Familial Cancer (2016) 15:371–384
DOI 10.1007/s10689-016-9878-4

ORIGINAL ARTICLE

# Müllerian intra-abdominal carcinomatosis in hereditary breast ovarian cancer syndrome: implications for risk-reducing surgery

**Murray Joseph Casey**[1] · **Agnes B. Colanta**[2]

Published online: 13 February 2016
© Springer Science+Business Media Dordrecht 2016

**Abstract** More than 40 years ago Lynch et al. described several multigenerational breast cancer family pedigrees which demonstrated autosomal dominant inheritance of a trait(s) that increased risks for both breast and ovarian cancers. Mutation carriers in at least 90 % of these hereditary breast ovarian cancer (HBOC) syndrome families have been linked to cancer-associated mutations in the genes *BRCA1* and *BRCA2*. This review focuses on the contributions of Lynch, colleagues and collaborators and pertinent literature, toward defining the HBOC syndrome, the cancer risks that the inherited adverse mutations convey, the gynecologic tissues and organs from which the malignancy may arise to disseminate throughout the pelvic and abdominal organs and peritoneum and how this information can be used to reduce the risk and morbidities of intra-abdominal carcinomatosis in effected individuals.

**Keywords** Intra-abdominal carcinomatosis · Hereditary breast ovarian cancer · Risk-reducing surgery

Presented during the Dr. Henry T. Lynch Symposium: Advances in Hereditary Cancer, Omaha, NE, USA, September 17–18, 2015.

✉ Murray Joseph Casey
mjcasey@creighton.edu; MurrayCasey@creighton.edu

[1] Departments of Obstetrics and Gynecology and Preventive Medicine, Creighton University School of Medicine, 601 N. 30th Street, Omaha, NE 68131, USA

[2] Department of Pathology, Creighton University School of Medicine and CHI Health Creighton University Medical Center - Bergan Mercy, Omaha, NE, USA

## Introduction

Lynch et al. [1–8] at Creighton University may best be known for their characterization over 40 years ago of autosomal dominant transmission of a susceptibility trait for non-polyposis colorectal cancer with predilection to the right colon and high risks for endometrial and ovarian cancers in female family members and also increased risks for carcinomas of the stomach, small bowel and hepatobiliary tract, pancreas, renal pelvis, ureter and brain tumors, particularly glioblastomas. This hereditary disease, marked by no other grossly recognizable phenotype, is now termed "Lynch syndrome" [9]. Less well recognized are the concurrent studies that Lynch and his group published during that time showing multigenerational family pedigrees with inordinate numbers of breast cancers leading to their identification of autosomal dominant hereditary susceptibility to both breast and ovarian cancers at unusually young ages in some of these kindreds [10–16].

Soon after Hall et al. [17, 18] reported linkage of early-onset breast cancer to a site in chromosome 17q, Narod and associates demonstrated that hereditary breast ovarian cancer (HBOC) susceptibility in families from the Creighton Hereditary Cancer Registry was linked to a locus at 17q12–q23. This gene and a separate gene locus on chromosome 13q12.3, also linked to the HBOC syndrome, have been cloned and designated *BRCA1* and *BRCA2*, respectively [19–22]. The Breast Cancer Consortium reported that over 90 % of their families with female breast cancer and two or more ovarian cancers were linked to mutations in *BRCA1* or *BRCA2* [23]. Meta-analysis of penetrance studies from Asia, North America and Europe reported a range of cumulative cancers by age 70 years of 47–66 % (mean 57 %) for breast cancer and 35–46 % (mean 40 %) for ovarian cancer in *BRCA1* mutation

carriers and of 40–57 % (mean 49 %) for breast cancer and 13–23 % (mean 18 %) for ovarian cancer in *BRCA2* mutation carriers [24].

Because of the high risk for ovarian cancer and 50 % likelihood that the deleterious autosomal dominant susceptibility trait would be inherited in HBOC syndrome families, Lynch and colleagues recommended that prophylactic oophorectomy should be considered by the female members [12]. In spite of the intent to prevent the morbid effects of ovarian cancer in families prone to this disease by prophylactic oophorectomy, it became evident in early studies that, although extirpated ovaries appeared grossly and histologically normal, a fraction of the women with hereditary predilection to gynecologic cancer still developed intra-abdominal carcinomatosis indistinguishable from metastatic ovarian carcinoma [25–27].

Our study of HBOC syndrome families linked to *BRCA1* or *BRCA2* mutations in the Creighton Hereditary Cancer Registry found only five mutation carriers who were diagnosed with intra-abdominal carcinomatosis in 238 individuals who had undergone prophylactic oophorectomy, giving a calculated cumulative risk of 3.5 % over 20 years post surgery [28]. Histological examination of the submitted ovarian specimens from these five cases found no preinvasive or invasive cancers in three, but superficial papillary serous borderline tumors, one with possible early invasion, were found on ovarian sections in two cases [28]. Recent clinical-pathological and molecular genetic studies favor different carcinogenic pathways for most borderline ovarian tumors contrasted with high grade carcinomas, such as serous intra-abdominal carcinomatosis in *BRCA1* and *BRCA2* linked HBOC families [29–31]. This model would not preclude malignant deterioration of superficial implants from extraovarian preinvasive or invasive serous carcinomas or the advance of ovarian intraepithelial serous lesions and tumors into full blown cancers by natural progression or by spontaneous or epigenetic loss of heterozygosity (LOH) in women who carry inherited deleterious mutations that predispose to "ovarian" cancer [29–33]. Microscopic malignancies, such as these, overlooked during routine surgical pathological examination, whether primarily arising from ovarian surface epithelium or tiny surface implants from other malignant sites, could account for some of those few cases of intra-abdominal carcinomatosis that occur many months or years after intended prophylactic surgery.

Following the speculation of Foyle et al. [34] that widespread peritoneal papillary serous carcinoma in ten of their female patients with no evidence of ovarian carcinoma arose primarily from "extraovarian mesothelium with the same müllerian potential as ovarian surface (germinal) epithelium", Tobacman et al. and Lynch et al. [25, 27] hypothesized that intra-abdominal carcinomatosis after oophorectomy in women at high genetic risk for ovarian cancers may result from malignant transformation of embryologically related epithelium of the müllerian system and coelomic epithelium of the peritoneum and ovarian surface. According with current concepts of normal human female embryology, primordial germ cells migrate from the yolk sac into mesenchyme posterior to the coelomic cavity during the fifth week of gestation to form bilateral thickened genital ridges just medial to the mesonephros and mesonephric ducts [35]. During the sixth week of gestation, cells from coelomic epithelium covering the genital ridges grow inward to invest the germ cells, and as embryo to fetal development progresses eventually surround germ cells to form primary follicles around individual oocytes. Meanwhile, a pair of paramesonephric ducts, more commonly called müllerian ducts in the female, form in a thickened band of proliferating mesoderm posterior to the coelomic cavity and lateral to the mesonephros and genital ridges [35]. As fetal growth and development continue, the primitive ovaries and bilateral müllerian systems descend caudally, both moving through coelomic lining epithelium, which becomes parietal peritoneum and the visceral peritoneum covering these pelvic organs and affiliated structures. Reaching the primitive pelvis, the distal müllerian ducts fuse in the midline and meet the invaginating urogenital sinus to form the upper vagina. The midline septum that resulted from fusion of the müllerian system then begins involution which continues cephalad until functionally resulting in a single uterine cervix and corpus and bilateral fallopian tubes [36]. Thereby, the epithelia of the endocervix, endometrium and endosalpinges derive from the müllerian system; while epithelium covering the pelvic viscera derives from coelomic epithelium.

## Fallopian tube neoplasms

Piek et al. [37] reported that 94 % of ovarian (42/45), fallopian tube (3/3) and peritoneal cancers (2/2) in *BRCA1* or *BRCA2* mutation carriers from the Amsterdam Family Cancer Clinic were invasive serous carcinomas compared to just 62 % of cases with this pathological histotype in the population based Netherlands Cancer Registry. Two of Piek's [37] three presumed cases of primary peritoneal serous carcinoma were in women who had undergone oophorectomy but not salpingectomy. Our 52 years review of gynecologic cancers in *BRCA1* and *BRCA2* mutation carriers from HBOC syndrome families in the Creighton Hereditary Cancer Registry found that 70 % of ovarian cancers (45/64), 86 % of fallopian tube cancers (12/14) and all of the cases classified as primary peritoneal cancers (8) were dedifferentiated serous or anaplastic carcinomas [38].

Among the early pedigrees of familial association of breast and ovarian carcinoma that Lynch and his associates reported in 1974 was one family member with papillary serous carcinoma involving both fallopian tubes and ovaries, and in 1975, Fraumeni et al. reported a primary fallopian tube carcinoma in a family with three breast and two ovarian cancers over two generations of first degree relatives [12, 39]. After linkage of most HBOC families to cancer-associated mutations in *BRCA1* or *BRCA2*, several cases of microscopic invasive and in situ fallopian tube carcinomas were reported in *BRCA1* and *BRCA2* mutation carriers, some with malignant peritoneal cytology [40–45]. A sub-study reported in 2002 by the Breast Cancer Linkage Consortium estimated a highly significant ($P < 0.001$) increased relative risk of 49.94 (95 % CI 22.48–110.94) for fallopian tube cancer in mutation carriers from breast and/or ovarian cancer families with at least one individual known to carry a pathogenic mutation in *BRCA1* compared with population incidence rates from the United Kingdom East Anglian Cancer Registry [46]. In 2003, Piek et al. [47] recounted that 37 % of the fallopian tubes that were prophylactically removed from women at high risk for breast and ovarian cancer showed dysplastic lesions, including one with in situ carcinoma, and they hypothesized that most hereditary serous carcinomas involving ovaries actually arise in fallopian tube epithelium Since then, the reports of occult invasive fallopian tube serous carcinomas and distinct noninvasive serous tubal intraepithelial carcinomas (STIC) in prophylactic surgical specimens from HBOC syndrome mutation carriers have continued to accumulate [48]. Many of these cases were associated with malignant cells in the peritoneal fluid, intra-abdominal carcinomatosis or later recurrent cancers [49–54]. Not only do STIC morphologically resemble high grade serous carcinomas (HGSC) involving pelvic and/or abdominal peritoneum and previously identified as "ovarian" or "primary peritoneal" cancers, but in more than 90 % of tested cases identical *T53* mutations were shared by STIC and the co-existing HGSC [55–58]. Immunohistochemical (IHC) staining for p53 is quite common in STIC, though not consistent [55, 59]. However, when staining for p53 is found in HGSC, as a surrogate for *T53* mutations, usually it is expressed in accompanying STIC, as well [55, 57]. On the other hand, complete absence of p53 expression in STIC correlates with frameshift mutations in *T53*, due to deletions, insertions, splicing junction and nonsense mutations [57]. Foci of p53 IHC straining found in otherwise morphologically normal tubal epithelium have been termed "p53 signatures", and some investigators have interpreted these as possible precursor lesions from which STIC may develop in genetically susceptible individuals; though this remains controversial [48, 56, 59]. Finally, when the entire fallopian tube could be examined, STIC have been identified in more than half of the HGSC cases classified as primary peritoneal cancers [58, 60]. Such evidence as the foregoing has led to a growing consensus that many, if not most, cases of serous intra-abdominal carcinomatosis in HBOC syndrome mutation carriers, originate from fallopian tube neoplasms, often to involve adjacent ovaries and disseminate to the peritoneum and intraperitoneal organs (Fig. 1) [50, 58, 60].

## Uterine neoplasms

Early attention to the possibility of increased susceptibility to uterine cancers in HBOC syndrome mutation carriers comes from a large study conducted by the multinational Breast Cancer Linkage Consortium, which included 11,847 individuals from 699 families with breast and/or ovarian and at least one member known to carry a pathogenic mutation in *BRCA1* [46]. This group calculated estimated increased relative risks of 2.86 (95 % CI 1.69–4.16) for uterine corpus cancer and 3.72 (95 % CI 2.26–6.10) for uterine cervix cancers which were highly significant ($P < 0.001$) compared with general population cancer risks specific to country, calendar period and 5-year age groups [46]. In that study, the relative risks for uterine corpus and cervix cancers exceeded even those for colorectal, biliary and pancreatic cancers but not fallopian tube cancers in *BRCA1* mutation linked families [46]. Although other hereditary factors could account for these increased cancer risks and the uterine cancer histotypes were not specified, this publication demands attention to uterine epithelium as

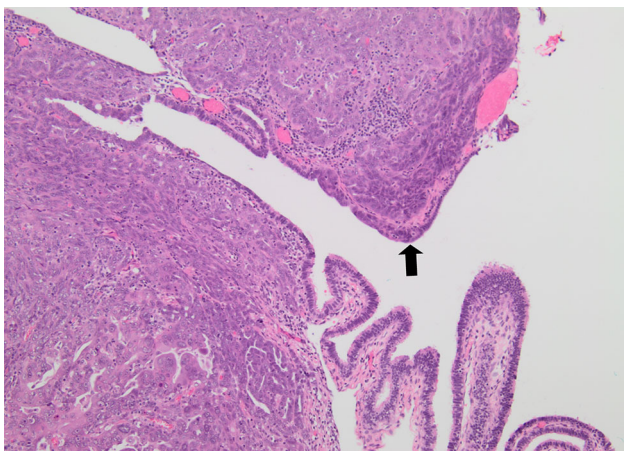

**Fig. 1** Distal fallopian tube prophylactically removed from *BRCA1* mutation carrier with high grade serous carcinoma arising in serous tubal intraepithelial carcinoma (STIC) (*arrow*) (H&E ×100). A single <1 mm implant was on the ipsilateral ovary. Four years after risk-reducing surgery the patient presented with disseminated serous intra-abdominal carcinomatosis

a possible site for malignant transformation that may lead to intra-abdominal carcinomatosis [46].

## Endometrium

Predilection of *BRCA1* and *BRCA2* mutation carriers to preinvasive and invasive serous fallopian tube carcinoma and a higher than expected overall 31 % (33/108) prevalence of *BRCA1* or *BRCA2* mutations in patients with fallopian tube cancers, especially a 59 % (10/17) prevalence in selected Jewish women who may carry one or another of the well defined Ashkenazi mutations in *BRCA1* (185delAG and 5382insC) or *BRCA2* (617delT) leads to question whether HBOC syndrome mutation carriers may be susceptible to serous carcinoma in other müllerian-derived epithelium which then seeds the peritoneum [31, 61]. Some 15 years ago, Hornreich et al. [62] reported cases of endometrial serous papillary carcinoma in a 53 year old woman of Ashkenazi descent and an ovarian papillary carcinoma in her 48 year old sister; both women carried the same *BRCA1* 5382insC mutation. A subsequent Israeli study of 20 consecutive Ashkenazi women with uterine serous papillary carcinomas found that four subjects (20 %), diagnosed at 65 years mean age, carried Ashkenazi *BRCA1* mutations (three 185delAG and one 5382insC) [63]. Members of this study group with others later reported uterine serous papillary carcinoma in a 65 year old Ashkenazi women who carried a *BRCA2* 617delT mutation [64]. Albeit, two early studies of uterine serous cancers in Canada (1994–2000) and endometrial serous carcinomas in New York Jewish women (1986–1998) found no *BRCA1* or *BRCA2* mutations in 56 and 17 patients, respectively [65, 66]. And a collaborative Israeli study over 26 years (1982–2008) found no Ashkenazi *BRCA1* or *BRCA2* mutations in 34 patients with endometrial serous carcinoma [67]. However, two other series of endometrial serous carcinomas in Israel (updated 1997–2007 and 1999–2008) found that 25.8 % (8/31) and 15.7 % (8/51) of those women, respectively, carried an Ashkenazi mutation, which was significantly higher than the 2.5 % incidence of these mutations in their Ashkenazi population [68, 69]. A more recent American study of 151 women with uterine serous carcinoma for mutations in 30 tumor suppressor genes, including *BRCA1* and *BRCA2*, found three subjects with mutations in *BRCA1*, a prevalence of 2 % in unselected women with this disease, which exceeds the expected frequency of 0.06 % *BRCA1* mutations in the general population [70]. An interesting report from the surgical arm of Gynecologic Oncology Group study GOG-0199 found six primary endometrial cancers among 966 "high risk" patients, including 326 *BRCA1* mutation carriers and 231 *BRCA2* mutation carriers who underwent risk-reducing salpingo-oophorectomy (RRSO) [53]. Only 515 of these patients also had hysterectomy [53]. Two endometrial cancers, both serous carcinomas, were diagnosed in *BRCA1* mutation carriers, and four endometrial cancers, two endometrioid and two mucinous carcinomas, were found in non-carriers. There were no endometrial cancers in *BRCA2* mutation carriers [53]. We found that eight cases (7.9 %) of endometrial cancer could be confirmed in 101 *BRCA1* and *BRCA2* mutation carriers with gynecologic and peritoneal cancers from HBOC syndrome families accrued to the Creighton Hereditary Cancer Registry over the past 55 years [71]. Three of these eight cases of endometrial cancer in HBOC syndrome mutation carriers were high grade pure serous carcinomas or contained greater that 10 % high grade elements of serous carcinoma mixed with poorly differentiated endometrioid carcinoma (Fig. 2). The other five patients had well or moderately well differentiated endometrioid carcinomas (Fig. 3) [71].

High grade serous carcinomas arising in endometrium are rare and aggressive tumors, making up fewer than 5 % to no more than 12 % of uterine cancers in population based international cancer registries and a large American group trial [72–76]. Even when small, superficial or a minor component admixed with endometrioid carcinoma, endometrial high grade serous carcinomas are prone to lymphatic involvement and/or transtubal dissemination [74–84]. Most endometrial serous carcinomas, whether invasive or intraepithelial, are characterized by *TP53* mutations, which often are shared with co-existing serous intra-abdominal carcinomatosis involving ovaries, fallopian tube serosa and peritoneum [81, 84]. Invasive endometrial serous carcinomas frequently coexist with endometrial intraepithelial carcinomas (EIC) [82]. Even when unaccompanied by invasive endometrial serous carcinoma, cases of EIC have been described variously with

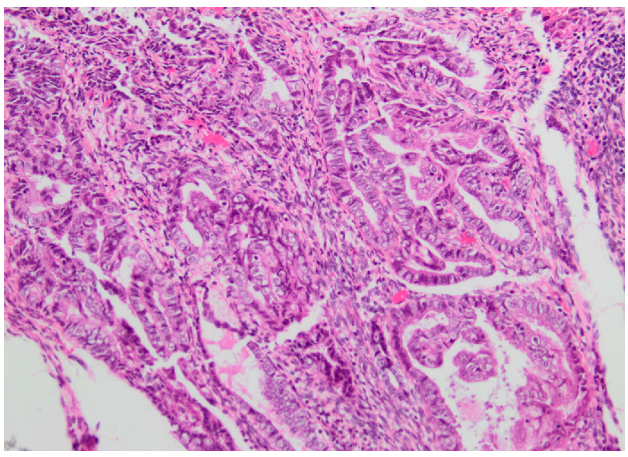

**Fig. 2** Endometrial high grade serous carcinoma in tamoxifen treated *BRCA1* mutation carrier presenting with disseminated serous intra-abdominal carcinomatosis (H&E ×200)

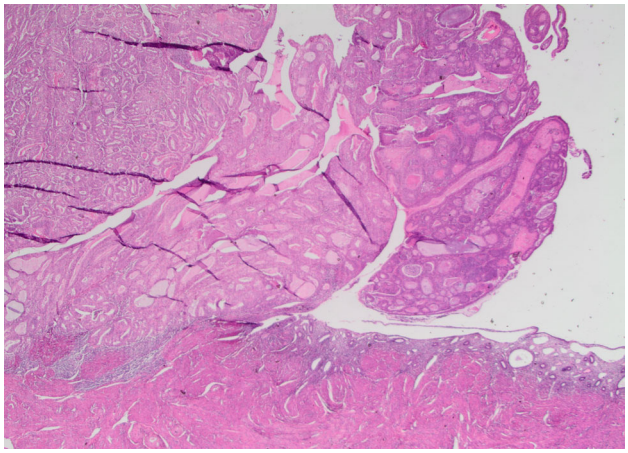

**Fig. 3** Endometrial endometrioid adenocarcinoma, FIGO grade 1, in a *BRCA1* mutation carrier previously treated with hormone replacement for 7 years (H&E ×100)

free-floating malignant cells in the fallopian tube, cancerous involvement of the ovary and metastases to pelvic and upper abdominal serosa and omentum [79, 81, 84] Simultaneous EIC and STIC have been reported with extrauterine extension or metastases [79, 82, 84], and shared *TP53* mutations in EIN and STIC have been demonstrated in a couple of the cases [79]. Extensive sectioning of the entire fallopian tube and endometrium in a recent Dutch study discovered EIC in 9/60 (15 %) and STIC in 23/54 (43 %) of 60 cases operated for ovarian serous carcinoma [85]. In six cases these intraepithelial carcinomas coexisted, and in 19 cases there were invasive serous carcinomas of the fallopian tube and/or endometrium [85]. Four (17 %) of the 23 cases of STIC were non-fimbrial [85]. These observations and studies would not preclude transit of transformed neoplastic cells from primary fallopian tube sites, the ovary or peritoneum into the endometrium from which EIC and invasive serous carcinoma are manifest. However, tumorous involvement of endosalpinx and ovarian surface with upper abdominal dissemination have been described in cases of EIC without the presence of STIC [79, 81]; while EIC have been reported with and without synchronous STIC but accompanied by extrauterine serous carcinomas that carried *TP53* mutations in common with EIC alone, STIC alone or both EIC and STIC [84]. Given the likelihood that EIC and STIC are preinvasive cancers capable of seeding peritoneum and intraperitoneal organs favors a concept that either lesion and their invasive counterparts could be sources of intra-abdominal carcinomatosis in susceptible individuals.

### Endocervix

Uterine endocervical epithelium, like endometrium and fallopian tube epithelium, is a müllerian derivative [34] We reported three cases of uterine cervix carcinoma in 95 HBOC syndrome mutation carriers with invasive gynecologic cancers in the Creighton Hereditary Cancer Registry [38]. Two of these cases demonstrated endocervical papillary serous carcinoma, one of which extended to endometrium [38]. The other primary cervical cancer in an HBOC syndrome mutation carrier was a minimally invasive (<3 mm) squamous carcinoma [38]. Serous carcinoma, the rarest cervical cancer histotype, is aggressively capable of lymphatic spread and/or dissemination to the peritoneum and to pelvic and abdominal organs [86, 87] Endocervical invasive serous carcinoma accompanied by intraepithelial serous carcinoma and then the diagnosis of peritoneal carcinomatosis 24 months later has been reported in a young woman in her fourth decade whose identical twin and mother also died at young ages with peritoneal carcinomatosis and whose maternal grand mother and aunt had bilateral breast cancers; but no genetic testing for mutations in *BRCA1* or *BRCA2* were done on any of these individuals [87]. Whether or not germline mutations in *BRCA1* or *BRCA2* enhance susceptibility to either endocervical or squamous cell carcinoma of the uterine cervix, cancer-associated defects in these genes certainly should not be expected to convey immunity against those diseases.

## Implications for risk-reducing surgery

The ultimate objectives of patient care are to prevent and relieve suffering from disease and to promote healthfulness. The present communication is directed toward preventing and relieving the morbidities of intra-abdominal carcinomatosis and mortality that may result therefrom in women with inherited susceptibility. This review has implicated several epithelial tissues as possible sites for primary malignant transformation from which intra-abdominal serous carcinomatosis may originate in mutation carriers from HBOC syndrome families: to wit, (1) ovarian surface and possibly inclusion cyst epithelium and the peritoneum which arise from the embryonic coelomic lining and (2) endosalpingeal, endometrial and endocervical epithelium that arise from the embryonic müllerian system.

Though several studies have shown statistically significant risk reductions for ovarian cancer with combined oral contraceptives (COC) used for more than a year in both *BRCA1* and *BRCA2* mutation carriers, use of these preparations for ovarian cancer chemoprophylaxis is guarded because they might be associated with increased risks for breast cancer in carriers of mutations in either gene [88, 89]. Also, the efficacy of presently available screening techniques intended to reduce morbidity and mortality attributed to serous ovarian cancers in high risk women is unproven [89, 90]. Therefore, prophylactic surgery

intended to reduce the risk of gynecologic serous carcinomas remains the standard for cancer prevention in HBOC syndrome mutation carriers [89, 91].

For more than a dozen years prophylactic oophorectomy and/or salpingo-oophorectomy have been known to significantly reduce the risk for both breast cancer and serous peritoneal, fallopian tube or ovarian cancers in women from HBOC syndrome kindreds who carry *BRCA1* or *BRCA2* mutations [92, 93]. As reviewed above, accumulating molecular, pathological and translational studies of organ and tissue specimens from women who carry cancer-associated mutations in *BRCA1* and *BRCA2* have concluded that many or most pelvic and peritoneal serous carcinomatosis of gynecologic origin arise from fallopian tube epithelium. This has led some authors to speculate whether risk-reducing surgery in premenopausal HBOC mutation carriers during their fifth decades of life could be confined to salpingectomy while conserving the ovaries [94, 95]. Sparing the ovaries should avoid symptoms associated with an abrupt decline of endogenous ovarian hormones, such as vasomotor hot flushes, night sweats and sleep disturbance, diminished libido and eventual vaginal dryness and dyspareunia, that are experienced by some women following premature surgical menopause and may be protective against osteoporosis, cardiovascular disease and cognitive impairment with aging [94, 95]. On the other hand, whatever protection against breast cancer attributable to risk-reducing salpingo-oophorectomy (RRSO) in mutation carriers may be lost if the ovaries are left in situ [96]. Prophylactic mastectomies alone reduce the risk for first primary breast cancer in HBOC syndrome mutation carriers by at least 90 % [97–99]. While the addition of RRSO to prophylactic mastectomies may enhance this protection against breast cancer and reduce overall mortality [98, 100–102]. Published results from a Markov Monte Carlo simulation model developed to compare (1) bilateral RRSO at age 40 years with (2) bilateral salpingectomy alone at age 40 years or (3) with bilateral salpingectomy at age 40 years and delayed oophorectomy till age 50 years in *BRCA1* and *BRCA2* mutation carriers showed that RRSO at age 40 years was associated with higher life expectancy and lower cost than the other alternatives [96]. According to this model, when compared to the second alternative, bilateral salpingectomy at age 40 years; the strategy of bilateral RRSO at age 40 years reduced the risk for ovarian cancer by 22.8 % in *BRCA1* and 20.5 % in *BRCA2* mutation carriers, and the risk for breast cancer was reduced 22.6 % in *BRCA1* and 39.7 % in *BRCA2* mutation carriers [96]. Whereas, with bilateral salpingectomy at age 40 years and delayed oophorectomy at age 50 years, the risk for ovarian cancer was reduced only 14.6 % in *BRCA1* and 13.1 % in *BRCA2* mutation carriers, and the risk for breast cancer was reduced only 0.4 % in *BRCA1* and 1.1 % in *BRCA2* mutation carriers [96]. When quality-of-life measures were included in the model, salpingectomy at age 40 years with delayed oophorectomy at age 50 years yielded the highest quality-adjusted life-expectancy, but the simulations did not include hormone replacement therapy (HRT), which if added may have improved quality-adjusted life expectancy with RRSO at age 40 years to exceed the predicted quality-adjusted life-expectancy with prophylactic salpingectomy at age 40 years and delayed oophorectomy to age 50 years [96].

Earlier simulation models also demonstrated improved life expectancy in *BRCA1* and *BRCA2* mutation carriers who undergo prophylactic oophorectomy [103–108]. These gains begin to diminish when prophylactic surgery is performed after age 30 years, especially if oophorectomy is delayed beyond age 40 years [103–108]. It is beyond the scope of this communication to discuss the merits and weigh the outcomes of various decision models. Suffice it to note that the reviewed reports concur in demonstrating improvements in life expectancy for regimens that include oophorectomy by age 40 years in women at high risk for breast and ovarian cancers.

Pending definitive investigations into early salpingectomy and delayed oophorectomy, some have advocated that with careful discussion and patients' understanding of risk, at least salpingectomy should be offered to mutation carriers who are set against premenopausal removal of their ovaries [95]. Surveys indicate interest for being engaged in such studies by women at increased hereditary risk for breast and ovarian cancers [109, 110], and at least one prospective trial is being set up to investigate cancer risk-reduction and quality of life with salpingectomy upon completion of childbearing and delayed oophorectomy and compare this with RRSO [111]. Already there is a published report of this planned approach in the care of a 41 year old carrier of the Ashkenazi 187delAG mutation in *BRCA1*, whose mother and maternal aunt carried the same mutation and were victims of breast cancer [112]. In spite of knowing this, the patient still was reluctant to have her ovaries removed; so after being advised of recommendations for RRSO, she instead chose minimally invasive salpingectomy [112]. Surgical pathology discovered a unilateral fallopian tube 2 mm serous carcinoma for which she was treated with hysterectomy-bilateral oophorectomy, pelvic and para-aortic lymphadenectomies and omentectomy, all with no other evident cancer [112]. After adjuvant platinum-based chemotherapy, the patient was reported to be disease-free 7 months following the diagnosis of occult cancer which likely would have gone unrecognized had not at least salpingectomy been carried out [112].

Review of cases that were reported during the past 5 years since adoption of rigorous surgical pathology

protocols to thoroughly examine the entire fallopian tube and ovarian specimens of RRSO from *BRCA1* and *BRCA2* mutation carriers, finds that 71 % of the occult preinvasive and/or invasive serous carcinomas involved only fallopian tubes, 14 % involved both fallopian tubes and ovaries, and 15 % involved only ovaries (Table 1) [49–54]. When peritoneal fluid was taken for cytology at the time of RRSO in these cases, 24 % of the occult preinvasive and 40 % of the occult invasive carcinomas were positive for malignancy (Table 2) [49–54]. But only 7 % of the preinvasive carcinomas compared with 27 % of the occult invasive carcinomas discovered at RRSO were accompanied by metastatic disease or diagnosed with recurrent pelvic-abdominal cancer during follow-up [49–54]. Because the objective of prophylactic gynecologic surgery in HBOC syndrome mutation carriers is to reduce the risk of disseminated cancer, it is judicious to eliminate the organ tissues from which the malignancies may arise and to which they first extend. A meta-analysis published in 2009 concluded that salpingo-oophorectomy reduced the risk for "ovarian" cancer by at least 80 % and the risk for breast cancer by some 50 % in mutation carriers from HBOC syndrome families [91]. And subsequent publications have reported even more impressive risk reductions of ovarian and breast cancers in *BRCA1* and *BRCA2* mutation carriers after RRSO [90, 100–102].

Observations and data support early removal of both fallopian tubes and ovaries by the end of the fifth decade of life to provide the most significant protective effect against ovarian cancer in HBOC syndrome mutation carriers. This is especially relevant for those who carry cancer-linked mutations in *BRCA1* for whom the risk of ovarian cancer is higher and the age of diagnosis is younger than it is in *BRCA2* mutation carriers [113, 114]. In a large international study of 1390 HBOC syndrome mutation carriers who had oophorectomy or salpingo-oophorectomy, 43 occult ovarian or fallopian tube cancers and one peritoneal cancer were diagnosed in *BRCA1* mutation carriers at prophylactic surgery [102]. The youngest of these patients with occult cancer was age 34 years; three occult cancers were diagnosed before age 40 years, and 19 of the occult cancers were diagnosed between ages 40 and 49 years [102]. Thus, half of the occult cancers diagnosed at surgery in *BRCA1* mutation carriers were discovered before age 50 years [102]. From a 1.5 % prevalence of occult cancers discovered in *BRCA1* mutation carriers before age 40 years and the cumulative prevalence over the next 10 years, the authors estimated that the chance of being diagnosed with occult cancer rises to 14 % if RRSO is delayed until age 50 years [102]. Only two occult cancers were diagnosed in *BRCA2* mutation carriers, both after age 60 years [102].

At least in the short term, HRT after oophorectomy probably does not increase the risk for breast cancer in HBOC syndrome mutation carriers. A collaborative cohort study of 462 *BRCA1* and *BRCA2* mutation carriers, adjusted for year of birth and mutated gene and prospectively followed for 3.6 years, demonstrated a significantly reduced hazards ratio 0.40 (95 % CI 0.18–0.92) for breast cancer in women who had undergone prophylactic oophorectomy at mean age 42.7 years (range 21.5–73.9 years) with 90 % being younger than 50 years [115]. Hormone replacement therapy did not alter the favorable results of reduced breast cancer risk in mutation carriers who had oophorectomies in that study [115]. In fact, women who underwent oophorectomy and took HRT had about one-third the risk for breast cancer as those who did not have oophorectomy and did not take HRT [115]. An earlier Markov decision model lumping together *BRCA1* and *BRCA2* mutation carriers also predicted that premenopausal oophorectomy lengthened life expectancy [106]. The simulated favorable effects associated with prophylactic oophorectomy were attributable mostly to reduced risks for both ovarian and breast cancers [106]. These good effects were somewhat obtunded by HRT, which was assumed to increase breast cancer risk over time, and the results improved when prophylactic mastectomy was concurrent with prophylactic oophorectomy [106]. In this model, life expectancy was not significantly affected when HRT was started after oophorectomy at age 35 years and continued until age 50 years; and life expectancy was slightly extended when oophorectomy was at age 40 years and HRT continued for 10 years, but this improvement did not approach the overall gain in life expectancy with prophylactic oophorectomy at age 40 years and no HRT [106]. Supporting expectations from the simulations, a case match control study of only *BRCA1* mutation carriers actually found significantly lower odds ratio OR 0.58 (95 % CI 0.35–0.96, $P = 0.02$) for breast

**Table 1** Proportion of occult intra-epithelial and invasive serous carcinomas[a] found involving fallopian tubes and/or ovaries from risk-reducing salpingo-oophorectomy on *BRCA1* and *BRCA2* mutation carriers

| Fallopian tube only | Fallopian tube and ovary | Total fallopian tube involvement | Ovary only | Total ovarian involvement |
|---|---|---|---|---|
| 74/105 (71 %) | 15/105 (14 %) | 89/105 (85 %) | 16/105 (15 %) | 31/105 (30 %) |

References [49–54]

[a] Serous intra-epithelial and invasive carcinomas and unspecified histotypes are included; neoplasms with other specified histotypes were excluded

**Table 2** Positive peritoneal cytology and metastatic or recurrent cancer after documented occult preinvasive and invasive ovarian and fallopian tube carcinomas in risk-reducing salpingo-oophorectomies

| Positive peritoneal cytology/cases tested | | Metastatic + recurrent cancers/cases reported |
|---|---|---|
| Preinvasive | Invasive | Preinvasive |
| 8/34 (24 %) | 20/50 (40 %) | 2/28 (7 %) |

References [49–54]

cancer in the group of subjects who ever used hormone therapy compared with those who had not [116]. Though the numbers of cases were few in which receptor status of the breast cancers were known, the findings in that study were not attributed to tumor type, as there was no significant difference in the use of hormone therapy reported by patients with ER-positive tumors 4/33 compared with those with ER-negative tumors 16/70 ($P = 0.29$) [116]. A study of 60 *BRCA1* and *BRCA2* mutation carriers disclosed the diagnosis of three breast cancers in 31 subjects (9.7 %) who took HRT after RRSO compared with nine breast cancers in 29 subjects (31 %) who did not use HRT after RRSO [117]. All three of the breast cancers in those who used HRT were in women who took estrogen only; two of these cancers were estrogen and progesterone receptor negative, and the receptor status of the other was unknown [117]. It is important to note that there are several known characteristics of breast cancers diagnosed in *BRCA1* mutation carriers which differ from breast cancers in general populations, and there are differences between the characteristics of breast cancers in *BRCA1* mutation carriers compared with *BRCA2* mutation carriers, including the proportions of histologic phenotypes, mitotic activity, differentiation, expression of ER and PR receptors, p53, HER2 and many other properties, as well as ages of onset and variables depending on age [118, 119].

A recent review of breast cancer risk modifiers reported significant reductions of this disease in both *BRCA1* and *BRCA2* mutation carriers who had used tamoxifen [88]. While a current multivariate analysis of endometrial cancer risk factors in a case control study of *BRCA1* and *BRCA2* mutation carriers by the Hereditary Breast Cancer Study Group found highly significant increased OR 3.50 (95 % CI 1.51–8.10, $P = 0.003$) for the diagnosis of endometrial cancer in *BRCA1* mutation carriers who had been treated for breast cancer or had any use of tamoxifen [120]. Though the OR for endometrial cancer diagnosis with tamoxifen treatment and use was increased in *BRCA2* mutation carriers, this was not significant [120]. These findings confirmed a previous prospective cohort study, reported in 2007, which had found significantly increased risks for endometrial cancer in both *BRCA1* and *BRCA2* mutation carriers who used tamoxifen but non-significant increased risks for those who did not, and the authors concluded that the increased risks for endometrial cancer in mutation carriers could be largely explained by tamoxifen treatment for previous breast cancers [121, 122]. All six endometrial cancers in the continuing study were endometrioid carcinomas though one was confirmed to have a serous component in the later 2013 report [121, 122]. Three of seven endometrial cancers in *BRCA1* mutation carriers from the Creighton Hereditary Cancer Registry were pure serous carcinomas (1) or mixed high grade serous and endometrioid carcinomas (2); the other four were grade 1 or grade 2 endometrioid carcinomas [71]. Two of these three patients with elements of serous carcinoma in their endometrial cancers had been prescribed tamoxifen for 5 and 7 years, respectively [71]. One *BRCA2* mutation carrier with endometrial cancer in our registry had a grade 2 endometrioid carcinoma [71]. Without regard to hereditary risk, tamoxifen use has been associated with development of more aggressive types of endometrial cancer, especially serous and clear cell carcinomas after five or more years of treatment [123].

Endometrial cancer is the most common gynecologic malignancy reported from industrialized countries; though cervical cancer is still prevalent in the less developed world [72, 124]. Whether or not HBOC syndrome mutation carriers are at increased risks for endometrial cancer and in particularly its highly aggressive serous carcinoma histotypes, currently available observations and data indicate that women from families who inherit cancer-associated mutations in either *BRCA1* or *BRCA2* are expected to bear at least population risks for endometrial and cervical intraepithelial and invasive carcinomas. Moreover, women who have had extended chemoprophylaxis or treatment with tamoxifen and those who opt to forego or delay mastectomies remain at high risk for future breast cancers and likely treatment with tamoxifen, which significantly increases the risk of endometrial cancer [88, 90, 120, 125]. Because of the residing risks for even the most common, readily treated histotypes of endometrial and cervical cancers together with the formidable consequences of advanced pelvic serous carcinoma and disseminated intra-abdominal serous carcinomatosis, unless there are prevailing contraindications, it seems prudent to remove the uterus when risk-reducing surgery is elected by HBOC syndrome mutation carriers. Embryologically, the

endosalpinx, endometrium and endocervix are müllerian derivatives and naturally remain in continuity through adult life. After childbearing, the uterus is an unnecessary and potentially dangerous organ in high risk patients. Including minimally invasive laparoscopic assisted vaginal hysterectomy (LAVH) along with RRSO can be accomplished by skilled laparoscopic surgeons with few if any complications, thereby prophylactically removing all müllerian derived epithelium at risk for malignant transformation [126, 127].

Expert opinion strongly favors that risk-reducing surgery for HBOC syndrome mutation carriers should consist of complete extirpation of the fallopian tubes and ovaries upon completion of childbearing and by age 40 years [89, 128, 129]. Several recent authoritative reviews have recommended short-term exogenous estrogen replacement for HBOC mutation carriers following risk-reducing removal of the ovaries during the fifth decade of life to alleviate acute menopausal symptoms and help protect against detrimental effects that can be associated with premature loss of endogenous hormones [89, 128, 129]. Whether effective or not, because of relatively high rates of osteopenia, osteoporosis and atraumatic fractures as well as their high risks for breast cancers and antineoplastic chemotherapy, many *BRCA1* and *BRCA2* mutation carriers who have undergone RRSO will be treated with tamoxifen [130–132]. Albeit, due to the adverse affects of tamoxifen on endometrium, this selective estrogen-receptor modulator (SERM) is largely being replaced in general populations by raloxifene, which may prove to be a better SERM for treatment of mutation carriers, as well [130–132]. Not only will RRSO–LAVH afford removal of the gynecological organs from which cancers may arise, be harbored and disseminate intra-abdominal carcinomatosis, but also removal of the uterus should simplify management decisions regarding HRT and treatment with SERMs.

## Conclusions

Women of HBOC syndrome kindreds who carry cancer-associated mutations in *BRCA1* or *BRCA2* are highly susceptible to both breast cancers and intra-abdominal serous carcinomatosis, which was previously ascribed to primary ovarian cancers. Rarely, intra-abdominal carcinomatosis has been diagnosed in women who had undergone prophylactic oophorectomy because they were understood to be at increased risk for ovarian cancer. Embryologically, fallopian tube epithelium, endometrium and endocervical epithelium are müllerian derivatives and naturally remain in continuity through adult life. Ovarian surface and follicle epithelium arise from epithelium of the coelomic cavity. Preinvasive and early invasive serous carcinomas of fallopian tubes and endometrium, individually and concurrently, have been associated with malignant peritoneal cytology and serous carcinoma implants on ovaries and the peritoneum. Presently available evidence indicates that fallopian tube epithelium, especially the distal tube and fimbria, is the primary site of malignant transformation for the majority of these cases. Prophylactic mastectomy and salpingo-ophorectomy during the fifth decade of life have proven to be the most effective approach for reducing breast and ovarian cancer risk and mortality in *BRCA1* and *BRCA2* mutation carriers. Without mastectomy, RRSO alone by age 40 years reduces the risk for "ovarian" cancer by at least 80 % and breast cancer by 50 % in mutation carriers. Occult preinvasive and invasive cancers have been demonstrated in endometrial and ovarian sections from prophylactic surgery and cases of disseminated serous cancer and intra-abdominal carcinomatosis. Tamoxifen use and HRT with exogenous estrogens increase the risk for endometrial cancer. It is as yet unclear whether *BRCA1* and *BRCA2* mutation carriers are at increased risk for primary endometrial serous carcinoma, and there is insufficient data to preclude ovarian surface and/or cyst epithelium as primary sites for malignant transformation. At least in the short run, estrogen-replacement therapy does not affect the reduction of breast cancer risk and may alleviate acute symptoms, protect against accelerated deterioration and improve longevity after early premenopausal oophorectomy. RRSO–LAVH and other minimally invasive surgery can be performed with few if any complications. After childbearing, the uterus is unnecessary and the endometrium remains a potential primary site for cancer. Including hysterectomy with RRSO will simplify decisions concerning the prescription of SERMs and HRT and may further reduce the risk for gynecologic cancer and intra-abdominal carcinomatosis in HBOC syndrome mutation carriers.

## References

1. Lynch HT, Shaw MW, Magnuson CW, Larsen AL, Krush AJ (1966) Hereditary factors in cancer: study of two large Midwestern kindreds. Arch Intern Med 117:206–212
2. Lynch HT, Krush AJ (1967) Heredity and adenocarcinoma of the colon. Gastroenterology 53:517–527
3. Lynch HT, Lynch PM (1979) The cancer-family syndrome: a pragmatic basis for syndrome identification. Dis Colon Rectum 22:106–110
4. Lynch HT, de la Chapelle A (1999) Genetic susceptibility to non-polyposis colorectal cancer. J Med Genet 36:801–818
5. Aarnio M, Sankila R, Pukkala E, Salovaara R, Aaltonen LA, de la Chapelle A, Peltomäki P, Mecklin J-P, Järvinen H-J (1999) Cancer risk in mutation carriers of DNA-mismatch-repair genes. Int J Cancer 81:214–218

6. Watson P, Lynch HT (2001) Cancer risk in mismatch repair gene mutation carriers. Fam Cancer 1:57–60
7. Lynch HT, Lynch JF, Lynch PM, Attard T (2008) Hereditary colorectal cancer syndromes: molecular genetics, genetic counseling, diagnosis and management. Fam Cancer 7:27–39
8. Watson P, Vasen HFA, Mecklin J-P, Bernstein I, Aarnio M, Järvinen HJ, Myrhøj T, Sunde L, Wijnen JT, Lynch HT (2008) The risk of extra-colonic, extra-endometrial cancer in the Lynch syndrome. Int J Cancer 123:444–449
9. Bellizzi AM, Frankel WL (2009) Colorectal cancer due to deficiency in DNA mismatch repair function: a review. Adv Anat Pathol 16:405–417
10. Lynch HT, Krush AJ (1971) Carcinoma of the breast and ovary in three families. Surg Gynecol Obstet 133:644–648
11. Lynch HT, Krush AJ, Lemon HM, Kaplan AR, Condit PT, Bottomley RH (1972) Tumor variation in families with breast cancer. JAMA 222:1631–1635
12. Lynch HT, Guirgis HA, Albert S, Brennan M, Lynch J, Kraft C, Pocekay D, Vaughns C, Kaplan A (1974) Familial association of carcinoma of the breast and ovary. Surg Gynecol Obstet 138:717–724
13. Lynch HT, Harris RE, Guirgis HA, Maloney K, Carmody MK, Lynch JF (1978) Familial association of breast/ovarian carcinoma. Cancer 41:1543–1548
14. Lynch HT, Watson P, Bewtra C, Conway TA, Hippee CR, Kaur P, Lynch JF, Ponder BAJ (1991) Hereditary ovarian cancer. Heterogeneity in age at diagnosis. Cancer 67:1460–1466
15. Lynch HT, Conway T, Lynch J (1991) Hereditary ovarian cancer. pedigree studies, Part II. Cancer Genet Cytogenet 53:161–183
16. Lynch HT, Watson P, Lynch JF, Conway TA, Fili M (1993) Hereditary ovarian cancer. Heterogeneity in age at onset. Cancer 71:573–581
17. Hall HJ, Lee MK, Newman B, Morrow JE, Anderson LA, Huey B, King MC (1990) Linkage of early-onset breast cancer to chromosome 17q21. Science 250:1684–1689
18. Narod SA, Feunteum J, Lynch HT, Watson P, Conway T, Lenoir GM (1991) Familial breast-ovarian cancer locus on chromosome 17q12–q23. Lancet 338:82–83
19. Miki Y, Swensen J, Shattuck-Eidens D, Futreal PA, Harshman K, Tavtigian S, Cochran C, Bennett LM, Ding W et al (1994) A strong candidate for the breast and ovarian cancer susceptibility gene BRCA1. Science 266:66–71
20. Wooster R, Neuhausen SL, Mangion J, Quirk Y, Ford D, Collins N, Nguyen K, Seal S, Tran T, Averill D et al (1994) Localization of a breast cancer susceptibility gene, BRCA2, to chromosome 13q12–13. Science 265:2088–2090
21. Wooster R, Bignell G, Lancaster J, Swift S, Seal S, Mangion J, Collins N, Gregory S, Gumbs C, Micklem G (1995) Identification of the breast cancer susceptibility gene BRCA2. Nature 378:789–792
22. National Center for Biotechnology Information. National Institutes of Health. www.ncbi.nlm.nih.gov/sites/entrez?db=gene. Accessed 1 Sept 2015
23. Ford D, Easton DF, Stratton M, Narod S, Goldgar D, Devilee P, Bishop DT, Weber B, Lenoir G, Chang-Claude J, Sobol H, Teare MD, Struewing J, Arason A, Scherneck S, Peto J, Rebbeck TR, Tonin P, Neuhausen S, Barkardottir R, Eyfjord J, Lynch H, Ponder BA, Gayther SA, Zelada-Hedman M et al (1998) Genetic heterogeneity and penetrance analysis of the BRCA1 and BRCA2 genes in breast cancer families. Am J Hum Genet 62:676–689
24. Chen S, Parmigiani G (2007) Meta-analysis of BRCA1 and BRCA2 penetrance. J Clin Oncol 25:1329–1333
25. Tobacman JK, Tucker MA, Kase R, Greene MH, Costa J, Fraumeni JF Jr (1982) Intra-abdominal carcinomatosis after prophylactic oophorectomy in ovarian-cancer-prone families. Lancet 2:795–797
26. Chen KT, Schooley JL, Flam MS (1985) Peritoneal carcinomatosis after prophylactic oophorectomy in familial ovarian cancer syndrome. Obstet Gynecol 66:93S–94S
27. Lynch HT, Bewtra C, Lynch JF (1986) Familial peritoneal ovarian carcinomatosis: a new clinical entity? Med Hypotheses 21:171–177
28. Casey MJ, Synder C, Bewtra C, Narod SA, Watson P, Lynch HT (2005) Intra-abdominal carcinomatosis after prophylactic oophorectomy in women of hereditary breast ovarian cancer syndrome kindreds associated with BRCA1 and BRCA2 mutations. Gynecol Oncol 97:457–467
29. Lakhani SR, Manek S, Penault-Llorca F, Flanagan A, Arnout L, Merrett S, McGuffog L, Steele D, Devilee P, Klijn JG, Meijers-Heijboer H, Radice P, Pilotti S, Nevanlinna H, Butzow R, Sobol H, Jacquemier J, Lyonet DS, Neuhausen SL, Weber B, Wagner T, Winqvist R, Bignon YJ, Monti F, Schmitt F, Lenoir G, Seitz S, Hamman U, Pharoah P, Lane G, Ponder B, Bishop DT, Easton DF (2004) Pathology of ovarian cancers in BRCA1 and BRCA2 mutation carriers. Clin Cancer Res 10:2473–2481
30. Wang C, Horiuchi A, Imai T, Ohira S, Itoh K, Nikaido T, Katsuyama Y, Konishi I (2004) Expression of BRCA1 protein in benign, borderline, and malignant epithelial ovarian neoplasms and its relationship to methylation and allelic loss of the BRCA1 gene. J Pathol 202:215–223
31. Casey MJ, Bewtra C (2004) Peritoneal carcinoma in women with genetic susceptibility: implications for Jewish populations. Fam Cancer 3:265–281
32. Vang R, Shih I-M, Kurman RJ (2009) Ovarian low-grade and high-grade serous carcinoma: pathogenesis, clinicopathologic and molecular biologic features, and diagnostic problems. Adv Anat Pathol 16:267–282
33. Werness BA, Parvatiyar P, Ramus SJ, Whittemore AS, Garlinghouse-Jones K, Oakley-Girvan I, DiCioccio RA, Wiest J, Tsukada Y, Ponder BAJ, Piver MS (2000) Ovarian carcinoma in situ with germline BRCA1 mutation and loss of heterozygosity at BRCA1 and TP53. J Natl Cancer Inst 92:1088–1091
34. Foyle A, Al-Jabi M, McCaughey WTE (1981) Papillary peritoneal tumors in women. Am J Surg Pathol 5:241–249
35. Schoenwolf GC, Bleyl SB, Brauer PR, Francis-West PH (2015) Development of the reproductive system. In: Schoenwolf GC (ed), Larsen's human embryology, 5th edn. Philadelphia, Elsevier/Churchill-Livingston. https://www.clinicalkey.com/#!/content/book/3-s2.0-B9781455706846000163. Accessed September 12, 2015
36. Healy A (2012) Embryology of the female reproductive tract. In: Mann GS, Blair JC, Garden AS (eds) Imaging of gynecological disorders in infants and children. Springer, Berlin, pp 21–30. doi:10.1007/174_2010_128. Accessed 10 Sept 2015
37. Piek JMJ, Torrenga B, Hermsen B, Verheijen RHM, Zweemer RP, Gille JJP, Kenemans P, van Diest PJ, Menko FH (2003) Histopathological characteristics of BRCA1- and BRCA2-associated intraperitoneal cancer: a clinic-based study. Fam Cancer 2:73–78
38. Casey MJ, Bewtra C, Lynch HT, Snyder C, Stacy M, Watson P (2013) Phenotypic heterogeneity of hereditary gynecologic cancers: a report from the Creighton hereditary cancer registry. Fam Cancer 12:719–740
39. Fraumeni JF Jr, Grundy GW, Creagan ET, Everson RB (1975) Six families prone to ovarian cancer. Cancer 36:364–369
40. Zweemer RP, van Diest PJ, Verheijen RHM, Ryan A, Gulle JJP, Sijmons RH, Jacobs IJ, Menko FH, Kenemans P (2000) Molecular evidence linking primary cancer of the fallopian tube to BRCA1 germline mutations. Gynecol Oncol 76:45–50

41. Rose PG, Shrigley R, Wiesner GL (2000) Germline BRCA2 mutation in a patient with fallopian tube carcinoma: a case report. Gynecol Oncol 77:319–320
42. Paley PJ, Swisher EM, Garcia RL, Agoff SN, Greer BE, Peters KL, Goff BA (2001) Occult cancer of the fallopian tube in BRCA-1 mutation carriers at prophylactic oophorectomy: a case for recommending hysterectomy at surgical prophylaxis. Gynecol Oncol 80:176–180
43. Leeper K, Garcia R, Swisher E, Goff B, Greer B, Paley P (2002) Pathologic findings in prophylactic oophorectomy specimens in high-risk women. Gynecol Oncol 87:52–56
44. Scheuer L, Kauff N, Robson M, Kelly B, Barakat R, Satagopan J, Ellis N, Hensley M, Boyd J, Borgen P, Norton L, Offit K (2002) Outcome of preventive surgery and screening for breast and ovarian cancer in BRCA mutation carriers. J Clin Oncol 20:1260–1268
45. Agoff SN, Mendelin JE, Grieco VS, Garcia RL (2002) Unexpected gynecologic neoplasms in patients with proven or suspected BRCA-1 or -2 mutations: implications for gross examination, cytology, and clinical follow-up. Am J Surg Pathol 26:171–178
46. Thompson D, Easton DF, the Breast Cancer Linkage Consortium (2002) Cancer incidence in BRCA1 mutation carriers. J Natl Cancer Inst 94:1358–1365
47. Piek JMJ, Verheijen RHM, Kenemans P, Massuger LF, Bulten H, van Diest PJ (2003) BRCA1/2-related ovarian cancers are of tubal origin: a hypothesis. Gynecol Oncol 90:491
48. Lee Y, Medeiros F, Kindelberger D, Callahan MJ, Muto M, Crum CP (2006) Advances in the recognition of tubal intraepithelial carcinoma: applications to cancer screening and the pathogenesis of ovarian cancer. Adv Anat Pathol 13:1–7
49. Manchanda R, Abdelraheim A, Johnson M, Rosenthal AN, Benjamin E, Brunell C, Burnell M, Side L, Gessler S, Saridogan E, Oram D, Jacobs I, Menon U (2011) Outcome of risk-reducing salpingo-oophorectomy in BRCA carriers and women of unknown mutation status. BJOG 118:814–824
50. Yates MS, Meyer LA, Deavers MT, Daniels MS, Keeler ER, Mok SC, Gershenson DM, Lu KH (2011) Microscopic and early-stage ovarian cancers in BRCA1/2 mutation carriers: building a model for early BRCA-associated tumorigenesis. Cancer Prev Res 4:463–470
51. Reitsma W, de Bock GH, Oosterwijk JC, Bart J, Hollema H, Mourits MJE (2013) Support of the 'fallopian tube hypothesis' in a prospective series of risk-reducing salpingo-oophorectomy specimens. Eur J Cancer 49:132–141
52. Powell CB, Swisher EM, Cass I, McLennan J, Norquist B, Garcia RL, Lester J, Karlan BY, Chen L (2013) Long term follow up of BRCA1 and BRCA2 mutation carriers with unsuspected neoplasia identified at risk reducing salpingo-oophorectomy. Gynecol Oncol 129:364–371
53. Sherman ME, Piedmonte M, Mai PL, Ioffe OB, Ronnett BM, Van Le L, Ivanov I, Bell MC, Blank SV, DiSilvestro P, Hamilton CA, Tewari KS, Wakeley K, Kauff ND, Yamada SD, Rodriguez G, Skates SJ, Alberts DS, Walker JL, Minasian L, Lu K, Greene MH (2014) Pathologic findings at risk-reducing salpingo-oophorectomy: primary results from Gynecologic Oncology Group Trial GOG-0199. J Clin Oncol 32:3275–3283
54. Conner JR, Meserve E, Pizer E, Garber J, Roh M, Urban N, Drescher C, Quade BJ, Muto M, Howitt BE, Pearlman MD, Berkowitz RS, Horowitz N, Crum CP, Feltmate C (2014) Outcome of unexpected adnexal neoplasia discovered during risk reduction salpingo-oophorectomy in women with germ-line BRCA1 or BRCA2 mutations. Gynecol Oncol 132:280–286
55. Kindelberger DW, Le Y, Miron A, Hirsch MS, Feltmate C, Medeiros F, Callahan MJ, Garner EO, Gordon RW, Birch C, Berkowitz RS, Muto MG, Crum CP (2007) Intraepithelial carcinoma of the fimbria and pelvic serous carcinoma: evidence for a causal relationship. Am J Surg Pathol 31:161–169
56. Carlson JW, Miron A, Jarboe EA, Parast MM, Hirsch MS, Lee Y, Muto MG, Kindelberger D, Crum CP (2008) Serous tubal intraepithelial carcinoma: its potential role in primary peritoneal serous carcinoma and serous cancer prevention. J Clin Oncol 26:4160–4165
57. Kuhn E, Kurman RJ, Vang R, Sehdev AS, Han G, Soslow R, Wang T-L, Shih l-M (2012) TP53 mutations in serous tubal intraepithelial carcinoma and concurrent pelvic high-grade serous carcinoma—evidence supporting the clonal relationship of the two lesions. J Pathol 226:421–426
58. Nik NN, Vang R, Shih I-M, Kurman RJ (2014) Origin and pathogenesis of pelvic (ovarian, tubal, and primary peritoneal) serous carcinoma. Annu Rev Pathol Mech Dis 9:27–45
59. Cass I, Walts AE, Barbuto D, Lester J, Karlan B (2014) A cautious view of putative precursors of serous carcinomas in the fallopian tubes of BRCA mutation carriers. Gynecol Oncol 134:492–497
60. Seidman JD, Zhao P, Yemelyanova A (2011) "Primary peritoneal" high-grade serous carcinoma is very likely metastatic from serous tubal intraepithelial carcinoma: assessing the new paradigm of ovarian and pelvic serous carcinogenesis and its implications for screening for ovarian cancer. Gynecol Oncol 120:470–473
61. Vicus D, Finch A, Cass I, Rosen B, Murphy J, Fan I, Royer R, McLaughlin J, Karlan B, Narod SA (2010) Prevalence of BRCA1 and BRCA2 germ line mutations among women with carcinoma of the fallopian tube. Gynecol Oncol 118:299–302
62. Hornreich G, Beller U, Lavie O, Renbaum P, Cohen Y, Levy-Lahad E (1999) Is uterine serous papillary carcinoma a BRCA1-related disease? Case report and review of the literature. Gynecol Oncol 75:300–304
63. Lavie O, Hornreich G, Ben-Arie A, Rennert G, Cohen Y, Keidar R, Sagi S, Lahad EL, Auslander R, Beller U (2004) BRCA germline mutations in Jewish women with uterine serous papillary carcinoma. Gynecol Oncol 92:521–524
64. Lavie O, Ben-Arie A, Pilip A, Rennert G, Cohen Y, Feiner B, Auslnader R (2005) BRCA2 germline mutation in a woman with uterine serous papillary carcinoma—case report. Gynecol Oncol 99:486–488
65. Goshen R, Chu W, Elit L, Pal T, Hakimi J, Ackerman I, Fyles A, Mitchell M, Narod SA (2000) Is uterine papillary serous adenocarcinoma a manifestation of the hereditary breast-ovarian cancer syndrome? Gynecol Oncol 79:477–481
66. Levine DA, Lin O, Barakat RR, Robson ME, McDermott D, Cohen L, Satagopan J, Offit K, Boyd J (2001) Risk of endometrial carcinoma associated with BRCA mutation. Gynecol Oncol 80:395–398
67. Barak F, Milgrom R, Laitman Y, Gemer O, Rabinovich A, Piura B, Anteby E, Baruch GB, Korach J, Friedman E (2010) The rate of the predominant Jewish mutations in the BRCA1, BRCA2, MSH2 and MSH6 genes in unselected Jewish endometrial cancer patients. Gynecol Oncol 119:511–515
68. Bruchim I, Amichay K, Kidron D, Attias Z, Biron-Shental T, Drucker L, Friedman E, Werner H, Fishman A (2010) BRCA1/2 germline mutation in Jewish patients with uterine serous carcinoma. Int J Gynecol Cancer 20:1148–1153
69. Lavie O, Ben-Arie A, Segev Y, Faro J, Barak F, Haya N, Auslender R, Gemer O (2010) BRCA germline mutations in women with uterine serous carcinoma—still a debate. Int J Gynecol Cancer 20:1531–1534
70. Pennington KP, Walsh T, Lee M, Pennil C, Novetsky AP, Agnew KJ, Thronton A, Garcia R, Mutch D, King M-C, Goodfellow P, Swisher EM (2013) BRCA1, TP53, and CHEK2

germline mutations in uterine serous carcinoma. Cancer 119:332–338
71. Casey MJ, Bewtra C, Lynch HT, Snyder CL, Stacey M (2015) Endometrial cancers in mutation carriers from hereditary breast ovarian cancer syndrome kindreds: report from the Creighton University Hereditary Cancer Registry with review of the implications. Int J Gynecol Cancer 25:650–656
72. Creasman WT, Odicino F, Maisonneuve P, Quinn MA, Beller U, Benedet JL, Heintz APM, Ngan HYS, Pecorelli S (2006) Carcinoma of the corpus uteri. FIGO 26th annual report on the results of treatment in gynecological cancer. Int J Gynaecol Obstet 95(Suppl 1):S105–S143
73. Brinton LA, Felix AS, McMeekin DS, Creasman WT, Sherman ME, Mutch D, Cohn DE, Walker JL, Moor RG, Downs LS, Soslow RA, Zaino R (2013) Etiologic heterogeneity in endometrial cancer: evidence from a Gynecologic Oncology Group trial. Gynecol Oncol 129:277–284
74. del Carmen MG, Birrer M, Schorge JO (2012) Uterine papillary serous cancer: a review of the literature. Gynecol Oncol 127:651–661
75. Semaan A, Mert I, Munkarah AR, Bandyopadhyay S, Mahdi HS, Winer IS, Nucci MR, Hussein Y, Quershi F, Hayek K, Tabassum F, Alosh B, Schultz DS, Cote ML, Vijver KK, Morris RT, Oliva E, Ali-Fehmi R (2013) Clinical and pathologic characteristics of serous carcinoma confined to the endometrium: a multi-institutional study. Int J Gynecol Pathol 32:181–187
76. Sagae S, Susumu N, Viswanathan AN, Aoki D, Backes FJ, Provencher DM, Vaughan M, Creutzberg CL, Kurzeder C, Kristensen G, Lee C, Kurtz J-E, Glasspool RM, Small W Jr (2014) Gynecologic Cancer InterGroup (GCIG) consensus review for uterine serous carcinoma. Int J Gynecol Cancer 24(9 suppl 3):S83–S89
77. Boruta DM II, Gehrig PA, Groben PA, Bae-Jump V, Boggess JF, Fowler WC Jr, Van Le L (2004) Uterine serous and grade 3 endometrioid carcinomas: is there a survival difference? Cancer 101:2214–2221
78. Zheng W, Schwartz PE (2005) Serous EIC as an early form of uterine papillary serous carcinoma: recent progress in understanding its pathogenesis and current opinions regarding pathologic and clinical management. Gynecol Oncol 96:579–582
79. Jarboe EA, Miron A, Carlson JW, Hirsch MS, Kindelberger D, Mutter GL, Crum CP, Nucci MR (2009) Coexisting intraepithelial serous carcinoma of the endometrium and fallopian tube: frequency and potential significance. Int J Gynecol Pathol 28:308–315
80. Massuger L, Roelofsen T, van Ham M, Bulten J (2010) The origin of serous ovarian cancer may be found in the uterus: a novel hypothesis. Med Hypothesis 74:859–861
81. Roelofsen T, van Kempen LCLT, van der Laak JAWM, van Ham MA, Bulten J, Massuger LFAG (2012) Concurrent endometrial intraepithelial carcinoma (EIC) and serous ovarian cancer: can EIC be seen as the precursor lesion? Int J Gynecol Cancer 22:457–464
82. Tolcher MC, Swisher EM, Medeiros F, Lima JF, Hilderbrand JL, Donovan JL, Garcia RL, Cliby WA, Dowdy SC (2015) Characterization of precursor lesions in the endometrium and fallopian tube epithelium of early-stage uterine serous carcinoma. Int J Gyencol Pathol 34:57–64
83. Stewart CJR, Doherty DA, Havlat M, Koay MHE, Leung YC, Naran A, O'Brien D, Ruba S, Salfinger S, Tan J (2013) Transtubal spread of endometrial carcinoma: correlation of intra-luminal tumour cells with tumour grade, peritoneal fluid cytology, and extra-uterine metastasis. Pathology 45:382–387
84. Jia L, Yuan Z, Wang Y, Cragun JM, Kong B, Zheng W (2015) Primary sources of pelvic serous cancer in patients with endometrial intraepithelial carcinoma. Mod Pathol 28: 118–127
85. Mingles MJJM, van Ham MAPC, de Kievit IM, Snijders MPML, van Tilborg AAG, Bulten J, Massuger LFAG (2014) Müllerian precursor lesions in serous ovarian cancer patients: using the SEE-Fim and SEE-End protocol. Mod Pathol 27:1002–1013
86. Zhou C, Gilks CB, Hayes M, Clement PB (1998) Papillary serous carcinoma of the uterine cervix: a clinicopathologic study of 17 cases. Am J Surg Pathol 22:113–120
87. Kaplan EJ, Caputo TA, Shen PUF, Sassoon RI, Soslow RA (1998) Familial papillary serous carcinoma of the cervix, peritoneum, and ovary: a report of the first case. Gynecol Oncol 70:289–294
88. Friebel TM, Domchek SM, Rebbeck TR (2014) Modifiers of cancer risk in BRCA1 and BRCA2 mutation carriers: systematic review and meta-analysis. J Natl Cancer Inst 106:dju091
89. Garcia C, Powell CB (2015) A comprehensive approach to the identification and management of the BRCA patient. Obstet Gynecol Surv 70:131–143
90. Nelson HD, Pappas M, Zakher B, Mitchell JP, Okinaka-Hu L, Fu R (2014) Risk assessment, genetic counseling, and genetic testing for BRCA-related cancer in women: a systematic review to update the U.S. Preventive Services Task Force recommendation. Ann Intern Med 160:255–266
91. Rebbeck TR, Kauff ND, Domchek SM (2009) Meta-analysis of risk reduction estimates associated with risk-reducing salpingo-oophorectomy in BRCA1 or BRCA2 mutation carriers. J Natl Cancer Inst 101:80–87
92. Kauff ND, Satagopan JM, Robson ME, Scheuer L, Hensley M, Hudi CA, Ellis NA, Boyd J, Borgen PI, Barakat RR, Norton L, Castiel M, Nafa K, Offit K (2002) Risk-reducing salpingo-oophorectomy in women with a BRCA1 or BRCA2 mutation. N Engl J Med 346:1609–1615
93. Rebbeck TR, Lynch HT, Neuhausen SL, Narod SA, van't Veer L, Garber JE, Evans G, Isaacs C, Daly MB, Matloff E, Olopade OI, Weber BL, the prevention and observation of surgical end points study group (2002) Prophylactic oophorectomy in carriers of BRCA1 or BRCA2 mutations. N Engl J Med 346: 1616–1622
94. Anderson CK, Wallace S, Guiahi M, Sheeder J, Bahbakht K, Spillman MA (2013) Risk-reducing salpingectomy as preventive strategy for pelvic serous cancer. Int J Gynecol Cancer 23:417–421
95. Schenberg T, Mitchell G (2014) Prophylactic bilateral salpingectomy as a prevention strategy in women at high-risk of ovarian cancer: a mini-review. Front Oncol 4:21
96. Kwon JS, Tinker A, Pansegrau G, McAlpine J, Housty M, McCullum M, Gilks CB (2013) Prophylactic salpingectomy and delayed oophorectomy as an alternative for BRCA mutation carriers. Obstet Gynecol 121:14–24
97. Lostumbo L, Carbine NE, Wallace J (2010) Prophylactic mastectomy for the prevention of breast cancer. Cochrane Database Syst Rev 10(11):CD002748
98. Zagouri F, Chrysikos DT, Sergentanis TN, Giannakopoulou G, Zografos CG, Papadimitriou CA, Zografos GC (2013) Prophylactic mastectomy: an appraisal. Am Surg 79:205–212
99. De Felice F, Marchetti C, Musella A, Palaia I, Perniola G, Musio D, Muzii L, Tombolini V, Panici PB (2015) Bilateral risk-reduction mastectomy in BRCA1 and BRCA2 mutation carriers: a meta-analysis. Ann Surg Oncol 22:2876–2880
100. Domchek SM, Friebel TM, Singer CF, Evans DG, Lynch HT, Isaacs C, Garber JE, Neuhausen SL, Matloff E, Eeles R, Pichert G, Van t'veer L, Tung N, Weitzel JN, Couch FJ, Rubinstein WS, Ganz PA, Daly MB, Olopade OI, Tomlison G, Schildkraut J, Blum JL, Rebbeck TR (2010) Association of risk-reducing

surgery in BRCA1 or BRCA2 mutation carriers with cancer risk and mortality. JAMA 304:967–975
101. Ingram SL, Sperrin M, Baildam A, Ross GL, Clayton R, Lalloo F, Buchan I, Howell A, Evans DGR (2013) Risk-reducing surgery increases survival in BRCA1/2 mutation carriers unaffected at time of family referral. Breast Cancer Res Treat 142:611–618
102. Finch APM, Lubinski J, Møller P, Singer CF, Karlan B, Senter L, Rosen B, Maehle L, Ghadiraian P, Cybulski C, Huzarski T, Eisen A, Foulkes WD, Kim-Sing C, Ainsworth P, Tung N, Lynch HT, Neuhausen S, Metcalfe KA, Thompson I, Murphy J, Sun P, Narod SA (2014) Impact of oophorectomy on cancer incidence and mortality in women with BRCA1 or BRCA2 mutation. J Clin Oncol 32:1547–1553
103. Schrag D, Kuntz KM, Garber JE, Weeks JC (1997) Decision analysis—effects of prophylactic mastectomy and oophorectomy on life expectancy among women with BRCA1 or BRCA2 mutations. N Engl J Med 336:1465–1471
104. van Roosmalen MS, Verhoef LCG, Stalmeier PFM, Hoogerbrugge N, van Daal WAJ (2002) Decision analysis of prophylactic surgery or screening for BRCA1 mutation carriers: a more prominent role for oophorectomy. J Clin Oncol 20:2092–2100
105. Grann VR, Jacobson JS, Thomason D, Hershman D, Heitjan DF, Neugut AI (2002) Effect of prevention strategies on survival and quality-adjusted survival of women with BRCA1/2 mutations: an updated decision analysis. J Clin Oncol 20:2520–2529
106. Armstrong K, Schwartz JS, Randall T, Rubin SC, Weber B (2004) Hormone replacement therapy and life expectancy after prophylactic oophorectomy in women with BRCA1/2 mutations: a decision analysis. J Clin Oncol 22:1045–1054
107. Kurian AW, Sigal BM, Plevritis SK (2010) Survival analysis of cancer risk reduction strategies for BRCA1/2 mutation carriers. J Clin Oncol 28:222–231
108. Sigal BM, Munoz DF, Kurian AW, Plevritis SK (2012) A simulation model to predict the impact of prophylactic surgery and screening on the life expectancy of BRCA1 and BRCA2 mutation carriers. Cancer Epidemiol Biomark Prev 21:1066–1077
109. Holman LL, Friedman S, Daniels MS, Sun CC, Lu KH (2014) Acceptability of prophylactic salpingectomy with delayed oophorectomy as risk-reducing surgery among BRCA mutation carriers. Gynecol Oncol 133:283–286
110. Arts-de Jong M, Harmsen MG, Hoogerbrugge N, Massuger LF, Hermens RP, de Hullu JA (2015) Risk-reducing salpingectomy with delayed oophorectomy in BRCA1/2 mutation carriers: patients' and professionals' perspectives. Gynecol Oncol 136:305–310
111. Harmsen MG, Arts-de Jong M, Hoogerbrugge N, Maas AHEM, Prins JB, Bulten J, Teerenstra S, Adang EMM, Piek JMJ, van Doorn HC, van Beurden M, Mourits MJE, Zweemer RP, Gaarenstroom KN, Slangen BFM, Vos MC, van Lonkhuijzen LRCW, Massuger LFAG, Hermens RPMG, de Hullu JA (2015) Early salpingectomy (TUbectectomy) with delayed oophorectomy to improve quality of life as alternative for risk-reducing salpingo-oophorectomy in BRCA1/2 mutation carriers (TUBA study): a prospective non-randomised multicentre study. BMC Cancer 15:593
112. Kim SH, Frey MK, Blank SV (2014) Occult tubal carcinoma found at risk reducing salpingectomy in a BRCA1 carrier. Gynecol Oncol Case Rep 9:1–2
113. Antoniou A, Pharoah PD, Narod S, Risch HA, Eyfijord JE, Hopper JL, Loman N, Olsson H, Johannsson O, Borg A, Pasini B, Radice P, Manoukian S, Eccles DM, Tang N, Olah E, Anton-Culver H, Warner E, Lubinski J, Gronwald J, Gorski B, Tulinius H, Thorlacius S, Eerola H, Nevanlinna H, Syrjäkoski K, Kallioniemi OP, Thompson D, Evans C, Peto J, Lalloo F, Evans DG, Easton DF (2003) Average risks of breast and ovarian cancer associated with BRCA1 or BRCA2 mutations detected in case series unselected for family history: a combined analysis of 22 studies. Am J Hum Genet 72:1117–1130
114. King M-C, Marks JH, Mandell JB, New York Breast Cancer Study Group (2003) Breast and ovarian cancer risks due to inherited mutations in BRCA1 and BRCA2. Science 302:643–646
115. Rebbeck TR, Friebel T, Wagner T, Lynch HT, Garber JE, Daly MB, Isaacs C, Olopade OI, Neuhausen SL, van't Veer L, Eeles R, Evans DG, Tomlinson G, Matloff E, Narod SA, Eisen A, Domchek S, Armstrong K, Weber BL, PROSE Study Group (2005) Effect of short-term hormone replacement therapy on breast cancer risk reduction after bilateral prophylactic oophorectomy in BRCA1 and BRCA2 mutation carriers: the PROSE study group. J Clin Oncol 23:7804–7810
116. Eisen A, Lubinski J, Gronwald J, Moller P, Lynch HT, Klijn J, Kim-Sing C, Neuhausen SL, Gilbert L, Ghadirian P, Manoukian S, Rennert G, Friedman E, Isaacs C, Rosen E, Rosen B, Daly M, Sun P, Narod SA, the Hereditary Breast Cancer Clinical Study Group (2008) Hormone therapy and the risk of breast cancer in BRCA1 mutation carriers. J Natl Cancer Inst 100:1361–1367
117. Gabriel CA, Tigges-Cardwell J, Stopfer J, Erlichman J, Nathanson K, Domchek SM (2009) Use of total abdominal hysterectomy and hormone replacement therapy in BRCA1 and BRCA2 mutation carriers undergoing risk-reducing salpingo-oophorectomy. Fam Cancer 8:23–28
118. Foulkes WD, Metcalfe K, Sun P, Hanna WM, Lynch HT, Ghadirian P, Tung N, Olopade OI, Weber BL, McLennan J, Olivotto IA, Bégin LR, Narod SA (2004) Estrogen receptor status in BRCA1- and BRCA2-related breast cancer: the influence of age, grade, and histological type. Clin Cancer Res 10:2029–2034
119. Eerola H, Heikkilä P, Tamminen A, Aittomäki K, Blomqvist C, Nevanlinna H (2005) Histopathological features of breast tumours in BRCA1, BRCA2 and mutation-negative breast cancer families. Breast Cancer Res 7:R93–R100
120. Segev Y, Rosen B, Lubinski J, Gronwald J, Lynch HT, Moller P, Kim-Sing C, Ghadirian P, Karlan B, Eng C, Gilchrist D, Neuhausen SL, Eisen A, Friedman E, Euhus D, Ping S, Narod SA, Hereditary Breast Cancer Study Group (2015) Risk factors for endometrial cancer among women with a BRCA1 or BRCA2 mutation: a case control study. Fam Cancer 14:383–391
121. Beiner ME, Finch A, Rosen B, Lubinski J, Moller P, Ghadirian P, Lynch HT, Friedman E, Sun P, Narod SA, Hereditary Ovarian Cancer Clinical Study Group (2007) The risk of endometrial cancer in women with BRCA1 and BRCA2 mutations. A prospective study. Gynecol Oncol 104:7–10
122. Segev Y, Iqbal J, Gronwald J, Lynch HT, Moller P, Ghadirian P, Rosen B, Tung N, Kim-Sing C, Foulkes WD, Neuhausen SL, Senter L, Singer CF, Karlan B, Ping S, Narod SA, Hereditary Breast Cancer Study Group (2013) The incidence of endometrial cancer in women with BRCA1 and BRCA2 mutations: an international prospective study. Gynecol Oncol 130:127–131
123. Narod SA, Pal T, Graham T, Mitchell M, Fyles A (2001) Tamoxifen and risk of endometrial cancer. Lancet 357:65–66
124. Quinn MA, Benedet JL, Odicino F, Maisonneuve P, Beller U, Creasman WT, Heintz APM, Ngan HYS, Pecorelli S (2006) Carcinoma of the cervix uteri. FIGO 26th annual report on the results of treatment in gynecological cancer. Int J Gynaecol Obstet 95(Suppl 1):S43–S103
125. Wuttke M, Phillips K-A (2015) Clinical management of women at high risk of breast cancer. Curr Opin Obstet Gynecol 27:6–13
126. Casey MJ, Bewtra C, Garcia-Padial J, Lynch HT (1995) Laparoscopic examination and assisted bilateral salpingo-oophorectomy hysterectomy for prophylactic removal of the ovaries and uterus in women at genetic risk for ovarian cancer. J Gynecol Tech 1:111–114

127. Casey MJ, Garcia-Padial J, Hakert D, Watson P (1998) Changing trends in surgical approaches to hysterectomy: an analysis of laparoscopic assisted vaginal hysterectomy in clinical practice. J Gynecol Surg 14:15–24
128. Finch A, Evans G, Narod SA (2012) BRCA carriers, prophylactic salpingo-oophorectomy and menopause: clinical management considerations and recommendations. Womens Health 8:543–555
129. Marchetti C, Iadarola R, Palaia I, di Donato V, Perniola G, Muzii L, Panici PB (2014) Hormone therapy in oophorectomized BRCA1/2 mutation carriers. Menopause 21:763–768
130. Garcia C, Lyon L, Conell C, Littell RD, Powell CB (2015) Osteoporosis risk and management in BRCA1 and BRCA2 carriers who undergo risk-reducing salpingo-oophorectomy. Gynecol Oncol 138:723–726
131. Cano A, Hermenegildo C (2000) The endometrial effects of SERMs. Hum Reprod Update 6:244–254
132. Gizzo S, Saccardi C, Patrelli TS, Berretta R, Capobianco G, Di Gangi S, Vacilotto A, Bertocco A, Noventa M, Ancona E, D'Antona D, Nardelli GB (2013) Update on raloxifene: mechanism of action, clinical efficacy, adverse effects, and contraindications. Obstet Gynecol Surv 68:467–481