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Editorial

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When two genes do not work properly

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BRCA1 and *BRCA2* are human genes that produce tumour suppressor proteins. These proteins help repair damaged DNA and, therefore, play a role in ensuring the stability of the cell's genetic material. When either of these genes is mutated, or altered, such that its protein product is not made or does not function correctly, DNA damage may not be repaired properly. As a result, cells are more likely to develop additional genetic alterations that can lead to cancer. A harmful *BRCA1* or *BRCA2* mutation can be inherited from a person's mother or father. Each child of a parent who carries a mutation in one of these genes has a 50 percent chance of inheriting the mutation. The effects of mutations in *BRCA1* and *BRCA2* are seen even when a person's second copy of the gene is normal.

Specific inherited mutations in *BRCA1* and *BRCA2* increase the risk of female breast and ovarian cancers, and they have been associated with increased risks of several additional types of cancer. Together, *BRCA1* and *BRCA2* mutations account for about 20 to 25 percent of hereditary breast cancers [1] and about 5 to 10 percent of all breast cancers [2]. In addition, mutations in *BRCA1* and *BRCA2* account for around 15 percent of ovarian cancers overall [3]. Breast cancers associated with *BRCA1* and *BRCA2* mutations tend to develop at younger ages than sporadic breast cancers. Moreover, harmful mutations in *BRCA1* and *BRCA2* increase the risk of several cancers in addition to breast and ovarian cancer. *BRCA1* mutations may increase a woman's risk of developing fallopian tube cancer and peritoneal cancer [4]. Men with *BRCA2* mutations, and to a lesser extent *BRCA1* mutations, are also at increased risk of breast cancer [5]. Men with harmful *BRCA1* or *BRCA2* mutations have a higher risk of prostate cancer [6]. Men and women with *BRCA1* or *BRCA2* mutations may be at increased risk of pancreatic cancer [7].

Several options are available for managing cancer risk in individuals who have a known harmful *BRCA1* or *BRCA2* mutation. These include enhanced screening, prophylactic (risk-reducing) and surgery.

Enhanced screening

Some women who test positive for *BRCA1* and *BRCA2* mutations may choose to start screening at younger ages than the general population or have more frequent screening. For example, some experts recommend that women who carry a harmful *BRCA1* or *BRCA2* mutation undergo clinical breast examinations beginning at age 25 to 35 years. And some expert groups recommend that women who carry such a mutation have a mammogram every year, beginning at age 25 to 35 years [8]. Unfortunately, no effective methods of ovarian cancer screening currently exist. Some groups recommend transvaginal ultrasound examinations, blood tests for the antigen CA-125, and clinical examinations for ovarian cancer screening in women with harmful *BRCA1* or *BRCA2* mutations, but none of these methods appears to detect ovarian tumours at an early enough stage to reduce the risk of dying from ovarian cancer [9]. The benefits of screening for breast and other cancers in men who carry harmful mutations in *BRCA1* or *BRCA2* is also not known, but some expert groups recommend that men who are known to carry a harmful mutation undergo regular mammography as well as testing for prostate cancer.

Prophylactic (Risk-reducing) Surgery. Prophylactic surgery involves removing as much of the "at-risk" tissue as possible. Women may choose to have both breasts removed (bilateral prophylactic mastectomy) to reduce their risk of breast cancer. Surgery to remove a woman's ovaries and fallopian tubes (bilateral prophylactic salpingo-oophorectomy) can help reduce her risk of ovarian cancer. Removing the ovaries also reduces the risk of breast cancer in premenopausal women by eliminating a source of hormones that can fuel the growth of some types of breast cancer. Prophylactic surgery does not completely guarantee that cancer will not develop because not all at-risk tissue can be removed by these procedures. Some women have developed breast cancer, ovarian cancer, or primary peritoneal carcinomatosis (a type of cancer similar to ovarian cancer) even after prophylactic surgery. Nevertheless, the mortality reduction associated with this surgery is substantial: one study showed that women who underwent bilateral prophylactic salpingo-oophorectomy had a nearly 80 percent reduction in risk of dying from ovarian cancer and a more than 50 percent reduction in risk of dying from breast cancer [10]. No evidence is available regarding the effectiveness of bilateral prophylactic mastectomy in reducing breast cancer risk in men with a harmful *BRCA1* or *BRCA2* mutation or a family history of breast cancer. Therefore, bilateral prophylactic mastectomy for men at high risk of breast cancer is considered an experimental procedure, and insurance companies will not normally cover it.

World Health Organization criteria for population screening for genetic predisposition to disease are that the disease is an important public health burden in the target population; that the risk of disease due to mutations in the screened genes is known; and that effective intervention exist to reduce morbidity and mortality among genetically susceptible individuals [11]. At present, the US Preventive Services Task Force (USPSTF) supports BRCA1 and BRCA2 testing based on family history and ancestry, but not for the entire female population, given the lack of data on risks for mutation carriers ascertained from the general population, rather than through a personal or family history of

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cancer [12]. This position was correct based on the data then available. However, a just-completed study now provides evidence that supports offering *BRCA1* and *BRCA2* sequencing to all women. Population-based screening enables mutation carriers to be identified independent of physician referral or family involvement. This is important, because at present, there is marked variability in practice in following the USPSTF guidelines. A recent survey revealed that only 19% of US primary care physicians accurately assessed family history for *BRCA1*/*BRCA2* testing [13].

Population-wide screening will require significant efforts to educate the public and to develop new counselling strategies, but this investment will both save women's lives and provide a model for other public health programs in genomic medicine. Women do not benefit by practices that "protect" them from information regarding their own health. They should have the choice to learn if they carry an actionable mutation in *BRCA1* or *BRCA2*.

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