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23

# The Role of Prophylactic Oophorectomy in the Management of Hereditary Breast & Ovarian Cancer Syndrome

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## 1. Introduction

### 1.1 Historical perspective of prophylactic-oophorectomy in ovarian and breast cancers before the era of BRCA1/BRCA2 testing

Prophylactic salpingo-oophorectomy (PO) entails removal of the ovaries prior to the clinical occurrence of cancer. Prophylactic removal of the ovaries, during hysterectomy or other abdominal surgery, to prevent ovarian cancer in postmenopausal women was popularised in the 1940s by Crossen, who stated "*the involuting ovaries have fulfilled their reproductive and endocrine function. They are....vestigial structures which carry a special tendency to cancer*" (Crossen, 1942). The first report of prophylactic oophorectomy for familial ovarian cancer was in 1950 when A.M Liber described a family of five sisters and their mother, all with histologically confirmed papillary adenocarcinoma of the ovary; it was recommended that family members should undergo frequent gynaecologic screening, and that prophylactic oophorectomy should be considered (Liber, 1950)

The role of oophorectomy in the management of breast cancer dates further back to 1889 when it was first proposed by Albert Schinzinger (Schinzinger, 1889); he observed that the prognosis for breast cancer appeared better in older women than younger women and postulated that oophorectomy would initiate atrophy of the breast and any cancer within the breast. Shinzinger suggested oophorectomy both as therapy for advanced breast cancer and prophylaxis against local recurrence, but he never actually performed the surgery; it was George Thomas Beatson who first performed a bilateral oophorectomy on a patient with metastatic breast cancer in 1895 , this was reported in the Lancet in 1896 (Beatson, 1896). A subsequent report detailed that this patient experienced remission of her disease and lived another four years. Beatson hypothesized that oophorectomy caused fatty degeneration of the malignant cells accounting for its beneficial effect in breast cancer (Beatson, 1896; Thomson, 1902). An English surgeon, Stanley Boyd performed the first oophorectomy as adjuvant breast cancer therapy in 1897 (Boyd, 1897). He commented "my working hypothesis is that internal secretion of the ovaries in some cases favors the growth of the cancer" and subsequently reported that that one third of breast cancer patients benefited from oophorectomy as adjuvant therapy (Boyd, 1900), in this way the rationale for hormonal treatment of breast cancer was first implied. In 1968 Feinleib observed that

premenopausal oophorectomy decreased the rate of subsequent breast cancer (Feinleib, 1968) however it was a further twenty years before Brinton proposed the potential of oophorectomy as a breast cancer *prevention* strategy, reporting that women, with a family history of breast cancer, who underwent oophorectomy before the age of 40 years had a 45% reduction in breast cancer risk compared with women who underwent natural menopause (Brinton et al, 1988). Meijer and van Lindert similarly reported that surgery performed before the age of natural menopause significantly reduced breast cancer risk (Meijer & van Lindert, 1992). These studies commented on patients with a family history of breast cancer, introducing the role of prophylactic salpingo-oophorectomy (PSO) as a risk reducing strategy in hereditary breast cancer. At this time the genetic etiologic association between breast and ovarian cancer was also being investigated; first put forward by Henry Lynch who collected pedigrees and samples from high risk breast and/or ovarian cancer families showing autosomal dominant inheritance patterns for breast cancer in the late 1960s (Lynch et al, 1972), and identifying HBOC families long before the discovery of breast cancer susceptibility genes. In the past two decades however, since the identification of increased genetic susceptibility to breast and ovarian cancer, in particular the BRCA1 and BRCA2 genetic mutations, the role of prophylactic oophorectomy has become more clearly defined, particularly in the setting of HBOC.

## 2. Identification of HBOC associated mutations and risks of breast and ovarian cancer

In the early nineties, the first breast cancer susceptibility gene – BRCA1 (Miki et al, 1994) and the second BRCA2 (Wooster et al, 1995) were identified as the cause of genetic predisposition in hereditary breast and ovarian cancer. This milestone in breast and ovarian cancer research was one of the most significant cancer discoveries of the twentieth century, both in terms of scientific impact and public interest. These breakthroughs were the culmination of five years of focused work based on the report in 1990 by Marie Claire King's group who undertook segregation analyses on breast cancer pedigrees and mapped a predisposing gene for both breast and ovarian cancer to chromosome 17q (Hall et al, 1990). Following this report a collaboration of international groups, termed "The Breast Cancer Linkage Consortium" further specified the site of the BRCA1 locus by linkage analysis (Easton et al, 1993). The 1994 report from Miki *et al* outlined the exact structure of the BRCA1 gene which had been determined by a team of scientists at the University of Utah using positional cloning techniques (Miki et al, 1994). The second predisposition gene, BRCA2 was mapped to chromosome 13 and reported by Wooster *et al* in the UK (Wooster et al, 1994; 1995).

At a molecular level, BRCA1 is a 100kb gene located on chromosome 17q21.1. It consists of 24 exons, 22 of which encode for a 1863 amino-acid nucleoprotein. BRCA2 is an even larger gene composed of 27 exons distributed over 70kb of genomic DNA on chromosome 13q12–q13, and enocoding for a protein of 3418 amino acids. The complete repertoire of function of the BRCA1 and BRCA2 proteins has not yet been determined, however several functions have been uncovered; both proteins are integral to the DNA damage response pathway and facilitate DNA damage repair through homologous recombination. BRCA1 also plays a role in cell-cycle control, gene expression control, protein ubiquination and chromatin remodelling (Aiyar et al, 2007; Foulkes 2010; Huen et al, 2010; Ma et al, 2010). In cells which are deficient in BRCA1 or BRCA2, double-strand breaks may be repaired in an erroneous

manner (non-homologous end-joining), which may lead to chromosomal rearrangements. The resultant chromosomal instability is a key feature of carcinogenesis. BRCA1 and BRCA2 are classified as tumour suppressor genes, and since their discovery, hundreds of different mutations have been reported in these genes. The prevalence of BRCA mutations in most European and North American countries is reported as 0.06 – 0.24% (Malone et al, 2006; Whittemore et al, 1997 & 2004). However there are specific populations in which the frequency of mutations are higher due to strong founder effect; these include ethnic and geographic populations worldwide including those of Norwegian, Dutch and Icelandic descent (Neuhausen et al, 2009). The Ashkenazi Jewish population is perhaps the best characterised example; three specific mutations; 185delAG and 5382insC in the BRCA1 gene, and 6174delT in BRCA2 are the most common mutations in this population and have been found to occur with frequencies of 2-2.5% which is at least five times that of the general population (Ferla et al, 2007; Neuhausen et al, 2009; Struewing et al, 1997; Warner et al, 1999), thus endowing this population with a significantly increased risk of breast and ovarian cancer.

The risk of breast and ovarian cancer in the general population is 10-13% and 1.7% respectively. This risk is significantly elevated in women carrying mutations of the BRCA1 or BRCA2 genes. BRCA1 and BRCA2 mutation carriers have a 54-85% and 45% lifetime risk of developing breast cancer, respectively and an 18-60% and 11-27% lifetime risk of developing ovarian cancer (Antoniou et al, 2003; Easton et al, 1995; King et al, 2003). Furthermore, BRCA1 mutation carriers are at increased risk for fallopian tube carcinoma (Paley et al, 2001; Zweemer et al, 2000), primary peritoneal carcinoma (Levine et al, 2003; Olivier et al, 2004), and uterine serous papillary carcinoma (Biron-shental et al, 2006). BRCA2 mutations are also associated with increased risk for a variety of other cancers including melanoma, pancreas, bone, hepatobiliary and pharyngeal cancer (Breast Cancer Linkage Consortium, 1999). Both BRCA1 and BRCA2 are associated with an increased risk of male breast cancer (Tai et al, 2007) and early onset prostate cancer (Agalliu et al, 2009; Mitra et al, 2008).

It is important to note that the breast and ovarian cancers in patients with a BRCA mutation exhibit phenotypic characteristics that are distinct from sporadic cancers, a fact that may have implications for local and systemic treatment. The ovarian cancers in families with BRCA mutations are predominantly histologically serous adenocarcinomas frequently exhibiting papillary changes; epithelial ovarian adenocarcinomas that occur in patients with transmitted germ-line BRCA1 mutations are characteristically high-grade with underpresentation of mucinous or borderline tumours (Kurian et al, 2005; Chiaffarino et al, 2007). Hereditary breast cancers due to BRCA mutations occur at a much younger age than sporadic cancers, and are more likely to be multi-focal and bilateral. BRCA 1 and BRCA2 related breast cancers however, have a distinct morphologic and molecular signature (Bane et al, 2007; Foulkes et al, 2003). The breast cancers that develop in BRCA2 gene mutation carriers are similar to sporadic breast cancers, they are more likely to exhibit the luminal phenotype of breast cancer and express the oestrogen receptor. Conversely, the breast cancers associated with BRCA1 mutation usually exhibit a distinct basal phenotype (Foulkes et al, 2003) characterised by lack of estrogen, progesterone and HER2/neu receptors and abundant expression of basal-type cytokeratins. The basal subtype of breast cancer is an aggressive form of tumour associated with increased metastatic potential and decreased overall survival (Billar et al, 2010; Dent et al, 2007) ; the poor prognosis and high recurrence

rate of these tumours has raised the question of whether BRCA1 breast cancers have a poorer outcome than sporadic breast cancers. The evidence supports an increased risk for contralateral breast cancer, but the data assessing local recurrence are inconsistent and overall survival appears to be similar (Liebens et al, 2007; Brekelmans et al, 2007). Breast conserving therapy should be employed with caution in women with hereditary BRCA related breast cancer in view of the increased likelihood of multicentricity and contralateral breast cancer.

## 3. Risk reducing effect of PSO on ovarian & breast cancer

Prophylactic salpingo-oophorectomy has been shown to decrease the risk of both breast cancer and ovarian cancer in BRCA1 and BRCA 2 mutation carriers (Domchek et al, 2006, 2010 ; Eisen et al, 2005; Finch et al, 2006; Kauff et al, 2002, 2008 ; Kramer et al, 2005; Rebbeck et al, 1999, 2002, 2009 ; Rutter et al, 2003) This evidence is predominantly based on the results of observational case control and cohort studies. There are no randomised clinical trials of PSO and these may not be feasible or ethically appropriate (Klaren et al, 2003). Rebbeck and colleagues were among the first to provide evidence of the risk reducing effect of PSO in BRCA mutation carriers; in 1999 they reported a 47% decreased risk of breast cancer in a series of 43 women with a BRCA1 mutation who underwent PSO compared to 79 matched controls who did not undergo PSO (Rebbeck et al, 1999). The findings from this relatively small series were enough to trigger a number of larger series, investigating health outcomes following PSO in patients with known BRCA mutations, in an effort to establish whether this risk-reducing effect was significant enough to incorporate PSO into routine clinical practice as a cancer prevention strategy.

### 3.1 Ovarian cancer reduction

In 2002, Rebbeck reported ovarian cancer incidence in a larger series of 551 BRCA mutation carriers, 259 who underwent PSO and 292 who did not (Rebbeck et al, 2002). After 8 years follow-up the risk of coelomic epithelial cancer was significantly reduced by 96% in the patients who had undergone prophylactic oophorectomy (HR=0.04, 95% CI 0.01-0.16). In the same issue of the New England Journal of Medicine, Kauff et al published their results from the first prospective series of 173 BRCA mutation carriers, of whom 101 underwent PSO (Kauff et al, 2002). In this series, PSO was associated with an 85% reduction in subsequent ovarian cancer. These findings have been substantiated in a number of subsequent series; in a prospective study of 1828 BRCA mutation carriers Finch *et al* reported a significantly lower ovarian cancer risk after PSO (HR 0.2, 95% CI 0.07-0.58) (Finch et al, 2006). A prospective multicentre study of 1079 BRCA mutation carriers demonstrated that PSO significantly reduced the risk of BRCA1 associated gynaecologic cancer risk (HR 0.15, 95% CI 0.04-0.56), however this reduction was not observed in patients with a BRCA2 mutation (Kauff et al, 2008). In 2009 a meta-analysis of the published literature, including 10 studies, was performed to assess the magnitude of the risk reduction effect (Rebbeck et al, 2009), the results of which showed an 80% reduction in ovarian/fallopian tube cancer risk associated with PSO in women carrying a BRCA1 or BRCA2 mutation.

The efficacy of prophylactic oophorectomy for reduction of ovarian cancer risk is somewhat compromised by the residual risk of papillary serous carcinoma of the peritoneum; this

refers to diffuse involvement of the peritoneal surfaces with a neoplasm bearing all the histological characteristics of papillary serous carcinoma of the ovary which can occur even after oophorectomy. This phenomenon was initially reported by Tobacman who reported an adenocacinoma indistinguishable from ovarian cancer after oophorectomy in women with a strong family history of ovarian cancer (Tobacman et al, 1982). The source of this extra-ovarian malignancy may be any of the following; microscopic foci of residual ovary, pre-existing carcinomatosis not detected at the time of prophylactic surgery, or multifocal origin of peritoneal tissue which shares a common embryonic origin with mullerian duct epithelium. The reported incidence of papillary serous adenocarcinoma in BRCA mutation carriers following PSO is 4.3% (Finch et al, 2006) and women should be counselled regarding this risk when making a decision regarding PSO.

### 3.2 Breast cancer reduction

The reduction in breast cancer risk associated with PSO in BRCA mutation carriers is approximately 50%. In the 2002 report from Rebbeck et al the incidence of breast cancer in patients who underwent PSO was 21.1% compared to 42.3 % in those who did not (Rebbeck et al, 2002). Kauff et al reported an even greater risk reduction of 68% in subsequent breast cancer for BRCA mutation carriers who underwent PSO (Kauff et al, 2002), they subsequently reported a 72% reduction in BRCA2 associated breast cancer risk following PSO, but no statistically significant reduction in BRCA1 associated breast cancer (Kauff et al, 2008). In a case control study of over 3,000 patients, Eisen et al reported a reduction in breast cancer risk of 56% in the BRCA1 mutation carriers, and 46% in the BRCA2 mutation carriers who underwent PSO (n=166) (Eisen et al, 2005). Kramer et al prospectively evaluated the risk of breast cancer in 98 patients with, and 353 without BRCA1 mutations, and found that among BRCA1 mutation carriers oophorectomy was associated with a 62% reduction in breast cancer risk (Kramer et al, 2005). In the 2009 meta-analysis performed by Rebbeck et al, PSO was associated with a statistically significant reduction in breast cancer risk of approximately 50% for both BRCA1 (HR 0.47, 95% CI 0.35-0.64) and BRCA2 (HR 0.47, 95% CI 0.26-0.84) mutation carriers (Rebbeck et al, 2009). Some of the prospective studies included in this meta-analysis had suggested that there may be a difference in risk reduction between BRCA1 and BRCA2 carriers depending on the specific mutation (Kramer et al, 2005, Kauff et al, 2008), however the data in retrospective series was inconsistent and insufficient to provide any definitive evidence in this regard. Thus, it was confirmed that there is a reduction in both ovarian and breast cancer risk following PSO in BRCA mutation carriers, but questions regarding the differential magnitude of risk reduction according to clinical variables such as the specific BRCA mutation (i.e. BRCA1 or BRCA2), or other factors in the patients clinical history.

It was with these questions in mind that Domcheck and colleagues prospectively analysed the largest cohort to date of BRCA mutation carriers, reporting risk reduction after PSO considering a number of different scenarios (Domcheck, 2010). The authors prospectively followed 2, 482 women with BRCA mutations identified between 1974 and 2008. The median follow up for patients who underwent prophylactic surgery was 3.65 years, and 4.29 years in those who did not opt for prophylactic surgery. A total of 993 women underwent PSO; of these 1.1% were subsequently diagnosed with ovarian cancer, 11.4% were subsequently diagnosed with breast cancer and the all cause mortality was 3%. This

represents a significant reduction when compared with women who did not undergo PSO, of whom 5.8% were diagnosed with ovarian cancer, 19.2% were diagnosed with breast cancer, and all cause mortality was 9.8%. These findings again confirmed the risk reducing effect of PSO in both breast and ovarian cancer. In this series, however a previous diagnosis of breast cancer was accounted for and it was found that the risk of ovarian cancer was reduced in BRCA mutation carriers with and without a history of breast cancer. However, the risk of breast cancer was reduced following PSO in those without prior breast cancer, but PSO had no effect on the risk of developing a second primary breast cancer in patients who had a previous breast cancer diagnosis. This is an interesting finding and may relate to the fact that patients who have previously been treated for breast cancer with cytotoxic chemotherapeutic agents inducing a menopausal state derive no further benefit from oophorectomy. Unfortunately this series was limited by insufficient adjuvant therapy data and this question may be further addressed in future prospective series. Another interesting finding in this series was the difference in breast cancer risk reduction following PSO in BRCA2 mutation carriers (64%) compared to BRCA1 mutation carriers (37%), which had previously been reported in smaller prospective studies (Kauff et al, 2008). It is possible that this difference relates to the distinction in breast cancer phenotype exhibited in BRCA1 and BRCA2 mutation carriers. In the BRCA2 cohort there is a high proportion of ER-positive breast tumours and it has been hypothesized that PSO may actually "treat" subclinical breast tumours present at the time of oophorectomy (Rebbeck et al, 2009). Such a treatment effect would not be evident in BRCA1 tumours which are predominantly ER-negative. The "protective" effect of PSO may take longer to become evident, thus a longer follow up time in addition to mechanistic studies may be required to definitively answer this question.

In conclusion, PSO has been proven to be associated with a reduction in ovarian cancer risk of approximately 80% and a reduction in breast cancer risk of approximately 50%, with the most recent analyses suggesting that the risk reducing effect may be more pronounced in BRCA2 mutation carriers (Domchek, 2010). Despite the uncertainties that remain to be addressed regarding the extent of risk reduction according to specific clinical variables, the evidence has sufficiently demonstrated a reduction in breast and ovarian cancer risk following PSO in patients with BRCA1 and BRCA2 mutations, that the National Comprehensive Cancer Network (NCCN) has incorporated this strategy into guidelines for recommended management of individuals carrying a BRCA mutation. These guidelines are as follows:

- Self-breast examination monthly starting at age 18 years
- Clinical breast examination semi-annually starting at age 25 years
- Annual mammogram and breast MRI starting at age 25 years or based on earliest age of onset in family
- Prophylactic oopherectomy between ages 35 and 40 years or upon completion of childbearing
- For individuals not electing a prophylactic oophorectomy, concurrent transvaginal ultrasound and CA125 levels semi-annually starting at age 35 years or 5-10 earlier than the first diagnosed case of ovarian cancer in the family
- Consider chemoprevention options (e.g tamoxifen)
- Consider research studies testing investigational imaging and screening options.

Clearly, such recommendations are meant to lower the woman's risk or identify a cancer as early as possible in the development of the disease. While PSO is an acceptable risk reduction strategy for many BRCA1/BRCA2 mutation carriers, the decision to undergo prophylactic surgery is a complex one, and there are a number of considerations which should be taken into account and discussed with patients during the decision making process.

## 4. Practical considerations: Timing & approach to surgery

### 4.1 Timing of PSO

As evidence supporting a risk reducing role for PSO in BRCA1 and BRCA2 mutation carriers accumulates, the clinical management of cancer risk in these patients remains complex and multifactorial; one issue that remains incompletely resolved is the optimum timing of PSO. Eisen *et al* reported improved risk reduction in BRCA mutation carriers who underwent PSO before the age of 50 years compared to those older than 50 years at the time of surgery (Eisen et al, 2005). These findings are supported by results from Domchek's series in which there was a reduction in breast cancer risk in patients who underwent PSO before the age of 50 years, but no significant reduction in women over 50 years of age. These studies are limited by small numbers in subgroup analyses and a limited follow-up time, leaving this question incompletely addressed by the currently available data. As outlined above, the current recommendations from the NCCN is that prophylactic oophorectomy should be offered to patients between the ages of 35 and 40 years, or when the woman has finished childbearing. The risk-reduction benefit of oophorectomy must be balanced against the side effects and potential morbidity associated with early menopause. This is highlighted by evidence suggesting that PSO in women under the age of 45 years is associated with increased mortality, particularly in patients who do not receive hormone replacement therapy (HRT) (Rocca et al, 2006). Women with a BRCA mutation have a unique risk and benefit profile which must be considered when making recommendations regarding the use of HRT following PSO in the premenopausal age-group. HRT is the most effective strategy for the management of postmenopausal symptoms and sequelae such as osteoporosis and cardiovascular risk in young females undergoing abrupt menopause through PSO. However, its use in patients with an increased risk of breast cancer has been questioned since the publication of Women's Health Initiative studies which provided evidence of a breast cancer risk associated with combined oestrogen and progestin hormone replacement therapy (Beral et al, 2003; Rossouw et al, 2002).

The PROSE study group in a prospective multicentre study of 462 patients with BRCA mutation found that the breast cancer risk reduction/protective effect attained following PSO was not significantly changed by the use of HRT (Rebbeck et al, 2005). Similarly, Eisen et al observed no increased risk of breast cancer associated with HRT use in patients following PSO (Eisen et al, 2005). Armstrong et al developed a Markov decision analytical model to calculate the impact of prophylactic oophorectomy and HRT use on breast and ovarian cancer risk, cardiac disease, osteoporosis and venous thrombosis (Armstrong et al, 2004). This model predicted that BRCA mutation carriers undergoing PSO between the ages of 30 and 40 years would obtain a significant gain in life expectancy irrespective of HRT use. However, this gain in life is predicted to decrease as the age at time of PSO increases. The short term use of HRT does not appear to increase breast cancer risk, and should be

considered in young patients to alleviate menopausal symptoms which may interfere with quality of life. In high-risk patients carrying a BRCA mutation, estrogen-only HRT is preferable.

### 4.2 Surgical approach

The extent of gynaecologic surgery in patients with BRCA1/2 mutations has been the subject of debate in view of the risk of proximal fallopian tube malignancy and subsequent peritoneal cancer of ovarian origin in patients post oophorectomy. For risk-reducing surgery to be successful all of the "at risk" tissue should be removed. It is essential that the fallopian tube is resected as close as possible to the uterine cornua to prevent the occurrence of proximal fallopian tube malignancy. Indeed the risk of proximal fallopian tube malignancy in the uterine fundus and the low risk of uterine papillary carcinoma in BRCA1/BRCA2 mutation carriers raises the question of whether these patients should undergo concomitant hysterectomy as part of risk reducing surgery (Biron-Shental et al, 2006; Hornreich et al, 1999; Paley et al, 2001). Removal of the entire fallopian tube can be optimally accomplished by performing a hysterectomy but the majority (92%) of fallopian tube malignancies occur in the mid and distal portions of the tube (Alvarado-Cabrero et al, 1999) thus there is little evidence to support systematic hysterectomy at the time of PSO on this basis. However there are other factors which may influence decisions regarding whether hysterectomy is performed at the time of salpingo-oophorectomy in BRCA1/2 mutation carriers:

**HRT use:** Post-PSO HRT does not appear to increase the risk of cancer in premenopausal women who undergo PSO (Rebbeck et al, 2005). However, unopposed oestrogen does pose a substantial risk of uterine cancer while combined HRT has been shown in the Women's Health Initiative studies to increase the risk of breast cancer (Beral et al, 2003; Grady et al, 1995; Rossouw et al, 2002). Hysterectomy at the time of PSO would negate the uterine cancer risk facilitating the use of unopposed oestrogen as HRT in these patients.

**Tamoxifen chemoprevention:** Tamoxifen is a selective oestrogen receptor modulator (SERM) which is routinely used as adjuvant therapy in women with estrogen receptor positive breast cancer to prevent the development of cancer in the contralateral breast and to prolong disease free survival (Osborne, 1998). Tamoxifen has also been shown to reduce the risk of developing cancer in high risk women without prior breast cancer and can be used as a chemoprevention strategy in these patients to reduce the risk of invasive ER positive breast cancer (Visvanathan et al, 2009). Regarding BRCA1/BRCA2 mutation carriers specifically, tamoxifen use has been shown to reduce the incidence of contralateral breast cancer in BRCA mutation carriers with a prior history of breast cancer (Metcalfe et al, 2004; Narod et al, 2000). The protective effect of tamoxifen in BRCA mutation carriers without prior breast cancer has been less well defined and the available evidence is extrapolated from subset analyses of large randomised trials evaluating the efficacy of chemoprevention for breast cancer in the general population. A subgroup analysis of the NSABP-P1 data (King et al, 2001) was performed; only 19 of the 288 women who developed breast cancer had BRCA1 or BRCA2 mutations, and tamoxifen use did not appear to have a significant effect on breast cancer risk in these patients. In a review of the evidence regarding Tamoxifen use as chemoprevention in patients with a BRCA mutation, the ASCO panel concluded that the "limited evidence precludes reliable evidence of Tamoxifen effects in this setting". However as it has a proven risk reduction benefit in BRCA patients with a history

of breast cancer and in women with an increased risk of breast cancer, Tamoxifen is frequently offered as chemoprevention to BRCA mutation carriers who do not choose to undergo prophylactic mastectomy (Eisen & Weber, 2001). Risks and side effects must be considered when proposing Tamoxifen as a chemopreventive strategy, and consist predominantly of vascular, thromboembolic and neoplastic events. Tamoxifen use has been shown to be associated with an increased risk of uterine malignancy, including early stage adenocarcinomas , endometriod, mucinous, clear cell and uterine sarcomas. A meta-analysis of the breast cancer prevention trials reported more than doubling of uterine cancer with tamoxifen use (Cuzick et al, 2003). This is a risk of malignancy that would be negated if the patient underwent concomitant hysterectomy at the time of PSO.

**Surgical Approach:** Laparoscopy has become the most commonly used approach to PSO as it offers many advantages in improved visualisation of the pelvic peritoneum, avoidance of a large abdominal incision, shorter hospital stay, decreased post-operative pain and a rapid recovery time (Hidlebaugh et al, 1996; Leetanaporn & Tintara, 1996). Traditionally, a total abdominal hysterectomy (TAH) and PSO has been associated with a higher morbidity and longer recovery time when compared with laparoscopic PSO, a factor which may influence the decision to undergo concomitant hysterectomy. However, the last decade has seen an increase in the laparoscopic approach to hysterectomy which has been successfully employed for endometrial and cervical malignancy with comparable surgical and oncologic outcomes to laparotomy (Cho et al, 2007; Eltabbakh et al, 2000). Laparoscopic vaginal hysterectomy combined with laparoscopic PSO is a feasible minimally invasive approach to risk reducing surgery in patients with BRCA1/2 mutations (Casey et al, 1998; Eltabbakh et al, 1999). Recent advances have seen the development of an even less invasive approach to laparoscopic surgery known as laparoendoscopic single-site surgery (LESS). This approach uses a single port which accommodates the camera and operating instruments, needing only a single incision (Canes et al, 2008). This approach to gynaecologic surgery has been pioneered by Escobar and colleagues in the Cleveland Clinic who have reported its use in benign and malignant gynaecologic conditions (Escobar et al, 2009 & 2010; Fader et al, 2009). This group have recently reported on a retrospective series of 58 patients at high risk for breast/ovarian cancer who underwent LESS PSO with (n=13) and without (n=45) hysterectomy (Escobar et al, 2010). All cases were performed successfully with LESS in a mean operative time of 38 minutes (35minutes without hysterectomy and 42 minutes with hysterectomy), and there were no surgical complications. The majority of patients had this procedure performed as day case surgery. Although larger prospective studies are required to validate these results, this single – port laparoscopic approach represents an advance in minimally invasive gynaecologic surgery that may become an attractive option for BRCA mutation carriers and breast cancer patients due to the favourable cosmetic outcome and rapid recovery time.

As outlined, there are a number of considerations which must be taken into account when planning and counselling a patient for PSO. The timing of surgery, surgical approach, use of HRT and the risks and benefits of hysterectomy at the time of PSO should all be discussed with patients on an individual basis to aid the decision making process.

## 5. Morbidity associated with prophylactic oophorectomy and issues of regret

Despite the lack of evidence that ovarian cancer screening is effective in reducing the risk of developing ovarian cancer or in reducing the risk of death from ovarian cancer (Stirling et

al, 2005; Olivier et al, 2006), the uptake of PSO in BRCA1/2 mutation carriers is variable across published datasets.

Patients considering PSO are faced with complex information regarding cancer risk and the risk/benefit profile of prophylactic surgery including factors such as surgical risk, hormonal deprivation and residual cancer risk. It is important that patients are supported in processing this information in order to help them make the best individual decision. Numerous variables have been identified as factors in this decision making process. Demographically older women, women with children and married women are more likely to opt for PSO (Madalinska et al, 2007; Miller et al, 2010), an association which is not unsurprising as this cohort of women may have completed their childbearing and may not have to deal with the sudden severe menopausal symptoms that are associated with surgical menopause in younger women. Interestingly, a lower level of education is also associated with an increased likelihood to opt for PSO. Proposed explanations for this are that such patients may be more inclined to follow a gynaecologists recommendation for surgery without seeking alternative options, or that they may prefer a more definitive solution (surgery) to regain a sense of control (Hallowell et al, 2004; Madalinska et al, 2007; Miller et al, 2010). Clinical predictors of PSO include a family history of ovarian cancer and a personal history of breast cancer (Miller et al, 2010). The most consistent psychosocial predictor of PSO uptake is the patients perception of their own health and the risk of ovarian cancer; patients who perceive their own health as poor, patients who overestimate their ovarian cancer risk and those who view ovarian cancer as an incurable disease are more likely to opt for PSO as a risk reducing strategy (Miller et al, 2010). Importantly, a physician/gynaecologists recommendation is a powerful determinant of PSO uptake (Madalinska et al, 2007) and it has been reported that failure to discuss this option with the patient may be perceived as a recommendation against this strategy (Madalinska et al, 2007; Tiller et al, 2002). Ideally, all patients with a BRCA1/2 mutation should be offered comprehensive counselling regarding the risks of breast and ovarian cancer and the surveillance and risk-reducing strategies which may be undertaken.

In the course of such counselling, it is also important that the side-effects and potential outcomes of risk reducing surgery be discussed; surgical risk, residual cancer risk and the effects of hormonal deprivation should all be clearly explained to every patient considering risk reducing surgery. It is crucial to consider the impact of this surgery on premenopausal women in particular; the effect of menopausal symptoms, cognitive changes, loss of fertility, osteoporosis, heart disease, vasomotor symptoms, urogenital symptoms and the effect on sexuality and body image are all important factors that the patient should be aware of prior to surgery (Taylor, 2001). Qualitiative studies indicate that post surgery, the majority of women are satisfied with their decision to undergo PSO (Miller et al, 2010). There are a number of positive quality of life changes reported following PSO including a reduced perception of ovarian cancer risk, reduced anxiety levels and an increased sense of control over ones' health (Elit et al, 2001; Miller et al, 2010; Robson et al, 2003; Tiller et al, 2002). The majority of patients do report side effects related to hormonal deprivation, including hot flushes, vaginal dryness, decreased sexual interest and decreased sexual pleasure. These symptoms are most common in younger women (Miller et al, 2010; Robson et al, 2003). There is conflicting evidence regarding the level of patients satisfaction with pre-operative counselling with some women reporting that they were fully informed and others feeling that they could have been provided with more information, particularly regarding the

option to use HRT post PSO (Hallowell et al, 2004; Miller et al, 2010). Campfield-Bonadies et al recently reported the results of a questionnaire based study of BRCA carriers who had undergone PSO regarding their post-operative symptoms, their recollection of pre-operative counselling, and what information they would have found helpful to have prior to surgery (Campfield-Bonadies et al, 2011). It was found that most patients were counselled pre-operatively regarding the impact of PSO on ovarian and breast cancer risk, the pros and cons of surgical approaches and the impact of surgery on menopause, however the most common surgical symptoms were vaginal dryness, changes in libido and sleep disturbances and the majority of women would have found it helpful to have more information regarding the impact of PSO on their sex life, the availability of sex counselling and the risk of coronary heart disease, which were not commonly discussed during pre-operative counselling. Despite this, the overall satisfaction with PSO remains high in this cohort of patients (Miller et al, 2010)

## 6. Alternatives to surgery – Surveillance & chemoprevention

Not all women who are diagnosed with a BRCA1/2 mutation will opt for PSO. Younger women who have not completed childbearing and wish to maintain fertility may seek alternative strategies to minimise risk or expedite diagnosis of a potential ovarian or breast cancer to improve survival.

The alternative options to risk reducing surgery for these women are: surveillance or chemoprevention.

### 6.1 Surveillance

**Breast cancer surveillance**

The goal of surveillance is early detection of cancer. In the case of breast cancer, this involves:

- Regular (monthly) self breast examination from age 18 years
- Annual or semi-annual clinical breast examination
- Annual mammography beginning at age 30 years
- Annual breast MRI beginning at age 30 years (Robson & Offit, 2007; Saslow et al, 2007)

The sensitivity of mammography to detect malignancy in women with a genetic predisposition to breast cancer is approximately 33%, MRI increases this to approximately 80%. Surveillance with alternating mammography and MRI six monthly has a sensitivity of 95% for the detection of breast cancer (Warner et al, 2001 & 2004).

**Ovarian cancer surveillance**

Screening for the early detection of ovarian cancer involves:

- Annual or semi-annual transvaginal pelvic ultrasonography from age 35 years or at 5 years younger than the earliest ovarian cancer diagnosis in the family
- Annual CA-125 testing (NCCN, 2007)

The advantages of surveillance are the fact that it is non-invasive, has no effect on fertility or childbearing, and leaves the other options for risk reduction available to the patient should

she choose them at any time (eg. when finished childbearing). However there are disadvantages, the most obvious being that there is no reduction in cancer risk for these patients, and in the case of ovarian cancer, there is no evidence that the recommended surveillance strategies even reduce cancer-related mortality. Furthermore, there is an inherent level of anxiety associated with surveillance and both breast MRI and pelvic USS can yield false positives which increase this anxiety (Spiegel et al, 2011). It has been recommended that women opting for surveillance should be provided with professional psychosocial support when necessary (Warner, 2011).

### 6.2 Chemoprevention

The development of effective prevention strategies for breast and ovarian cancers is predominantly based on hormonal responsiveness. As discussed above, selective oestrogen receptor modulators (SERMS) have emerged as the first class of therapeutic agents in breast cancer chemoprevention trials (Fisher et al, 1998; Vogel et al, 2010). However, their efficacy in reducing breast cancer risk in BRCA1/2 mutation carriers is unclear, and questionable in BRCA1 carriers in whom breast cancers are predominantly ER negative. The potential of the aromatase inhibitor exemestane as a chemopreventive agent has been evaluated in a randomized, placebo-controlled, double-blind trial in 4560 women at high risk of breast cancer (Goss et al, 2011). There was a with a 65% relative reduction in the annual incidence of invasive breast cancer in the exemestane group indicating that this agent may have a role to play in breast cancer chemoprevention. There is no data to date regarding the protective effect of aromatase inhibitors in patients with BRCA1/2 mutations, but again it is doubtful that there will be a significant benefit in BRCA1 patients at risk of developing ER negative breast cancers. In the event that SERMs or aromatase inhibitors are deemed effective as chemoprevention for BRCA1/2 mutation carriers their benefit must be weighed against the side effect profiles including an increased risk of endometrial cancer with tamoxifen and the potential for thromboembolic events.

The oral contraceptive pill (OCP) has been shown to be effective in reducing epithelial ovarian cancer risk by 40-50% (McLaughlin et al, 2007; Narod et al, 2001). This strategy is well tolerated and inexpensive however OCP use also increases the risk of thromboembolic events and is associated with a slightly increased risk of breast cancer in BRCA mutation carriers if used for more than 5 years (Milne et al, 2005).

Translational research in breast cancer is largely focused on the development of targeted therapy. In addition to targeting the oestrogen pathway, researchers are continually investigating novel approaches to preventive therapy for breast cancer. Agents which have shown promise in breast cancer risk reduction include: non-steroidal anti-inflammatory drugs (NSAIDS) (Harris et al, 2003), bisphosphonates (Chlebowski et al, 2010; Rennert et al, 2010) and metformin (Bodmer et al, 2010; Bosco et al, 2011). The data to date however is all observational and prospective trials are underway to confirm a protective effect before these agents can be considered or recommended for clinical use (Cuzick et al, 2011). In the context of BRCA mutation carriers, the investigation of novel strategies to target ER negative breast cancers is most likely to yield a potentially effective agent. Perhaps the most promising agents under investigation at present are the poly-ADP ribose polymerase (PARP) inhibitors which induce synthetic lethality in homozygous BRCA-deficient cells. Recent reports of phase II trials have shown efficacy and tolerability for PARPs, or poly ADP (adenosine

diphosphate)-ribose polymerase inhibitors, in BRCA mutation carriers with advanced breast and ovarian cancers (Audeh et al, 2010; Tutt et al, 2010), and BRCA1/2 mutation status is the best predictor of clinical response to PARP inhibitor treatment in patients with breast or ovarian cancer, highlighting the potential for these agents as therapeutic and future preventive agents in this cohort of patients.

## 7. Conclusions

Prophylactic oophorectomy is proven to be an effective risk-reducing strategy in hereditary breast and ovarian cancer. In women diagnosed with a BRCA1/2 mutation the decision of whether to undergo risk reducing surgery is a complex one. Adequate consideration must be given to the risks and benefits of surgery, particularly in relation to timing of surgery, fertility, reduction in cancer risk, the need for hysterectomy and the symptoms of early menopause. Patients should be adequately counseled by regarding the options available to them including surveillance and risk reducing strategies.

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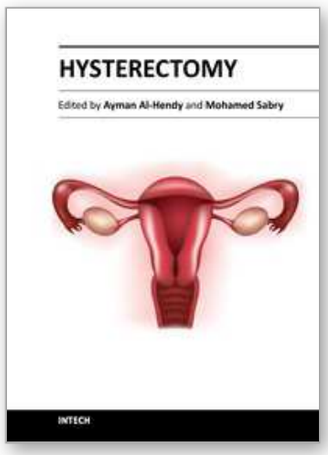


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This book is intended for the general and family practitioners, as well as for gynecologists, specialists in gynecological surgery, general surgeons, urologists and all other surgical specialists that perform procedures in or around the female pelvis, in addition to intensives and all other specialities and health care professionals who care for women before, during or after hysterectomy. The aim of this book is to review the recent achievements of the research community regarding the field of gynecologic surgery and hysterectomy as well as highlight future directions and where this field is heading. While no single volume can adequately cover the diversity of issues and facets in relation to such a common and important procedure such as hysterectomy, this book will attempt to address the pivotal topics especially in regards to safety, risk management as well as pre- and post-operative care.

**How to reference**

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