of women with breast cancer diagnosed in 1998, Control 2 = participants diagnosed with breast cancer between 1996-2002, participating in a prospective study of gene mutation | **Disease-free and overall survival in 89 patients**11/93 patients with breast cancer had relapse, 7/11 were mutation carriers5 patients had distant metastasis, all were mutation carriers4 patients died, 9.7% (3/31) *BRCA1* and 6.3% (1/16) *BRCA2*Cumulative metastasis-free and overall survival at 6 years in 43 mutation carriers with invasive cancer were 84% and 93%, other groups had 100% cumulative survival | Sensitivity of MRI superior to mammography for detection of breast cancer in women at increased risk. *BRCA1*- associated cancers have younger age at diagnosis, lower mammographic sensitivity, high number of interval cancers, low number of DCIS, and unfavorable tumor size at diagnosis. | Dutch government; Cancer Genomics Center |

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| **Author, year** **Quality** | **Design** | **Purpose** | **Population/setting** | **Inclusion/exclusion criteria** |
| **Ovarian Cancer** |  |  |  |  |
| ***Current Review*** |  |  |  |  |
| Evans, 200832NA | Prospective cohort, 1-arm (for staging and survival, prevalent and post-prevalent cases compared) | To assess the effectiveness of annual ovarian cancer screening with TVUS and CA-125 in reducing mortality from ovarian cancer in women at increased genetic risk | Five cancer genetics centers in the U.K., the Netherlands, and NorwayWomen at increased risk of ovarian cancer | Inclusion: All women with ≥10% lifetime risk of ovarian cancer based on family history were offered genetic testing and screeningExclusion: NR |
| Rosenthal et al., 2013217UK FOCSS Phase INA | Prospective cohort, 1-arm (for staging and survival compared women diagnosed within a year of screening to those diagnosed later) | To establish the performance characteristics of annual TVUS and CA-125 screening for women at high risk of ovarian or fallopian tube cancer | U.K.High-risk women recruited at 37 regional centers | Inclusion: Women with estimated minimum 10% lifetime ovarian cancer risk based on family history of ovarian and breast cancer or mutation in predisposing genes including BRCAExclusion: History of BSO, age <35 years, or participating in another ovarian cancer screening trial |
| Rosenthal et al., 2017218UK FOCSS Phase IINA | Prospective cohort, 1-arm (for staging compared women diagnosed within a year of screening to those diagnosed later) | To establish the performance of screening with CA-125 and TVUS for women at high risk of ovarian or fallopian tube cancer. | U.K.Recruited at 42 National Health Service centers | Inclusion: Women ≥35 years old at high risk for ovarian cancer, based on personal or family history of cancer or genetic predisposition to cancerExclusion: History of bilateral oophorectomy, or negative result for a pathologic mutation found in affected family member |
| ***2013 Review*** |  |  |  |  |
| Hermsen et al., 2007198NA | Prospective cohort, 1-arm (staging vs. 2 external comparison groups; unscreened family members with cancer and combined data from multiple studies) | To assess efficacy of annual gynecological screening, accounting for compliance to protocol. | The NetherlandsWomen with BRCA mutation screened at 6 University Family Cancer Clinics | Inclusion: Women with *BRCA1/2* mutation screened at one of participating centersExclusion: 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 definitions** | **N** | **Baseline demographics** |
| **Ovarian Cancer** |  |  |  |
| ***Current Review*** |  |  |  |
| Evans, 200832NA | All estimated ≥10% lifetime ovarian cancer risk, based on family history | 981 *BRCA1/2*3532 overall | Not reportedScreening offered starting at 30 or 35 years of age |
| Rosenthal et al., 2013217UK FOCSS Phase INA | All estimated ≥10% lifetime ovarian cancer risk, based on BRCA and other predisposing mutations in patient or family, or history of ovarian, breast, and colorectal cancer in family | 282 *BRCA1*250 *BRCA2*3563 overall | Median age, years (all participants): 44.6 (range 35 to 81) |
| Rosenthal et al., 2017218UK FOCSS Phase IINA | Some results reported separately for BRCA carriers; other indicators of risk include mutations in other cancer-related genes, family history of ovarian, breast, and other cancers, and Ashkenazi Jewish ethnicity | 804 *BRCA1/2*4348 overall | Median age, years (all participants): 45.5 (range 34.2 to 84.8) |
| ***2013 Review*** |  |  |  |
| Hermsen et al., 2007198NA | Based on BRCA status | 883 (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) |

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| **Author, year Quality** | **Screening method and interval** | **Scoring criteria** | **Duration/followup** |
| **Ovarian Cancer** |  |  |  |
| ***Current Review*** |  |  |  |
| Evans, 200832NA | A) Annual CA-125B) Annual TVUS | Not reported | Enrolled 1991 to 2007Followup not reportedScreened for up to 16 years |
| Rosenthal et al., 2013217UK FOCSS Phase INA | UK Familial Ovarian Cancer Screening Study (UK FOCSS), Phase I:A) Annual CA-125B) Annual TVUS | CA-125: premenopausal 35 IU/mL, postmenopausal 30 IU/mLTVUS: Normal, Equivocal, or Suspicious based on ovarian morphology; all suspicious scans and those with ovarian volume > 60 mL considered abnormal | Recruited 2002 to 200811,366 women-years for 3563 women, mean followup 3.2 years |
| Rosenthal et al., 2017218UK FOCSS Phase IINA | UK Familial Ovarian Cancer Screening Study (UK FOCSS), Phase II:A) CA-125 every 4 months, interpreted using risk of ovarian cancer algorithm (ROCA)B) TVUS annually, or within 2 months of an abnormal ROCA result | CA-125: Normal, Intermediate, or Elevated; no fixed threshold; initial ROC based on initial CA-125 level and age-specific ovarian cancer incidence; later ROC based on both CA-125 level and rate of change; menopausal status incorporated as wellTVUS: Normal, Unsatisfactory, or Abnormal | 2007 to 201213,728 women-years for 4,348 women; median followup 4.8 years |
| ***2013 Review*** |  |  |  |
| Hermsen et al., 2007198NA | All women underwent: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 familyNote: Biannual screens were done in some centers during the study period, but this was not systematically adopted | CA-125: >35kU1-1 abnormal if resulted in extra screen visit or diagnostic operationTVUS: Abnormal or normal | 1993 to 20051473 person-years |

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| **Author, year** **Quality** | **Outcome: test characteristics** | **Cancer incidence** |
| **Ovarian Cancer** |  |  |
| ***Current Review*** |  |  |
| Evans, 200832NA | Not reported | 49 ovarian cancers diagnosed among 981 BRCA carriers (21 prevalent, 28 post-prevalent, 9 interval)64 ovarian cancers diagnosed overall |
| Rosenthal et al., 2013217UK FOCSS Phase INA | Based on 538 BRCA carriers, incident cancers only**Test characterstics (95% CI), A+B**Sensitivity: 76.9 (46.2 to 95.0)Specificity: 99.2 (97.9 to 99.8)PPV: 71.4 (41.9 to 91.6)NPV: 99.4 (98.2 to 99.9)Note: estimates reported here include occult cancers as false negatives | 20 cancers diagnosed among 538 BRCA carriers (6 prevalent, 10 incident screen-detected, 2 screen-negative, 2 occult). Note: These include only cancers detected within 365 days of last screening test and included in test performance analysis. |
| Rosenthal et al., 2017218UK FOCSS Phase IINA | Based on 804 BRCA carriers**Test characterstics (95% CI), A+B**Sensitivity: 64.3 (35.1 to 87.2)Specificity (occults NA): 99.3 (98.9 to 99.6)PPV: 36.0 (18.0 to 57.5)NPV: 99.8 (99.5 to 99.9)Note: estimates reported here include occult cancers as false negatives | 14 cancers diagnosed among 804 BRCA carriers (1 prevalent, 8 incident, 5 occult) |
| ***2013 Review*** |  |  |
| Hermsen et al., 2007198NA | 15 cancers diagnosed in cohortBased on 459 women with data on each visit: 7 cancers diagnosed (2 prevalent, 2 interval, 3 incident)**Sensitivity (95% CI), A vs. B vs. A+B**All cancers: 42% (14 to 70) vs. 25% (1 to 50) vs. 42% (14 to 70)Excluding occult cancers: 71% (38 to 100) vs. 43% (6 to 80) vs.71% (38 to 100)**Specificity (95% CI) A vs. B vs. A+B**All cancers: 99% for all (CI range 98 to 100)Excluding occult cancers: 99% for all (CI range 98 to 100) **PPV (95% CI), A vs. B vs. A+B**All cancers: 33% (9 to 57) vs. 20% (0 to 40) vs. 23% (5 to 40)Excluding occult cancers: 33% (9 to 57) vs. 20% (0 to 40) vs. 23% (5 to 40)**NPV (95% CI), A vs. B vs. A+B**All cancers: 99% (99 to 100) for allExcluding occult cancers: 100% for all (CI range 99 to 100) | 10 cancers diagnosed during followup 5 screen detected6.5 cases expectedBased on 459 women with data on each visit: 7 cancers diagnosed (2 prevalent, 2 interval, 3 incident)**SIR (95% CI)**Overall: 1.5 (0.7 to 2.8)*BRCA1*: 1.7 (0.8 to 3.1)*BRCA2*: unable to estimate, no event observedOptimally screened women-years (interval between screen visits <13 months): 1.6 (0.5 to 3.6)Note: Expected number of cases based on data from population-based studies of breast cancer cases, families of *BRCA1/2* carriers; SIR =expected/observed cases based on reference curves derived from refitting BOADICEA model of genetic susceptibility to breast cancer and including data from population-based studies of breast cancer families and cases |

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| **Author, year Quality** | **Outcome: cancer characteristics Interval cancers** | **Outcome: disease-free survival Mortality** | **Conclusions** | **Funding source** |
| **Ovarian Cancer** |  |  |  |  |
| ***Current Review*** |  |  |  |  |
| Evans, 200832NA | **Stage 3 or 4**:*BRCA1*: 71% (30/42)*BRCA2*: 71% (5/7)*BRCA1/2* prevalent: 81% (17/21)*BRCA1/2* post-prevalent: 61% (17/28)**Interval**: n=9 among BRCA carriers | Among 49 BRCA carriers diagnosed with ovarian cancer:5-year survival: 59% (95% CI 51% to 66%)10-year survival: 36% (95% CI 27% to 45%)Deaths among prevalent cases: 57% (12/21)1Deaths among post-prevalent cases: 39% (11/28) | Annual surveillance by TVUS and CA-125 in women at increased familial risk of ovarian cancer is ineffective in detecting tumors at an early enough stage to affect survival in BRCA carriers | National Institute for Health Research, Central Manchester Foundation Trust |
| Rosenthal et al., 2013217UK FOCSS Phase INA | Among all participants excluding those with Lynch Syndrome:**Stage**: 26% (6/23) of cancers in women screened in the year before diagnosis were stage IIIc to IV, vs. 86% (6/7) of those in women not screened in year before diagnosisAmong BRCA carriers:**Interval** **cancers**: n=2 screen-negative cancers within one year of screening. | Survival (all participants):71.9 months (95% CI 60.7 to 83.2) in women screened in year before diagnosis48.4 months (95% CI 39.4 to 57.4) in women not screened in year before diagnosis, p=0.233Based on 11 deaths from ovarian, fallopian tube, or peritoneal cancer | Screening more frequently than annually in a high-risk population with prompt surgical intervention offers a better chance of early-stage detection of ovarian cancer | Cancer Research UK, the UK Department of Health, the Eve Appeal, the National Cancer Institute, the UK National Institute for Health Research, and University College London |
| Rosenthal et al., 2017218UK FOCSS Phase IINA | Based on 4,348 participants**Stage**: 37% (7/19) stage IIIb to IV of cancers diagnosed within a year of last UK FOCSS Phase II screening, vs. 94% (17/18) of those diagnosed later**Interval cancers**: n=0 clinically presenting interval cancers  | Survival analysis not performed3 deaths among 37 women with invasive cancer at end of study (including those diagnosed within one year of screening and later) | ROCA-based screening is an option for women at high risk of ovarian cancer who defer or decline RRSO, given its high sensitivity and significant stage shift. Effects on survival are unknown. | Cancer Research UK, The Eve Appeal, and the UK National Institute for Health Research |
| ***2013 Review*** |  |  |  |  |
| Hermsen et al., 2007198NA | **Stage:** 80% (8/10) stage III/IV (4/5 incident, 4/5 interval cancers) vs. 77% (20/26) in unscreened family members with cancer**Interval cancers**: n=5 | After mean followup 28 months from diagnosis3/15 cases died of ovarian cancer | Annual screening with TVUS and serum CA-125 is an ineffective method for detecting ovarian cancer in women at increased risk due to family history | Biocare Foundation |

\*Incident plus interval cancer

**Abbreviations:** BIRADS=Breast Imaging Reporting and Data System; BMI=Body mass index; BOADICEA=Breast and Ovarian Analysis of Disease Incidence and Carrier Estimation Algorithm; BRCA=breast cancer susceptibility gene; BRCAPRO= breast cancer susceptibility gene prediction model; CA-125=cancer antigen-125; CBE=clinical breast exam; CE=contrast enhanced; CI=confidence interval; cm=centimeter; DCIS=ductal carcinoma in situ; FDR=first degree relative; MARIBS=Magnetic Resonance Imaging for Breast Screening; mm=Millimeter; MRI=magnetic resonance imaging; MRISC=Magnetic resonance imaging screening study; NA=not applicable; NPV=negative predictive value; NR=not reported; PPV=positive predictive value; ROCA=Risk of Ovarian Cancer Algorithm; SIR=standard incidence ratio; TP53=tumor protein 53; TVUS=transvaginal ultrasound; U.K.=United Kingdom; UK FOCSS=United Kingdom Familial Ovarian Cancer Screening Study; U.S.=United States