

Information for Carriers of *BRCA1* and *BRCA2* Gene Mutations



BASSER CENTER FOR BRCA

Revolutionizing *BRCA1* and *BRCA2* Research.

A gift to the University of Pennsylvania from alumni Mindy and Jon Gray established the Basser Center for BRCA, a center focused solely on the prevention and treatment of cancers that are associated with hereditary *BRCA1* and *BRCA2* mutations.

The Basser Center for BRCA has a broad mission: to use cutting edge research in basic and clinical sciences to advance the care of individuals living with *BRCA1* and *BRCA2* mutations. Alongside our research work, the Basser Center serves as a center of excellence for *BRCA1/2* positive individuals and their families, providing a place for carriers to go for clinical care, referrals to centers of excellence in their geographic area, as well as support and advice.

To read about the Basser Center's team and gain additional information on *BRCA1/2* research, cancer risks and management, and support, as well as BRCA news, Basser events, and patient stories visit us at Basser.org or call **215.349.9093** for an appointment.

This booklet provides information for carriers of *BRCA1* and *BRCA2* mutations.

Throughout this booklet, words that might be new to you are shown in bold and blue. Definitions for these and other terms related to cancer and genetics begin on page 32.

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“We hope that the Basser Center for *BRCA* will eliminate *BRCA*-related cancers and, in so doing, provide a road map for curing other genetic diseases.”

Mindy & Jon Gray,
Basser Center Founders

Cancer Risks Associated with *BRCA1* and *BRCA2* mutations

When an individual undergoes genetic testing and receives a positive ***BRCA1*** or ***BRCA2*** result, this means that they have an inherited **mutation** that puts them at increased risk for certain cancers. The **cancer risks** associated with *BRCA1* and *BRCA2* are presented as ranges (see [Table 1](#)), since cancer risk may vary in different families or population groups. Some studies and laboratories report slightly higher or lower risks than summarized in [Table 1](#). This is because as more individuals undergo genetic testing and more studies that assess risk are published, our understanding of cancer risk in individuals with *BRCA1* and *BRCA2* mutations continues to evolve. For these reasons, risk estimates may vary from one source to the next and may vary as research advances. At present, we cannot predict where in the risk range any individual will fall. There are other genetic and lifestyle factors that can influence or modify cancer risk associated with mutations in *BRCA1* and *BRCA2*. Discovering these factors and refining our understanding of the risks associated with them may help us provide a more accurate individual **risk assessment**.

People with mutations in *BRCA1* or *BRCA2* may develop none, one, or several cancers. Unfortunately, being diagnosed with one type of cancer does not mean other cancer risks no longer apply.

For example, women with *BRCA* mutations who have developed one breast cancer, are at increased risk of developing a second breast cancer as well as ovarian and other cancers. The risk to develop a second breast cancer depends on a person's age at diagnosis of the first breast cancer, type of breast cancer, family history and whether a person has a *BRCA1* or *BRCA2* mutation. Therefore, depending on these risk factors, the risk of developing a second breast cancer can range from less than 20% to 50% over one's lifetime. This should be discussed with your doctor.

Table 1: Cancer Risk Ranges for *BRCA1* and *BRCA2* carriers

Lifetime <i>BRCA1</i> and <i>BRCA2</i> Cancer Risks for Women			
TYPE OF CANCER	Woman with <i>BRCA1</i> Mutation	Woman with <i>BRCA2</i> mutation	Average woman in US without mutation
Breast	60-80%	50-70%	13%
Ovarian	30-45%	10-20%	1-2%
Pancreatic	2-3%	3-5%	1%
Melanoma	-	3-5%	1-2%
Uterine	1	-	2-3%

¹ Limited data suggest a higher chance to develop serious uterine cancer in *BRCA1* mutation carriers. The overall chances are still low but may be higher than average risk women. More research is needed before this association is fully understood.

Lifetime <i>BRCA1</i> and <i>BRCA2</i> Cancer Risks for Men			
TYPE OF CANCER	Man with <i>BRCA1</i> Mutation	Man with <i>BRCA2</i> mutation	Average man in US without mutation
Breast	1-5%	5-10%	0.1%
Prostate	2	15-25%	16%
Pancreatic	2-3%	3-5%	1%
Melanoma	-	3-5%	1-2%

² Although there is no convincing evidence of overall increased risk of prostate cancer in men with *BRCA1* mutations, they may develop prostate cancer at a younger age than men in the general population. *BRCA2* mutations are associated with an increased risk of prostate cancer, which also can be of earlier onset.

In addition to the cancers specifically listed in [Table 1](#) (page 3), men and women with BRCA mutations appear to have slightly increased risk of developing cancers in general. Therefore, regular medical follow-up with prompt attention to symptoms is strongly encouraged. For example, symptoms of unexplained weight loss and persistent pain, swollen lymph nodes, and/or sores that do not heal should be evaluated by a physician.

General Population Cancer Screening

General cancer screening recommendations should also be followed by carriers. In addition to the more intensive cancer surveillance recommended for BRCA-related cancers, Multiple organizations and panels make recommendations for cancer screening for the general population, most notably The United States Preventative Task Force (USPSTF). The USPSTF systematically reviews the evidence of effectiveness of screening methods and develops recommendations for clinical preventive services. Recommendations change regularly and are generally tailored given your personal or family history, so ask your doctor about the following general cancer screening tests.

General cancer screening in women includes cervical cancer screening. Cervical cancer screening guidelines depend on several factors, including age and if there are any signs of high risk human papillomavirus (HPV). In addition, upon reaching **menopause**, all women should be informed about the risk and symptoms of uterine cancer and encouraged to report any unexpected bleeding or spotting to their physicians. Please discuss this with your gynecologist.

General cancer screening for men and women includes **colonoscopy**. Colonoscopy screening generally starts around 45-50 years of age but may begin earlier depending on your personal and family history. Please discuss this with your primary care physician or gastroenterologist.

For people aged 20 or older having periodic health exams including a cancer-

related check-up and health counseling is recommended. Depending on a person's age and gender, exams for cancers of the thyroid, oral cavity, skin, lymph nodes, and testes as well as for some non-malignant (non-cancerous) diseases are recommended.

In addition, if you have a significant history of smoking you should also ask your doctor about lung cancer screening.

Lifestyle and Environmental Factors

Smoking remains a significant risk factor for developing cancer. Smoking and exposure to second-hand smoke should be avoided as a part of a healthy lifestyle.

In addition to avoiding smoking, a healthy lifestyle includes exercising, maintaining a healthy weight, having a healthy diet, and limiting alcohol intake. Choosing foods, beverages, and exercise in amounts that help you achieve and maintain a healthy weight is important. The American Cancer Society recommends that adults get at least 150 minutes of moderate intensity exercise or 75 minutes of vigorous intensity activity each week, preferably spread out throughout the week. When it comes to diet, ensuring a good variety of fruits, vegetables, and whole grains and limiting processed foods and red meats is recommended. Alcohol is associated with increased risk for a wide range of cancers and should therefore be limited.

Lastly, exposure to radiation can increase cancer risk. Therefore, unnecessary radiation risk should be avoided. For example, ultraviolet radiation via sun exposure can be limited through proper clothing and sunscreen, and tanning beds should be avoided entirely. Radiation is often employed as a part of medical tests, including mammography, and also as a form of therapy for cancers. Radiation under these circumstances is often appropriate once the benefits and risks are considered together. For example, in women who carry BRCA mutations between the ages of 25 to 29, mammography is often postponed because the radiation risk outweighs the benefit given that the risk of cancer is low, and breasts are dense and hard to image on mammogram during this period of life.

Cancer Risk Management

A personalized cancer risk management plan can be developed for individuals known to be at increased cancer risk due to a mutation in *BRCA1* or *BRCA2*. A cancer risk management plan is typically tailored to a person's unique circumstances and preferences. You and your doctors will ultimately decide what plan makes the most sense for you.

Cancer risk management generally includes the following categories:

- Intensive screening to increase the chances of early detection, should cancer develop (pp. 6-11).
- Consideration of risk-reducing, or **prophylactic**, surgical removal of ovaries and possibly breast tissue (pp. 12-18).
- Chemoprevention, which is taking a medicine shown to lower the risk of developing cancer (pp. 19-20).

Cancer Screening for BRCA Carriers

Generally, cancer that is detected at earlier stages is more easily treated, and outcomes are often better. Screening recommendations for women and men with *BRCA1* and *BRCA2* mutations are detailed in [Table 2](#). Note that screening recommendations for *BRCA1/2* mutation carriers may change as research evolves and we develop better methods for detecting cancer early.

Table 2:

Screening for Women with Mutations in <i>BRCA1</i> or <i>BRCA2</i>			
TYPE OF CANCER	Screening Procedure	Starting Age	Frequency
	Breast ¹	Breast MRI	25 years
Mammogram		30 years	Every 12 months
Physician Breast Exams		25 years	Every 6 months
Ovarian	Breast Awareness ¹	18 years	Once every month
	CA-125 Blood Test Ovarian Ultrasound Note: There is not a strong recommendation for these screenings because they have not been proven effective at diagnosing ovarian cancer.	Consider at age 30-35 Upon completion of childbearing, removal of ovaries and fallopian tubes ideally between ages 35-40 is recommended.	Consider every 6-12 months

¹ Women should be familiar with their breasts and promptly report changes to their health care provider. Periodic, consistent breast self-exam (BSE) may facilitate breast awareness. Premenopausal women may find BSE most informative when performed at the end of menses.

Table 2 Continued:

Screening for Men with Mutations in <i>BRCA1</i> or <i>BRCA2</i>			
TYPE OF CANCER	Screening Procedure	Starting Age	Frequency
Breast	Physician Breast Exams	35 years	Every 12 months
Prostate	Prostate Exam and PSA Blood Test	40 years ²	Once every year

² Recommend prostate cancer screening for *BRCA2* carriers start between ages 40-45. Screening could be considered for *BRCA1* mutation carriers.

Breast Cancer Screening

Screening for breast cancer will not decrease the chance that cancer will develop. However, breast cancer screening aims to detect breast cancer early, when it is most treatable. Both men and women with *BRCA1/2* mutations should be screened for breast cancer. However, since lifetime breast cancer risk and anatomy differs between women and men, breast cancer screening for women and men are discussed separately below.

Breast Cancer Screening for Women

Over the years, researchers have developed specialized breast cancer screening strategies for *BRCA1/2* carriers. This means starting screening at an earlier age and using several different screening methods more frequently. Intensive breast cancer screening starts at age 25 for *BRCA*-positive women; although, it may be recommended an individual start screening at an earlier age based on the youngest age of breast cancer in the family. For women, screening involves a clinical breast exam every 6-12 months and an annual breast MRI starting at age 25. At age 30, annual mammography is added and is alternated with breast MRI every six months.

A **mammogram** is a low-dose X-ray that creates images of the inside of the breasts. Mammography can detect some suspicious breast changes that are too small or too deep to be felt on breast examination. A newer technology called 3-dimensional (3D) mammography, or breast **tomosynthesis**, can be done in combination with traditional mammography. How much this modality adds in individuals already getting breast MRI is unknown.

A breast MRI (Magnetic Resonance Imaging) uses a magnetic field to create clear detailed pictures of the inside of your breasts. The breast is mildly compressed during the procedure while you are lying on your stomach. An intravenous injection of a contrast agent that increases the quality of the imaging is required. A substance called gadolinium is often used for this purpose and although it is very sensitive for the detection of invasive breast cancer, it is also associated with a high rate of false positive results that can lead to unnecessary procedures and increased anxiety. In addition, the Food and Drug Administration requires that patients and providers be warned regarding gadolinium-based contrast agents because the metal remains in the body, including the brain, for months or years, after receiving these drugs. Gadolinium retention has not been directly linked to adverse health effects in patients who have normal kidney function and the FDA concluded that the benefit of all approved gadolinium-based contrast agents continues to outweigh any potential risks. Gadolinium levels in the body are lowest after administration with certain agents, specifically Dotarem, Gadavist, and ProHance.

Women with *BRCA1/2* mutations should have “breast awareness,” meaning they should be familiar with their breasts and promptly report changes to their healthcare provider. Periodic, consistent breast self-exam (BSE) may facilitate breast awareness. Premenopausal women may find BSE most informative when performed at the end of their menses. Given that many women will not undergo genetic testing until age 25, breast self-exam should be considered by all women from families with *BRCA1/2* mutations.

Breast Cancer Screening for Men

For men with *BRCA1/2* mutations, breast cancer screening generally starts at age 35 with annual clinical breast exams. In a clinical breast exam, a medical provider examines the chest wall by touch to detect any lumps or differences. Men are also recommended to receive breast self-exam training and education starting at age 35. Breast self-exam can help men become familiar with their breast tissue in order to promptly report changes to their healthcare provider.

Ovarian Cancer Screening

Ovarian cancer screening involves a transvaginal ultrasound and a blood test called CA-125, which can be considered every 6-12 months starting between ages 30-35.

Ultrasound is an imaging technique that uses sound waves to create a picture.

By inserting an ultrasound probe into a woman's vagina, doctors can look at the ovaries. However, transvaginal ultrasound often fails to detect ovarian cancer at an early stage and can detect changes in the ovaries that are not actually cancer.

CA-125 is a protein in the blood shed from damaged ovary cells and is often elevated in women with ovarian cancer. However, CA-125 can also be elevated for other reasons unrelated to cancer and many early stage ovarian cancers do not cause an elevated CA-125.

These available methods for ovarian cancer screening often fail to detect ovarian cancer at an early stage. Therefore, it is at the discretion of the doctor and woman whether these methods are used to screen for ovarian cancer before a woman decides to have surgery to remove her ovaries and fallopian tubes.

Prostate Cancer Screening

It is recommended that men with *BRCA2* mutations initiate prostate cancer screening between ages 40 and 45. Men with *BRCA1* mutations may also consider starting prostate cancer screening by age 45. Prostate cancer screening includes Prostate Specific Antigen (PSA) blood test and digital rectal exam (DRE). In men with *BRCA* mutations, in particular *BRCA2* mutations, prostate cancers tend to occur at a younger age and may be more aggressive than prostate cancer in men without mutations. Prostate cancer screening remains controversial for men in the general population, although screening may be more beneficial for men with *BRCA* mutations due to the increased risk of prostate cancer and the increased proportion of those cancers that are aggressive in nature.

Pancreatic Cancer Screening

There are no consensus guidelines for pancreatic cancer screening, even in *BRCA* mutation carriers. Individuals with a strong family history of pancreatic cancer and a *BRCA1* or *BRCA2* mutation may consider screening for pancreatic cancer. The goal of pancreatic screening is to identify pancreatic cancer at earlier and more treatable stages. Although the goal of pancreatic cancer screening is early detection, there is currently very limited data to suggest that pancreatic cancer screening consistently detects pancreatic cancers at an early, treatable stage.

We recommend that if pancreatic cancer screening is pursued, it be done as a part of a clinical research study at a center with significant experience and expertise in pancreatic cancer screening.

Screening for pancreatic cancer is typically performed by upper endoscopic ultrasound or abdominal MRI. Upper endoscopic ultrasound involves placing an instrument called an endoscope down your throat while you are under sedation. The endoscope uses sound waves to produce images of your pancreas. Abdominal MRI uses a magnetic field to create detailed pictures of your pancreas. If any suspicious findings are seen on either of these tests, additional tests may be required. Screening can lead to invasive diagnostic procedures like biopsies which themselves increase the chance for pancreatitis (painful inflammation of the pancreas), or even a surgery that reveals only benign findings.

For these reasons, prior to undergoing pancreatic cancer screening, an in-depth discussion is advised to consider the potential benefits, risks and limitations of the procedures.

At the University of Pennsylvania, our screening protocols employ endoscopic ultrasound. In addition, there may be clinical trials of new methods of pancreatic cancer screening that you can learn more about as a part of your consultation.

Note that clinical trials of pancreatic cancer screening do not generally cover the cost of endoscopic ultrasound or imaging, which are billed to you or your insurance as a part of your clinical care. While pancreatic cancer screening is considered primarily for individuals with a *BRCA* mutation and a family history of pancreatic cancer, there may be some options for individuals with *BRCA* mutations without a family history of pancreatic cancer. For current studies and more detailed information, please visit the Pancreatic Cancer section of the following Penn Medicine website: www.pennmedicine.org/cancer/navigating-cancer-care/programs-and-centers/gastrointestinal-cancer-genetics-and-risk-evaluation-program/clinical-trials-and-research.

Research Screening Options

There are multiple research studies currently being conducted through the Bassett Center for *BRCA* aimed at finding better methods for detecting *BRCA*-related cancers early. It is hoped these studies will find even better ways to manage high-risk individuals. Current cancer screening opportunities for which you are eligible will be discussed with you as part of your genetic counseling sessions.

Surgical Options for Women with *BRCA1/2* Mutations

Risk-reducing (prophylactic) mastectomy is the removal of healthy breast tissue. It is the most aggressive and effective strategy available to reduce breast cancer risk. Some women with *BRCA1/2* mutations choose this option. We and others have completed studies showing this procedure lowers breast cancer risk by at least 90 percent in women with *BRCA1* and *BRCA2* mutations. The estimated risk of developing a breast cancer after risk-reducing mastectomy is 1-2%.

However, breast cancer screening is a reasonable alternative to risk-reducing mastectomy. Screening for breast cancer is usually effective in finding breast cancer at an early stage, particularly when MRI is used as one of the screening components. Some types of breast cancer, even if found at an early stage, may still require chemotherapy. This may impact the decisions of some women regarding risk-reducing mastectomy. Increased breast cancer screening can also be used in combination with medications shown to reduce breast cancer risk.

Reviewing a person's breast cancer risk by age or decade with a genetic counselor can be helpful in determining when to consider the option of prophylactic surgery (see [Graphs 1 and 2](#)). Surgery is a very personal decision and we recommend women fully investigate all their options.

For women considering a prophylactic mastectomy, it is often helpful to consult with a plastic surgeon to learn about options for breast reconstruction.

Options for breast reconstruction include implant and tissue-based reconstruction. It is important to discuss your options with your surgeon, including the pros and cons of different types of surgery, recovery time, and potential risks of surgery.

Implant-based reconstruction is a one- or two-step procedure that takes place over two to six months. In some situations, implants can be placed at the time of mastectomy in a one-step procedure. In two-step reconstruction, a **tissue expander**, which is a balloon device, is placed underneath the skin and muscles of the chest wall. Then, over a period of several months, the expanders are inflated in the office to stretch the muscles and tissue to accommodate the implants. In the second step, the tissue expander is replaced with an implant. Recovery time from these two surgeries is generally two to four weeks.

In autologous or free "flap" surgery, the breast is reconstructed from an individual's own tissue, using skin, fat, and occasionally muscle from another part of the body, often the lower abdomen. This is performed in a single surgery. The hospital stay and recovery time are longer than for implant reconstruction surgery, with a recovery time of approximately six to eight weeks.

Implant and free-flap options also have different potential complications. For example, implants are not permanent and require maintenance. All implants have a concern for "rupture" and it is recommended that implants be replaced every 10-15 years, on average. In addition, there is a risk of infection, hardened scar tissue (called capsular contracture), and a rare implant-associated lymphoma (mostly with textured implants). For free flap surgery, major potential risks are complications of the abdomen including scar and hernia. There is also a risk that the tissue fails.

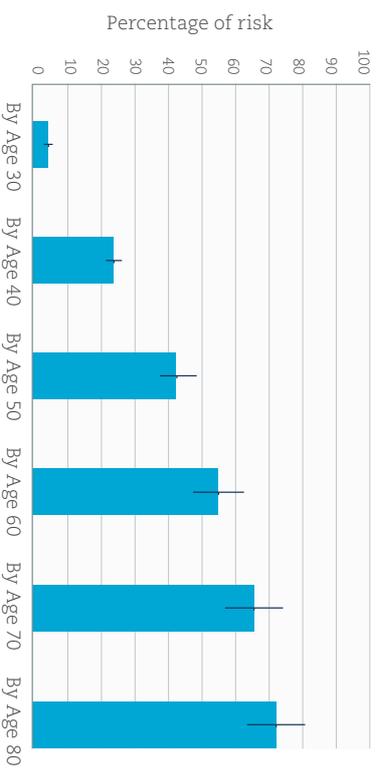
Given these complexities, we encourage all women considering risk-reducing mastectomy to gather detailed information from their plastic surgeons and take the time they need to make a thoughtful decision.

In addition to deciding whether to have risk-reducing mastectomy, individuals must consider the timing of such procedures in terms of age and breast cancer risk. Although the lifetime risk for breast and ovarian cancer are high in *BRCA1* and *BRCA2* mutation carriers, they vary across ages.

The below graphs of breast and ovarian cancer risk by age are from a large study that combined patients from multiple institutions (Kuchenbaecker et al. 2017 in *JAMA*). The risks presented are up to age 80. Like the cancer risks cited earlier in the booklet, the risks below may differ from other sources.

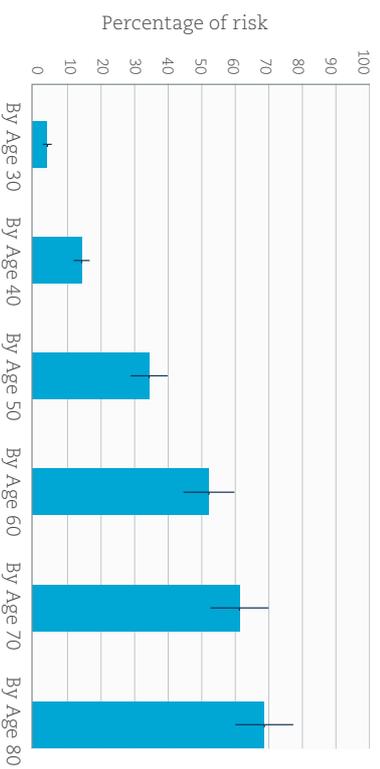
Nonetheless, the graphs of cancer risk by decade are helpful for understanding the trends in cancer risk over a lifetime and may help inform decisions about the timing of surgeries.

Graph 1: BRCA1 Breast Cancer Risk by Decade



The blue bars indicate the average risk (percent change) that a woman with a *BRCA1* mutation will develop breast cancer by each age noted across the bottom. The vertical line on each bar is called an “error bar” and represents the range in which the true risk likely falls.

Graph 2: BRCA2 Breast Cancer Risk by Decade



The blue bars indicate the average risk (percent change) a woman with a *BRCA2* mutation will develop breast cancer by each age noted across the bottom. The vertical line on each bar is called an “error bar” and represents the range in which the true risk likely falls.

Risk-Reducing Bilateral Salpingo-Oophorectomy

Risk-reducing **bilateral salpingo-oophorectomy (BSO)** is the removal of healthy ovarian and fallopian tube tissue. We strongly recommend risk-reducing BSO surgery after childbearing has been completed. The major decision is the timing of the procedure.

Current guidelines recommend salpingo-oophorectomy by age 35–40, although the recommendations around the timing of this procedure do vary because in general, ovarian cancer onset is earlier in *BRCA1* than *BRCA2*, as discussed below. Recent studies suggest this approach will reduce ovarian cancer risk by as much as 70–90 percent.

Fallopian tube cancers are very rare but occur more frequently in women with *BRCA1* and *BRCA2* mutations. It is routine for fallopian tubes to be removed at the time of oophorectomy. There is some evidence that ovarian cancers start in the fallopian tubes. Given this, some women ask about having a **salpingectomy**, a surgery where the fallopian tubes, but not the ovaries, are removed. Salpingectomy is not a standard of care for risk reduction, although clinical trials of this surgery as an interim step with delayed oophorectomy are ongoing. It is not known if salpingectomy with delayed oophorectomy is equally effective at reducing ovarian cancer risk as the standard approach of removing the ovaries and fallopian tubes at the same time.

Despite pursuing risk-reducing bilateral salpingo-oophorectomy, a small number of women will still develop cancer of the lining of the abdomen, known as primary peritoneal cancer. This is a disease that behaves like advanced ovarian cancer.

In addition to significantly reducing ovarian cancer risk, it appears removing the ovaries from premenopausal women also reduces breast cancer risk, though to what degree risk is reduced and whether *BRCA1* and *BRCA2* mutation carriers both gain this benefit is unknown.

Therefore, the overall benefit of risk-reducing salpingo-oophorectomy is very significant. This is important since screening for ovarian cancer is very limited and usually does not detect ovarian cancer in the early stages.

For premenopausal women, risk-reducing salpingo-oophorectomy reduces estrogen levels which can impact bone and heart health and bring about menopausal symptoms such as hot flashes, vaginal dryness, mood swings, and sleep disturbances.

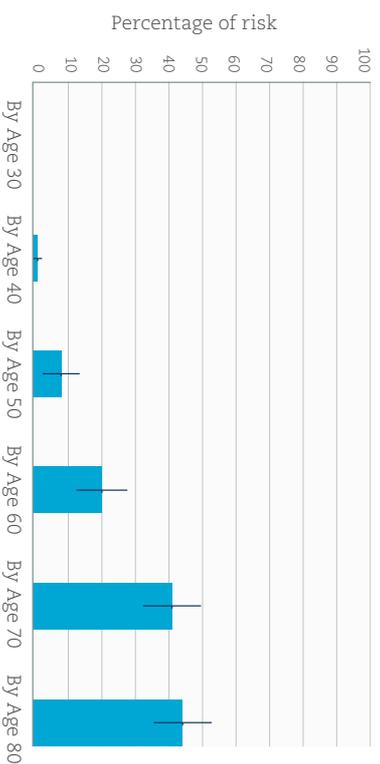
However, once a woman has gone through natural menopause (no periods for over a year), her ovaries are not expected to produce estrogen. Therefore, removing healthy ovaries in a woman who has naturally gone through menopause is not expected to have an impact on her symptoms of menopause.

The potential side effects of risk-reducing salpingo-oophorectomy are detailed in later sections on hormone replacement therapy in premenopausal and postmenopausal women (pp.18-19).

In deciding on the timing of risk-reducing salpingo-oophorectomy, it can be helpful to consider how the risk of ovarian cancer varies across ages and depending on whether a woman carries a *BRCA1* and *BRCA2* mutation. The risk of ovarian cancer and the average age at the time a woman is diagnosed with ovarian cancer does differ between *BRCA1* and *BRCA2* mutation carriers. Ovarian cancer risk becomes more significant for women in their 40s, 50s, and beyond. Even in women with *BRCA1/2* mutations, it is uncommon to be diagnosed with ovarian cancer before the age of 40. It is important to discuss these issues with your providers and how they relate to the timing of risk-reducing BSO. The below graphs ([Graph 3](#) and [Graph 4](#)) provide information on ovarian cancer risk by age for carriers of *BRCA1* and *BRCA2* mutations.

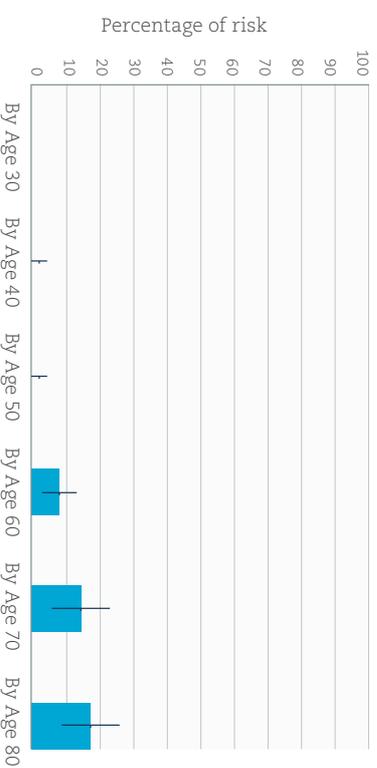
As noted earlier, the below graphs of ovarian cancer risk by age are from a large study that combined patients from multiple institutions (Kuchenbaecker et al. 2017 in JAMA). The risks presented are up to age 80 and like the cancer risks cited earlier, the risks below may differ from other sources.

Graph 3: BRCA1 Ovarian Cancer Risk by Age



The blue bars indicate the average risk (percent chance) a woman with a *BRCA1* mutation will develop ovarian cancer by each age noted across the bottom. The vertical line on each bar is called an "error bar" and represents the range in which the true risk likely falls.

Graph 4: BRCA2 Ovarian Cancer Risk by Age



The blue bars indicate the average risk (percent chance) a woman with a *BRCA2* mutation will develop ovarian cancer by each age noted across the bottom. The vertical line on each bar is called an "error bar" and represents the range in which the true risk likely falls.

Consideration of hysterectomy at time of prophylactic BSO

Some women choose to have their uterus removed at the same time their ovaries and fallopian tubes are removed. There are both advantages and disadvantages to this approach.

In terms of advantages, removal of the uterus decreases a woman's chance of developing uterine cancer. Limited data suggest a higher chance to develop serous uterine cancer in *BRCA1* mutation carriers. The overall chances remain low but may be higher than average risk women and more research is needed before this association is fully understood. Regardless, the medications like tamoxifen that are considered to reduce breast cancer risk in women who carry *BRCA* mutations are associated with a slightly increased risk for uterine cancer. This may factor into surgical decisions for women who plan to manage their risk with chemoprevention medications which are discussed in detail below.

Furthermore, since the fallopian tube connects the ovaries to the uterus, there is a possible chance of fallopian tube cancer developing where the tubes have been removed from the uterus. Although possible, it is unlikely to happen given that most fallopian tube cancers do not start in the side of the tube which attaches to the uterus.

The last possible advantage of **hysterectomy** in premenopausal women who carry BRCA mutations is that it helps to simplify hormone replacement after risk-reducing oophorectomy, as detailed below. This is because the type of hormone replacement therapy (HRT) prescribed for premenopausal women who have had their ovaries removed depends on whether a woman still has her uterus, as detailed below.

In addition, for women with considerations such as abnormal bleeding, symptomatic fibroids, or abnormal PAP smears, there may be additional benefits to hysterectomy. It is therefore important to review your personal history with your doctor.

However, there are disadvantages of hysterectomy for women to consider.

The recovery time for surgery involving the removal of both the uterus and the ovaries and fallopian tubes is longer than for surgery to remove only the ovaries and tubes alone. Removal of the uterus may also result in more complications and a longer recovery time than removal of the ovaries and tubes alone. The only “required” surgery for BRCA1/2 mutation carriers is the removal of the ovaries and fallopian tubes. We encourage you to discuss these issues in more detail with your providers.

Hormone Replacement Therapy in Premenopausal Women after Risk-Reducing Salpingo-Oophorectomy

While risk-reducing salpingo-oophorectomy significantly reduces ovarian cancer risk, there are additional health issues that need to be addressed. Reducing estrogen levels at a young age increases a woman’s risk of osteoporosis and heart disease. Post-surgery, some women may also experience menopausal symptoms such as hot flashes, vaginal dryness, mood swings, and sleep disturbances. To help address menopausal symptoms, women with BRCA1/2 mutations and no history of breast cancer typically have the option of hormone replacement therapy for several years after having their ovaries removed.

We recognize many women at high risk of breast cancer will feel anxious about taking hormonal medications. Discussions with the clinicians at Penn Medicine’s Bassett Center, along with your personal physicians are usually helpful in making these difficult decisions.

Hormone Replacement Therapy in Postmenopausal Women with BRCA1/2 Mutations

In women without BRCA1/2 mutations there is not routine use of HRT in the postmenopausal period. Postmenopausal women over the age of 50 with a BRCA1/2 mutation and intact breast tissue should discuss the pros and cons with their doctors. Lastly, women with a previous breast cancer diagnosis are discouraged from using HRT.

Therefore, pre- and postmenopausal women should discuss alternative non-hormonal interventions with their doctors. Options include acupuncture, and non-hormonal medications that can be discussed with their providers.

Chemoprevention: Medications that Reduce Breast Cancer Risk

Chemoprevention, taking a medicine in an attempt to lower cancer risk, can provide additional choices for high-risk women. There is very limited data on these medications specifically in BRCA1 and BRCA2 mutation carriers. Three common examples are tamoxifen, raloxifene (Evista), and aromatase inhibitors (AIs).

Tamoxifen

Tamoxifen has been used for more than 40 years to treat women with breast cancer. Usage is also associated with reduced numbers of breast cancer occurrences in the opposite breast. A national study of over 13,000 healthy women at increased risk determined tamoxifen can lower the risk of developing breast cancer by 49 percent. This finding was very significant, and tamoxifen is the first FDA approved medication shown to lower breast cancer risk in healthy women. Tamoxifen was also associated with some protection from bone loss in postmenopausal women. Drawbacks to taking tamoxifen include a small increased risk for uterine cancer and a small increased risk for pulmonary embolism (a blood clot in the lung), deep vein thrombosis (a blood clot in a major vein), and cataracts.

Raloxifene. Medications continued from page 19

Raloxifene

In postmenopausal women, raloxifene (also called Evista) has been shown to decrease the risk of breast cancer and to benefit bone density and cholesterol levels. Therefore, this option can be an excellent choice for women with bone loss. Raloxifene is not associated with an increased risk for uterine cancer. Like tamoxifen, raloxifene has risks that must be weighed against the benefits in consultation with your physician.

Aromatase Inhibitors

Aromatase inhibitors (AIs) are another class of medications being investigated for their ability to reduce breast cancer risk in post-menopausal women.

In the future, there will likely be additional medications available for chemoprevention in those with mutations in *BRCA1* and *BRCA2*. It is important to know all current options, including the risks and benefits of each option before making a decision.

When a new medicine for chemoprevention is tested to determine how much it can reduce cancer risk, it is typically offered as part of a clinical trial. People found to have a *BRCA1/2* mutation should be informed about all the chemoprevention trials available, including the risks and benefits, before deciding about this option. Participation in these trials is strongly encouraged.

Birth Control Pills in Women with *BRCA1/2* Mutations

There have been several studies published examining the safety of birth control pills in women with a *BRCA1/2* mutation. Birth control pills, also known as oral contraceptives, work in part by preventing a woman from ovulating. Preventing a woman from ovulating is usually associated with a decreased risk for ovarian cancer. Some studies suggest the risk reduction for ovarian cancer can be as much as 50%.

There are some conflicting findings about the association between birth control pills and breast cancer risk. Some studies have shown there may be a small

increased risk of breast cancer associated with these medications. More research is underway to help answer these important questions.

Ultimately, balancing the potential risk of breast cancer (for which we do have effective screening) against the significantly reduced risk for ovarian cancer and the potential need for effective birth control is complex.

In addition, it is important to consider the other benefits and risks of birth control pills. Birth control pills can effectively prevent pregnancy when taken as instructed. They may also help regulate the menstrual cycle, reduce menstrual cramps, and lighten periods. Birth control pills can cause side effects like altered levels of sexual desire, spotting or bleeding between periods, and sore breasts, but these generally go away after two to three months. Rare, serious side effects of birth control include blood clots and heart attack. Given the wide range of benefits and risks, discussion on an individual basis is strongly encouraged.

Family Planning and Reproductive Options

There are some considerations for *BRCA* carriers planning to start or expand their family. Decisions regarding family planning are very personal; there is no wrong or right approach.

A man or woman who has a mutation in *BRCA1* or *BRCA2* has a 50% chance of passing down the mutation to each of their children (son or daughter). A parent with a *BRCA* mutation may pass the mutation along to one, some or none of their children. Many families with a known *BRCA* mutation accept the 50% risk of passing on the *BRCA* mutation to their children and do not pursue any interventions.

Couples also have the option to consider reproductive technologies to greatly reduce the chance of passing a known mutation to their children. PGT-M (**preimplantation genetic testing for monogenic/single gene** defects such as *BRCA1* and *BRCA2*) can be performed prior to a pregnancy used in combination with **in vitro fertilization (IVF)** to test fertilized eggs for a specific gene mutation.

There are several steps involved in PGT-M and IVF. One of the first steps in being able to consider PGT-M is to identify the genetic mutation in the parent. One of the next steps involves creating a specific PGT-M test probe at a specialty laboratory which is unique to each family. This process may involve obtaining DNA samples from other members in

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the family. Once the eggs are fertilized, they will be tested to determine which of the fertilized eggs do not have the gene mutation. This is done using the specific PGT-M test created for your family and once tested, the fertilized eggs that do not have the gene mutation can then be implanted. This process is not always straightforward and it can be useful to discuss this further with genetic counselors with specialized expertise in reproductive genetic testing.

PGT-M does not guarantee transferred fertilized eggs will lead to a full-term, healthy pregnancy. PGT-M and IVF can be costly and coverage can vary greatly depending on insurance plan. Those who are interested in PGT-M may discuss it in greater detail with their genetics providers and may be referred to a fertility clinic specializing in this service for more information.

Fanconi Anemia

Fanconi Anemia is a rare condition, occurring in 1 in 360,000 births, characterized by skeletal differences including underdeveloped or absent thumbs, short stature, developmental delay, bone marrow failure (inability to make red and white blood cells as well as platelets), and risk for blood and non-blood related cancers. Symptoms may be present at birth, or in early childhood, and signs of bone marrow failure are often present by ages 7 or 8. Inheriting two *BRCA2* mutations (a *BRCA2* gene mutation from mother and a *BRCA2* gene mutation from father) is one cause of Fanconi Anemia. This type of inheritance is called autosomal recessive inheritance.

A person with a *BRCA2* mutation has about a 1 in 1,200 chance of having a child with Fanconi Anemia. This is based on the general population chance of having a *BRCA2* mutation (1 in 300) and the chance that if both parents are carriers, they will have an affected child (1 in 4). If there is reason to believe your chances are significantly higher than this, then it will be individually discussed. Those who are concerned about risks for conditions affecting future children may benefit from consultation with a prenatal genetics program around the time of pregnancy planning.

Implications for Family Members

Hereditary breast and ovarian cancer syndrome can be passed down through the family by both men and women. There is a 50% (1 in 2) chance that a person with a *BRCA* mutation will pass the mutation to each of their children. This is called autosomal dominant inheritance. Testing relatives will determine whether or not they inherited the *BRCA* mutation. Relatives who do not have the mutation and who do not have a significant family history of cancer on the other side of their family are NOT at increased risk for *BRCA*-associated cancers and would only need to follow cancer surveillance recommendations for the general population, and cannot pass the family mutation on to their children.

We strongly encourage individuals to share information about their positive genetic testing result with other female and male relatives (including children, siblings, parents, aunts/uncles, and cousins) given its significance for their health. Often genetic counselors can provide resources such as a letter to help share your results with relatives. Family members will need a copy of your genetic test report (listing your specific mutation) in order to have their testing properly arranged.

Learning about the presence of an inherited mutation that increases risk for cancer can also possibly impact family relationships. While we strongly encourage people to share genetic testing information with relatives, ultimately each family member will need to choose whether or not to be tested.

Children (Individuals under age 18)

Sharing information about cancer with children can be challenging to navigate.

For individuals looking for guidance, there are specific resources that have been developed to help parents make decisions about how and when to share cancer risk information with their children. For example, the patient support and advocacy group, FORCE, has developed a booklet on “Talking About BRCA In Your Family Tree” that can be accessed at www.facingourrisk.org/understanding-brca-and-hboc/publications/documents/booklet-talking-about-brca-family.pdf

It is important to keep in that mind that children are not currently candidates for BRCA testing since there is no known cancer risk or medical intervention that takes place during childhood, and testing may be psychologically difficult for children. In addition, all individuals should be given the chance to make their own informed decision about testing, and to decide when the timing is right to obtain that information.

“The Basser Center for BRCA truly advanced our work and is bringing us closer to the day when we can stop BRCA-related cancers before they ever appear.”

Susan Domchek, MD
Basser Professor in Oncology
Executive Director, Bassar Center for BRCA

Future of BRCA1/2 Research

The Basser Center infuses powerful resources to support cancer care and research at every stage from risk assessment and genetic counseling to prevention, early detection, treatment, and survivorship. We are very grateful to the families who have participated in research studies aimed at understanding *BRCA1/2*, as they have made it possible to advance our knowledge of *BRCA1/2*-related cancer risk, risk reduction, and treatment. Their contributions have been critical in the identification of mutations in the *BRCA1/2* genes and in the development of better methods to manage *BRCA1/2* cancer risk, and to treat *BRCA1/2* cancers. The ultimate goal of the Basser Center is to provide better options for *BRCA1/2* mutation carriers for the treatment and prevention of cancer.

Resources

Many resources are available in the community to provide information about cancer. The following list should serve as a basic guide; more specific information may be available through these and other organizations.

Abramson Cancer Center

Penn Medicine's Abramson Cancer Center is one of a select group of cancer centers in the country awarded the prestigious designation of *Comprehensive Cancer Center* by the National Cancer Institute. This status reflects our outstanding research, clinical services, educational and informational services, and community outreach.

Abramson Cancer Center physicians and scientists are dedicated to increasing knowledge about preventing and curing cancer. The Abramson Cancer Center offers multidisciplinary evaluation centers, so patients can receive diagnosis and treatment options in one visit, as well as comprehensive treatment programs for all types of cancer. As part of Penn Medicine, the ACC is able to build upon the resources of one of the nation's foremost medical centers while addressing all patients' medical needs. Visit PennMedicine.org/Abramson.

Basser Center for BRCA

A gift to the University of Pennsylvania from alumni Mindy and Jon Gray has established the Basser Center for BRCA, a center focused solely on research and education on the prevention and treatment of cancers associated with inherited *BRCA1/2* mutations. The Basser Center is part of Penn Medicine's Abramson Cancer Center and funds research on the *BRCA1* and *BRCA2* genes at Penn and external institutions, in addition to providing expert care and support to *BRCA1/2* mutation carriers. Call **215.349.9093** for an appointment or visit www.Basser.org.

Young Leadership Council of the Bassler Center for BRCA

The Young Leadership Council of the Bassler Center for BRCA serves as a forum for young adults to become more engaged with the mission of the Bassler Center, stay informed about the latest advances in BRCA-related cancer research, and advocate and raise awareness of the Center. Through personal philanthropy and fundraising events, this committed group supports innovative BRCA-related cancer research, patient care, and educational priorities. Contact Carolyn Brown at **215.573.0550** to get involved or visit www.bassler.org/about-us/young-leadership-council

Mariann and Robert MacDonald Cancer Risk Evaluation Center

Penn Medicine's Cancer Risk Evaluation Program (CREP) is a clinical service for anyone who wants more information about personal risk for breast and ovarian cancer. This program offers genetic counseling and testing, and follow-up care for those at high risk. For more information, call **1.800.789.PENN (7366)** or **215.349.9093** or visit PennMedicine.org/Abramson.

Oncolink®

Oncolink® is the Abramson Cancer Center's award-winning Internet resource. It contains information about all aspects of cancer, the latest treatments, research advances, clinical trials, and related issues. Oncolink has a section dedicated to complementary and alternative therapies where users can find the latest information, as well as the research discoveries related to complementary therapies and cancer. For more information, please visit www.oncolink.org.

Organizations

American Cancer Society (ACS)

The ACS is a national, non-profit organization that supports research and educational efforts, as well as many local support groups. The ACS can be reached at **1.800.ACS.2345** or www.cancer.org.

Cancer Support Community of Greater Philadelphia

Formerly known as The Wellness Community, The Cancer Support Community offers free of charge psychological and emotional support, educational workshops, exercise, stress management and social activities for people with cancer and their families. Please check the locations (Philadelphia and Bucks County Branches): **215.879.7744** or www.cancersupportphiladelphia.org.

Facing Our Risk of Cancer Empowered (FORCE)

FORCE provides support, education, and awareness to help those facing hereditary breast, ovarian, and related cancers know their health care options and make informed decisions. This well-known and respected organization has helped guide critical research and policy issues that impact the hereditary breast cancer and ovarian cancer community. FORCE can be reached by calling **866.288.RISK (7475)** or visit www.facingourrisk.org.

HIS Breast Cancer Awareness

HIS was co-founded by a brother and sister who are both breast cancer survivors and carry a BRCA2 gene mutation. The organization aims to inform, educate, bring awareness and help with prevention and assist those diagnosed with male breast cancer. www.hisbreastcancer.org.

Imerman Angels

Imerman Angels provides free personalized one-on-one support for cancer fighters, survivors, and caregivers, as well as people at a high risk for developing cancer. Please visit imermanangels.org.

Living Beyond Breast Cancer (LBBC) Survivors Helpline

A non-profit education and support organization, LBBC is dedicated to empowering all women affected by breast cancer to live as long as possible with the best quality of life. Volunteers offer peer support and information in a confidential setting. To contact LBBC, please call **888.753.LBBC (5222)** or visit www.lbbc.org

National Cancer Institute (NCI)

The National Cancer Institute is a government organization that supports research and education, and has a vast amount of information about cancer diagnoses, treatment, clinical trials and cancer genetics. The NCI also maintains an informative website. For more information, please call **1.800.4.CANCER** or visit www.cancer.gov.

National Human Genome Research Institute (NHGRI)

An institute of the National Institutes of Health (NIH), NHGRI provides information about genetics public policy, including information on health insurance and workplace legislation. Please visit www.nhgri.nih.gov.

Sharsheret

Sharsheret is a national not-for-profit organization supporting women and their families of all Jewish backgrounds facing breast and ovarian cancer. Sharsheret offers a community of support to Jewish women who are diagnosed with breast or ovarian cancer or at increased genetic risk by fostering culturally relevant individualized connections with networks of peers, health professionals, and related resources. For more information, please call **1.866.474.2774** or visit www.sharsheret.org.

Susan G. Komen Breast Cancer Foundation

This national organization sponsors research, education and the annual "Race for the Cure" held in many cities across the country. More information about the Komen Foundation is available at **1.800.462.9273** or www.komen.org.

For other support and resources visit the Patients & Families section of our website at basser.org.

Glossary

Bilateral Salpingo-oophorectomy (BSO): The surgical removal of ovarian and fallopian tube tissue.

BRCA1 and BRCA2: The names for the first two genes to be discovered that increase risk for breast and ovarian cancer.

Cancer: A term for more than 100 diseases that have in common the uncontrolled, abnormal growth of cells. Cancer cells can spread through the blood stream and lymphatic system to other parts of the body.

Colonoscopy: A medical procedure where a long, flexible, tubular instrument called the colonoscope is used to view the entire inner lining of the colon (large intestine) and the rectum. Usually performed to detect and remove colon polyps which lead to colon cancer and to detect colon cancer.

Gene: An individual unit of hereditary information that is located at a specific position within the chromosome. A gene provides coded information for a specific characteristic, trait, or body function.

Hysterectomy: The surgical removal of the uterus.

In vitro fertilization (IVF): A procedure in which mature eggs are retrieved from a woman's ovaries and fertilized by sperm in a lab.

Mastectomy: The surgical removal of a breast.

Menopause: When periods have ceased for over a year.

Mutation: A change in the normal sequence, or chemical spelling, of DNA, the genetic material.

Oophorectomy: Surgical removal of a woman's ovaries. A salpingo-oophorectomy removes a woman's ovaries and fallopian tubes.

Preimplantation Genetic Testing for monogenic/single gene defects (PGT-M):

A special test created uniquely for each family that is performed prior to pregnancy to greatly reduce the risk of having a child with a specific genetic mutation, such as a *BRCA1* or *BRCA2* gene mutation.

Prophylactic: Risk reducing treatment, such as surgical removal of healthy tissue, in the hopes of preventing cancer.

Risk Assessment: The process of assessing personal medical and family history to determine the chance that cancer could develop.

Salpingectomy: A surgery where the fallopian tubes, but not the ovaries, are removed.

Tissue expander: A tissue expander is a balloon device that is placed underneath the skin and muscles of the chest wall during breast reconstruction to create space for an eventual implant.

Tomosynthesis: Tomosynthesis is a newer technology for imaging breasts. Like a mammogram, it is a low-dose X-ray but renders a 3-dimensional (3D) image instead of a 2-dimensional one.

WE TAKE CANCER PERSONALLY.

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