CONFERENCES WITH PATIENTS AND DOCTORS

Management of Women With BRCA Mutations
A 41-Year-Old Woman With a BRCA Mutation and a Recent History of Breast Cancer

Nadine Tung, MD, Discussant

DR LIBMAN: Ms E is a 41-year-old woman who was diagnosed as having breast cancer at age 37 years in June 2006 after presenting with an asymptomatic lump in her left axilla. Mammography revealed only dense breast tissue, but breast magnetic resonance imaging (MRI) demonstrated suspicious axillary nodes as well as a mass in the tail of her left breast (FIGURE). Pathological examination showed a 1.5-cm grade 3 invasive ductal carcinoma that did not overexpress the estrogen receptor (ER) or progesterone receptor (PR) and did not express human epidermal growth factor receptor 2 (HER2) (ie, it was triple-negative). Seven axillary nodes contained metastatic tumor. She was treated with wide excision and adjuvant chemotherapy with doxorubicin and cyclophosphamide followed by paclitaxel and radiation therapy. Since that time, she has been followed up regularly by her oncologist. She is asymptomatic with no evidence of recurrence.

Because of her young age, Ms E was referred for genetic counseling and testing soon after diagnosis and found to have a 5382insC BRCA1 mutation. Her eggs were harvested prior to beginning chemotherapy. She subsequently underwent preimplantation genetic diagnosis and had an embryo free of the BRCA1 mutation implanted. After a full-term pregnancy, she gave birth to a healthy boy in June 2010.

Ms E's menarche was at age 13 years. She is gravida 2, para 1. She took oral contraceptives for about 20 years. Ms E has a history of mitral valve prolapse. She is otherwise in good health.

There is no known family history of breast or ovarian cancer. However, Ms E's father was an adopted only child, and his biological mother died at a young age of tuberculosis. Ms E's father died at age 55 years from complications following a cholecystectomy. Her mother is alive and healthy at age 64 years with her ovaries in place. Ms E's maternal ancestry is English and her paternal ancestry is uncertain. She is unaware of any Ashkenazi Jewish heritage.

Ms E works in the banking business. She is married. She does not smoke cigarettes and drinks alcohol infrequently.

Ms E, a 41-year-old BRCA1 mutation carrier, was diagnosed 4 years ago as having breast cancer and opted for breast-conserving therapy. Prior to receiving chemotherapy, she harvested her eggs through in vitro fertilization and subsequently used preimplantation genetic diagnosis; 3 months ago she delivered a healthy boy. This review examines the prevalence of BRCA mutations in women with breast cancer, as well as current recommendations for surgery and systemic therapy in these women. In particular, the risk of a contralateral breast cancer is reviewed to help guide the choice of prophylactic mastectomies vs breast-conserving therapy. The technology of preimplantation genetic diagnosis and genetic testing in relatives of mutation carriers is discussed.

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MS E: HER VIEW

I learned that I had breast cancer at the age of 37, which was a little over 4 years ago. I had some pain under my armpit and did not think it could be breast cancer. However, within 6 weeks the lump got a little bit larger. My gynecologist ordered a mammogram that did not pick it up, but the MRI and ultrasound did. I had a biopsy and found out that it was breast cancer. It was definitely a shock. I had a successful lumpectomy, but I knew that I would have to go through chemotherapy and radiation. During that time frame, we let the oncologist and surgeon know that we were in the process of trying to have a child through in vitro fertilization.

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I knew something was wrong, but I didn’t think about breast cancer, probably because I was very young. I think it was very important to find out why this happened to me. I met with the geneticist and we decided to move forward to find if I was carrying the breast cancer gene. When we found that I was positive for BRCA1, I knew right away that it had to be my father’s side. I was slightly apprehensive to do the testing because I honestly thought that it would become public record. I also thought that the insurance companies would deny me coverage if I lost my job or if I moved to another company. When we learned the results, I also found out that we could test our embryos for the gene, and knowing that made a difference.

The results of the genetic test have been extremely important for us. The idea of knowing is so much more important than not knowing. For us to have children at this stage in life and understand that we are not passing the gene on outweighs any possible negative consequences.

**AT THE CROSSROADS:**

**QUESTIONS FOR DR TUNG**

What percentage of breast cancer is attributable to BRCA mutations? What women should consider genetic testing for breast cancer susceptibility and at what age? How does a BRCA mutation affect management of breast cancer? What malignancies other than breast cancer are BRCA mutation carriers at risk of and how should that risk be managed? What is pre-implantation genetic diagnosis and how is it used clinically? What breast cancer prevention strategies are appropriate for a mutation carrier who has not yet developed breast cancer?

**Epidemiology and Testing Recommendations**

Dr Tung: Germline mutations in the tumor suppressor genes BRCA1 (NG_005905.2) and BRCA2 (NG_012772.1) are responsible for 3% to 5% of all breast cancer and 10% to 15% of ovarian cancer. Lifetime estimates of breast cancer risk in BRCA1/2 carriers range from 36% to 90%, and ovarian cancer risk ranges from 24% to 59% in BRCA1 carriers and 8% to 35% in BRCA2 carriers. Cancer risk estimates in carriers from high-risk clinics with strong family histories of cancer are generally higher than those in carriers unselected for family history. Whether this observation is related to shared environmental or other genetic factors among family members is unknown.

Guidelines for BRCA1/2 testing include the following features of family history: multiple breast cancers, early-onset...
breast cancer (age <50 years), ovarian cancer (any age), coexistence of 2 breast cancers or breast and ovarian cancer in a single individual, and male breast cancer (Box). 7,9 There are more than a dozen statistical and empirical models to calculate an individual’s risk of carrying a BRCA mutation. 10 The sensitivity of these models is lower in individuals with smaller families. 11 Although the American Society of Clinical Oncology (ASCO) previously recommended testing only for persons with at least a 10% likelihood of carrying a mutation, it is currently recommended for any individual with a suggestive personal or family history provided that the results will affect medical management. 12 Ms E’s young age at diagnosis qualified her for genetic testing. However, her case illustrates the limitations of relying on family history to identify appropriate candidates for testing since half of her family history was unknown.

BRCA1/2 mutations are common in Ashkenazi Jews. Mutations exist in 2.5% of the Jewish population and are responsible for 10% to 12% of breast cancer. 13-15 In contrast, in the non-Jewish population, BRCA1/2 mutations are estimated to exist in 0.1% to 0.25% and account for 3% to 5% of breast cancer. 16 In addition, whereas more than 1000 mutations have been identified in the BRCA1 and BRCA2 genes, approximately 95% of the mutations found in Jewish individuals occur in 3 locations: 2 in BRCA1 (187delAG and 5382insC) and 1 in BRCA2 (6174delT), 17 which are called “founder mutations.” Ms E has 1 of these founder mutations but was unaware of any Jewish heritage. These Ashkenazi founder mutations have been identified in other populations, likely due to intermarriage or, possibly, separate mutational events. Furthermore, the 5382insC mutation found in Ms E originated in Europe and is also common in non-Ashkenazi populations. 18 A higher frequency of specific mutations also exists in several other ethnic populations (eg, Icelandic, Dutch, and French Canadian). 19

Incorporating information about the pathologic features of a breast cancer can improve the ability to predict whether a BRCA mutation is present. 20-22 Ms E’s pathology is typical of BRCA1-related breast cancers, since 80% lack the ER, the PR, and amplification of HER2, known as triple-negative breast cancers (TNBCs). An analysis concluded that it is cost-effective to perform genetic testing in women with TNBCs diagnosed before age 50 years. 23 BRCA1 breast cancers also tend to be high-grade, frequently have p53 mutations, and often stain for the epithelial “basal” cytokeratins 5/6 and 14. In contrast, there are no consistent pathologic features of BRCA2-associated breast cancers; like nonhereditary cancers, they are most often ER-positive. 24

Management of Breast Cancer in BRCA1 and BRCA2 Carriers

Surgery. Women such as Ms E with a BRCA mutation and newly diagnosed breast cancer face the difficult decision of whether to undergo breast-conserving therapy (excision of the tumor and postoperative radiation), unilateral mastectomy, or prophylactic bilateral mastectomies to prevent future breast cancers. For women without mutations, breast-conserving therapy results in survival equal to that of unilateral mastectomy because of the low rate of local tumor recurrence. 25 Most studies have shown that local recurrence rates do not differ significantly between mutation carriers and noncarriers after breast-conserving therapy. 26-29 However, the incidence of another tumor developing in the treated breast does increase in mutation carriers with longer follow-up. Pierce et al 26 found that the rate of tumor occurrence in the treated breast increased from 11% at 10 years to 30% at 20 years. Of interest, 70% of the tumors that occurred in the ipsilateral breast after breast-conserving therapy were new cancers, rather than a recurrence of the original, since they occurred after a median interval of 8.7 years and developed in a quadrant of the breast different than the original cancer.

A major decision with which mutation carriers struggle is whether to undergo bilateral prophylactic mastectomies to also prevent a future contralateral breast cancer (CBC). The risk of CBC in mutation carriers is 1.5% to 3.1% per

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Box. National Comprehensive Cancer Network Criteria for BRCA1/2 Testing

- Individual from a family with known BRCA1/2 mutation
- Individual with breast or ovarian cancer
  - Personal history of ovarian cancer
  - Personal history of male breast cancer
  - Personal history of female breast cancer plus ≥1 of the following:
    - Diagnosed age ≤45 years
    - Diagnosed age ≤50 years with ≥1 relatives with breast cancer diagnosed age ≤50 years and/or ovarian cancer at any age
    - Two primary breast cancers with the first diagnosed age ≤50 years
    - Diagnosed at any age with ≥2 relatives with breast and/or ovarian cancer at any age
    - Relative with male breast cancer
    - Personal history of ovarian cancer
  - No additional family history may be needed if ethnicity is one associated with higher mutation frequency (eg, Ashkenazi Jewish)
- Family history only (individual without breast/ovarian cancer)
  - Individual has a first- or second-degree relative meeting above criteria
  - Individual has a third-degree relative with breast and/or ovarian cancer with ≥2 relatives with breast cancer (1 diagnosed age ≤50 years) and/or ovarian cancer

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1 Epithelial ovarian cancer, fallopian tube cancer, or primary peritoneal cancer.
2 Invasive breast cancer or ductal carcinoma in situ.
3 First-, second-, or third-degree relatives.
4 Personal history of male breast cancer.
5 Personal history of breast cancer at any age.
Several risk factors influence CBC risk in mutation carriers. The younger the age at first breast cancer diagnosis, the higher the risk of subsequent CBC. At 25 years, the risk of CBC for BRCA1 carriers diagnosed before age 40 years, like Ms E, is 62.9% (95% confidence interval [CI], 50.4%-75.4%) vs 19.6% (95% CI, 5.3%-33.9%) if diagnosed at older than 50 years. Charts for determining cumulative risks of a CBC based on age at diagnosis of initial breast cancer, BRCA1 vs BRCA2 mutation, and interval since diagnosis have been published. Several studies have found a 1.3- to 1.8-fold higher risk of CBC in mutation carriers after oophorectomy than that seen in women without a mutation. With longer follow-up, the risk of CBC in BRCA1/2 carriers was reported to be 47.4% at 25 years.

Several risk factors influence CBC risk in mutation carriers. The younger the age at first breast cancer diagnosis, the higher the risk of subsequent CBC. At 25 years, the risk of CBC for BRCA1 carriers diagnosed before age 40 years, like Ms E, is 62.9% (95% confidence interval [CI], 50.4%-75.4%) vs 19.6% (95% CI, 5.3%-33.9%) if diagnosed at older than 50 years. Charts for determining cumulative risks of a CBC based on age at diagnosis of initial breast cancer, BRCA1 vs BRCA2 mutation, and interval since diagnosis have been published. Several studies have found a 1.3- to 1.8-fold higher risk of CBC in mutation carriers after oophorectomy than that seen in women without a mutation. With longer follow-up, the risk of CBC in BRCA1/2 carriers was reported to be 47.4% at 25 years.

Despite the significant risk of a second breast cancer in mutation carriers, no difference in survival has yet been found whether a contralateral prophylactic mastectomy was performed, though the number of women studied is small (Table 2). Updated results were reported at the European Breast Cancer Conference in 2010. No significant difference in the rate of metastatic disease or survival has been detected between 138 mutation carriers who opted for prophylactic mastectomy and 252 who did not, with a median follow-up of 6 years. It is possible that longer follow-up is needed to detect a survival benefit from prophylactic mastectomies in carriers who must first survive their initial breast cancer.

Although there is no evidence that prophylactic mastectomy improves breast cancer survival for mutation carriers, weighing the emotional sequelae of a subsequent breast cancer and the need for further treatment must be considered when making this decision. The prognosis of the initial breast cancer is also a factor; if the risk of systemic relapse from breast cancer is high, then major prevention surgery may not seem warranted initially but should be reconsidered in several years if the patient remains disease-free.

Studies have shown that the great majority of women who choose prophylactic mastectomy are satisfied with their decision and that psychosocial outcomes are similar to women at increased risk of breast cancer who do not choose prophylactic mastectomy and tamoxifen may also induce an early menopause.

As such, there is no evidence that oophorectomy, tamoxifen, and chemotherapy are additive in reducing the risk of CBC. Ms E’s risk of CBC should be substantially reduced if she undergoes risk-reducing salpingo-oophorectomy (RRSO) before menopause. Whether the chemotherapy she received would further reduce that risk is unclear.

**Table 1. Interventions Associated With Decreased Risk of Contralateral Breast Cancer (CBC) in BRCA1/2 Mutation Carriers**

<table>
<thead>
<tr>
<th>Intervention and Source</th>
<th>Study Design</th>
<th>No. Exposed</th>
<th>No. With BRCA Mutation</th>
<th>Follow-up, y</th>
<th>RR of CBC (95% CI)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oophorectomy</td>
<td></td>
<td></td>
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<td></td>
<td></td>
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<tr>
<td>Metcalfe et al, 2004</td>
<td>Retrospective cohort</td>
<td>107</td>
<td>229</td>
<td>97</td>
<td>9.2</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>224</td>
<td>112</td>
<td></td>
<td></td>
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<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>HR, 0.41 (0.18-0.90)</td>
<td></td>
<td>.03</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Aged &lt;50 y old at diagnosis: HR, 0.24 (0.07-0.77)</td>
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<td>.02</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Aged ≥50 y at diagnosis: HR, 0.91 (0.26-3.21)</td>
<td></td>
<td>NA</td>
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<tr>
<td>Tamoxifen</td>
<td></td>
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<td></td>
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<tr>
<td>Pierce et al, 2006</td>
<td>Matched retrospective cohort</td>
<td>NA</td>
<td>NA</td>
<td>123</td>
<td>37</td>
<td>Median, 7.9 (range, 0.5-23.4)</td>
</tr>
<tr>
<td>Gronwald et al, 2006</td>
<td>Matched case-control</td>
<td>220</td>
<td>816</td>
<td>848</td>
<td>188</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>222</td>
<td>57</td>
<td>228; BRCA1: 57</td>
<td>Cases: 5.7; controls: 7.4</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>BRCA1: 4.9 (2.8); BRCA2: 5.0 (3.0)</td>
<td>Controls: BRCA1, 4.2 (2.7); BRCA2: 4.5 (2.5)</td>
<td>.001</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>BRCA1 carriers: OR, 0.47 (0.30-0.74)</td>
<td>BRCA2 carriers: OR, 0.42 (0.17-1.02)</td>
<td>.01</td>
</tr>
<tr>
<td>Chemotherapy</td>
<td></td>
<td></td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Reding et al, 2010</td>
<td>Matched case-control</td>
<td>123</td>
<td>58</td>
<td>109</td>
<td>72</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>67; BRCA1: 41</td>
<td></td>
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</tr>
<tr>
<td></td>
<td></td>
<td>4.7 (2.8); BRCA2: 5.0 (3.0)</td>
<td>Controls: BRCA1, 4.2 (2.7); BRCA2: 4.5 (2.5)</td>
<td>RR, 0.5 (0.2-1.0)</td>
<td>BRCA1 carriers: RR, 0.5 (0.1-1.6)</td>
<td>.04</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>BRCA2 carriers: RR, 0.3 (0.1-1.0)</td>
<td></td>
<td>.05</td>
</tr>
</tbody>
</table>

**Abbreviations:** CI, confidence interval; HR, hazard ratio; NA, not available; OR, odds ratio; RR, relative risk.

Follow-up data are reported as mean or mean (SD) unless otherwise indicated.
mastectomy.\textsuperscript{41,42} Mutation carriers often report decreased anxiety about developing cancer after prophylactic mastectomy. However, negative effects on body image and sexuality have also been reported.\textsuperscript{42}

Ms E opted for breast-conserving therapy. Given the high-risk features of her breast cancer and the lack of demonstrated survival benefit of prophylactic mastectomies, this was an understandable choice. Since the diagnosis of breast cancer was made more than 4 years ago and Ms E remains disease-free, much of the risk of systemic recurrence, however, has elapsed, and prevention surgery may be even more appropriate now.

Chemotherapy. Recent retrospective studies have demonstrated that prognoses are similar for women with BRCA-related and sporadic (noninherited) breast cancers, especially if chemotherapy is administered.\textsuperscript{13,44}

There is reason to expect that breast cancers without functional \(BRCA1/2\) may be more sensitive to DNA-damaging chemotherapy since these genes are essential to multiple aspects of DNA repair and in preventing apoptosis.\textsuperscript{45} However, there are limited clinical data addressing the relative sensitivity of \(BRCA\)-related and sporadic breast cancers to the standard chemotherapy that Ms E received (ie, anthracycline and alkylator-based). Kriege et al\textsuperscript{46} retrospectively studied response rates to chemotherapy that Ms E received (ie, anthracycline and alkylator-based). There are limited clinical data addressing the relative sensitivity of \(BRCA\)-related and sporadic breast cancers to the standard chemotherapy that Ms E received (ie, anthracycline and alkylator-based). Kriege et al\textsuperscript{46} retrospectively studied response rates to chemotherapy that Ms E received (ie, anthracycline and alkylator-based). There are limited clinical data addressing the relative sensitivity of \(BRCA\)-related and sporadic breast cancers to the standard chemotherapy that Ms E received (ie, anthracycline and alkylator-based). Kriege et al\textsuperscript{46} retrospectively studied response rates to chemotherapy that Ms E received (ie, anthracycline and alkylator-based).

Recent data have raised the question of whether cisplatin, an unconventional breast cancer agent, should be used instead of standard chemotherapy to treat newly diagnosed breast cancer in mutation carriers. In early breast cancer, the response of a tumor to chemotherapy administered prior to excision of the cancer (neoadjuvant chemotherapy) can be measured at the time of surgery; pathologic complete response is often considered the gold standard of response to a regimen and correlates with long-term disease-free survival. In a retrospective cohort study, Byrski et al\textsuperscript{47} found that of 51 mutation carriers treated with conventional neoadjuvant doxorubicin and cyclophosphamide, 11 (22\%) had a pathologic complete response. In comparison, 18 of 25 mutation carriers (72\%) demonstrated pathologic complete response in a prospective trial using cisplatin.\textsuperscript{48,49} Two \(BRCA1\) carriers in a second report also had a pathologic complete response to neoadjuvant cisplatin.\textsuperscript{50} Cisplatin is a DNA cross-linking agent that causes double-strand (DS) DNA breaks. While most cells in a mutation carrier still have 1 functioning copy of \(BRCA1\) or \(BRCA2\) (depending on the mutation), cancer cells have lost both functioning alleles. \(BRCA1/2\) proteins are critical in repair of DS DNA breaks through the process of homologous recombination. However, this apparent superior response to cisplatin compared with nonplatinum chemotherapy requires confirmation. Likewise, preclinical models have shown decreased sensitivity to chemotherapy agents such as taxanes that require intact homologous recombination to work.\textsuperscript{45} Currently, for patients like Ms E, standard adjuvant therapy rather than cisplatin should generally be used outside of a clinical trial.

### Table 2. Effects of Prophylactic Mastectomy in Women With \(BRCA1/2\) Mutations

<table>
<thead>
<tr>
<th>Source</th>
<th>Study Design</th>
<th>No. Exposed</th>
<th>No. With (BRCA) Mutation</th>
<th>No. of Events</th>
<th>Mean Follow-up, y</th>
<th>HR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Brekelmans et al,\textsuperscript{27} 2006</td>
<td>Retrospective cohort</td>
<td>37</td>
<td>133</td>
<td>0</td>
<td>NR</td>
<td>4.3\textsuperscript{b}</td>
</tr>
<tr>
<td>Brekelmans et al,\textsuperscript{24} 2007</td>
<td>Retrospective cohort</td>
<td>51</td>
<td>209</td>
<td>170</td>
<td>90</td>
<td>NR</td>
</tr>
<tr>
<td>van Sprundel et al,\textsuperscript{27} 2005</td>
<td>Retrospective cohort</td>
<td>79</td>
<td>69</td>
<td>115</td>
<td>33</td>
<td>14</td>
</tr>
<tr>
<td>Rebbeck et al,\textsuperscript{26} 2004</td>
<td>Matched cohort</td>
<td>102</td>
<td>378</td>
<td>382</td>
<td>101</td>
<td>186</td>
</tr>
<tr>
<td>Meijers-Heijboer et al,\textsuperscript{37} 2001</td>
<td>Prospective cohort</td>
<td>78</td>
<td>63</td>
<td>120</td>
<td>19</td>
<td>8</td>
</tr>
<tr>
<td>Domchek et al,\textsuperscript{28} 2010</td>
<td>Prospective cohort</td>
<td>247</td>
<td>1372</td>
<td>1032</td>
<td>587</td>
<td>98</td>
</tr>
</tbody>
</table>

Abbreviations: CI, confidence interval; HR, hazard ratio; NR, not reported; PM, prophylactic mastectomy.

\textsuperscript{a}Risk in carriers with previous breast cancer by age and mutation status was also estimated by Kurian et al\textsuperscript{20} in a Monte Carlo model.

\textsuperscript{b}Median duration of follow-up.

\textsuperscript{c}Hazard ratio for breast cancer–specific survival.

\textsuperscript{d}Hazard ratio for overall mortality.
**PARP Inhibitors.** Poly (ADP-ribose) polymerase 1 (PARP) inhibitors are novel agents that exploit the defect in homologous recombination that exists in *BRCA*-related breast and other cancers. PARP inhibitors block the repair of single-strand (SS) DNA breaks through the base excision repair pathway. During cell replication, these unrepaired SS DNA breaks are converted to DS DNA breaks that cannot be repaired in the *BRCA*-deficient cancer cells (see interactive Figure illustrating the mechanism of action of PARP inhibitors at http://www.jama.com). A phase 2 trial in patients with metastatic breast cancer demonstrated a +1% response rate with olaparib, an oral PARP inhibitor, when used at the optimal dose. Adverse effects were minimal, and responses were seen in women who had previously received multiple chemotherapy regimens. The success of PARP inhibitors in treating *BRCA*-related metastatic breast cancer underscores the importance of genetic testing in appropriate patients with advanced breast cancer. Trials comparing combinations of chemotherapy and PARP inhibitors with single-agent PARP inhibitors and chemotherapy alone are under way. It is not yet clear whether Ms E would have benefited from PARP inhibitor treatment because trials in *BRCA*-carriers with early breast cancer have not yet begun.

**Breast Cancer Surveillance in BRCA1/2 Carriers.** When deciding whether to undergo prophylactic mastectomy, mutation carriers must consider the effectiveness of breast cancer surveillance. The goal of screening is to detect breast cancer before it becomes invasive (e.g., ductal carcinoma in situ [DCIS]) or at least when it is small (<1 cm) and before it has spread to axillary lymph nodes. Ms E’s breast cancer was not seen on mammography even when palpable. Studies have demonstrated that breast MRI is approximately twice as sensitive as mammography for detecting breast cancer in women at increased risk, and annual MRI has been incorporated into screening guidelines for mutation carriers. Magnetic resonance imaging is considered complementary to mammography, however, since 2 large trials found mammography to be more sensitive than MRI at detecting DCIS in women at increased risk of breast cancer. In contrast, Kuhl et al found that the sensitivity of breast MRI far exceeded that of mammography in women at increased risk, and annual MRI has been incorporated into screening guidelines for mutation carriers. Magnetic resonance imaging is considered complementary to mammography, however, since 2 large trials found mammography to be more sensitive than MRI at detecting DCIS in women at increased risk of breast cancer. In contrast, Kuhl et al found that the sensitivity of breast MRI far exceeded that of mammography in detecting DCIS. The sensitivity of combined MRI and mammography in women at increased risk is 80% to 100%.

Two studies have evaluated surveillance with combined MRI and mammography in 329 mutation carriers, one-third of whom had a history of breast cancer like Ms E. They demonstrated that 24% of the cancers detected were DCIS, and of the 25 invasive cancers, 83% were node-negative, 52% were smaller than 1 cm, and only 2 (8%) were larger than 2 cm at diagnosis. The Dutch MRI screening study reported that surveillance with annual mammography and breast MRI may be less effective in detecting early breast cancer in *BRCA1* compared with in *BRCA2* carriers. In 599 mutation carriers without prior breast cancer, the cancers found in *BRCA1* carriers were larger, less often DCIS, and more often undetected by surveillance. These differences may reflect the higher proliferative rate of triple-negative breast cancers that occur in *BRCA1* carriers, like Ms E, and the difficulty of detecting these cancers when they are small or preinvasive.

However, the increased sensitivity of breast MRI comes at the expense of decreased specificity. Specificity of combined mammogram and MRI is 73% to 90% in high-risk women, although in prospective studies it is generally greater than 95%. Women who choose surveillance rather than prophylactic mastectomy must consider the additional imaging and biopsies that may follow from the pursuit of abnormal imaging findings. In high-risk women, the frequency of additional imaging is 11% and of biopsies; 5% to 11%. However, these rates decrease with ongoing screening because abnormal findings are most common on initial MRI.

**Ovarian Cancer Risk Management in BRCA1/2 Carriers**

Although it has been recommended that use of transvaginal ultrasound and cancer antigen 125 blood tests be considered starting at age 35 years in mutation carriers, screening for ovarian cancer is widely believed to be ineffective since it often detects cancer only when it is advanced and does not improve survival.

All mutation carriers, including those with a diagnosis of breast cancer such as Ms E, should undergo RRSO when childbearing is completed, ideally by age 35 to 40 years. Laparoscopic RRSO can be performed as an outpatient procedure in most cases. Although no randomized trials have been performed, observational studies demonstrate that in mutation carriers with a history of breast cancer, like Ms E, RRSO is associated with a decrease in breast cancer—specific (HR, 0.35; 95% CI, 0.19-0.67) and overall (HR, 0.30; 95% CI, 0.17-0.52) mortality. A significant decrease was seen in the distal fallopian tube. Unfortunately, even when RRSOs are performed prophylactically, ovarian cancer is found in 2% to 4% of cases and early serous tubal carcinomas are detected in 4% to 10% of specimens with careful fallopian tube sectioning. The residual risk of primary peritoneal cancer after RRSO is estimated to be 4.3% at 20 years, since the cells lining the peritoneal cavity arise from the same embryologic origin as the epithelial cells of the ovary and fallopian tubes.

The role of oophorectomy in decreasing the risk of CBC was discussed previously. Risk-reducing salpingo-oophorectomy performed in a premenopausal mutation carrier is also associated with a reduction in the risk of primary breast cancer by approximately 50% (eTable). and 1 report concluded that the benefit was greater if it was performed before age 40 years. While 2 studies have found that breast cancer risk reduction is greater after RRSO for...
BRCA2 carriers,65,68 a meta-analysis demonstrated that the benefit was similar for BRCA1 and BRCA2 carriers.71

**Hormone Therapy**

Mutation carriers who undergo RRSO at a young age face medical problems such as osteoporosis, as well as quality-of-life issues associated with menopause. This consideration raises the question of whether it is safe to treat mutation carriers with hormone therapy, an option typically not offered to women with a prior diagnosis of breast cancer like Ms E. Two retrospective studies in mutation carriers without prior cancer did not find an increased risk of breast cancer in those who had used hormone therapy.71,73 However, given the small numbers of women studied and the short follow-up, additional trials are needed to assess the optimal use of hormone therapy in this population. Alternatively, nonhormonal therapies exist to treat bone loss and menopause-induced symptoms.

**Other Cancers in BRCA1/2 Carriers**

When counseling Ms E and her relatives, it is important to emphasize that an increased risk of other cancers has been found in both male and female mutation carriers. In BRCA1 carriers, the risk of prostate cancer is 33% to 39% by age 70 years,76 the risk of pancreatic cancer is 3% to 4%,77 and the risk of male breast cancer is 1.2%.78 Data are inconsistent regarding the risk of uterine cancer,77,79,80 and colon cancer31,37,81 in BRCA1 carriers. In BRCA2 carriers, studies have found an increased risk of male breast cancer, with a lifetime risk of 7%78,81, pancreatic cancer, 4% to 8%27,77, prostate cancer, 19% to 39%76,82; and melanoma, 5%.78 Men with BRCA2 mutations develop a particularly aggressive form of prostate cancer and have a shorter survival than men with sporadic or BRCA1-related prostate cancer.82,83 An increased risk of gastric cancer has also been found in BRCA2 carriers.85 Despite lack of any demonstrated benefit, adherence to appropriate screening guidelines for these cancers has been recommended.7

**Preimplantation Genetic Diagnosis**

Ms E harvested her eggs prior to chemotherapy and used preimplantation genetic diagnosis (PGD) on her stored embryos. Preimplantation genetic diagnosis involves removing a single cell from a 3-day-old embryo when it is at the 8-cell stage and every cell is totipotent. Genetic testing is performed, results return within 24 to 48 hours, and embryos without the BRCA1/2 mutation can then be selected for reimplantation. This process results in a nearly 100% chance that the offspring will not have the mutation, rather than a 50% chance when it is not performed. However, PGD is expensive, adding $3500 to $4000 to the cost of in vitro fertilization, and currently is not covered by most US insurance plans.

The use of PGD in general has raised ethical concerns about the use of genetic testing to create “designer babies” since PGD can be used not only to avoid serious genetic diseases (eg, cystic fibrosis) but for sex selection and selection of embryos with traits unrelated to disease. Critics of PGD for BRCA carriers argue that a mutation merely predisposes to but does not guarantee the development of cancer and that most cancers would not develop until adulthood. Various consensus groups (eg, the American Society for Reproductive Medicine, the Human Fertilization and Embryology Authority, and the National Comprehensive Cancer Network) support consideration of PGD for individuals with cancer predisposition mutations.7 Studies of patients’ opinions consistently find that 60% to 75% of BRCA carriers support the use of PGD, though fewer would personally consider using the procedure.84,85

While physician acceptance of PGD for patients with hereditary cancer syndromes is high, knowledge is limited.86 Therefore, BRCA mutation carriers who are making reproductive decisions, like Ms E, should be advised of PGD as an option and referred to reproductive specialists for consultation if they are interested.

**Genetic Testing and Risk Management in BRCA1/2 Carriers Without Cancer**

BRCA1/2 mutations are inherited in an autosomal dominant fashion; each first-degree relative of a carrier has a 50% chance of having a mutation. While Ms E’s mutation was most likely inherited from her now-deceased father, genetic testing of her mother would clarify whether there are additional relatives who should undergo genetic counseling and testing.

Managing the Increased Risk of Breast Cancer in Carriers Without Prior Cancer.

Breast cancer screening in mutation carriers should begin at age 25 years.7 Since the risk of radiation-induced breast cancer from mammography may outweigh the screening benefit in younger women,87 some clinicians delay mammography until age 30 years. However, surveillance with breast MRI can begin at age 25 years.

Prophylactic mastectomy is extremely effective in unaffected mutation carriers and reduces the residual lifetime risk of breast cancer to less than 5% (Table 2).36,37,65 However, the survival benefit of prophylactic mastectomy in this population is small. Compared with surveillance of BRCA 1/2 carriers who undergo RRSO, it is estimated that survival is increased by at most 3% with prophylactic mastectomy performed at age 40 years.39 Since this estimate is model-based, prospective studies addressing the survival advantage of prophylactic mastectomies in unaffected mutation carriers are needed.

Only 1 study has evaluated the benefit of tamoxifen, a selective estrogen receptor modulator (SERM), for primary breast cancer prevention in BRCA1/2 carriers. This unplanned subset analysis did not show a significant risk reduction, possibly because of the small number of mutation carriers identified (8 BRCA1 and 11 BRCA2).88 No studies have examined the effectiveness of raloxifene, another SERM, for chemoprevention in mutation carriers. The Aromasin Prevention Study (APreS) is evaluating the role of the aromatase inhibitor exemestane for primary breast cancer prevention in mutation carriers. Aromatase inhibitors block the conversion of androgens to estrogen in postmenopausal women, and in noncarriers have been associated with a 70% to 80% decrease in CBC.89

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Several studies have found that oral contraceptive use in mutation carriers is associated with a 50% to 60% decrease in the risk of ovarian cancer and that longer use is associated with a greater protective effect. However, the data are inconsistent as to whether oral contraceptive use is associated with an increased risk of breast cancer.01-04

Timing of Genetic Testing. The opportune time for an unaffected relative to be tested generally is when medical care, including screening, will be affected. BRCA1/2 mutations do not increase the risk of childhood malignancy, and ASCO guidelines support “delaying genetic testing until an individual is of sufficient age to make an informed decision.” As discussed, RRSO should be performed when childbearing is completed, preferably between ages 35 and 40 years. Since breast cancer screening should begin at age 25 years, many individuals contemplate testing at this age. Individuals who potentially have a BRCA mutation may also want to undergo genetic testing when they are contemplating parenthood since those who have a BRCA mutation may choose to use PGD.

What the Future Holds
The optimal chemotherapy for mutation carriers with breast cancer, as well as any survival benefit for prophylactic mastectomy in these women, will need to be determined in future studies. The role that specific BRCA mutations, environmental and lifestyle factors, and other genetic factors play in modifying the risk of particular cancers should be determined. As an increasing number of mutation carriers undergo RRSO, the long-term medical consequences of premature menopause will be elucidated. Controversy exists regarding the need for hysterectomy at the time of RRSO, and more data to inform this clinical decision are needed.00 Given the limitations of patient-reported family history and the demonstration that many mutation carriers are not identified using current guidelines, genetic testing for higher-risk populations (eg, Ashkenazi Jews) has been proposed04; the consequences of such an approach need to be considered thoughtfully. Finally, with the success of PARP inhibitors in mutation carriers with advanced breast cancer, the future will likely see the evaluation of these agents in treatment of early breast cancer and prevention of cancer in BRCA1/2 carriers. Hopefully, someday the use of these or other agents exploiting the unique biological defects in BRCA-related cancers will serve as effective prevention and enable mutation carriers to avoid prophylactic surgeries.

QUESTIONS AND DISCUSSION

QUESTION: What protections are in place against discrimination resulting from genetic testing?

DR TUNG: Few, if any, examples of overt discrimination as a result of BRCA1/2 genetic testing exist, yet fear of discrimination deters many women. Genetic information is considered to be protected health information and is covered by the Privacy Rule of the Health Information Portability and Accountability Act of 1996. In 2008, the federal government passed the Genetic Information Nondiscrimination Act, which protects against the use of genetic information to discriminate in issues of employment or health insurance but does not specifically cover life insurance, disability insurance, and long-term care insurance. This act sets a minimum level of protection; most states have passed their own laws with varying additional protection against discrimination.

QUESTION: Is there evidence that triple-negative breast cancers (TNBCs) in women without a BRCA1/2 mutation should be treated similarly to BRCA1-related TNBCs?

DR TUNG: It is important to remember that although 80% of the breast cancers that develop in BRCA1 carriers are TNBCs, treatments effective in BRCA-related breast cancers may not necessarily have the same benefit in sporadic TNBC. Cisplatin resulted in only a 15% pathologic complete response rate in 26 non–mutation carriers with TNBC, and PARP inhibitors have shown little to no benefit in sporadic breast cancers.00

QUESTION: Are there any detrimental effects associated with long-term use of breast MRI in mutation carriers starting at age 25 years?

DR TUNG: Unlike mammography, breast MRI does not use ionizing radiation; therefore, there is no known risk of cancer induction from its long-term use. However, the use of gadolinium-based contrast agents for contrast-enhanced breast MRI in patients with severe renal failure increases the risk of developing nephrogenic systemic fibrosis/nephrogenic fibrosing dermopathy, a rare but potentially fatal scleroderma-like illness.100

QUESTION: What are the cost implications of genetic testing programs? The process of genetic counseling is time-intensive and requires trained counselors. As more genetic predispositions for diseases are identified, how will genetic programs be financed?

DR TUNG: Unfortunately, most genetic counseling programs cost more than they generate in revenue. Since the demand for BRCA1/2 testing has increased, many physicians in the community now offer genetic testing with or without the aid of trained counselors, and testing companies market directly to community-based physicians. However, several studies have shown that many clinicians lack sufficient knowledge to counsel adequately.101,102 In a survey of nonacademic physicians, those assisted by a trained genetic counselor or nurse-geneticist, those who spent at least 60 minutes counseling, and medical oncologists were more likely to discuss important counseling issues.103 We need to understand the relative effectiveness of counseling offered in academic-based genetic counseling programs compared with that offered in the community, especially for the dissemination of complex information such as uninformative negative results (eg, a negative result in a family without a known mutation) and genetic variants of uncertain significance. The need to understand the implications of other genetic changes (eg, al-
lele polymorphisms) for cancer risk has become even more critical since companies now market directly to consumers. As identification of disease predisposition genes occurs at an accelerating rate, the burden on physicians to understand and absorb this information is prodigious. Determining how best to compensate hospitals and physicians for trained genetic counselors is essential.

Conflict of Interest Disclosures: The author has completed and submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest and none were reported.

Online Only Material: The interactive figure illustrating the mechanism of action of PARP inhibitors and the eTable are available at http://www.jama.com.

Additional Contributions: We thank the patient for sharing her story and for providing permission to publish it.

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