Risk-Reducing Appendectomy and the Elimination of BRCA1-Associated Intraperitoneal Cancer

James V. Sitzmann, MD; Eric A. Wiebke, MD, MBA

Risk-reducing bilateral salpingo-oophorectomy (RRBSO) and risk-reducing mastectomy are widely used for BRCA1 and BRCA2 mutation carriers to reduce the risk of ovarian and breast cancer. To our knowledge, no risk-reduction therapy has addressed the BRCA1/2 carrier lifetime risk of intra-abdominal peritoneal carcinoma from an appendix source. We identified a BRCA1 carrier in a hereditary breast and ovarian cancer kindred who developed a low-grade malignant appendiceal mucocele 2 years after risk-reducing salpingo-oophorectomy. Our retrospective meta-analysis assessed the risk of intraperitoneal appendiceal cancer in BRCA1/2 carriers after RRBSO to determine whether elective risk-reduction appendectomy could reduce the incidence of intraperitoneal cancer. Data sources included the case report and 12 reports of BRCA1 and BRCA2 carriers after RRBSO with ovarian, fallopian tube, breast, and peritoneal cancer published from January 1, 1985, through April 30, 2012. Main outcome measures were nonovarian, non–fallopian tube, nonbreast, positive intra-abdominal peritoneal carcinoma in previously cancer-free BRCA1/2 carriers after RRBSO. The source of intraperitoneal cancer in BRCA1/2 carriers after risk-reducing salpingo-oophorectomy is highly likely the appendix. Use of risk-reduction appendectomy with RRBSO in younger BRCA1/2 carriers may reduce lifetime risk of malignant tumor and eliminate intraperitoneal cancer.


The well-documented penetrance of ovarian cancer (OC) in BRCA1 (OMIM 113705) mutation carriers is 11% to 54%, and the OC penetrance in BRCA2 (OMIM 600185) carriers is 11% to 23%. Clinical therapy for OC prevention has progressed to routine use of risk-reducing bilateral salpingo-oophorectomy (RRBSO) in women with hereditary breast cancer and OC (HBOC) kindreds. Risk-reduction operative ablative procedures have been reported in more than 8000 women resulting in reduction of risk of OC in HBOC kindreds by 80%. Multiple studies have noted that BRCA1/2 carriers after BSO retain a lifetime risk of intraperitoneal cancer from 1% to 10%. The peritoneal cancer occurrence in BRCA1/2 cohorts presents an unknown, unanswered mortality question related to the pathologic origin site of the intraperitoneal tumor: ovarian or fallopian tube or gastrointestinal (GI) intra-abdominal primary sites remain the most common suggested sources.

An element of diagnostic difficulty is using only histologic examination in determining the primary organ source of malignant tumor in intraperitoneal carcinomatosis. On the basis of the histology of intraperitoneal cancers, the primary site has been reported to be an ovary, a fallopian tube, or the appendix and other possible GI sources, such as the colon, stom-
ach, bile duct, or pancreas. All the peritoneal cancers from GI sources have been documented to produce histologically quite similar serous intraepithelial mucoid cells. The appendiceal source of low-grade mucoid tumor follows a clinical course of origin and growth within the appendix progressing to appendiceal rupture and peritoneal surface dissemination with carcinomatosis, which has been called pseudomyxoma peritonei (PMP) for decades. Many published reports of intraperitoneal cancer occurrence in BRCA1/2 cohorts suggest that after RRBSO a pathology laboratory error has occurred.

The multiple primary cancer sites associated with BRCA1/2 carriers result in lifetime cancer risk for HBOC kindred of 85% compared with 38% in the general population. The current case report of BRCA1 HBOC kindred developing a low-grade malignant appendiceal mucocoele 2 years after RRBSO is notable. The clinical presentation reveals an unsuspected malignant appendiceal mucocoele before rupture without intraperitoneal dissemination. This case is an example of a potential major cause of intraperitoneal cancer in BRCA1 mutation carriers in which rupture of the appendix results in PMP. This clinical case prompted a retrospective meta-analysis literature review to assess the relationship of BRCA1/2 mutation carriers after RRBSO and risk-reducing bilateral mastectomy (RRBM) who develop intraperitoneal cancer and to determine whether elective risk-reduction appendectomy would reduce the residual intraperitoneal cancer risk in female BRCA1/2 carriers.

To estimate the risk of nonovarian, non–fallopian tube, primary appendix origin of intraperitoneal cancer in BRCA1/2 mutation carriers, a review of published studies of BRCA1/2 cohorts was conducted. The review yielded 12 nonoverlapping studies reporting the incidence of intraperitoneal cancer. These studies included BRCA1/2 carriers after RRBSO and RRBM with no history of breast, ovarian, fallopian tube, or uterine cancer. These studies form the basis of a meta-analysis estimate of intraperitoneal cancer risk from a suspected primary appendiceal source in BRCA1/2 carriers who were documented to be free of all other primary cancer sites.

**METHODS**

The Indiana University institutional review board provided expedited approval of the study (full review of case studies and meta-analyses is not required by this board). Methods and case report clinical data were obtained, de-identified from hospital records of the BRCA1 patient and her HBOC kindred.

**META-ANALYSIS CRITERIA**

Intraperitoneal cancer primary site of origin is a diagnosis of exclusion reached by a process of elimination, which is the method used to identify the intraperitoneal cancer source of the highest probability. The method of elimination is iterative. The possible primary site of origin of intraperitoneal cancer in every patient considered for enrollment in this meta-analysis was identified. Every case enrolled from published cohorts into the present meta-analysis had established resections of several primary sites (breast, ovary, fallopian tube, and uterus), thus eliminating these as primary site possibilities. This left only 4 intra-abdominal sites of intraperitoneal cancer: appendix, colon, GI tract, or pancreas. The latter GI sources (colon, GI tract, and pancreas) cannot be accepted as probable primary sites with no primary organ mass and no symptoms, which leads to greater than 99.99% diagnosis before classification as intraperitoneal cancer. Any BRCA1/2 mutation carrier reported to have colon, gastric, or pancreatic cancer was excluded from the analysis.

**META-ANALYSIS DATA ACCRUAL**

Meta-analysis patient-specific clinical data were extracted from the case report, and 12 reports published from January 1, 1985, through April 30, 2012, were obtained from a PubMed search of BRCA1/2 mutation carriers followed up after RRBSO and/or RRBM who developed peritoneal cancer.

Cohort studies and prospective studies with retrospective elements were reviewed, and the case familial series report was included. The basic design of the 12 published studies used to extract data was that of a prospective cohort study of BRCA1 and BRCA2 female carriers. The case report qualified as a familial cohort series. Randomized control trials were excluded. The major effect of pathologic determination within any reported cohort series was derived from specific data on individual patient cancer site identification, and there was no overlap with prior reports.

Length of follow-up by definition was more than 5 years after RRBSO and/or RRBM in order to have a patient develop intraperitoneal cancer with no risk of peritoneal metastatic cancer from these common sources. This study used process of elimination to lead to a conclusion. All other consensus primary-origin sites of intraperitoneal cancer (of the breast, uterus, fallopian tube, ovary, pancreas, colon, and stomach) were methodically excluded from any patient included in this meta-analysis.

**DATA EXTRACTION METHOD**

The method used an extensive limitation of inclusion criteria. The “extraction criteria” eliminated all other consensus-accepted primary pathologic sources of reported intraperitoneal cancers in female patients. This method assumes that breast, ovarian, fallopian tube, uterus, pancreatic, colon, or stomach primary cancer had been identified and reported in the manuscripts used in the meta-analysis. For the published studies to be accepted in this meta-analysis, all cancer sources in all patients had to be identified. In publications accepted into the meta-analysis, all breast, ovarian, and fallopian tube cancers found in resected tissues in the patients were reported, and these specific patients were excluded from the analysis. Only previously cancer-free patients and those with intraperitoneal cancer with no other primary-site cancer identified were extracted from series for inclusion in this study. All reports of any other cancer site or mortality from all other causes resulted in exclusion of the patient from the current meta-analysis.

**RISK ANALYSIS**

A meta-analysis estimate of risk and mortality reduction was stratified by BRCA1 and BRCA2 mutation status, intraperitoneal carcinoma incidence, sex, OC status, breast cancer status, other cancer site status, and age to evaluate the risk and benefit of a novel intraperitoneal cancer risk-reduction strategy: elective appendectomy. The analysis cohort was restricted to women, and all cases of OC or breast cancer of any stage identified before or after RRBSO were excluded. Also, all patients with any other cancer present before or at the time of RRBSO and/or RRBM were excluded. Therefore, all patients with extraperitoneal cancer or with intraperitoneal cancer that could represent OC or breast cancer or fallopian tube cancer progression were excluded.
variable before applying Cox proportional risk assessment. Statistical modeling used data censoring and Cox proportional analysis and has been widely used in BRCA studies. Data censoring was performed to remove variables and narrowed to a specific variable (intraperitoneal cancer) assessment over time. Censoring was performed to remove variables and narrowed to a specific variable (intraperitoneal cancer) assessment over time.

oc. The patient did well after RRBSO. Subsequently, the meta-analysis estimates of risk of primary peritoneal cancers for HBOC kindred women with no breast, no ovarian, and no fallopian tube cancers after RRBSO, by age and mutation type, are presented in Table 1. The risk of peritoneal cancer following RRBSO was significantly higher for BRCA1 mutation carriers than for BRCA2 mutation carriers (11.6% vs. 0.9%; P < .01) (Table 1). Also notable is that intraperitoneal cancer incidence increased with age. There was 0% risk before age 40 years. No case of intraperitoneal cancer in BRCA1/2 cohorts younger than 40 years was reported.

The annualized BRCA1 carrier intraperitoneal cancer hazard risk of 0.06% rose from the youngest reported case (age 42 years) in a cumulative fashion, which summed to 5% per decade after the fifth decade of life (40-49 years of age). The cumulative hazard rate reached 11.6% penetrance after the seventh decade (Figure). This represents 30 years of exposure after age 40. This steady increase in intraperitoneal cancer correlation with age may relate to increased occurrence due to timeline exposure or due to years’ delay in clinical presentation. Hazard risk analysis revealed 6.8% annualized risk in BRCA1 carriers older than 40 years and 0.5% risk in BRCA2 carriers older than 40 years. Total BRCA1/2 carriers have 6.7% annual hazard risk of intraperitoneal cancer (Table 2)

Statistical modeling predicts that widespread use of elective risk-reduction appendectomy in HBOC kindred BRCA1 mutation carriers combined with early RRBSO would result in 99% reduction of the lifetime risk

## RESULTS

### CASE REPORT

A 44-year-old woman presented with a 40-day history of increasing right lower quadrant abdominal pain. Her medical history was significant for RRBSO and risk-reducing mastectomy as a carrier of BRCA1 mutation 2 years before this presentation. Both her mother and sister were kindred BRCA1/2 carriers who had developed OC. The patient did well after RRBSO. Subsequently, evaluation of the new abdominal pain included a computed tomographic scan that demonstrated a large appendiceal mass. At exploratory laparotomy, she was found to have an appendiceal mass, which was resected with appendectomy and partial cecectomy. This was malignant. Pathologic evaluation revealed a nonperforated, low-grade, mucinous appendiceal neoplasm with negative colonic margins and no nodal involvement in the 5 lymph nodes evaluated. The patient was discharged 24 hours after the operation and has done well in 1 year of follow-up. The case reveals the clinical presentation of an unsuspected appendiceal mucocoele before progression to intraperitoneal cancer in a BRCA1 mutation carrier from a well-documented HBOC kindred.

### META-ANALYSIS ESTIMATE

The meta-analysis estimates of risk of primary peritoneal cancers for HBOC kindred women with no breast, no ovarian, and no fallopian tube cancers after RRBSO, by age and mutation type, are presented in Table 1. The risk of peritoneal cancer following RRBSO was significantly higher for BRCA1 mutation carriers than for BRCA2 mutation carriers (11.6% vs. 0.9%; P < .01) (Table 1). Also notable is that intraperitoneal cancer incidence increased with age. There was 0% risk before age 40 years. No case of intraperitoneal cancer in BRCA1/2 cohorts younger than 40 years was reported.

The annualized BRCA1 carrier intraperitoneal cancer hazard risk of 0.06% rose from the youngest reported case (age 42 years) in a cumulative fashion, which summed to 5% per decade after the fifth decade of life (40-49 years of age). The cumulative hazard rate reached 11.6% penetrance after the seventh decade (Figure). This represents 30 years of exposure after age 40. This steady increase in intraperitoneal cancer correlation with age may relate to increased occurrence due to timeline exposure or due to years’ delay in clinical presentation. Hazard risk analysis revealed 6.8% annualized risk in BRCA1 carriers older than 40 years and 0.5% risk in BRCA2 carriers older than 40 years. Total BRCA1/2 carriers have 6.7% annual hazard risk of intraperitoneal cancer (Table 2). Statistical modeling predicts that widespread use of elective risk-reduction appendectomy in HBOC kindred BRCA1 mutation carriers combined with early RRBSO would result in 99% reduction of the lifetime risk

### Table 1. Meta-analysis: Intraperitoneal Cancer in Otherwise Cancer-Free BRCA1/2 Patients After RRBSO

<table>
<thead>
<tr>
<th>Rank</th>
<th>Source</th>
<th>BRCA1 Carriers</th>
<th>BRCA2 Carriers</th>
<th>BRCA1/2 Carriers</th>
<th>Mean Age, y</th>
<th>Risk, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>Case report</td>
<td>3</td>
<td>1</td>
<td>4</td>
<td>45</td>
<td>1</td>
</tr>
<tr>
<td>1</td>
<td>Finch et al</td>
<td>374</td>
<td>113</td>
<td>487</td>
<td>51</td>
<td>487</td>
</tr>
<tr>
<td>2</td>
<td>Scheur et al</td>
<td>77</td>
<td>40</td>
<td>117</td>
<td>48</td>
<td>117</td>
</tr>
<tr>
<td>3</td>
<td>Olivier et al</td>
<td>26</td>
<td>12</td>
<td>38</td>
<td>48</td>
<td>38</td>
</tr>
<tr>
<td>4</td>
<td>Kauff et al</td>
<td>56</td>
<td>42</td>
<td>98</td>
<td>48</td>
<td>98</td>
</tr>
<tr>
<td>5</td>
<td>Rebbeck et al</td>
<td>114</td>
<td>22</td>
<td>136</td>
<td>52</td>
<td>136</td>
</tr>
<tr>
<td>6</td>
<td>Powell et al</td>
<td>55</td>
<td>46</td>
<td>101</td>
<td>63</td>
<td>101</td>
</tr>
<tr>
<td>7</td>
<td>Maehle et al</td>
<td>48</td>
<td>1</td>
<td>49</td>
<td>56</td>
<td>49</td>
</tr>
<tr>
<td>8</td>
<td>Donmetch et al</td>
<td>342</td>
<td>123</td>
<td>465</td>
<td>46</td>
<td>465</td>
</tr>
<tr>
<td>9</td>
<td>Rutter et al</td>
<td>7</td>
<td>0</td>
<td>7</td>
<td>48</td>
<td>7</td>
</tr>
<tr>
<td>10</td>
<td>Kauff et al</td>
<td>325</td>
<td>184</td>
<td>509</td>
<td>47</td>
<td>509</td>
</tr>
<tr>
<td>11</td>
<td>Casey et al</td>
<td>65</td>
<td>13</td>
<td>78</td>
<td>56</td>
<td>78</td>
</tr>
<tr>
<td>12</td>
<td>Rhiem et al</td>
<td>91</td>
<td>83</td>
<td>174</td>
<td>47</td>
<td>174</td>
</tr>
<tr>
<td>Totals</td>
<td>1583</td>
<td>680</td>
<td>2263</td>
<td>59.4</td>
<td>2263</td>
<td>45</td>
</tr>
</tbody>
</table>

Abbreviation: RRBSO, risk-reducing bilateral salpingo-oophorectomy.

Indicates a mean value.
for intraperitoneal cancer. Risk-reduction appendectomy would not reduce peritoneal cancer if the source were gastric, biliary, pancreatic, or other colonic sites as typically found in other familial cancer cohorts, such as familial adenomatous polyposis. Risk-reduction appendectomy, when combined with RRBSO and risk-reducing mastectomy, may also complete a “trifecta” resulting in an 80% reduction of total lifetime cancer risk.

The BRCA1/2 mutation carries a 1000-fold increased risk of peritoneal cancer compared with the risk in the general population. Also, BRCA1 mutation carries a specific 11.6% lifetime risk of intra-abdominal peritoneal cancer. Aging increases the risk of peritoneal cancer in BRCA1/2 mutation carriers. This study indicates that age greater than 40 years carries a 1000-fold increase risk of mucinous peritoneal cancer in HBOC kindred women. In BRCA1 carriers, aging steadily increased the risk of intraperitoneal cancer by 0.5% per year after the age of 40 years was reached (Figure). The cohort of women with BRCA1 mutations who are older than 40 years have a significantly increased incidence of intraperitoneal cancer compared with the general population.

Table 2. Hazard Risk of Intraperitoneal Cancer in BRCA1/2 Carriers After Risk-Reducing Bilateral Salpingo-oophorectomy

<table>
<thead>
<tr>
<th>Variable</th>
<th>BRCA1</th>
<th>BRCA2</th>
<th>BRCA1/2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hazard risk assessment</td>
<td>2.721518987</td>
<td>0.147058824</td>
<td>2.03269956</td>
</tr>
<tr>
<td>Annual risk</td>
<td>0.068037975</td>
<td>0.004901961</td>
<td>0.067756665</td>
</tr>
<tr>
<td>Annual risk, %</td>
<td>6.803797468</td>
<td>0.490196078</td>
<td>6.775666519</td>
</tr>
</tbody>
</table>

Women who carry the BRCA1 and/or BRCA2 genetic mutations have a well-documented increased risk of breast, ovarian, and fallopian tube cancers. Individual lifetime OC risk is estimated to range from 36% to 63% but is elevated to 95% if both maternal and sibling BRCA1 carriers have already developed OC. Additional cancer risk has also been reported to include an increased association of intra-abdominal peritoneal malignant tumors with OC. Some highly selective BRCA1/2 cohort studies based on primary therapy RRBSO in young patients and brief follow-up with or without chemotherapy report a low incidence of intraperitoneal cancer. Other larger, longer-term studies have identified peritoneal carcinomatosis in 2% to 3% of BRCA1/2 HBOC kindred cohorts after RRBSO with no prior OC diagnosis.

Multiple studies have observed that female carriers of BRCA1 or BRCA2 germline mutations are at an increased risk of developing breast, ovarian, salpingo-fallopian tube, and/or peritoneal malignant tumors. Management strategies for genetically susceptible women include genetic counseling, chemoprevention, radiologic and tumor-marker surveillance, and risk-reducing surgery, such as mastectomy and bilateral salpingo-oophorectomy.

Identification of the source organ in intraperitoneal cancer is frequently inaccurate because the pathology nomenclature classification includes primary papillary serous carcinoma of the peritoneum with no identification of the primary organ site. Papillary serous carcinoma of the peritoneum is considered a rare tumor found predominantly in elderly and postmenopausal women. Papillary serous carcinoma of the peritoneum has histologic characteristics similar to serous ovarian papillary carcinoma, serous fallopian tube cancer, and PMP arising from the appendix. These histologic similarities render an extracorporeal pathologic identification of organ origin site quite difficult, with primary site investigation limited to radiologic imaging and histologic analysis without pathologic examination of the primary organ site following excision or resection. Although the pathogenesis of papillary serous carcinoma of the peritoneum remains unclear, documentation or exclusion of GI sources has not been complete. Several published familial studies have included peritoneal carcinoma in the HBOC syndrome, which also includes breast, ovarian, and fallopian tube neoplasms.

Many published reports of intraperitoneal cancer in BRCA1/2 cohorts suggest that occurrence after RRBSO indicates that a pathology laboratory analysis error has occurred. The possible errors include that OC or fallopian tube cancer was not found or that cancer was missed owing to a sampling error or poor pathology processing. The diffuse peritoneal cancer primary source of origin has commonly been suggested to be an ovary, a fallopian tube, or the appendix (PMP) or to be a pancreatic intraductal papillary mucinous neoplasm, or a low-grade colon mucoid epithelial tumor. The total cancer risk for a BRCA HBOC kindred is increased for gastric cancer, gallbladder and biliary tract cancer, and melanoma.

Multiple other primary sites of metastatic intraperitoneal mucoid epithelial serous cancers may originate from GI sources. Low-grade, mucinous, adenomatous, intraperitoneal colon cancer syndromes include Lynch syndrome, familial adenomatous polyposis, attenuated familial adenomatous polyposis, MYH-associated polyposis, familial colon rectal cancer, Peutz-Jeghers syndrome, juvenile polyposis syndrome, hereditary mixed polyposis syndrome, and hyperplastic polyposis syndrome. The BRCA1/2 gene mutations have never been linked to any of these syndromes nor has BRCA1/2 been directly linked to colon cancer except in 1 case report. Also, no ovar-
ian, breast, or fallopian tube cancers have been reported in any of the colon cancer syndrome cohorts.

Many studies have identified multiple variable genetic expressions in histologically similar or identical tumors in appendiceal and ovarian tumors. The incidence of appendiceal cancer is rare, occurring in less than 0.5% of all general population GI tumors. Appendiceal mucocoele incidence is reported to occur rarely, in less than 0.3% of all appendectomies, and occurs in less than 0.0001% of the general population based on data about lifetime risk from the Surveillance, Epidemiology, and End Results program of the National Cancer Institute. These tumors may represent appendiceal tumors, which progress to locoregional peritoneal carcinomatosis, which is characteristic of PMP. Most intra-abdominal tumors in OC patients are reported as low-grade, mucinous, intraperitoneal cancers.

A mucocoele is characterized by the accumulation of mucoid material in the appendiceal lumen. The designation of mucocoele has been proposed for a neoplasm that is pathologically benign, premalignant, or malignant. Epithelial appendiceal tumor histology has been subclassed as 4 types: (1) a simple appendiceal mucocoele, (2) a mucocoele with epithelial hyperplasia, (3) a cystadenoma, and (4) a cystadenocarcinoma. The latter 2 are more aggressive neoplasms. Dissemination of necrotic cells producing mucoid material in the abdominal cavity typically occurs following appendiceal perforation, which results in PMP. This has been reported in 10% to 15% of appendiceal epithelial tumors. Metastatic dissemination of appendiceal low-grade epithelial tumors by vascular or lymphatic invasion has not been reported. These appendiceal benign or malignant proliferative pathologic features either can remain asymptomatic for a lifetime or present clinically with abdominal pain associated with intraperitoneal volume space reduction due to increasing tumor volume. The most common initial clinical manifestation is pain in the right lower iliac fossa. The appendiceal epithelial proliferative pathology diagnosis is most frequently based on intraoperative observation without histologic evaluation.

To our knowledge, this report presents the first case of a documented HBOC kindred BRCA1 carrier presenting with an appendiceal mucocoele tumor 2 years after RRBSO before developing PMP. This analysis provides strong clinical evidence that BRCA1 mutation carriers older than 40 years carry an additional 11% lifetime risk of appendiceal mucinous neoplasm, which is the most likely source of reported intraperitoneal cancer in BRCA1 and BRCA2 carriers. The data also strongly suggest that appendiceal tumors are the predominant source of intraperitoneal cancer in BRCA1/2 mutation carriers who have undergone RRBSO and have no fallopian tube cancer or OC.

Treatment of appendiceal tumor is excision appendectomy. Appendectomy is curative for a simple appendiceal mucocoele, for an appendiceal mucocoele with epithelial hyperplasia, and for cystadenoma with an intact appendiceal base; cecal resection is indicated for cystadenoma with appendiceal base involvement or invasion. Right hemicolectomy remains the elective oncologic staging and treatment for appendiceal cyst adenocarcinoma. Elective appendectomy carries no risk of functional loss and total operative risk of less than 0.01%. Elective appendectomy performed during RRBSO would not result in significant complications specifically related to appendectomy.

These facts, the strong statistical correlation of appendiceal mucinous peritoneal malignant tumor with OC, and the increased risk of intra-abdominal carcinomatosis in BRCA1 carriers support the proposed clinical treatment mandate of risk-reduction surgery to include prophylactic elective appendectomy with RRBSO in all BRCA1 carriers older than 40 years.

This meta-analysis confirms that BRCA1/2 mutation carrier cohorts older than 40 years have significantly increased incidence and risk of intraperitoneal cancer compared with the general population. The BRCA1 mutation carrier has a 6.8% annualized cumulative hazard risk of intraperitoneal cancer compared with a 1% risk in BRCA2 carriers. The BRCA1 risk of 11.6% is increased 1000-fold above that of PMP or other intraperitoneal cancer risk in the general population, whose risk is 1 in 100,000 (0.001%). On the basis of the risk assessment, the addition of risk-reduction appendectomy to RRBSO and RRBM in the cohort of women older than 40 years with BRCA1 or BRCA2 mutations is predicted to reduce the annual 6.7% risk of intraperitoneal cancer. This may also contribute a 12% total reduction in lifetime malignant tumor risk after eliminating the breast, fallopian tube, ovary, and appendix as intraperitoneal cancer primary source risks. The statistical model predicts that widespread use of risk-reduction appendectomy with RRBSO and risk-reducing mastectomy in HBOC kindred BRCA1 mutation carriers would result in a 99% reduction of the lifetime risk for peritoneal cancer and also lower total lifetime cancer risk from 95% to 20%.

Accepted for Publication: September 8, 2012.
Correspondence: James V. Sitzmann, MD, Surgical Service (112), Indianapolis Veterans Affairs Medical Center, 1001 W 10th St, Indianapolis, IN 46202 (jvsitzma@iupui.edu).

Author Contributions: Study concept and design: Sitzmann. Acquisition of data: Sitzmann. Analysis and interpretation of data: Sitzmann and Wiebke. Drafting of the manuscript: Sitzmann and Wiebke. Critical revision of the manuscript for important intellectual content: Sitzmann and Wiebke. Statistical analysis: Sitzmann. Administrative, technical, and material support: Sitzmann and Wiebke. Study supervision: Wiebke.

Conflict of Interest Disclosures: None reported.

References

The Appendix

A Culprit for BRCA1-Associated Intraperitoneal Cancer?

Women with inherited BRCA1/2 mutations have substantially elevated risks of breast and ovarian cancer, with 60% to 85% cumulative lifetime risk of invasive breast cancer and 10% to 63% risk of ovarian cancer.1-3 Prophylactic mastectomy and risk-reducing bilateral salpingo-oophorectomy (RRBSO) reduce the risk of both cancers and of cancer-specific and all-cause mortality in these patients.1-3

Women with BRCA1 mutations also have an increased risk of intra-abdominal carcinomatosis, which is reduced but not abrogated following RRBSO. The estimated risk for intra-abdominal carcinomatosis following RRBSO is less than 5%.4-5 The origins of intra-abdominal carcinomatosis after RRBSO remain unclear; dissemination of occult ovarian, fallopian tube, and possibly endometrial neoplasms has been suggested.

Here, Sitzmann and Wiebke6 review 12 studies examining outcomes among female BRCA1/2 mutation carriers. They report a 2% incidence (46 of 2262 patients) of intraperitoneal cancer following RRBSO; most cases occurred in BRCA1 mutation carriers. The authors raise the interesting possibility that the appendix may be the source of intraperitoneal cancer following RRBSO.

Although this hypothesis is intriguing, the data are far from convincing. The authors make the assumption that all cases of intraperitoneal cancer after RRBSO must be secondary to an appendiceal source because other potential sources were previously resected (ovaries and fallopian tubes) or “should” present with a primary lesion (colon, stomach, or pancreas). However, in the case of at least 1 patient included in this study, occult borderline serous papillary tumor was found in 1 ovary removed during RRBSO.4 It is also unknown how many of the patients with intraperitoneal cancer after RRBSO in this study had an appendix in situ because appendectomy is among the most commonly performed surgeries in the United States with an estimated 250,000 to 300,000 cases in 2010. The title “Risk-Reducing Appendectomy and the Elimination of BRCA1-Associated Intraperitoneal Cancer” is misleading because no patients included in this study underwent prophylactic appendectomy.

It therefore remains to be seen whether the appendix is a significant contributor to intra-abdominal cancer following RRBSO or whether occult gynecologic sources (ovaries, fallopian tubes, or endometrium) are the major players. If the authors’ theory can be verified, a question that still must be addressed before widespread adoption of appendectomy at the time of RRBSO is whether the intraperitoneal cancer risk-reduction benefit of prophylactic appendectomy justifies its attendant surgical risks.

Emily Z. Keung, MD
Stanley W. Ashley, MD

Author Affiliations: Department of Surgery, Brigham and Women’s Hospital/Harvard Medical School, Boston, Massachusetts.

Correspondence: Dr Ashley, Department of Surgery, Brigham and Women’s Hospital/Harvard Medical School, ASBH-3, 75 Francis St, Boston, MA 02115 (sashley@partners.org).

Conflict of Interest Disclosures: None reported.


JAMA SURG/VOL 148 (NO. 3), MAR 2013 WWW.JAMASURG.COM
©2013 American Medical Association. All rights reserved.