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Malignancies following bilateral salpingo-oophorectomy (BSO)

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Abstract

Aims: Prophylactic bilateral salpingo-oophorectomy (BSO) is an effective risk reducing measure in ovarian cancer susceptible women. Yet, a small subset of women develop primary peritoneal carcinomatosis (PPC) after BSO. The rates of PPC following non-risk reducing BSO have sparingly been reported.
Methods: Women who underwent BSO for non-cancer reasons from 1/1/1984 to 12/31/2000 were crossed with the list of cancer diagnoses reported to the Israel National Cancer Registry until 12/31/2001.
Results: Overall, 4128 women at a mean age of 58 ± 12 years were analyzed. After a mean of 7.2 ± 4 years following BSO, 147 women (3.6%) were diagnosed with cancer: breast cancer in 50 women 62 ± 50 months after BSO, and one patient developed PPC, whereas the expected was 0.15 cases. The Standardized Incidence Ratio (SIR) of developing breast cancer was statistically significant lower than expected (SIR 0.71, 95% C.I. 0.44–0.78).
Conclusion: The rate of post-oophorectomy PPC in average risk population is low, and BSO appears to lower the rate of breast cancer in average risk women.

Keywords: Bilateral salpingo-oophorectomy; Cancer risk; Primary peritoneal carinomatosis; Prophylactic surgery

Introduction

Ovarian cancer is the leading cause of death from gynecological malignancies and the fourth most common cause of cancer death in women in western countries, with a lifetime risk for developing this malignancy of 1.8%.[1,2] No reliable screening tools are available for early detection of ovarian cancer in the general population, and about 75% of cases are diagnosed at an advanced stage, with a 5-year survival of 27%.[3,4] The poor prognosis of advanced ovarian cancer coupled with the lack of effective means for detecting early stage disease, has led to recommending risk reducing bilateral salpingo-oophorectomy (BSO) for high risk women.[5–7] Of the known and putative factors associated with an increased risk for developing ovarian cancer, the most significant one is having a family history of ovarian or breast cancer.[8] Germline mutations in either *BRCA1* (MIM# 113705) or *BRCA2* (MIM# 600185) can be detected in the majority of families with inherited breast/ovarian cancer [reviewed in Ref. 9]. The value of prophylactic BSO in risk reduction in high risk populations is well established, for both ovarian and breast cancer.[10–14] Yet, prophylaxis is incomplete: about 1–5% of high risk women undergoing prophylactic BSO develop an intraperitoneal tumor – primary peritoneal carcinomatosis (PPC) – following prophylactic surgery.[15,16] This tumor is clinically, phenotypically and biologically indistinguishable from ovarian cancer.[12] BRCA mutation carriers were reported to have an increased risk for developing PPC, with a lifetime risk estimated at 1.3%.[17,18]

Given the efficacy of prophylactic BSO in high risk population and the grim prognosis of advanced ovarian cancer

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in the average risk population, a debate is ongoing as to the rationale and value of offering BSO to all women after their reproductive cycle has been completed.[19] Proponents stress the efficacy of the procedure in risk reduction, whereas opponents emphasize the hazards of surgery offered to healthy women to reduce the risk of a rare disease.[6] A key component in trying to settle the debate is determining the rate of PPC in average risk women who underwent the procedure for non-cancerous reasons and not as a risk reduction measure. In a study from Greece, Kontoravdis et al.[13] report that ovarian cancer was diagnosed in 520/5262 women (9.9%) who underwent hysterectomies a mean of 7.2 years prior to ovarian cancer diagnosis. These authors conclude that BSO should be offered to all women aged 40 years or older who completed their reproductive cycle that are undergoing hysterectomy for non-cancerous reasons. In contrast, Charoenkwan,[14] estimated that one or two cases of an annual load of the more than 1200 ovarian cancer cases would be prevented annually in Thailand, if BSO would routinely be preformed in Thai women aged 45 and over who undergo hysterectomy.

To shed light on this issue, we retrospectively ascertained all cases of cancer, primarily PPC and breast cancer, encountered among Israeli women who underwent BSO over an 18-year period in a single tertiary referral medical center in Israel.

Methods

Patient ascertainment

All women who underwent oophorectomy (ICD 9-CM code 65.0) or oophorectomy and hysterectomy (ICD 9-CM codes 68.0–68.9) at the Department of Gynecology, Sheba Medical Center from January 1, 1984 to December 31, 2000 were initially enrolled. These patients were ascertained from the Medical Records unit at the medical center by selecting those who fit the above-mentioned ICD diagnoses. Each record was retrieved, and the exact diagnosis at the time of surgery based on the pathology report, as well as previous diagnoses was recorded. Exclusion criteria included surgery to therapeutically remove a malignant ovarian, fallopian tube, or primary peritoneal tumor (ICD-O Version. 3 codes C56.9, C57.0, C48.2, C57.4), inaccurate diagnosis, or inability to confirm the lack of ovarian cancer at the time of surgery. The list of eligible patients generated was then crossed with the database of cancer diagnoses from January 1, 1984 to December 31, 2001 reported to the central Israeli Cancer registry. All cancer diagnoses in Israel are reported by law to this registry, and the lag time from reporting to being available on the database is about 3–4 months. This crossing resulted in names and cancer diagnoses of all study participants.

Results

Study participants characteristics

Overall from January 1, 1984 to December 31, 2000 4128 women underwent bilateral salpingo-oophorectomy (BSO) at the Department of Gynecology, Sheba Medical center. The indication for surgery was acquired by review of the charts of the first 719 patients that were operated from January 1, 1984 to December 31, 1989. The reasons for undergoing BSO were associated with surgery for removal of uterine myomas (41%), endometrial cancer (21%) or removal of ovarian cysts (15%). The mean (±SD) age at surgery was 58 ± 12 years (range 16–94).

Cancer diagnoses post-BSO

Of 4128 study participants, 147 (3.6%) had cancer diagnosed after BSO, with a mean follow-up period of 7.2 ± 4 years (range 1–18). Notably, 50 (1.2%) patients had breast cancer diagnosed following BSO, with a mean time from BSO to breast cancer diagnosis of 62 ± 50 months. Of these patients, 39 (78%) developed breast cancer at or over the age of 50, and a minority of 22% prior to the age of 50. In order to get some insight as to the potential effect of menopausal status at the time of oophorectomy on the risk of breast cancer, we noted that 1269 patients (31%) underwent the oophorectomy prior to the age of 50 years, and 460 of these, or only 11% of all the patients, before the age of 45 years. Only one patient developed primary peritoneal carcinoma during the follow-up, 31 months after oophorectomy. She was a 53-year-old patient, G10P7, with no family history of cancer, who had undergone a laparoscopic assisted vaginal hysterectomy with bilateral salpingo-oophorectomy in March 1997 for symptomatic fibroid uterus. Pathology of the surgical specimen was reviewed at the time of diagnosis of PPC and no ovarian or fallopian tube primary could be identified. In October 1999, PPC was diagnosed clinically manifested with ascites, palpable abdominal masses, and elevated CA 125 at 3000 IU. The patient died in August 2001, 21 months after diagnosis. Notably she had no family history of cancer and she did not carry any of the predominant Jewish mutations in *BRCA1 BRCA2*.[20] The other common cancer types observed were colon cancer ($n = 26$, 0.63%), malignant melanoma ($n = 12$, 0.29%) and lung cancer ($n = 11$, 0.26%).

Statistical analyses

The adjusted expected number of cases of PPC in the entire Israeli population was calculated and compared it to the findings in the present study. The Standardized Incidence Ratio (SIR) of PPC was 6.67 (95% confidence interval 0–19.73) where there was an expected of 0.15 cases versus the one case in our cohort. Though mathematically it seems an excess of PPCs, no conclusions can be made based on

a single observed case. The same calculation was applied for breast cancer incidence, and the resultant SIR was 0.71 (95% C.I. 0.44–0.78). This result indicates that our cohort of women that underwent BSO had an average 29% reduction in breast cancer incidence.

Discussion

In this study, the rate at which PPC and other malignant tumors occurred after BSO in unselected Jewish Israeli women was evaluated. The main outcome of this study is that PPC rate among Jewish Israeli women who undergo BSO is low – 1:4000 – 0.025%. Initially the reported rates of PPC after BSO were reported to be 10% (3/28) in ovarian cancer-prone families.[21] Subsequent studies encompassing more patients have reported lower rates: a rate of 1.3% was reported among high risk *BRCA1* mutation carriers,[18] and 1.8% among high risk women who were not genotyped for *BRCA1*.[15] The rate of developing PPC in the present study is significantly lower. In essence, this low to negligible rate of PPC in average risk population may indicate that prophylactic BSO in high risk women does indeed lower the risk of ovarian cancer but does not affect the residual risk of PPC. Indeed, ovarian cancer risk reduction from prophylactic BSO is quoted at 90% or higher (from 20–50% to 1.3%).[18] Compared with that risk reduction, the rate of PPC in high risk women undergoing prophylactic BSO is basically unchanged and significantly higher than that of the general population, although one study performed on Jewish Israeli women[22] reported that the odds ratio for developing PPC post-prophylactic BSO was 0.12 (95% C.I. 0.06–0.24), in high risk women.

From the practical viewpoint the results of this study, if confirmed by others in ethnically diverse populations, may impact the information transmitted during genetic testing for high risk women regarding risk reductions and residual cancer risk. It may also be taken by proponents of prophylactic oophorectomy to the general population,[19] as an indication that the residual risk for PPC in the average risk population is negligible.

The rate of breast cancer was significantly lower than the rate in the average risk, non-oophorectomized Israeli population, leading to a 29% risk reduction (SIR 0.71, 95% C.I. 0.44–0.78). Among high risk individuals, there is little doubt as to the efficacy of prophylactic BSO as a means of risk reduction of both ovarian and breast cancer.[23–25] The results of the present study show that even in average risk population, BSO may provide some protection from breast cancer risk. In an unselected Swedish population[26] breast cancer risk reduction of 50% was evident for premenopausal women who underwent BSO before the age of 50 years, whereas no risk reduction was noted for Swedish women aged 50 and over or post-menopausal women. The finding of breast cancer risk reduction by BSO should not be an indication to offer this intervention to the general population as a risk reducing measure for breast cancer, but the information needs to be transmitted to the patient in order for her to make an informed decision concerning her adnexa prior to pelvic surgery.

The limitations of this study should be pointed out: this is a retrospective analysis from a single, tertiary referral medical center in central Israel that may not equally represent the entire Israeli population. Data regarding other breast cancer risk factors [e.g., use of oral contraceptives (OC), hormone replacement therapy (HRT)], as well the pathological characteristics of the breast cancer (i.e., grade, stage, estrogen and progesterone receptor status) are not available. This lack of information partially stems from the lack of uniformly performing these determinations in Israel in the late 1980s and early 1990s, from the fact that the majority of breast cancer patients were operated in other hospitals, and from the lack of adequate information in the available files regarding if and for how long OC and HRT were used. A recent survey of the National Cancer Registry reported a 92.9% overall adequacy in reporting cancer cases to the Registry in Israel.[27]

These obvious inherent limitations hinder drawing firm conclusions from the results presented. Yet, the data support a significantly lower risk of PPC following BSO in the average risk population as compared to the high risk population, and a decrease in the risk of breast cancer, supporting the data from Scandinavia.[26]

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