ABSTRACT

Objective: Recent evidence has supported the concept that epithelial ovarian cancer (EOC) arises from the cells of the fallopian tube or endometrium. This study investigated current practice in Japan with respect to performing opportunistic bilateral salpingectomy (OBS) during gynecological surgery for benign disease for Ovarian Cancer Prevention.

Methods: We mailed a questionnaire to 767 hospitals and clinics, comprising 628 accredited training institutions of the Japan Society of Obstetrics and Gynecology (JSOG), Japan Society of Gynecologic Oncology (JSGO), or Japan Society of Gynecologic and Obstetric Endoscopy and Minimally Invasive Therapy (JSGOE) and 139 private institutions with at least one JSGOE-certified licensed gynecologic laparoscopist.

Results: Among the 767 institutions, 444 (57.9%) provided responses, including 91 (20.6%) that were both JSGOE and JSGO accredited, 71 (16.0%) that were only JSGO accredited, 88 (19.8%) that were only JSGOE accredited, and 194 (43.7%) that were unaccredited. It was found that awareness and performance of OBS largely depended on the JSGO and/or JSGOE accreditation status. OBS was only performed at 54.0% of responding institutions and just 6.8% of the institutions were willing to participate in randomized controlled trials to validate this method for reducing the incidence of ovarian cancer.

Conclusion: The JSOG Gynecologic Tumor Committee will announce its opinion on salpingectomy for ovarian cancer prevention to all JSOG members and will develop a system for monitoring the number of OBS procedures in Japan.

Keywords: Ovarian Neoplasms; Salpingectomy; Prevention & Control
INTRODUCTION

Epithelial ovarian cancer (EOC) is the most devastating of all gynecological malignancies. In Japan, it is estimated that 9,384 new cases of EOC occurred in 2012 and there were 4,840 deaths from this cancer in 2014 [1]. The majority of ovarian cancers are diagnosed when the disease is advanced due to lack of effective screening tests for early detection. While women who are carriers of BRCA and Lynch syndrome mutations are known to have an elevated risk of ovarian malignancy, approximately 90% of ovarian cancer occurs sporadically [2]. Despite advances in treatment, particularly new chemotherapy agents, there has been little improvement of the overall survival of ovarian cancer patients during recent decades [3,4]. Serous EOC is the most common histological subtype in the USA and EU, being found in approximately 70% of patients. This subtype shows various morphological similarities to serous papillary cancer of the peritoneum and fallopian tube [5]. Evidence has been reported to suggest that serous EOC, traditionally considered to originate from the ovarian epithelium, may actually arise from the distal fallopian tube [6]. Histological examination of fallopian tube specimens obtained either during prophylactic surgery in high-risk women or during resection of serous ovarian/peritoneal cancer has demonstrated that a significant proportion of clinically occult malignancies and intraepithelial carcinomas originate from the fallopian tube rather than the ovary. These lesions are known as serous tubal intra-epithelial carcinoma (STIC) and demonstrate numerous molecular similarities to high-grade serous ovarian cancer. A strong association between the presence of STIC and development of high-grade serous pelvic tumors has been reported [7]. In addition, tubal ligation has a specific protective effect against endometrioid and clear cell carcinoma of the ovary, supporting the theory that these tumors may arise from retrograde transport of endometrial cells during menstruation [8]. In Japan, clear cell carcinoma accounts for around 25% of ovarian cancer [9], which is very different from the proportion in the USA and EU. Therefore, performing prophylactic opportunistic bilateral salpingectomy (OBS) or tubal ligation during another surgical procedure (e.g., hysterectomy or Caesarean section) may be effective for reducing the risk of ovarian cancer among Japanese women.

A recent population-based cohort study demonstrated that bilateral salpingectomy achieves greater ovarian cancer risk reduction than tubal ligation alone [10]. Several other studies have demonstrated lower ovarian cancer rates in women who have undergone tubal ligation, providing further evidence of the malignant potential of the fallopian tubes in relation to ovarian cancer [11]. There is no known benefit to retaining the fallopian tubes in the post-reproductive period and the tubes have no known physiological role after hysterectomy or tubal ligation. For these reasons, recognition of the malignant potential of the fallopian tube has led to changes in surgical practice, particularly in Canada and the USA [12].

However, the current practice of Japanese gynecologists regarding OBS is unclear and is difficult to assess due to the lack of a national registry or a specific surgical code for salpingectomy, as exists in other countries. Therefore, the primary objective of this survey was to assess current Japanese practice with respect to performing or discussing OBS in women undergoing gynecological surgery for benign disease.

MATERIALS AND METHODS

The questionnaire for this study was designed by members of the Gynecologic Oncology Committee of the Japan Society of Obstetrics and Gynecology (JSOG). In September 2016,
we mailed the questionnaire (Appendix) to 767 hospitals or clinics (628 accredited training institutions of the JSOG, Japan Society of Gynecologic Oncology [JSGO], or Japan Society of Gynecologic and Obstetric Endoscopy and Minimally Invasive Therapy [JSGOE] and 139 private institutions with at least one JSGOE-certified licensed gynecologic laparoscopist), and the last date for receipt of responses was set as January 4th, 2017. The following parameters were assessed: 1) institutional characteristics and accreditation status (JSOG, JSGO, and/or JSGOE), 2) annual number of hysterectomies for benign disease (laparotomy or laparoscopy), 3) annual number of OBS procedures in patients undergoing surgery for benign disease, 4) annual number of tubal ligations, 5) awareness of the theory of epithelial ovarian carcinogenesis suggesting that serous, endometrioid, and clear cell carcinoma are derived from the fallopian tube or endometrium rather than from the ovary and the opinion of the American College of Obstetricians and Gynecologists (ACOG) Committee on Salpingectomy for Ovarian Cancer Prevention, 6) whether OBS is offered to patients with benign disease, 7) the institutional criteria for performing OBS in patients with benign disease, 8) the cost of OBS for ovarian cancer prevention in patients with benign disease, 9) performance of oophorectomy at the time of hysterectomy for benign disease, and 10) participation in randomized controlled trials for validation of OBS as a strategy to reduce the incidence of ovarian cancer. Most questions are multiple choice type and encouraged to be answered objectively. After discussed among doctors in each institution, chief physicians were asked to answer the questionnaire.

**Statistical analysis**

All statistical analyses were 2-tailed, and p-values of less than 0.05 were considered significant. The Statistical Package for the Social Sciences (SPSS version 17.0; SPSS Inc., Chicago, IL, USA) was used. Chi-square test was employed to compare replies among institutions with differences of the accreditation status.

**RESULTS**

Among the 767 institutions that were sent the questionnaire, 444 (57.9%) provided responses. The responding institutions included 90 academic centers (20.3%) such as university hospitals, 303 general hospitals (68.2%), 12 cancer centers (2.7%), and 39 private hospitals (8.9%). With regard to JSGO, JSGO and JSGOE accreditation (Table 1), 91 institutions (20.6%) were accredited by both the JSGOE and JSGO, 71 (16.0%) were only accredited by the JSGO, 88 (19.8%) were only accredited by the JSGOE, and 194 (43.7%) were unaccredited.

**Table 1** shows survey results of OBS during benign gynecological surgery for ovarian cancer prevention. 1) The annual number of hysterectomies performed for benign diseases at institutions responding to this questionnaire confirms that more hysterectomies were performed for benign indications than at JSGO accredited institutions and unaccredited institutions at JSGOE accredited institutions (JSGO/JSGOE and only JSGOE) (p<0.001). However, hysterectomy for benign indications was even frequent at unaccredited institutions. 2) OBS was performed more frequently at JSGO and/or JSGOE accredited institutions than at unaccredited institutions. 3) Tubal ligation (>20 procedures) was performed at 0%–3.8% of institutions, depending on the category. 4) The theory that EOC arises from the fallopian tube or endometrium and not directly from the ovary was widely known at almost 100% of institutions accredited by the JSGO or by both the JSGO and
Table 1. Survey results of OBS during benign gynecological surgery for ovarian cancer prevention

<table>
<thead>
<tr>
<th>Accreditation</th>
<th>Both JSGO &amp; JSGOE</th>
<th>JSGO only</th>
<th>JSGOE only</th>
<th>None</th>
<th>Total</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>A. Hysterectomies per year</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>More than 100</td>
<td>48 (52.7)</td>
<td>13 (18.3)</td>
<td>29 (33.0)</td>
<td>26 (13.7)</td>
<td>116 (26.4)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>50–100</td>
<td>29 (31.9)</td>
<td>36 (50.7)</td>
<td>35 (28.6)</td>
<td>65 (34.8)</td>
<td>166 (37.0)</td>
<td></td>
</tr>
<tr>
<td>No more than 50</td>
<td>14 (15.4)</td>
<td>22 (31.0)</td>
<td>24 (27.3)</td>
<td>98 (51.6)</td>
<td>158 (35.9)</td>
<td></td>
</tr>
<tr>
<td><strong>B. OBS per year</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median (max–min)</td>
<td>27.5 (0–200)</td>
<td>20.0 (0–200)</td>
<td>20.0 (0–203)</td>
<td>10.0 (0–120)</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td><strong>C. Tubal ligation per year</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>0.415</td>
</tr>
<tr>
<td>More than 20</td>
<td>2 (2.2)</td>
<td>0 (0)</td>
<td>3 (3.5)</td>
<td>7 (3.8)</td>
<td>12 (2.8)</td>
<td></td>
</tr>
<tr>
<td>≤20</td>
<td>87 (97.8)</td>
<td>67 (100.0)</td>
<td>82 (96.5)</td>
<td>177 (96.2)</td>
<td>413 (97.2)</td>
<td></td>
</tr>
<tr>
<td><strong>D. New theory of ovarian carcinogenesis</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>0.005</td>
</tr>
<tr>
<td>Known</td>
<td>90 (98.9)</td>
<td>71 (100.0)</td>
<td>82 (93.2)</td>
<td>171 (90.5)</td>
<td>418 (94.4)</td>
<td></td>
</tr>
<tr>
<td>Unknown</td>
<td>1 (1.1)</td>
<td>0 (0)</td>
<td>6 (6.8)</td>
<td>18 (9.5)</td>
<td>25 (5.6)</td>
<td></td>
</tr>
<tr>
<td><strong>E. ACOG Committee opinion</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Known</td>
<td>71 (79.8)</td>
<td>48 (71.6)</td>
<td>56 (64.4)</td>
<td>120 (53.4)</td>
<td>279 (63.1)</td>
<td></td>
</tr>
<tr>
<td>Unknown</td>
<td>18 (21.2)</td>
<td>19 (28.4)</td>
<td>31 (35.6)</td>
<td>89 (46.6)</td>
<td>163 (36.9)</td>
<td></td>
</tr>
<tr>
<td><strong>F. Offering the information to patients</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Yes</td>
<td>71 (80.7)</td>
<td>48 (71.6)</td>
<td>54 (64.3)</td>
<td>98 (52.4)</td>
<td>277 (63.8)</td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>16 (18.2)</td>
<td>19 (28.4)</td>
<td>30 (35.7)</td>
<td>89 (47.6)</td>
<td>157 (36.2)</td>
<td></td>
</tr>
<tr>
<td><strong>G. Performance of OBS</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Not resected</td>
<td>9 (9.9)</td>
<td>4 (5.6)</td>
<td>16 (18.2)</td>
<td>48 (24.7)</td>
<td>77 (17.7)</td>
<td></td>
</tr>
<tr>
<td>Resected</td>
<td>63 (69.2)</td>
<td>46 (64.8)</td>
<td>47 (53.4)</td>
<td>84 (43.3)</td>
<td>240 (54.0)</td>
<td></td>
</tr>
<tr>
<td>Depends on surgeons</td>
<td>18 (25.4)</td>
<td>18 (25.4)</td>
<td>24 (27.3)</td>
<td>58 (29.9)</td>
<td>119 (26.8)</td>
<td></td>
</tr>
<tr>
<td>Others</td>
<td>0 (0)</td>
<td>3 (4.2)</td>
<td>1 (1.1)</td>
<td>4 (2.1)</td>
<td>4 (2.1)</td>
<td></td>
</tr>
<tr>
<td><strong>H. Resection of ovaries at the time of hysterectomy</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>0.506</td>
</tr>
<tr>
<td>Resected at certain criteria</td>
<td>41 (46.1)</td>
<td>28 (41.8)</td>
<td>36 (41.9)</td>
<td>83 (43.5)</td>
<td>188 (43.4)</td>
<td></td>
</tr>
<tr>
<td>Depends on patient’s opinion</td>
<td>17 (19.1)</td>
<td>13 (19.4)</td>
<td>25 (29.1)</td>
<td>50 (26.2)</td>
<td>105 (32.3)</td>
<td></td>
</tr>
<tr>
<td>Others</td>
<td>31 (34.8)</td>
<td>26 (38.8)</td>
<td>25 (29.1)</td>
<td>58 (30.4)</td>
<td>140 (32.3)</td>
<td></td>
</tr>
<tr>
<td><strong>I. Willingness to participate in RCT</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Yes</td>
<td>13 (17.8)</td>
<td>2 (3.2)</td>
<td>4 (5.1)</td>
<td>8 (4.4)</td>
<td>27 (6.8)</td>
<td></td>
</tr>
<tr>
<td>Cohort survey is better</td>
<td>21 (28.8)</td>
<td>22 (34.9)</td>
<td>12 (15.4)</td>
<td>21 (11.5)</td>
<td>76 (19.1)</td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>7 (9.6)</td>
<td>13 (20.6)</td>
<td>20 (25.6)</td>
<td>60 (32.8)</td>
<td>100 (25.2)</td>
<td></td>
</tr>
<tr>
<td>Others</td>
<td>73 (43.8)</td>
<td>26 (41.3)</td>
<td>42 (53.8)</td>
<td>94 (51.4)</td>
<td>194 (48.9)</td>
<td></td>
</tr>
</tbody>
</table>

All values were expressed as number (%).

ACOG, American College of Obstetricians and Gynecologists; JSGO, Japan Society of Gynecologic Oncology; JSGOE, Japan Society of Gynecologic of Obstetric Endoscopy and Minimally Invasive Therapy; OBS, opportunistic bilateral salpingectomy; RCT, randomized controlled trial.

Salpingectomy for ovarian cancer prevention in Japan

JSGOE, as well as at about 90% of institutions accredited by the JSGOE or not accredited.

5) In 71.6%–79.8% of institutions accredited by the JSGO or by both the JSGO and JSGOE, the opinion of the ACOG Salpingectomy for Ovarian Cancer Prevention Committee was also known. Conversely, the opinion of this committee was not known in around 50%–65% of institutions that were accredited by the JSGOE or not accredited. 6) The percentages of institutions where patients were given information about salpingectomy for prevention of ovarian cancer at the time of hysterectomy for benign disease was provided to patients at 70%–80% of JSGO accredited institutions vs. 50%–65% of institutions not accredited by the JSGO (p<0.001). 7) In regard to the criteria for performing salpingectomy at the time of hysterectomy for benign disease in relation to institutional accreditation status, OBS was performed in 65%–70% of JSGO-accredited institutions vs. 40%–50% of institutions not accredited by the JSGO (p<0.001). At 87.9% (211/240) of the institutions where OBS was performed, there was no additional fee for the procedure. 8) Regardless of the accreditation status, oophorectomy was recommended according to certain criteria at 40%–45% of all institutions. In 61.1% (179/293) of the institutions where oophorectomy was recommended, there was no additional fee for the procedure. 9) We examined the willingness to participate in trials depending on the accreditation status of the institutions. Although
17.8% of institutions accredited by both the JSGO and JSGOE were willing to participate in randomized controlled trials of OBS, the rate was only 3.2% among JSGO-accredited institutions, which preferred cohort studies (34.9%). Also, only 4.4% of unaccredited institutions were willing to participate (p<0.001).

**DISCUSSION**

In spite of emerging evidence that cell from the fallopian tube or endometrium is often the source of EOC, the present survey conducted by the JSOG Gynecologic Oncology Committee showed that awareness of and performance of OBS in Japanese patients undergoing hysterectomy for benign disease largely depended on the JSGO and/or JSGOE accreditation status of the treating institution. Although this theory of ovarian carcinogenesis was known at 94.4% of all institutions, 36.9% were unaware of the ACOG Committee opinion recommending OBS. Awareness of this opinion was dependent on the JSGO and/or JSGOE accreditation status, even though all JSOG members can access information about ACOG committee opinions advocated by the JSOG Public Relations Committee. Wider adoption of this method for ovarian cancer prevention should be promoted by the JSOG, which is chief association among those involved in obstetrics and gynecology subspecialties in Japan.
This survey showed that OBS was performed at only 54.0% of the responding institutions. Moreover, a very low 6.8% were participating in randomized controlled trials of OBS for ovarian cancer prevention. Judging from the present results, many hospitals were discussing whether or not to conduct a randomized controlled trial (RCT), but it seems that the concept of clinical trials on OBS for ovarian cancer prevention might not be well understood among Japanese hospitals providing obstetrics and gynecology services. Clinical trials can provide answers to many current questions. However, sufficient randomized trials of OBS may be never performed in the future because of the low participation rate (6.8%) revealed by this survey. Even for cohort studies, the participation rate was only 19.1%. Moreover, the other institutions that were not currently involved in had no plans to perform any studies in the future. Therefore, it is necessary to plan methods for recommending OBS to surgeons and for measuring the efficacy of OBS in the future. We are now preparing an opinion of the JSOG Gynecologic Tumor Committee on Salpingectomy for Ovarian Cancer Prevention in order to inform all JSOG members about this new theory of ovarian carcinogenesis. In addition, we need an objective method of assessing the actual uptake of OBS, such as a registry or a unique surgical identification code. While it was shown that 63.8% of the institutions responding to our survey are currently offering OBS or discussing it with patients (Table 1), the actual rate of performing OBS cannot be determined under the current health care system because we do not have an OBS registry or a unique surgical code to identify OBS cases. If there was a separate item number for bilateral salpingectomy in Japan, as exists in Sweden, it would become possible to identify women choosing to undergo this additional procedure [10]. Therefore, we could obtain data on the number of women undergoing this procedure for prevention of ovarian cancer and a national registry could be established to assess the short-term and long-term outcomes. Such data would be helpful for determining the true benefit of this procedure.

The JSOG Committee opinion will also provide details about the risks of additional operative complications [13] and the ovarian function of women who undergo OBS [14-16]. While the short-term results of studies have been encouraging, there has been no long-term follow-up of these women, so we need to conduct long-term cohort studies of OBS to define the surgical complications and ovarian function.

Another issue that currently remains unresolved is how detailed examination of the resected fallopian tube should be. At present, the Sectioning and Extensively Examining the Fimbria (SEE-FIM) protocol is commonly employed by pathologists specializing in gynecological malignancies because it allows histological assessment of the greatest surface area of the tube. This protocol is particularly utilized when examining specimens obtained from high-risk women undergoing risk-reduction surgery or patients with suspected ovarian cancer [17]. However, the SEE-FIM protocol is not routinely employed to examine the fallopian tubes of low-risk women who undergo OBS during gynecological surgery for benign disease. As a result, it is possible that many STIC lesions may be missed and the prevalence of such disease could be severely underestimated, although the clinical relevance is unclear because of uncertainty regarding the management of pathologically detected lesions in asymptomatic women with no genetic risk factors.

Another interesting finding of our survey was the quite low rate (0%–3.8%) of tubal ligation (>20 patients per year) at the responding institutions. It was reported that tubal ligation is common in the USA [18,19]. Therefore, this finding suggests that there is a large difference of contraceptive methods after delivery between Japan and the USA. Combined
oophorectomy at the time of hysterectomy for benign disease was not performed according to specific criteria because there is still no consensus about handling the ovaries under these circumstances. This should be decided by taking into consideration the risks and benefits of bilateral oophorectomy for prevention of ovarian cancer and the role of ovarian hormones in regulating the aging process.

In summary, the JSOG Gynecologic Tumor Committee will announce its opinion on Salpingectomy for Ovarian Cancer Prevention to all JSOG members and will develop a system for monitoring the number of OBS procedures in Japan. In addition, the clinical outcome of OBS for prevention of ovarian cancer in Japan will be estimated by comparison with the national registry of ovarian cancer patients.

REFERENCES


Appendix. Questionnaire survey on opportunistic bilateral salpingectomy (OBS) during benign gynecological surgery for ovarian cancer prevention

Gynecologic Oncology Committee of Japan Society of Obstetrics and Gynecology (JSOG)

The JSOG Gynecologic Oncology Committee is conducting a questionnaire survey on opportunistic bilateral salpingectomy (OBS) during benign gynecological surgery for ovarian cancer prevention. We would like to ask you questions about the principle and current status of your institutions for OBS. The results will be reflected in future Gynecologic Oncology Committee activities for OBS. Please answer the following questions.

We would like to ask your institution’s head and other responsible persons to consult with each other in detail before answering our questions.

<table>
<thead>
<tr>
<th>Question</th>
<th>Options</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Institutional characteristics and accreditation status</td>
<td>Accredited by: Both JSOG &amp; Japan Society of Gynecologic Oncology (JSOG) ( ), JSOG only ( ), Japan Society of Gynecologic of Obstetric Endoscopy and Minimally Invasive Therapy (JSOGE) only ( ), None ( )</td>
</tr>
<tr>
<td>2. Annual number of hysterectomies for benign disease (laparotomy or laparoscopy)</td>
<td>No more than 50 cases ( ), 50–100 ( ), More than 100 ( )</td>
</tr>
<tr>
<td>3. Annual number of OBS procedures in patients undergoing surgery for benign disease</td>
<td>( ) cases</td>
</tr>
<tr>
<td>4. Annual number of tubal ligations</td>
<td>Less than 20 ( ), 20 and more ( )</td>
</tr>
<tr>
<td>5. Are you aware of the theory of epithelial ovarian carcinogenesis suggesting that serous, endometrioid, and clear cell carcinoma are derived from the fallopian tube or endometrium rather than from the ovary?</td>
<td>Yes ( ), No ( )</td>
</tr>
<tr>
<td>6. Are you aware of the opinion of the American College of Obstetricians and Gynecologists (ACOG) Committee on Salpingectomy for Ovarian Cancer Prevention?</td>
<td>Yes ( ), No ( )</td>
</tr>
<tr>
<td>7. Are you offering the information of OBS to patients with benign disease?</td>
<td>Yes ( ), No ( )</td>
</tr>
<tr>
<td>8. The institutional principle for performing OBS in patients with benign disease</td>
<td>Not resected ( ), Resected ( ), Depend on surgeons ( ), Others ( )</td>
</tr>
<tr>
<td>9. The cost of OBS for ovarian cancer prevention in patients with benign disease</td>
<td>Free ( ), At patient’s own expense ( ), Covered by health insurance ( ), Others ( )</td>
</tr>
<tr>
<td>10. Performance of oophorectomy at the time of hysterectomy for benign disease</td>
<td>Resect at certain criteria ( ), Depends on patient’s opinion ( ), Others ( )</td>
</tr>
<tr>
<td>11. Are you willing to participate in randomized controlled trials for validation of OBS as a strategy to reduce the incidence of ovarian cancer?</td>
<td>Yes ( ), Cohort survey is better ( ), No ( ), Others ( )</td>
</tr>
</tbody>
</table>