

## Editorial

# Preventing Breast, Ovarian Cancer in BRCA Carriers: Rational of Prophylactic Surgery and Promises of Surveillance

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Women with inherited mutations in the BRCA1 or BRCA2 (BRCA) genes face a high lifetime risk of developing breast and ovarian cancer. Breast cancer is the most common female malignancy in the Western world; 275,000 women will receive a new diagnosis of breast cancer this year in the United States.<sup>1</sup> Given that BRCA carriers make up 5 to 10% (13,750-27,500 women in the USA) of all breast cancer cases, increasing is the interest for the management of these women. As genetic test, with the power to identify these high-risk women, has been widely available and preventive surgical and non-surgical choices abound, there is growing controversy and uncertainty about prevention choice.

Ideally, prevention strategy should provide the best combination of cancer protection, survival and quality of life (QoL). Goal of prophylactic surgery is to eliminate risk of cancer, by removing the organ(s) targeted by the BRCA mutated genes, namely breasts and ovaries, before the disease clinically occurs. By contrast, preservation or surgical resection of these target organs only when screening-detected early-stage cancer occurs represents the principal aim of close surveillance. In the absence of data from randomized controlled trials (RCTs) for apparent reasons, prevention management should be guided by other nonrandomized reports.<sup>2</sup> The evident high risk of cancer for BRCA carriers urgently suggests the need for intervention. But for which prevention option are there the most convincing data?

Wide variation in risk estimates, diverse impacts of surgical and nonsurgical prevention measures on sur-

vival and QoL and insufficient data, make decision for prevention of BRCA mutation carriers too complicated and challenging. As new data become available over the last year regarding lifetime risk,<sup>3</sup> the efficacy and limitations of surgical and nonsurgical procedures,<sup>4-6</sup> and decision analysis,<sup>7</sup> critical analysis on the light of these new findings may help women and their physician to deal with this dilemma.

Ten years after the discovery of BRCA genes an explosion of research on understanding the molecular mechanisms of BRCA pathway has been noted. But the expectation that this elucidation could lead to effective chemoprevention of the most common noninherited (sporadic) cancer has been proven elusive. Although the BRCA genes themselves appear unconnected to common, nonhereditary cancers, advances in understanding BRCA genes' biological function,<sup>8-10</sup> suggest that defects in other parts of the BRCA pathway might be critical not only driving breast cancer but other cancers as well.<sup>9,10</sup>

Uncertainty about risk magnitude is a major obstacle in making decision. Most, but not all, women with inherited mutations that affect one allele of either BRCA1 or BRCA2, will develop breast and/or ovarian cancer. This risk varies considerably between 40% to 85% for breast cancer and 11% to 65% for ovarian cancer.<sup>3,8,11,12</sup> This variation is depended on mutated gene (BRCA1 or BRCA2 and different mutations in the same gene), family history (strong or weak), as well as genetic and external factors that modify genetic risk.<sup>8</sup> Data available suggest that among women with BRCA mutations, those with a strong family history have a higher risk<sup>13</sup> than those without such a family history.<sup>14,15</sup>

However, a recent study published in *Science*<sup>3</sup> may overturn this widely accepted status.<sup>16</sup> In the New York Breast Cancer Study (NYBCS) on 1,008 New York-area Ashkenazi Jewish women diagnosed with incident, breast cancer, 104 (10.3%) female probands carried an

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ancient mutation in BRCA1 or BRCA2. By comparing age, family history, cancer status, and other factors, King et al.<sup>3</sup> determined that the overall lifetime risks for breast cancer were 82% for BRCA1 or BRCA2 carriers and for ovarian cancer were 54% for BRCA1 carriers and 23% for BRCA2 mutation carriers. These findings confirm the very high lifetime risk of breast and ovarian cancer. The exciting new is that all women with BRCA mutations, even those who are distant relatives from both mother's side and father's side, of a breast cancer case may face a high lifetime risk.

### **Surgical and Nonsurgical Preventive Options**

Prophylactic surgery includes bilateral mastectomy (BM), bilateral salpingo-oophorectomy (BSO) and resection of both breasts and ovaries. By removing the BRCA-targeted organ(s) surgery can dramatically reduce an overall cancer risk.<sup>17</sup> Indeed, although BRCA mutated genes are found in every cell in the body of carriers, they target nearly exclusively breast tissue, and to a lesser extent, the ovary, and fallopian tube. Small appears to be the risk of other cancers, such as pancreatic, colorectal and stomach of women with inherited mutations.<sup>15,18,19</sup>

Early on, prophylactic BM in women with family history of breast cancer had been suggested. With the availability of genetic testing, surgery is performed only to women with evident BRCA mutations. In a recent report, 483 women with BRCA1/2 mutations were studied. After a mean follow-up of 6.4 years breast cancer was diagnosed in two (1.9%) of 105 women who had bilateral prophylactic mastectomy and in 184 (48.7%) of 378 matched controls who did not have the procedure. Rebbeck et al. conclude that bilateral prophylactic mastectomy reduces the risk of breast cancer in women with BRCA1/2 mutations by approximately 90%.<sup>4</sup> In a prospective study of 139 women with BRCA1 or BRCA2 mutations, after a mean follow-up of 3 years, breast cancer was developed in 8 of 63 women who had elected surveillance but in none of the 76 BRCA mutations carriers who had undergone prophylactic surgery.<sup>20</sup> High morbidity in up to 30% after BM and reconstruction<sup>21</sup> and adverse effects on psychosocial status have been reported. However, recent studies show low rate of complications after reconstruction, less than 10%.<sup>22</sup> Furthermore, the majority of women were satisfied with their decision, more those women with reconstruction, to undergo BM and were not experiencing abnormal levels of psychological distress, low levels of sexual activity, or difficulties with body image.<sup>23</sup>

Nonsurgical interventions reliably attract research interest for a better QoL without increasing risk of cancer death of high-risk women. But data are few and suggest

major limitations. The addition of magnetic resonance imaging (MRI), to the modest efficacy regular clinical breast examination and annual mammography, could increase the rate of early detection. In a latest prospective study,<sup>5</sup> at a mean follow-up of 2.9 years, 23 of 358 women with BRCA mutations developed ductal or invasive breast cancer. MRI significantly increased the rate of early detection, but the rate of tumors larger than 1 cm was 43% and only 63% of patients had node-negative disease.<sup>5</sup> More frequent mammographic and MRI screening, for example every six months, might decrease late diagnosis due early detection of "interval cancers" increasing thereby early-stage cancer. But evidence is still lacking. Because of its low specificity, MRI increases the unneeded additional investigations and biopsies.<sup>5</sup>

Tamoxifen, an antiestrogenic modifier of genetic risk,<sup>8</sup> can reduce breast cancer risk. But tamoxifen is effective only in estrogen-receptors (ER) positive tumors in the general population and probably also in BRCA-associated tumors. Indeed, in the NSABP-P1 trial, tamoxifen chemoprevention reduced breast cancer incidence in BRCA2 carriers only but not to those with BRCA1 mutations.<sup>24</sup> Research is ongoing to confirm these findings and to determine whether other estrogen receptor modulators and aromatase inhibitors are more effective than tamoxifen. Other nongenetic factors may also modify genetic risk.<sup>8</sup> Pregnancy, physical exercise as adolescent, healthy weight<sup>4</sup> and breast-feeding<sup>25</sup> are all factors that may delay the onset or even reduce the risk of cancer.

Ovarian cancer, beyond breast cancer, is also a principal goal of prevention strategies for women with inherited mutations. Since breast tumorigenesis is causatively linked with estrogen,<sup>26</sup> it is not surprising that BSO reduces the risk of both ovarian cancer and breast cancer. This protective effect of BSO has been suggested by previous small studies and decision analysis<sup>27,28</sup> and is confirmed by recent reports. In a large, retrospective analysis of 551 BRCA carriers, BSO reduced the risk of ovarian cancer by 96% and of breast cancer by 53% at a mean follow-up of 9 years.<sup>29</sup> Similar findings provided a prospective study of 170 BRCA carriers. During a mean follow-up of 2 years, incidence of ovarian or peritoneal cancer and breast cancer was significantly greater in women who selected surveillance than in those who choose to undergo BSO.<sup>30</sup> Laparoscopic BSO is associated with low morbidity (4%)<sup>30</sup> and all benefits of a minimal-access surgery. High efficacy, minimal invasiveness and noneffective surveillance explain an increasing trend towards BSO in recent years. Intensive screening with ultrasonography and CA-125 in BRCA carriers detection of ovarian cancer at early stage has

been failed.<sup>30</sup> A recent analysis of studies published between 1998 and 2003 provided a convincing biological basis to explain the failure of such a screening. Most ovarian cancers in women with inherited mutations are high-grade serous cancers, and these are infrequently screen at an early stage.<sup>6</sup> The use of hormone replacement therapy (HRT) after BSO arises some concerns<sup>(31)</sup>, although HRT-associated adverse effects – increased risk of breast cancer, coronary disease and thromboembolism – observed in general population,<sup>32</sup> were not found among BRCA carriers in a recent Markov decision analysis.<sup>7</sup>

### Choosing Prevention Intervention

Penetrance, and impacts of prevention strategies on cancer risk, survival, and QoL are the key criteria considered for making a good decision. It is however, elusive to believe that a certain prevention option can fully meet all these expectations together in an individual woman. On one hand, nonsurgical procedures provide good QoL but may be associated with increased risk of advanced-stage cancer and mortality, on the other surgery ensures a very high protection from cancer but it is associated with all the disadvantages of invasiveness, non-reversibility, surgical morbidity and adverse effects on QoL.<sup>33</sup>

Ideally, surveillance may result in lifelong preservation of target organs or its surgical resection only when cancer becomes clinically evident. Unfortunately, individual women who will benefit from close screening and/or chemoprevention cannot be identified. This identification can emerge only due understanding signalling pathways and identifying genetic and environmental modifiers.<sup>26</sup> Genomics-based diagnostic techniques, such as gene-array analysis and research focused on evaluating molecular pathways<sup>34</sup> will help to identify those BRCA carriers who will develop breast or ovarian cancer. Exciting findings using gene-expression profiles based on tissue-array analysis in clinically evident breast cancer are already available.<sup>35,36</sup>

Despite the rational focus of research on developing effective nonsurgical interventions, in current clinical practice prophylactic surgery is clearly superior to surveillance. The high protective index, over 90% by surgery, despite a possible overestimation<sup>37</sup> and advances in surgical techniques have resulted in an increasing acceptance of surgical prevention among both oncologists and women with BRCA mutations.<sup>23</sup>

Which surgical procedure is the best? Of three surgical approaches available, radical removal of both breast and ovaries provides the highest cancer protection but because of its major invasiveness and complications, it is

preferred by few women. Most BRCA carriers choose between BM and BSO, but it is a great challenge because of their various effects on efficacy and QoL.<sup>38</sup> The efficacy of BSO to reduce risk of both breast cancer by 50% and ovarian cancer by 90%,<sup>27–30</sup> the more extensive surgery and increased morbidity with BM and reconstruction,<sup>21,22</sup> the advantages of laparoscopic BSO, and the absence of effective ovarian-cancer screening, strongly convince for the superiority of BSO.<sup>6,7,39</sup> A careful and individualized decision about use of HRT after BSO is advised.

Separate decision for BRCA1 and BRCA2 carriers appears useful. For BRCA1 carriers there is little or no room for discussion. The evident very high lifetime risk of both breast cancer (65–82%) and ovarian cancer (39–54%)<sup>3,12,14,15</sup> along with failure response to tamoxifen chemoprevention,<sup>24</sup> suggest the urgent need for surgical prophylaxis. Compared with BRCA1 carriers, women with BRCA2 mutation face a lower probability of developing cancer in the breast (45–82%) or ovary (11–23%). But this risk remains high, much higher than in general population, and despite the tamoxifen effectiveness – most BRCA2 are ER positive tumors – the uncertainty about cancer mortality persists.

The wide availability and power expand the clinical applications of genetic testing. Since 5% to 10% of women with a new breast cancer diagnosis carry BRCA mutations and initial surgical treatment of breast cancer differs between carriers and non-carriers, genetic risk assessment may affect surgical decision.<sup>40</sup> Breast-conserving surgery<sup>41</sup> and mastectomy, which are currently used for breast cancer treatment, may be inappropriate procedures for BRCA carriers. The mutated genes continue to target the available breast tissue and there is increased risk of developing cancer in the preserved breast and/or the contralateral breast<sup>42</sup>

In summary, with the discovery of BRCA genes enormous progress has been made and multiple prevention options are available. However, right individualized decision at the right time is elusive. Intensive research on nonsurgical prevention strategies provides the best promises for the future. But at present, demands and preferences of women with BRCA mutations to avoid removal of breasts and/or ovaries cannot be satisfied without risk. Surveillance strategy is associated with a high risk of late diagnosis of breast cancer and particularly of ovarian cancer and mortality in some women, who despite advances in molecular research and image technology cannot be identified.

In current clinical practice, rational is a surgical approach. Prophylactic surgery does not cure the cause, namely the mutated genes. But with complete resection

of target organ(s), surgery provides a very high efficacy regarding cancer prevention and survival. As surgery evolves, postoperative morbidity rates and adverse effects on QoL have dramatically been reduced. Laparoscopic bilateral salpingo-oophorectomy after completion of childbearing provides today the best risk-benefit ratio and it is increasingly acceptable by both doctors and their patients toward improving primarily survival and QoL.

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