

Susan M. Domchek, MD

*LDI Senior Fellow,
Associate Professor of Medicine
University of Pennsylvania*

Timothy R. Rebbeck, PhD

*Professor of Epidemiology
University of Pennsylvania*

Preventive surgery is associated with reduced cancer risk and mortality in women with BRCA1 and BRCA2 mutations

Editor's Note: Women who have inherited mutations in the *BRCA1* or *BRCA2* (*BRCA1/2*) genes have a substantially elevated risk of developing breast and ovarian cancer. For more than 10 years, researchers have studied whether preventive surgery (to remove breasts, ovaries, and/or fallopian tubes) can reduce the cancer and mortality risk in *BRCA1/2* mutation carriers. This Issue Brief summarizes the results of the latest, largest, multinational study on the effects of preventive surgery in these women. The results are consistent with earlier studies and provide strong evidence for the use of preventive surgery as an effective approach to managing this genetic risk.

Women with a BRCA1 or BRCA2 mutation face difficult decisions about how to reduce their risk of breast or ovarian cancer

BRCA1/2 mutations confer a significant risk of breast and ovarian cancer. Clinical management options for these high-risk women include preventive salpingo-oophorectomy, (removal of the ovaries and fallopian tubes), preventive mastectomy, regular cancer screening, and chemoprevention. Each woman faces a complex and difficult decision about these options.

- *BRCA1* and *BRCA2* mutation carriers have a lifetime risk for breast cancer of 56%-84%; the lifetime risk for ovarian cancer is 36%-63% for *BRCA1* mutation carriers and 10%-27% for *BRCA2* mutation carriers. These risks are substantially higher than in women in the general population, and reach the level that preventive measures must be considered to reduce the substantial risks of morbidity and mortality faced by these women.
- Preventive removal of both breasts (bilateral mastectomy) has been shown to reduce breast cancer risk by about 90%. However, the choice of this treatment option is complicated by concerns about quality of life and body image. Screening with yearly mammography or breast magnetic resonance imaging (MRI) is another option, although this strategy is designed to detect breast cancer early, rather than to prevent it. Chemopreventive options are also available for primary prevention of breast cancer.
- No effective screening strategies exist for ovarian cancer. Because of this and the high mortality rate associated with ovarian cancer, women are now advised to have risk-reducing salpingo-oophorectomy (RRSO) after their childbearing is completed and prior to age 35-40. Studies have shown that RRSO, which is the surgical removal of both ovaries and the fallopian tubes, reduces the risk of both ovarian and breast cancer.

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- RRSO has become the standard of care for women with *BRCA1/2* mutations, although many women do not choose this option. Premenopausal women face the difficult decision of undergoing a treatment that will cause abrupt and premature menopause and its attendant consequences on bone and cardiovascular health.

Meta-analysis of studies between 1999 and 2007 reveals that RRSO is strongly associated with reductions in the risk of breast, ovarian, and fallopian tube cancers

To provide an overall estimate of the risk reduction from RRSO, Rebbeck and colleagues conducted a meta-analysis of 10 studies of RRSO published between 1999 and 2007.

- The pooled results of 5,703 participants across four separate studies indicate that RRSO is associated with a 50% reduction in the risk of breast cancer in *BRCA1* and *BRCA2* mutation carriers.
- The pooled results of 2,840 women across three separate studies indicate that RRSO is associated with an 80% reduction in the risk for ovarian/fallopian tube cancer in *BRCA1* and *BRCA2* mutation carriers.
- The data are lacking to evaluate the effects of birth cohort or timing of surgery.
- Limited data are available about differences for *BRCA1* vs. *BRCA2* mutation carriers in the efficacy of RRSO or risk-reducing mastectomy. However, it is clear that risk reduction is substantial in women with either mutation.

Prospective study conducted at 22 centers in Europe and North America

To clarify some of these remaining issues about the outcomes of preventive surgery, Domchek and colleagues analyzed data from the Prevention and Observation of Surgical Endpoints (PROSE) study, an international consortium of research centers. PROSE participants were ascertained between 1974 and 2008.

- The study included 2,482 women with *BRCA1* or *BRCA2* mutations at 22 clinical and research genetics centers in Europe and North America. Some of the women had a prior diagnosis of breast cancer (i.e., one reason for undergoing genetic testing), while others did not.
- Women were eligible for the study if they had no prior ovarian cancer diagnosis and no diagnosis of cancer in the first six months of follow-up.
- Women who declined preventive mastectomy or RRSO were offered increased surveillance according to established guidelines. In the US, this consisted of annual mammography and MRI for those with breast tissue, and transvaginal ultrasound and CA 125 blood testing for those with ovaries. CA 125 measures a blood protein often elevated in ovarian cancer. However, CA 125 is not sufficiently sensitive or specific to be recommended for routine screening for ovarian cancer.
- Patients were followed prospectively from the time of their preventive surgery, or time they were identified for this study. The median time of follow-up was 3.7 years for those who underwent surgery, and 4.3 years for those who did not.

Preventive surgery highly effective in reducing cancer risk and mortality

Overall, 10% of study participants chose risk-reducing mastectomy and 38% opted for RRSO. After adjusting for patient age and the ascertainment site, the authors found that preventive surgery was associated with large decreases in the incidence of cancer and in deaths from cancer and deaths from any cause.

- None of the 247 women who underwent prophylactic mastectomy developed breast cancer in the three years of follow-up, compared with 7% of women who did not have the surgery.
- Just 1% of women undergoing RRSO developed ovarian cancer, compared to 6% of women who did not have the surgery. Women having RRSO also had a reduced risk of developing breast cancer (11% vs. 19%).
- Undergoing RRSO (compared to those who did not) was associated with lower mortality from any cause (3% vs. 10%), lower mortality from breast cancer (2% vs. 6%) and lower mortality from ovarian cancer (0.4% vs. 3%).
- RRSO was associated with reduced risks for both *BRCA1* and *BRCA2* carriers, and in those with and without a prior diagnosis of breast cancer. See table below for specific risk reductions.

Risk Reduction Among Those Undergoing RRSO		
	<i>BRCA1</i> carriers	<i>BRCA2</i> carriers
<i>Prior history of breast cancer</i>	85% reduction in ovarian cancer risk No reduction in breast cancer risk	0 cases of ovarian cancer detected No reduction in breast cancer risk
<i>No prior history of breast cancer</i>	70% reduction in ovarian cancer risk 37% reduction in breast cancer risk	0 cases of ovarian cases detected 64 % reduction in breast cancer risk

Synopsis of management strategies

The following table summarizes the management strategies available to women with *BRCA1/2* mutations.

Management Option	Strategy	Advantage	Limitation
<i>Ovarian cancer</i>			
<i>Chemoprevention</i>	Oral contraceptive pills	Likely 30%-60% reduction in ovarian cancer risk	Potential increase risk of breast cancer
<i>Screening</i>	Transvaginal ultrasound, serum CA 125	Allows for screening prior to RRSO	Unproven efficacy
<i>Risk-reducing surgery</i>	Bilateral RRSO	About an 80% decrease in risks of ovarian and fallopian tube cancers	Infertility and premature menopause
<i>Breast Cancer</i>			
<i>Chemoprevention</i>	Selective estrogen receptor modulators (tamoxifen, raloxifene)	May reduce risk of breast cancer	Very limited data in <i>BRCA1/2</i> mutation carriers
<i>Screening</i>	Yearly MRI Yearly mammogram Self/clinical breast examination	About 80% sensitive for detection of malignancy	Issues of specificity (false positives) Does not prevent cancer, goal is early detection
<i>Risk-reducing surgery</i>	Bilateral RRSO Mastectomy, with or without breast reconstruction	About a 50% decrease in breast cancer risk About a 90% reduction in breast cancer risk	Premature menopause, iatrogenic infertility Body image and quality-of-life issues

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POLICY IMPLICATIONS

The clinical management of cancer risk in *BRCA1* and *BRCA2* mutation carriers is complex and should consider patient preferences. These preferences can be informed by accurate knowledge of the risks and benefits of the interventions considered.

- It is now clear that effective strategies exist for managing the elevated risks once the *BRCA1/2* carrier status is known. Cancer risk estimates, and approaches to reducing those risks, should be incorporated into counseling for women who are *BRCA1/2* mutation carriers. Data on risks and benefits should be presented to help each woman make the best decision for herself.
- These results can also help women make the initial decision about genetic testing for breast cancer.
- A number of clinically relevant issues remain and warrant further research. The effect of age at RRSO remains unresolved. Some preliminary evidence suggests that the effects of RRSO on breast cancer risk reduction are greater before age 50 than after age 50. Another issue is the use of hormone replacement therapy after RRSO and its effect on the association of RRSO and reduced cancer risk.
- Insurance coverage for risk-reducing surgery in *BRCA1/2* mutation carriers is warranted. Many insurers now provide such coverage, although Medicare has no national coverage decision to that effect. Because the data on effectiveness are unequivocal, all public and private insurers should cover preventive surgery in these women.

This Issue Brief is based on the following articles: S.M. Domchek et al. Association of Risk-Reducing Surgery in BRCA1 or BRCA2 Mutation Carriers With Cancer Risk and Mortality. Journal of the American Medical Association, September 1, 2010, vol. 304, pp. 967-975; T. R. Rebbeck, N.D. Kauff, S.M. Domchek. Meta-analysis of Risk Reduction Estimates Associated with Risk-Reducing Salpingo-oophorectomy in BRCA1 or BRCA 2 Mutation Carriers. Journal of the National Cancer Institute, January 2009, vol. 10, pp. 80-87. This Issue Brief was supported, in part, by the National Cancer Institute grant #5RC2CA148310-02, Comparative Effectiveness in Genomic Medicine.

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Janet Weiner, MPH, Associate Director for Health Policy, Editor
David A. Asch, MD, MBA, Executive Director*

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3641 Locust Walk
Philadelphia, PA 19104-6218
215.898.5611
fax 215.898.0222
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