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| **Author, year**  **Quality** | **Design** | **Purpose** | **Sample size** | **Population/setting** | **Demographics** |
| **Mastectomy** |  |  |  |  |  |
| ***Current Review*** |  |  |  |  |  |
| Flippo-Morton et al., 2016174  Fair | Retrospective cohort | To analyze the uptake and outcomes of surgery and surveillance in *BRCA1/2* patients. | Eligible patients without cancer diagnosis: 100  Analyzed: 87 | 1996 to 2011  All patients testing positive for a BRCA mutation at a single center in the U.S. (North Carolina). | Age at BRCA testing among 87 women analyzed: 59% >35 years, 41% ≤ 35 years |
| Heemskerk-Gerritsen et al., 2013177  Fair | Prospective cohort | To prospectively assess the effect of BRRM when compared with surveillance on breast cancer risk and mortality in healthy *BRCA1/2* mutation carriers. | Eligible patients: 570  *BRCA1* : 405  *BRCA2* : 165 | 1994 to 2011  All patients testing positive for a BRCA mutation and with no cancer history at a single center in the Netherlands. | Age at BRCA testing, years: BRRM: 33 (range 18 to 64)  Surveillance: 36 (range 18 to 75) |

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| **Author, year**  **Quality** | **Inclusion/exclusion criteria** | **Risk definition** | **Followup** |
| **Mastectomy** |  |  |  |
| ***Current Review*** |  |  |  |
| Flippo-Morton et al., 2016174  Fair | Inclusion: All patients testing positive for a BRCA mutation. Study included patients with breast cancer or a combination of breast and ovarian cancers (n=118, not reported here), as well as women without a diagnosis of cancer at the time of testing (n=87).  Exclusion: Male patients, patients with a malignancy other than breast, and patients without complete followup data. | BRCA status | Median followup 30.4 months among 87 patients analyzed  RRM: median followup 36 months (range 12 to 132 months), no invasive breast cancers developed  Surveillance: median time to cancer development 30 months (range 3 to 76 months) |
| Heemskerk-Gerritsen et al., 2013177  Fair | Inclusion: *BRCA1* or *BRCA2* carrier, no history of cancer at the time of DNA testing, both breasts and both ovaries in situ at the time of DNA testing, and followup at one site in the Netherlands.  Exclusion: Women with symptomatic breast cancer at baseline. | BRCA status | Median followup, years:  BRRM: 8.5 (range 0.6 to 17.8), 6.3 after surgery (range 0.1 to 17.4), 1379 PYO  Surveillance: 4.1 (range 0.1 to 16.1), 2037 PYO |

| **Author, year**  **Quality** | **Results** | **Conclusions** | **Funding source** |
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| **Mastectomy** |  |  |  |
| ***Current Review*** |  |  |  |
| Flippo-Morton et al., 2016174  Fair | **RRM ± RRSO (n=38) vs. RRSO alone (n=13) vs. surveillance (n=36)**  Number of invasive breast cancers: 0 vs. NR vs. 14% (5/36)  Note: 13% (5/38) of women undergoing RRM had breast neoplasia identified on pathology (DCIS or atypical hyperplasia). | Bilateral prophylactic mastectomy is an effective means of breast cancer prevention. | Carolinas Medical Center/Levine Cancer Institute; no outside funding |
| Heemskerk-Gerritsen et al., 2013177  Fair | **BRRM (n=212) vs. surveillance (n=358)**  Number of incident breast cancers: 0 vs. 57 (20% in *BRCA1,* 7% in *BRCA2* )  Incidence rate per 1000 PYO: 0 vs. 28  10-year breast cancer-free survival: 100% vs. 74% (p<0.001)  All-cause mortality, BRRM vs. surveillance: HR 0.20 (95% CI 0.02 to 1.68)  Breast cancer mortality: HR 0.29 (95% CI 0.03 to 2.61)  Note: one patient in BRRM group described as presenting with metastases in 2001 and dying of breast cancer in 2006; not clear why she was not included in analyses. | In healthy *BRCA1/2* mutation carriers, BRRM when compared with surveillance reduces breast cancer risk substantially, while longer followup is warranted to confirm survival benefits. | The Dutch Cancer Society and the Dutch Pink Ribbon Foundation. |

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| **Author, year**  **Quality** | **Design** | **Purpose** | **Sample size** | **Population/setting** | **Demographics** |
| **Mastectomy** |  |  |  |  |  |
| ***2013 Review*** |  |  |  |  |  |
| Domchek et al., 201098  Fair | Prospective cohort | To assess the relationship of RRM or RRSO with cancer outcomes. | Eligible: 2482  Analyzed: 1458 with no prior breast cancer (935 *BRCA1* , 523 *BRCA2* ) | 1974 to 2008  U.K., Europe and North America Women from 22 centers in the PROSE consortium. | Not reported |
| Evans et al., 2009173  all sites  Fair | Prospective cohort, one-arm | To assess effectiveness of risk- reducing surgery in women at high risk of breast cancer, including carriers and noncarriers of *BRCA1/2* mutation. | All RRM enrolled: 550  Bilateral (unaffected): 57% (314/550)  *BRCA1/2*: 37% (202/550) | 1987 to 1992  Europe  Multidisciplinary family history clinics established at 10 centers. | Age range of women undergoing mastectomy, years: 21 to 72  Mean age: NR |

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| **Author, year**  **Quality** | **Inclusion/exclusion criteria** | **Risk definition** | **Followup** |
| **Mastectomy** |  |  |  |
| ***2013 Review*** |  |  |  |
| Domchek et al., 201098  Fair | Inclusion: Women with *BRCA1/2* mutations, no prior ovarian cancer, no salpingo-oophorectomy at time of ascertainment, and minimum 6 months followup.  Exclusion: Women with cancer diagnosis within first 6 months of followup, women who had undergone RRM prior to ascertainment excluded from all breast cancer end points, and women with occult ovarian cancer during RRSO excluded from ovarian cancer end points. | BRCA status | Patients followed until end of 2009.  Median followup 3.65 years for those who had surgery and 4.29 years for those who did not.  **Mastectomy & breast cancer outcomes**  *BRCA1* followed mean 2.7 years to censoring  *BRCA2* followed mean 2.5 years to censoring |
| Evans et al., 2009173  all sites  Fair | Inclusion: Eligible for bilateral RRM if lifetime breast cancer risk in excess of 25% or eligible for unilateral RRM if already had a diagnosis of in situ or invasive breast cancer in the contralateral breast. Paris center offered surgery to *BRCA1/2* carriers only.  Exclusion: Not reported | Lifetime risk of breast cancer >25% based on family history with or without mutation or diagnosis of breast cancer in contralateral breast. | Followup among all women with RRM, years: Median 7.5; Mean 6.1; 3,334 women years  Followup among women undergoing bilateral RRM: 2,155 women years |

| **Author, year Quality** | **Results** | **Conclusions** | **Funding source** |
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| **Mastectomy** |  |  |  |
| ***2013 Review*** |  |  |  |
| Domchek et al., 201098  Fair | Number of cancer cases in women with no history of breast cancer; surgery vs. no surgery  Risk-reducing mastectomy and risk of first occurrence of breast cancer  Total: 0% (0/75) vs. 5.8% (34/585)  *BRCA1*: 0% (0/43) vs. 5.1% (19/372)  *BRCA2*: 0% (0/32) vs. 7.0% (15/213) | Among a cohort of women with BRCA mutations, RRM was associated with a lower risk of breast cancer. | Public Health Service; University of Pennsylvania Cancer Center; Cancer Genetics Network; Marjorie Cohen Research Fund; SPORE grant from the Dana- Farber/Harvard Cancer Center; the U.S. Department of Defense; Utah Cancer Registry; Utah State Department; Nebraska State Cancer and Smoking-Related Diseases Research Program grants; Cancer Research U.K. Grant; National Cancer Institute; Dr. Olopade received funding as the Doris Duke Distinguished Clinical Scientist; Dr. Eeles received funding from the National Institute for Health Research |
| Evans et al., 2009173  all sites  Fair | Bilateral RRM: N=307 among women with followup (314 total)  Expected cancers: 21.30  Cancers diagnosed: 0 | Risk-reducing surgery is highly effective. | NR |

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| **Author, year**  **Quality** | **Design** | **Purpose** | **Sample size** | **Population/setting** | **Demographics** |
| **Mastectomy** |  |  |  |  |  |
| ***2013 Review*** |  |  |  |  |  |
| Evans et al., 2009173  Manchester site  Fair | Prospective cohort | To assess effectiveness of risk-reducing surgery in women at high risk of breast cancer, including carriers and noncarriers of *BRCA1/2* mutation. | All RRM enrolled: 245  Bilateral (unaffected): 73% (179/245)  *BRCA1/2:* 36% (87/245) | 1987 to 1992  United Kingdom  Multidisciplinary family history clinic in Manchester. | Mean age of women undergoing mastectomy, years: 41 (range: 21 to 60) |
| Hartmann et al., 1999175  Fair | Retrospective cohort | To define the effect of RRM on incidence of breast cancer and risk of death from breast cancer. | Eligible: 639  Analyzed: 639 | 1960 to 1993 U.S.  Mayo Clinic medical records of women who underwent RRM. | Mean age at surgery 42 (range: 18 to 79) |

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| **Author, year**  **Quality** | **Inclusion/exclusion criteria** | **Risk definition** | **Followup** |
| **Mastectomy** |  |  |  |
| ***2013 Review*** |  |  |  |
| Evans et al., 2009173  Manchester site  Fair | Inclusion: Eligible for bilateral RRM if lifetime breast cancer risk in excess of 25% or eligible for unilateral RRM if already had a diagnosis of in situ or invasive breast cancer in the contralateral breast.  Exclusion: Not reported | Lifetime risk of breast cancer >25% based on family history with or without mutation or diagnosis of breast cancer in contralateral breast. | Followup among all women with RRM, years: Median 7.3; 1,673 women years Followup amongst women undergoing bilateral RRM: 1,274 women years Followup among control women; 2,438 women years |
| Hartmann et al., 1999175  Fair | Inclusion: Women with a family history of breast cancer who underwent bilateral RRM.  Exclusion: Breast cancer detected in surgically treated breast; Surgery undertaken for augmentation of reduction.  High-risk Comparison Group Inclusion: Sisters of high-risk subjects were recruited to the study. | High risk: ≥2 first-degree relatives with breast cancer; 1 first-degree relative and ≥2 second-degree or third-degree relatives with breast cancer; 1 first-degree relative with breast cancer before the age of 45 years and 1 other relative with breast cancer; 1 first-degree relative with breast cancer and ≥1 relatives with ovarian cancer; 2 second-degree or third-degree relatives with breast cancer and ≥1 with ovarian cancer; 1 second-degree or third-degree relative with breast cancer and ≥2 with ovarian cancer; ≥3 second-degree or third-degree relatives with breast cancer; 1 first-degree relative with bilateral breast cancer; Breast cancer in male family members  Moderate risk: Women who did not meet these criteria. | Median 14 years, with a minimum of 2 years for 99% of the subjects. |

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| **Author, year**  **Quality** | **Results** | **Conclusions** | **Funding source** |
| **Mastectomy** |  |  |  |
| ***2013 Review*** |  |  |  |
| Evans et al., 2009173  Manchester site  Fair | **Bilateral RRM (N=179) vs. no mastectomy (N=367)**  Breast cancers expected based on life tables: 12.12 vs. 20.8 Cancers diagnosed: 0 vs. 21 | Risk-reducing surgery is highly effective. | Not reported |
| Hartmann et al., 1999175  Fair | Overall: 425 subjects were classified moderate risk, 214 subjects high risk. 95% were alive at the time of the study. 7 were diagnosed with breast cancer (4 moderate risk, 3 high risk); all cases occurred after subcutaneous mastectomy.  Cancer Diagnosis: 37 in the moderate-risk group (based on Gail model estimates) and 53 in the high-risk group (based on the high-risk comparison group) were expected to develop breast cancer had they not undergone mastectomy. RRM reduced risk in the moderate-risk group by 89.5% (p<0.001) and in the high-risk group by 90% to 94% (depending on adjusted analysis). 2 women in the high-risk group were diagnosed with ovarian cancer.  Death Reduction: 10 in the moderate-risk group (based on Gail model estimates) and 31 in the high-risk group (based on the high-risk comparison group) were expected to die from breast cancer had they not undergone mastectomy. Death was reduced in the moderate-risk group by 100% (no deaths) (95% CI 70 to 100) and in the high-risk group by 81% to 94% (depending on adjusted analysis) (2 deaths). | In women with high risk of breast cancer on the basis of family history, RRM can significantly reduce the incidence of breast cancer. | Department of Defense; National Cancer Institute; Donaldson Charitable Trust |

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| **Author, year**  **Quality** | **Design** | **Purpose** | **Sample size** | **Population/setting** | **Demographics** |
| **Mastectomy** |  |  |  |  |  |
| ***2013 Review*** |  |  |  |  |  |
| Hartmann et al., 2001176  Fair | Retrospective cohort | To report the effect of RRM on breast cancer risk in *BRCA1/2* carriers identified from a high-risk cohort. | 18 *BRCA1/2* | *BRCA1/2* mutation carriers undergoing RRM and enrolled as high-risk participants in prior study (Hartmann, 1999). | Mean age at surgery 41 (range 20 to 75) |
| Skytte et al., 2011183  Good | Prospective cohort | To compare incidence of breast cancer after RRM in healthy BRCA mutation carriers versus non-operated mutation carriers and background population. | Eligible: 307 with mutation (201 *BRCA1* , 106 *BRCA2*) | January 1996-February 2008  Denmark  Women from clinical genetics departments at multiple sites with mutation status diagnosed. | Median age at entry into study, years: 36.2 (range: 17.9 to 86.3)  Mean age at group entry, years (mastectomy vs. no mastectomy): 37.1 vs. 37.7  <40 years: 67% (64/96) vs. 60% (127/211)  Note: age at group entry = age at mastectomy for mastectomy group and age at BRCA diagnosis for no mastectomy group. |

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| **Author, year**  **Quality** | **Inclusion/exclusion criteria** | **Risk definition** | **Followup** |
| **Mastectomy** |  |  |  |
| ***2013 Review*** |  |  |  |
| Hartmann et al., 2001176  Fair | Inclusion: Women with *BRCA1/2* mutations who underwent bilateral RRM mastectomy. | BRCA status | 13.1 years |
| Skytte et al., 2011183  Good | Inclusion: *BRCA1* or *BRCA2* mutation positive and women who did not undergo mastectomy or salpingo-oophorectomy prior to study.  Exclusion: Diagnosis of breast or ovarian cancer before BRCA testing and women who opted for risk- reducing surgery before receiving test result. | BRCA status | Median time from study entry to mastectomy: 7.7 years  Total at-risk time in mastectomy group: 378.7 years  Total at-risk time in no mastectomy group: 934.6 years |

| **Author, year**  **Quality** | **Results** | **Conclusions** | **Funding source** |
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| **Mastectomy** |  |  |  |
| ***2013 Review*** |  |  |  |
| Hartmann et al., 2001176  Fair | **Expected risk reduction**  Easton model (a high-penetrance model): 6.1 cases  Struewing model (a low-penetrance model): 4.5 cases  **Mastectomy resulted in risk reduction**  Eastern model: 89.5% or 100% (95% CI 41.4 to 99.7 and CI 68 to 100)  Struewing model: 85% or 100% (95% CI 15.6 to 99.6 and CI 54.1 to 100) | Risk-reducing mastectomy is associated with a substantial reduction in the incidence of breast cancer in known *BRCA1/2* mutation carriers. | Not reported |
| Skytte et al., 2011183  Good | **Number of breast cancer cases (incidence per person-year)**  Mastectomy vs. no mastectomy: 3/96 (0.8%) vs. 16/211 (1.7%); HR 0.394 (95% CI 0.115 to 1.355) p=0.14  Note: 3/3 women with breast cancer in the mastectomy group and 12/16 women in no mastectomy group were *BRCA1* positive.  Note: all women diagnosed with cancer in mastectomy group had also undergone bilateral salpingo-oophorectomy; 1 woman diagnosed with breast cancer on date of mastectomy, contributed to the "no mastectomy" group at risk time and cancer incidence.  Adjusting for age did not change significance (HR 0.455, p=0.224)  Effect of age was significant (p=0.008), in both groups, 1 year age difference was associated with 4.2% increase in breast cancer risk  Annual incidence of breast cancer after mastectomy by carrier status: 1.1% for *BRCA1* (n=67); 0 for *BRCA2* (n=29) | Study of 307 healthy *BRCA1/2* carriers suggests bilateral RRM reduces risk of breast cancer but does not completely eliminate it. Study size too small to show a significant difference. | Not reproted |

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| **Author, year Quality** | **Design** | | **Purpose** | | **Sample size** | | **Population/setting** | | **Demographics** | |
| **Oophorectomy or salpingo- oophorectomy** | | | | |  | |  | |  | |
| ***Current Review*** |  | |  | |  | |  | |  | |
| Heemskerk-Gerritsen et al., 2015178  HEBON Study  Fair | Retrospective cohort and prospective cohort | | To assess potential bias in estimated breast cancer risk reduction after RRSO. Multiple analytic methods tested and a new one proposed. | | Eligible patients: 822  *BRCA1* : 589  *BRCA2* : 233 | | From the ongoing Hereditary Breast and Ovarian Cancer in the Netherlands (HEBON) study, selected *BRCA1/2* mutation carriers with no cancer history when DNA tested. | | **Median age at start of observation, years**  RRSO: 44 (range 30 to 66)  Non-RRSO: 33 (range 30 to 66) | |
| Kotsopoulos et al., 2017179  Fair | | Prospective cohort | | Given concerns regarding methods of previous case-control studies, conducted a prospective analysis of oophorectomy and breast cancer risk in BRCA carriers with no history of cancer. | | Eligible patients: 3722  *BRCA1* only 2969  *BRCA2* only: 725 | | Enrollment dates NR  BRCA carriers identified at 78 centers in 12 countries | | **Mean age at baseline**:  46.2 (range 21 to 88) among 1552 women with oophorectomy  33.4 (range 13 to 85) among 2170 women without oophorectomy |

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| **Oophorectomy or salpingo- oophorectomy** | |  |  |
| ***Current Review*** |  |  |  |
| Heemskerk-Gerritsen et al., 2015178  HEBON Study  Fair | Inclusion: Female *BRCA1/2* mutation carriers with no history of cancer and both ovaries and both breasts intact at the date of DNA test result, and no cancer diagnosis within the first six months of study observation.  Exclusion: Women with breast or ovarian cancer before DNA testing. | BRCA status | Median followup, years: 3.2 for all 822 patients **Mean followup, years**  RRSO: 6.8 (range 0.5 to 17.4)  Non-RRSO: 3.1 (range 0.1 to 15.9) |
| Kotsopoulos et al., 2017179  Fair | Inclusion: BRCA carrier, family history of breast or ovarian cancer  Exclusion: personal history of any cancer or of bilateral prophylactic mastectomy | BRCA status | **Mean followup, years**: 5.6 (range 0 to 21.2)  All: 20,700 person-years  Oophorectomy: 7648 person-years  No oophorectomy: 13,052 person-years |

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| **Author, year**  **Quality** | **Results** | **Conclusions** | **Funding source** |
| **Oophorectomy or salpingo- oophorectomy** | |  |  |
| ***Current Review*** |  |  |  |
| Heemskerk-Gerritsen et al., 2015178  HEBON Study  Fair | **RRSO (n=346) vs. non-RRSO (n=476)**  Breast cancer incidence: 12.1% (42/346) vs. 9.9% (47/476)  Incidence rate per 1000 PYO: 25.6 vs. 21.5, HR 1.09 (95% CI 0.67 to 1.77)  *BRCA1* : 29.1 vs. 24.2, HR 1.21 (95% CI 0.72 to 2.06*)*  *BRCA2* : 14.9 vs. 13.8, HR 0.54 (95% CI 0.17 to 1.66)  Age <51 years: rates NR, HR 1.11 (95% CI 0.65 to 1.90)  Age ≥51 years: rates NR, HR 1.78 (95% CI 0.52 to 6.15)  Note: in addition to requiring no history of cancer, mastectomy, or oophorectomy at baseline, authors' analysis attempted to reduce bias by allocating both person-time before surgery in the RRSO group and a 3- month latency period to the non-RRSO group. | In previous studies, breast cancer risk reduction after RRSO in *BRCA1/2* mutation carriers may have been overestimated because of bias. Using a design that maximally eliminated bias, we found no evidence for a protective effect. | Dutch Cancer Society, the Netherlands Organization of Scientific Research, Pink Ribbon grant, and Biobanking and Biomolecular Resources Research Infrastructure grant |
| Kotsopoulos et al., 2017179  Fair | **With oophorectomy (n=1552) vs. without oophorectomy (n=2170)**  Annual incidence of new first primary breast cancers, all women: 1.87% vs. 1.59%, HR 0.89 (95% CI 0.69 to 1.14)  *BRCA1*: 2.02% vs. 1.57%, HR 0.97 (95% CI 0.73 to 1.29)  *BRCA2*: 0.97% vs. 2.32%, HR 0.68 (95% CI 0.38 to 1.21)  Breast cancer diagnosed before age 50 years:  *BRCA1*: 1.99% vs. 1.46%, HR 0.84 (95% CI 0.58 to 1.21)  *BRCA2*: 0.53% vs. 1.70%, HR 0.17 (95% CI 0.05 to 0.61)  Note: HRs adjusted for country, age, family history, and reproductive factors | Findings from this large prospective study support a role of oophorectomy for the prevention of premenopausal breast cancer in *BRCA2*, but not *BRCA1* mutation carriers | National Cancer Institute at the National Institutes of Health and the Canadian Cancer Society Research Institute |

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| **Author, year Quality** | **Design** | **Purpose** | **Sample size** | **Population/setting** | **Demographics** |
| **Oophorectomy or salpingo- oophorectomy** | | |  |  |  |
| ***Current Review*** |  |  |  |  |  |
| Mavaddat et al., 2013180  EMBRACE  Fair | Prospective cohort | To examine the effect of bilateral prophylactic oophorectomy on cancer risk in *BRCA1/2* mutation carriers. | Eligible patients without breast or ovarian cancer history: 988  *BRCA1:* 501  *BRCA2:* 485 | From the ongoing EMBRACE study established in 1998  U.K. and Ireland  28 centers; included *BRCA1/2* carriers with either no breast or ovarian cancer history (reported here), or with history of unilateral breast cancer. | **Age at enrollment of women without cancer history, years**  Mean: 41.2  Median: 39.5  Interquartile range: 14.6 |
| Rebbeck et al., 2002181  Fair | Prospective cohort | To investigate whether bilateral prophylactic oophorectomy reduces the risk of ovarian and breast cancers in women with BRCA mutations | Eligible patients, ovarian cancer study: 551  *BRCA1*: 459  *BRCA2*: 94  Eligible patients, breast cancer subgroup: 241  *BRCA1*: 204  *BRCA2*: 39 | Enrollment dates NR  Identified from 11 North American and European registries | **Mean age at time of surgical subjects’ oophorectomy, years:**  Ovarian cancer study:  42.0 (range 21.2 to 74.8) with oophorectomy  40.9 (range 19.6 to 79.1) without oophorectomy  Breast cancer study:  40.1 (range 21.3 to 66.4) with oophorectomy  38.9 (range 18.6 to 69.9) without oophorectomy |

| **Author, year**  **Quality** | **Inclusion/exclusion criteria** | **Risk definition** | **Followup** |
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| **Oophorectomy or salpingo- oophorectomy** | |  |  |
| ***Current Review*** |  |  |  |
| Mavaddat et al., 2013180  EMBRACE  Fair | Inclusion: Women, aged at least 18 years at interview, carriers of a pathogenic *BRCA1* or *BRCA2* mutation, either unaffected at date of baseline questionnaire or diagnosed with unilateral breast cancer.  Exclusion: Not reported | BRCA status | **Followup time for women without cancer history, years**  Mean: 3.3  Median: 2.6  Interquartile range: 3.7 |
| Rebbeck et al., 2002181  Fair | Inclusion: women with confirmed BRCA mutations who reported having prophylactic oophorectomy and controls without oophorectomy matched for BRCA mutation, center, and birth year  Exclusion: history of unilateral oophorectomy, BRCA variant of unknown significance, or history of ovarian cancer; for study of breast cancer risk, women with history of breast cancer or mastectomy excluded | BRCA status | **Mean followup, years:**  In study of ovarian cancer:  Oophorectomy: 8.2  No oophorectomy: 8.8  In subgroup followed for breast cancer:  Oophorectomy: 10.7  No oophorectomy: 11.9  Subjects who had undergone prophylactic oophorectomy were followed from date of oophorectomy until occurrence of cancer or until censoring |

| **Author, year**  **Quality** | **Results** | **Conclusions** | **Funding source** |
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| **Oophorectomy or salpingo- oophorectomy** | |  |  |
| ***Current Review*** |  |  |  |
| Mavaddat et al., 2013180  EMBRACE  Fair | **Number of women with new breast cancer, with oophorectomy (n=309) vs. without oophorectomy (n=679)**  All carriers: 5.8% (18/309) vs. 6.8% (46/679), HR 0.62 (95% CI 0.35 to 1.09)  *BRCA1* : 5.6% (9/162) vs. 7.7% (26/339), HR 0.52 (95% CI 0.24 to 1.13)  *BRCA2* : 6.2% (9/146) vs. 5.9% (20/339), HR 0.79 (95% CI 0.35 to 1.80)  Note: HRs adjusted for reproductive factors were similar and not reported.  Stratified by age:  All carriers < 45: HR 0.39 (95% CI 0.17 to 0.87)  All carriers ≥ 45: HR 1.14 (95% CI 0.50 to 2.61)  *BRCA1* < 45: HR 0.38 (95% CI 0.13 to 1.13)  *BRCA1* ≥ 45: HR 0.83 (95% CI 0.26 to 2.63)  *BRCA2* < 45: HR 0.44 (95% CI 0.14 to 1.38)  *BRCA2* ≥ 45: HR 1.74 (95% CI 0.59 to 5.15)  Note: patient numbers reported incorrectly in Supplementary Table 4 (compared with Table 4) and not reported here. | Oophorectomy carried out at less than 45 years of age was associated with a greater reduction in cancer risks than oophorectomy carried out at ages 45 years or older. | Cancer Research U.K., National Institute for Health Research, Medical Research Council |
| Rebbeck et al., 2002181  Fair | **Ovarian or peritoneal cancer, with oophorectomy (n=259) vs. without oophorectomy (n=292)**  All carriers: 0.8% (2/259) vs. 19.9% (58/292), HR 0.04 (95% CI 0.01 to 0.16)  Note: 2 peritoneal cancers; excludes 6 occult ovarian cancers found at oophorectomy  All carriers, by age at oophorectomy (years):  <35 (n=124): No events  35 to 50 (n=348): HR 0.03 (95% CI <0.01 to 0.20)  ≥50 (n=79): HR 0.11 (95% CI 0.02 to 0.76)  Women without personal history of breast cancer (n=351): HR 0.06 (95% CI 0.01 to 0.25)  **Breast cancer, with oophorectomy (n=99) vs. without oophorectomy (n=142)**  All carriers: 21.2% (21/99) vs. 42.3% (60/142), HR 0.47 (95% CI 0.29 to 0.77)  All carriers, by age at oophorectomy (years):  <35 (n=76): HR 0.39 (95% CI 0.15 to 1.04)  35 to 50 (n=146): HR 0.49 (95% CI 0.26 to 0.90)  ≥50 (n=19): HR 0.52 (95% CI 0.10 to 2.70) | Bilateral prophylactic oophorectomy reduces the risk of ovarian and peritoneal cancer and breast cancer in women with BRCA mutations | Public Health Service, University of Pennsylvania Cancer Center, Breast Cancer Research Foundation, Dana-Farber Women’s Cancers Program, Department of Defense, Utah State Department of Health, and the Nebraska State Cancer and Smoking-Related Diseases Research Program |

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| **Author, year**  **Quality** | **Design** | **Purpose** | **Sample size** | **Population/setting** | **Demographics** |
| **Oophorectomy or salpingo- oophorectomy** | | |  |  |  |
| ***Current Review*** |  |  |  |  |  |
| Shah et al., 2009182  Fair | Prospective cohort | To examine the combined effects of oophorectomy and intensive surveillance on breast cancer incidence in a prospective cohort of *BRCA1/2* carriers. | Analyzed: 93  *BRCA1:* 55% (51/93)  *BRCA2:* 44% (41/93) | 2003 to 2008  U.S.  University of Pennsylvania protocol for MRI screening in  *BRCA1/2* carriers. | Median age at enrollment, years: 47 |

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| **Author, year**  **Quality** | **Inclusion/exclusion criteria** | **Risk definition** | **Followup** |
| **Oophorectomy or salpingo- oophorectomy** | |  |  |
| ***Current Review*** |  |  |  |
| Shah et al., 20099182  Fair | Inclusion: Women over 25 years with known *BRCA1/2* mutation, or prior probability of a mutation of >75%. Required to be at least 3 months from any breast biopsies, lactation, radiation treatments, and chemotherapy treatments; women with prior breast cancer otherwise eligible.  Exclusion: Patients who were pregnant, had a contraindication to MRI, had bilateral mastectomies, those with unresolved actionable clinical or mammogram findings, or with new or recurrent ovarian cancer within 4 years. | Known deleterious mutation in *BRCA1* or *BRCA2,* or prior probability of a mutation of >75% | Median followup from study entry, years: 3.2 |

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| **Author, year**  **Quality** | **Results** | **Conclusions** | **Funding source** |
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| ***Current Review*** |  |  |  |
| Shah et al., 2009182  Fair | **With oophorectomy (n= 80) vs. no oophorectomy (n=13)**  Number of women with breast cancer: 11% (9/80) vs. 15% (2/13), p=NS  **With oophorectomy ≤40 years (n=25) vs. no oophorectomy ≤ 40 years (n=68)**  Number of women with breast cancer: 12% (3/25) vs. 12% (8/68), p=NS  All cancers diagnosed in *BRCA1* carriers | The breast cancer risk reduction from oophorectomy may be greater in *BRCA2* than in *BRCA1* mutation carriers | Cancer Genetics Network, the Marjorie Cohen Foundation, the QVC Network-Fashion Footwear Association of New York, and the National Institutes of Health |

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| **Author, year Quality** | **Design** | **Purpose** | | **Sample size** | | **Population/setting** | | **Demographics** | |
| **Oophorectomy or salpingo- oophorectomy** | | |  | |  | |  | |  |
| ***2013 Review*** |  |  | |  | |  | |  | |
| Domchek et al., 201098  Fair | Prospective cohort | To assess the relationship of RRM or RRSO with cancer outcomes. | | Eligible: 2482  Analyzed: 1458 with no prior breast cancer (935 *BRCA1* , 523 *BRCA2* ) | | 1974 to 2008  U.K., Europe and North America Women from 22 centers in the PROSE consortium. | | Not reported | |

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| ***2013 Review*** |  |  |  |
| Domchek et al., 201098  Fair | Inclusion: Women with *BRCA1/2* mutations, no prior ovarian cancer, no salpingo-oophorectomy at time of ascertainment, and minimum 6 months followup.  Exclusion: Women with cancer diagnosis within first 6 months of followup, women who had undergone RRM prior to ascertainment excluded from all breast cancer end points, and women with occult ovarian cancer during RRSO excluded from ovarian cancer end points. | BRCA status | Patients followed until end of 2009.  **Median followup, years**  Those who had surgery: 3.65  those who did not have surgery: 4.29  **Oophorectomy & breast cancer outcomes**  *BRCA1* followed mean 4.7 years to censoring  *BRCA 2* followed mean 4.7 years to censoring  **Oophorectomy & ovarian cancer outcomes**  *BRCA1* followed mean 5.6 years to censoring  *BRCA2* followed mean 5.8 years to censoring |

| **Author, year**  **Quality** | **Results** | **Conclusions** | **Funding source** |
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| **Oophorectomy or salpingo-oophorectomy** | |  |  |
| ***2013 Review*** |  |  |  |
| Domchek et al., 201098  Fair | **Number of cancer cases in women with no history of breast cancer; surgery vs. no surgery**  Risk-reducing salpingo-oophorectomy and ovarian or primary peritoneal cancer risk  Total: 1.3% (6/465) vs. 5.8%( 63/1092), HR 0.28 (95% CI 0.12 to 0.69)  *BRCA1*: 1.8% (6/342) vs. 7.4% (49/661), HR 0.31 (95% CI 0.12 to 0.82)  *BRCA2*: 0% (0/123) vs. 3.2% (14/431), HR N/A  Note: HR adjusted for year of birth, oral contraceptive use, and stratified by center.  Risk-reducing salpingo-oophorectomy and breast cancer risk  Total: 12% (39/336) vs. 22% (223/1034), HR 0.54 (95% CI 0.37 to 0.79)  *BRCA1* : 14% (32/236) vs. 20% (129/633), HR 0.63 (95% CI 0.41 to 0.96)  *BRCA2* : 7% (7/100) vs. 23% (94/401), HR 0.36 (95% CI 18.1 to 82.7)  Note: HR adjusted for year of birth and stratified by center.  Risk-reducing salpingo-oophorectomy and all-cause mortality  Total: 1.8% (8/447) vs. 5.9% (60/1011), HR 0.45 (95% CI 0.21 to 0.95)  *BRCA1* : 2.4% (8/327) vs. 7.1% (43/608), HR 0.52 (95% CI 0.24 to 1.14)  *BRCA2* : 0%(0/120) vs. 4.2% (17/403), HR N/A  Note: HR adjusted for year of birth and stratified by center.  Risk-reducing salpingo-oophorectomy and breast cancer specific mortality  Total: 0.5% (2/441) vs. 2.3% (22/973), HR 0.27 (95% CI 0.05 to 1.33)  *BRCA1*: 1.0% (2/321) vs. 2.8% (16/581), HR 0.30 (95% CI 0.06 to 1.53)  *BRCA2*: 0% (0/120) vs. 1.5% (6/392), HR N/A  Note: HR adjusted for year of birth and stratified by center.  Risk-reducing salpingo-oophorectomy and ovarian cancer specific mortality  Total: 0.7% (3/442) vs. 2.5% (24/975), HR 0.39 (95% CI 0.12 to 1.29)  *BRCA1*: 0.9% (3/322) vs. 3.4% (20/585), HR 0.46 (95% CI 0.08 to 2.72)  *BRCA2*: 0% (0/120) vs. 1.0% (4/390), HR N/A  Note: HR adjusted for year of birth, oral contraceptive use, and stratified by center. | Among a cohort of women with BRCA mutations, RRSO was associated with a lower risk of ovarian cancer, first diagnosis of breast cancer, all-cause mortality, breast cancer specific mortality, and ovarian cancer specific mortality. | Public Health Service; University of Pennsylvania Cancer Center; Cancer Genetics Network; Marjorie Cohen Research Fund; SPORE grant from the Dana- Farber/Harvard Cancer Center; the U.S. Department of Defense; Utah Cancer Registry; Utah State Department; Nebraska State Cancer and Smoking-Related Diseases Research Program grants; Cancer Research U.K. Grant; National Cancer Institute; Dr. Olopade received funding as the Doris Duke Distinguished Clinical Scientist; Dr. Eeles received funding from the National Institute for Health Research |

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| ***2013 Review*** |  |  |  |  |  |
| Kramer et al., 200599  Fair  Note: only oophorectomy performed | Prospective cohort | To assess whether population differences in oophorectomy prevalence might significantly influence breast cancer penetrance estimates in *BRCA1* mutation families. | Eligible: 673 (98 *BRCA1* positive, 23 from *BRCA1* families) | Year: NR  U.S.  Women from self-referred and physician-referred families affected by hereditary breast/ovarian cancer with a *BRCA1* mutation and participating in ongoing studies at the National Cancer Institute. | Not reported  Mean 2.7 cases of breast cancer and 3.0 cases of ovarian cancer per family diagnosed before ascertainment. |
| Olson et al., 2004100  NA  Note: only oophorectomy performed | Retrospective cohort | To estimate the potential risk reduction of breast cancer for women who underwent oophorectomy and had a family history of breast cancer but unknown BRCA status. | Eligible: 851  Analyzed: 634 | 1970 to 1994  U.S./review of Mayo Clinic Surgical Index  Followup survey completed by patient or surrogates (if patient deceased). | **Surrogate respondent vs. self-respondent**  Age at surgery, years (n)  21-30: 4% (1/27) vs. 3% (16/607)  31-40: 4% (1/27) vs. 14% (88/607)  41-50: 41% (11/27) vs. 53% (319/607)  51-60: 52% (14/27) vs. 30% (184/607)  Age at questionnaire response (followup) of self-respondents, years (n)  31-40: 1% (9/634)  41-50: 8% (48/634)  51-60: 28% (172/634)  61-70: 38% (231/634)  71-80: 20% (124/634)  81-90: 3% (20/634)  Deceased: n=30 |

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| **Oophorectomy or salpingo- oophorectomy** | | |  |  |
| ***2013 Review*** |  |  | |  |
| Kramer et al., 200599  Fair  Note: only oophorectomy performed | Inclusion: Female, bloodline family member from *BRCA1* positive family, no history of breast cancer before ascertainment, no history of bilateral mastectomy, age ≥20 years by study closing date.  Exclusion: Breast cancer diagnosed before family ascertainment and families with variants of uncertain significance. | BRCA status | | **Mean followup**: 16.5 years; 11,105 PYO  **Mean followup per patient, years**  *BRCA1* positive: 14.1  *BRCA1* negative: 17.6  *BRCA1* unknown: 15.8 |
| Olson et al., 2004100  NA  Note: only oophorectomy performed | Inclusion: Women <60 years old with bilateral oophorectomy during study dates.  Exclusion: Women who underwent hysterectomy alone or only had one ovary removed, underwent prophylactic mastectomy at any time, or had any history of cancer prior to surgery, aside from nonmelanoma skin cancer. | High-risk: ≥1 first-degree relative with breast cancer before age 50 or 1 first-degree relative with ovarian cancer at any age and ≥1 other first or second- degree relative with either diagnosis at any age.  Moderate-risk: Only 1 first-degree relative with breast cancer at any age.  Low- risk: No breast or ovarian cancer family history. | | NA |

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| ***2013 Review*** |  | |  |  |
| Kramer et al., 200599  Fair  Note: only oophorectomy performed | **Number of breast cancer cases, oophorectomy vs. no oophorectomy**  *BRCA1* positive (n=98): 18% (6/33) vs. 42% (27/65), HR 0.38 (95% CI 0.15 to 0.97), p=0.043  *BRCA1* negative (n=353): 2.9% (1/34) vs. 1.3% (4/319), HR NR  *BRCA1* status unknown (n=222): 0% (0/18) vs. 2.5% (5/204), HR NR  Absolute risk reduction among women who underwent oophorectomy was most prominent when surgery was done at a younger age (<40 years), figure representation. | | Among a cohort of *BRCA1* mutation carriers from multiple case families, oophorectomy was associated with decreased risk of breast cancer; affect was strongest in younger women; oophorectomy status affects breast cancer penetrance. | Intramural Research Program of National Cancer Institute; Funding source not specifically reported |
| Olson et al., 2004100  NA  Note: only oophorectomy performed | **Expected vs. observed number of cancer cases**  Age of surgery <60 years  High-risk (n=55): 5.4 vs. 3, RR 0.56 (95% CI 0.11 to 1.33)  Moderate-risk (n=193): 10.9 vs. 9, RR 0.83 (95% CI 0.38 to 1.44)  Age of surgery <50 years  High-risk (n=41): 3.9 vs. 1, RR 0.26 (95% CI 0.001 to 0.99)  Moderate-risk (n=130): 7.7 vs. 5, RR 0.65 (95% CI 0.21 to 1.32)  Age of surgery <60 years and premenopausal before surgery  High-risk (n=52): 5.1 vs. 3, RR 0.59 (95% CI 0.12 to 1.41)  Moderate-risk (n=186): 10.4 vs. 7, RR 0.67 (95% CI 0.27 to 1.24)  Age of surgery <50 years and premenopausal before surgery  High-risk (n=40): 3.8 vs. 1, RR 0.26 (95% CI 0.00 to 1.00)  Moderate-risk (n=126): 7.4 vs. 3, RR 0.41 (95% CI 0.08 to 0.98) | | The number of observed breast cancers among women in the cohort was lower than expected for nearly all levels of risk, and especially for those <50 years old and premenopausal prior to surgery. | Fraternal Order of the Eagles and the National Cancer Institute |

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| ***2013 Review*** |  |  |  |  |  |
| Struewing et al., 1995184  Poor | Prospective cohort | To determine the incidence of post- oophorectomy carcinomatosis and quantify the effectiveness of risk- reducing surgery. | Eligible: 16 families  Analyzed: 12 families (390 first-degree relatives of breast or ovarian cancer cases) | Women with high genetic risk of ovarian cancer and oophorectomies matched to high- risk women who did not undergo surgery from National Cancer Institute, Creighton University, and U.K. | Not reported |

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| ***2013 Review*** |  |  | |  |
| Struewing et al., 1995184  Poor | Inclusion: Families with ≥3 cases of ovarian cancer or ≥2 cases of ovarian cancer and ≥1 case of breast cancer before age 50.  Exclusion: Families fitting criteria for Lynch Syndrome II. | Results presented by those with an affected first- degree relative and those with an affected second-degree relative. | | **Surgery vs. no surgery**  Ovarian cancer incidence  1st degree relative: 460 vs. 1665 person-years  2nd degree relative: 106 vs. 2123 person-years  Breast cancer incidence  1st degree relative: 484 vs. 1587 person-years  2nd degree relative: 106 vs. 2131 person-years |

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| ***2013 Review*** |  | |  |  |
| Struewing et al., 1995184  Poor | **Surgery vs. no surgery**  *Preliminary Analysis from National Cancer Institute only*  Ovarian cancer incidence  1st degree relative: 2/44 vs. 8/346  2nd degree relative: 0 vs. 1  Note: incidence includes post-oophorectomy ovarian carcinomatosis  Breast cancer incidence  1st degree relative: 3/44 vs. 14/346  2nd degree relative: 0 vs. 3 | | Findings suggest that there is a finite risk of post- oophorectomy carcinomatosis. Preliminary analysis suggests a statistically nonsignificant protective effect of surgery for ovarian cancer. | Not reported |

**Abbreviations:** BRCA=breast cancer susceptibility gene; BRRM=Bilateral risk-reducing mastectomy; CI=confidence interval; DCIS=ductal carcinoma in situ; DNA=deoxyribonucleic acid; EMBRACE=Epidemiological Study of Familial Breast Cancer; HEBON=Hereditary Breast and Ovarian Cancer in the Netherlands; HR=hazard ratio; MRI=magnetic resonance imaging; NA=not applicable; NR=not reported; NS=not significant; PROSE=Prevention and Observation of Surgical End Points; PYO=person years of observation; RRM=risk-reducing mastectomy; RRSO=risk-reducing salpingo-oophorectomy; U.K.=United Kingdom; U.S.=United States