
Pathologic findings at risk-reducing surgery.

Mourits MJ(1), de Bock GH(2), Hollema H(2).

Author information:
(1)University of Groningen, University Medical Center Groningen, Groningen, the Netherlands m.j.e.mourits@umcg.nl. (2)University of Groningen, University Medical Center Groningen, Groningen, the Netherlands.

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The impact of risk-reducing gynaecological surgery in premenopausal women at high risk of endometrial and ovarian cancer due to Lynch syndrome.

Moldovan R(1), Keating S, Clancy T.

Author information:
(1)Department of Psychology, Babes-Bolyai University, No. 37 Republicii Street, 400015, Cluj-Napoca, Romania, ramonamoldovan@psychology.ro.

Women with Lynch syndrome (LS) have a significantly increased lifetime risk of endometrial cancer (40-60 %) and ovarian cancer (7-12 %). Currently there is little evidence to support the efficacy of screening for the early detection of these cancers. Another option is risk-reducing hysterectomy and/or bilateral salpingo-oophorectomy (BSO). Research on the impact of BSO in premenopausal women with a non-LS associated family history cancer has generally shown that women have a high level of satisfaction about their decision to undergo surgery. However, debilitating menopausal symptoms and sexual dysfunction are common post-surgical problems. We used a mixed methods study to explore the impact of risk-reducing gynaecological surgery in women with LS: 24 women were invited to take part; 15 (62.5 %) completed validated questionnaires and 12 (50 %) participated in semi-structured interviews. Our results suggest that risk reducing surgery does not lead to significant psychological distress and the women tend not to think or worry much about developing cancer. However, they tend to be distressed about the physical and somatic symptoms associated with menopause; their social well-being is somewhat affected, but sexual difficulties are minimal. The women reported being overwhelmingly satisfied with their decision to have surgery and with the quality of information they received prior to the operation. However, they felt underprepared for menopausal symptoms and received conflicting advice about whether or not to use HRT. Recommendations from the study include that professionals discuss the menopause, its side effects and HRT in detail prior to surgery.

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Long-term outcomes of risk-reducing surgery in unaffected women at increased familial risk of breast and/or ovarian cancer.

Heiniger L(1), Butow PN, Coll J, Bullen T, Wilson J, Baylock B, Meiser B, Price MA.

Author information:
(1)Centre for Medical Psychology and Evidence-Based Decision-Making (CeMPED), School of Psychology, University of Sydney, Level 6 North, Chris O'Brien Lifehouse (C392), Sydney, NSW, 2006, Australia.

This study prospectively investigated long-term psychosocial outcomes for women who opted for risk-reducing mastectomy (RRM) and/or risk-reducing salpingo-oophorectomy (RRSO). Unaffected women from high-risk breast cancer families who had completed baseline questionnaires for an existing study and subsequently underwent RRM and/or RRSO, completed measures of perceived breast and ovarian cancer risk, anxiety, depression, cancer-related anxiety, body image, sexual functioning, menopausal symptoms, use of hormone replacement therapy and decision regret 3 years post-surgery. Outcomes were compared to age- and risk-matched controls. Participants (N = 233) were 17 women who had RRM (39 controls), 38 women who had RRSO (94 controls) and 15 women who had RRM + RRSO (30 controls). Women who underwent RRM and those who underwent RRM + RRSO reported reductions in perceived breast cancer risk and perceived breast and ovarian cancer risk respectively, compared to their respective controls. RRM women reported greater reductions in cancer-related anxiety compared with both controls and RRSO women. RRSO women reported more sexual discomfort than controls and more urogenital menopausal symptoms than controls and RRM only women. No differences in general anxiety, depression or body image were observed. Regret was associated with greater reductions in body image since surgery and more sexual discomfort, although overall regret levels were low. Women who undergo RRM experience psychological benefits associated with reduced breast cancer risk. Although women who undergo RRSO experience some deterioration in sexual and menopausal symptoms, they do not regret their surgery decision. It is vital that women considering these procedures receive detailed information about potential psychosocial consequences.

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Risk-reducing surgery in hereditary gynecological cancer: Clinical applications in Lynch syndrome and hereditary breast and ovarian cancer.

Adachi M(1), Banno K(1), Yanokura M(1), Iida M(1), Nakamura K(1), Nogami Y(1), Umene K(1), Masuda K(1), Kisu I(1), Ueki A(1), Hirasawa A(1), Tominaga E(1), Aoki D(1).

Author information:
(1)Department of Obstetrics and Gynecology, School of Medicine, Keio University, Tokyo 160-8582, Japan.

Risk-reducing surgery (RRS) is defined as a prophylactic approach with removal of organs at high risk of developing cancer, which is performed in cases without lesions or absence of clinically significant lesions. Hereditary gynecological cancers for which RRS is performed include hereditary breast and ovarian cancer.
(HBOC) and Lynch syndrome. For HBOC, RRS in the United States (US) is recommended for women with mutations in the breast cancer susceptibility (BRCA)1 and BRCA2 genes and bilateral salpingo-oophorectomy (BSO) is generally performed. This procedure may reduce the risk of breast, ovarian, Fallopian tube and primary peritoneal cancer, although ovarian deficiency symptoms occur postoperatively. For Lynch syndrome, RRS in the US is considered for postmenopausal women or for women who do not desire to bear children and BSO and hysterectomy are usually performed. This approach may reduce the risk of endometrial and ovarian cancer, although ovarian deficiency symptoms also occur. For RRS, there are several issues that must be addressed to reduce the risk of cancer development in patients with HBOC or Lynch syndrome. To the best of our knowledge, this is the first review to discuss RRS with a focus on hereditary gynecological cancer.

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Personalized assessment and management of women at risk for breast cancer in North America.

Pruthi S(1), Heisey R, Bevers T.

Author information:
(1)Division of General Internal Medicine, Mayo Clinic, 200 First Street SW, Rochester, MN 55905, USA.

Many women at increased risk for breast cancer would benefit from referral for genetic testing, enhanced screening, preventive therapy or risk-reducing surgery. We present a visual model and a step-wise approach to assist with a personalized risk stratification and management of these women. We present current recommendations with respect to lifestyle behaviors and mammographic screening, and we review the current evidence regarding enhanced screening and risk-reducing therapies. We discuss the usefulness of three risk-assessment tools in determining whether a woman qualifies for genetic testing, enhanced screening or preventive therapy and present four cases to demonstrate the usefulness of this approach in the clinical setting.

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Managing symptoms and maximizing quality of life after preventive interventions for cancer risk reduction.

Chapman JS(1), Jacoby V, Chen LM.

Author information:
(1)Department of Obstetrics, Gynecology, and Reproductive Sciences bThe Helen Diller Family Comprehensive Cancer Center at the University of California San Francisco, San Francisco, California, USA.

PURPOSE OF REVIEW: The prevention of breast, ovarian and endometrial cancer
frequently involves hormonal or surgical interventions. Each of these may have noncancerous sequelae and can affect quality of life in women with hereditary cancer syndromes. The purpose of this review is to discuss the medical management of hormonal suppression and surgical menopause in hereditary breast and ovarian cancer syndromes and in Lynch syndrome.

RECENT FINDINGS: As we gain a better understanding of genetic cancer risk, we are able to reduce the development of cancer with risk-reducing surgery. Understanding the significance of noncancer outcomes helps improve surveillance and treatment strategies and improves our understanding of the interaction between our interventions and their effects on quality of life.

SUMMARY: Advances in our understanding of the pathogenesis of hereditary breast and ovarian cancer, as well as the difference in ovarian ageing in these high-risk women, allow us to improve our counselling and interventions for family planning and risk-reducing surgery. Studies are ongoing regarding the optimal surveillance of cardiovascular and bone health after risk-reducing salpingo-oophorectomy, although more studies are needed regarding the optimal management of sexual health and other quality of life measures.

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Management of ovarian and endometrial cancers in women belonging to HNPCC carrier families: review of the literature and results of cancer risk assessment in Polish HNPCC families.

Dębniak T(1), Gromowski T(1), Scott RJ(2), Gronwald J(1), Huzarski T(1), Byrski T(1), Kurzawski G(1), Dymerska D(1), Górski B(1), Paszkowska-Szczer K(1), Cybulski C(1), Serrano-Fernandez P(1), Lubiński J(1).

Author information:
(1)Department of Genetics and Pathology, International Hereditary Cancer Center, Pomeranian Medical University, Szczecin, Poland. (2)Discipline of Medical Genetics, Faculty of Health, University of Newcastle and Hunter Medical Research Institute, Newcastle, NSW Australia.

BACKGROUND: Over half the cancer deaths in HNPCC families are due to extra-colonic malignancies that include endometrial and ovarian cancers. The benefits of surveillance for gynecological cancers are not yet proven and there is no consensus on the optimal surveillance recommendations for women with MMR mutations.

METHODS: We performed a systematic review of the literature and evaluated gynecological cancer risk in a series of 631 Polish HNPCC families classified into either Lynch Syndrome (LS, MMR mutations detected) or HNPCC (fulfillment of the Amsterdam or modified Amsterdam criteria).

RESULTS: Published data clearly indicates no benefit for ovarian cancer screening in contrast to risk reducing surgery. We confirmed a significantly increased risk of OC in Polish LS families (OR=4.6, p<0.001) and an especially high risk of OC was found for women under 50 years of age: OR=32.6, p<0.0001 (95% CI 12.96-81.87). The cumulative OC risk to 50 year of life was calculated to be 10%. Six out of 19 (32%) early-onset patients from LS families died from OC within 2 years of diagnosis. We confirmed a significantly increased risk of EC (OR=26, 95% CI 11.36-58.8; p<0.001). The cumulative risk for EC in Polish LS families was calculated to be 67%.
CONCLUSIONS: Due to the increased risk of OC and absence of any benefit from gynecological screening reported in the literature it is recommended that prophylactic oophorectomy for female carriers of MMR mutations after 35 year of age should be considered as a risk reducing option. Annual transvaginal ultrasound supported by CA125 or HE4 marker testing should be performed after prophylactic surgery in these women. Due to the high risk of EC it is reasonable to offer, after the age of 35 years, annual clinical gynecologic examinations with transvaginal ultrasound supported by routine aspiration sampling of the endometrium for women from either LS or HNPCC families. An alternative option, which could be taken into consideration for women preferring surgical prevention, is risk reducing total hysterectomy (with bilateral salpingo-oophorectomy) for carriers after childbearing is complete.

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PMID: 25606063 [PubMed]

Hereditary cancer syndromes with high risk of endometrial and ovarian cancer: surgical options for personalized care.
McCann GA(1), Eisenhauer EL.

Author information:
(1)Department of Obstetrics and Gynecology, University Of Texas Health Science Center, San Antonio, Texas.

Cancer genomics has increased our recognition of specific hereditary cancer mutations. Hereditary breast and ovarian cancer (HBOC) syndrome and Lynch syndrome are two such entities in which women carrying specific mutations may be at high risk for developing breast, ovarian, and/or endometrial cancers. Risk reducing surgery such as prophylactic mastectomy, oophorectomy, and/or hysterectomy may allow women to decrease these risks after completing childbearing. Background, indications, and consequences of these procedures are reviewed.

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Intentions for risk-reducing surgery among high-risk women referred for BRCA1/BRCA2 genetic counseling.

Author information:
(1)Lombardi Comprehensive Cancer Center/Georgetown University, Oncology, Washington, DC, USA.

OBJECTIVE: Genetic testing for breast and ovarian cancer susceptibility is now part of routine clinical practice. Although rates of risk-reducing surgery following genetic testing have been increasing, little is known about attitudes
This study examines correlates of patient intentions to undergo risk-reducing mastectomy (RRM) and risk-reducing oophorectomy (RRO).

METHODS: Participants were 696 women, ages 21-85, who sought breast cancer gene 1 and 2 (BRCA1/2) genetic counseling and had at least a 10% risk of carrying a mutation. The sample included women who were affected with breast or ovarian cancer and unaffected women with a known familial BRCA1/2 mutation. Participants completed a precounseling telephone questionnaire.

RESULTS: Prior to receiving genetic counseling, 23.3% of participants were considering RRM and 42.5% were considering RRO. Variables that were independently associated with RRM intentions were cancer-specific distress (OR=1.14, 95% CI=1.03-1.26), perceived risk of breast cancer (OR=1.16, 95% CI=1.05-1.28), education (OR=1.76, 95% CI=1.03-2.99), and age (OR=0.96, 95% CI=0.95-0.98). Predictors of RRO intentions were perceived risk for ovarian cancer (OR=1.25, 95% CI=1.14-1.37), perceived risk of carrying a BRCA1/2 mutation (OR=1.74, 95% CI=1.15-2.62), marital status (OR=1.92, 95% CI=1.34-2.76), and age (OR=1.02, 95% CI=1.00-1.03).

CONCLUSIONS: Because precounseling intentions predict subsequent risk-reducing surgery decisions, this study identified patient factors associated with surgical intentions. These factors reinforce the critical role for pretest genetic counseling in communicating accurate risk estimates and management options, and addressing psychosocial concerns, to facilitate informed decision making regarding RRM and RRO.

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Impact of Prophylactic Mastectomy in BRCA1/2 Mutation Carriers.

Rhiem K(1), Schmutzler R(1).

Author information:
(1)Center for Hereditary Breast and Ovarian Cancer, University Hospital Cologne, Germany.

Unlike the general decrease in invasive oncologic care, the trend for prophylactic bilateral mastectomy in healthy women and prophylactic contralateral mastectomy in women with unilateral breast cancer is steadily rising. This is even more surprising when considering that for e.g. prophylactic contralateral mastectomy no clear survival benefit has been demonstrated so far. The decision-making process around risk-reducing surgery may be influenced by several conflicting parameters such as the patient's fears and desire to achieve a survival advantage, the surgeon's financial motivations, or the oncologist's paternalistic approach to the above trend. Physicians should support their patients throughout the decision-making process, guide them through the dense fog of information, and encourage them to reconsider all options and alternatives before embarking on an irreversible surgical intervention. Healthy and diseased women should be comprehensively informed about their absolute individual risks for cancer, the benefits and harms of the surgery, alternative preventive strategies, and last but not least the competing risks of preceding carcinomas and cancer in general. Within the framework of non-directive counseling in the
specialized centers of the German Consortium for Hereditary Breast and Ovarian Cancer (GC-HBOC), decision-making aids are being developed with grants from the Federal Ministry of Health and the German Cancer Aid to support women in making conclusive and satisfactory decisions.

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Features of ovarian cancer in Lynch syndrome (Review).
Author information:
(1)Department of Obstetrics and Gynecology, School of Medicine, Keio University, Tokyo 160-8582, Japan.
Lynch syndrome is a hereditary ovarian cancer with a prevalence of 0.9-2.7%. Lynch syndrome accounts for 10-15% of hereditary ovarian cancers, while hereditary breast and ovarian cancer syndrome accounts for 65-75% of these cancers. The lifetime risk for ovarian cancer in families with Lynch syndrome is ~8%, which is lower than colorectal and endometrial cancers, and ovarian cancer is not listed in the Amsterdam Criteria II. More than half of sporadic ovarian cancers are diagnosed in stage III or IV, but ≥80% of ovarian cancers in Lynch syndrome are diagnosed in stage I or II. Ovarian cancers in Lynch syndrome mostly have non-serous histology and different properties from those of sporadic ovarian cancers. A screening method for ovarian cancers in Lynch syndrome has yet to be established and clinical studies of prophylactic administration of oral contraceptives are not available. However, molecular profiles at the genetic level indicate that ovarian cancer in Lynch syndrome has a more favorable prognosis than sporadic ovarian cancer. Inhibitors of the phosphatidylinositol 3-kinase/mammalian target of the rapamycin pathway and anti-epidermal growth factor antibodies may have efficacy for the disease. To the best of our knowledge, this is the first review focusing on ovarian cancer in Lynch syndrome.

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PMID: 25279173 [PubMed]

12. Health Psychol. 2014 Sep 22. [Epub ahead of print]
Effects of False-Positive Cancer Screenings and Cancer Worry on Risk-Reducing Surgery Among BRCA1/2 Carriers.
Portnoy DB, Loud JT, Han PK, Mai PL, Greene MH.
Objective: Female BRCA1/2 mutation carriers are at increased risk of breast and ovarian cancer. Annual breast and semiannual ovarian cancer screening is recommended for early detection, which frequently leads to false-positive test results (FPTR). FPTR may influence cancer risk perceptions and worry, which in turn may affect an individual's decision to undergo risk-reducing bilateral salpingo-oophorectomy (RRSO) or risk-reducing bilateral mastectomy (RRBM). The purpose of this study was to examine: (a) the effect of false-positive breast and ovarian cancer screening test results on perceived cancer risk and cancer worry,
and (b) the joint effects of FPTR, risk perceptions, and worry on the choice of risk-reducing surgery among BRCA1/2 mutation carriers undergoing an intensive cancer screening protocol. Method: BRCA1/2 mutation carriers (N = 170) reported cancer risk perceptions and cancer worry during a prospective 4-year screening protocol (2001-2007) at the U.S. National Cancer Institute. FPTR and risk-reducing surgeries were objectively recorded. Results: FPTR at baseline were associated with transient elevations in worry; cumulative FPTR across the entire study were not associated with opting for risk-reducing surgery. However, cancer-specific worry was a strong predictor of surgery (RRSO: OR = 6.15; RRBM: OR = 4.27). Conclusions: In women at inherited risk of breast and ovarian cancer, FPTR were not associated with large increases in cancer risk perception, cancer worry, or increased uptake of risk-reducing surgery. However, cancer-specific worry was an independent predictor of uptake of risk-reducing surgery and warrants consideration when counseling high-risk women regarding risk-reducing interventions. (PsycINFO Database Record (c) 2014 APA, all rights reserved).

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Maximising survival: the main concern of women with hereditary breast and ovarian cancer who undergo genetic testing for BRCA1/2.

Jeffers L(1), Morrison PJ(2), McCaughan E(3), Fitzsimons D(4).

Author information:
(1)Belfast Health and Social Care Trust, Department of Genetics, Belfast City Hospital, Lisburn Road, Belfast BT9 7AB, UK. Electronic address: lisa.jeffers@belfasttrust.hscni.net. (2)Belfast Health and Social Care Trust, Department of Genetics, Belfast City Hospital, Lisburn Road, Belfast BT9 7AB, UK. (3)Institute of Nursing Research, University of Ulster, Coleraine BT52 1SA, UK. (4)Institute of Nursing Research, University of Ulster, Jordanstown BT37 0QB, UK; Belfast Health and Social Care Trust, Belfast City Hospital, Lisburn Road, Belfast BT9 7AB, UK.

PURPOSE: Little is known about how women with hereditary breast and/or ovarian cancer who test positive for a BRCA gene manage the impact of a positive test result on their everyday lives and in the longer term. This study defined the experience and needs of women with hereditary breast and ovarian cancer and a positive BRCA test over time.

METHODS: A grounded theory approach was taken using qualitative interviews (n = 49) and reflective diaries. Data collected from December 2006 until March 2010 was analysed using the constant comparative technique to trace the development of how women manage their concerns of inherited cancer.

RESULTS: A four stage substantive theory of maximising survival was generated that defines the experience of women and how they resolve their main concerns. The process of maximising survival begins prior to genetic testing in women from high risk families as they expect to get a cancer diagnosis at some time. Women with cancer felt they had experienced the worst with a cancer diagnosis and altruistically tested for the sake of their children but a positive test result temporarily shifted their focus to decision-making around their personal health needs.

CONCLUSION: This study adds to clinical practice through raising awareness and adding insights into how women cope with living with inherited cancer risk and the personal and familial ramifications that ensue from it. A clear
multi-professional structured care pathway for women from genetic testing result disclosure to undergoing risk-reducing surgery and/or surveillance should be developed.

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Acceptability of prophylactic salpingectomy with delayed oophorectomy as risk-reducing surgery among BRCA mutation carriers.

Holman LL(1), Friedman S(2), Daniels MS(3), Sun CC(3), Lu KH(3).

Author information:
(1)Department of Gynecologic Oncology and Reproductive Medicine, The University of Texas MD Anderson Cancer Center, Houston, TX, USA. Electronic address: lholman@mdanderson.org. (2)Facing Our Risk of Cancer Empowered (FORCE), Tampa, FL, USA. (3)Department of Gynecologic Oncology and Reproductive Medicine, The University of Texas MD Anderson Cancer Center, Houston, TX, USA.

OBJECTIVE: Given the emerging evidence for the fimbria as the site of origin for many serous carcinomas in BRCA mutation carriers, consideration is being given in studying prophylactic salpingectomy with delayed oophorectomy (PSDO) as a risk-reducing surgery. We aimed to determine the interest in a study of PSDO among these women.

METHODS: We evaluated the results of an online survey conducted by Facing Our Risk of Cancer Empowered (FORCE), a patient advocacy group, from October 2010 to August 2012. Premenopausal BRCA mutation carriers with no history of ovarian cancer or prior bilateral salpingo-oophorectomy (BSO) were included.

RESULTS: Of the 204 women meeting inclusion criteria, median age was 35 years, 92.5% were white, 25.7% were Jewish, and 16.7% had a history of breast cancer. Overall, 34.3% reported interest in a study of salpingectomy, 35.3% were unsure, and 30.4% were not interested in the study. Women noted the possibility of lowering ovarian cancer risk without menopause as a compelling reason to participate (83.8%). Reasons for not participating in a salpingectomy study included surgical complications (46.6%), potential ovarian damage (42.2%), planning BSO soon (32.4%), and surgical costs (32.8%). Acceptable study risks included the need for two surgeries (77.2%), possibility of not lowering ovarian cancer risk (68%), and disruption of ovarian blood supply (66.5%).

CONCLUSIONS: One-third of BRCA mutation carriers indicated definite interest in a PSDO study. Potential study risks were acceptable to most women. These findings suggest that patient accrual for a clinical trial of prophylactic salpingectomy with delayed oophorectomy is possible.

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The impact of risk-reducing hysterectomy and bilateral salpingo-oophorectomy on survival in patients with a history of breast cancer--a population-based data linkage study.

Obermair A(1), Youlde DR, Baade PD, Janda M.

Author information:
(1)Queensland Centre for Gynaecological Cancer School of Medicine, The University of Queensland, Royal Brisbane and Women's Hospital, Brisbane, QLD, Australia.

Prophylactic surgery including hysterectomy and bilateral salpingo-oophorectomy (BSO) is recommended in breast cancer susceptibility gene (BRCA)-positive women, whereas in women from the general population, hysterectomy plus BSO may increase the risk of overall mortality. The effect of hysterectomy plus BSO on women previously diagnosed with breast cancer is unknown. We used data from a population-based data linkage study of all women diagnosed with primary breast cancer in Queensland, Australia between 1997 and 2008 (n = 21,067). We fitted flexible parametric breast cancer-specific and overall survival models with 95% confidence intervals (also known as Royston-Parmar models) to assess the impact of risk-reducing surgery (removal of uterus, one or both ovaries). We also stratified analyses by age 20-49 and 50-79 years, respectively. Overall, 1,426 women (7%) underwent risk-reducing surgery (13% of premenopausal women and 3% of postmenopausal woman). No women who had risk-reducing surgery compared to 171 who did not have risk-reducing surgery developed a gynaecological cancer. Overall, 3,165 (15%) women died, including 2,195 (10%) from breast cancer. Hysterectomy plus BSO was associated with significantly reduced risk of death overall [adjusted hazard ration (HR), 0.69; 95% confidence interval (CI), 0.53-0.89; p = 0.005]. Risk reduction was greater among premenopausal women, whose risk of death halved (HR, 0.45; 95% CI, 0.25-0.79; p < 0.006). This was largely driven by reduction in breast cancer-specific mortality (HR, 0.43; 95% CI, 0.24-0.79; p < 0.006). This population-based study found that risk-reducing surgery halved the mortality risk for premenopausal breast cancer patients. Replication of our results in independent cohorts and subsequently randomised trials are needed to confirm these findings.

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Human ovarian tissue cortex surrounding benign and malignant lesions.

Pavone ME(1), Hirshfeld-Cytron J, Tingen C, Thomas C, Thomas J, Lowe MP, Schink JC, Woodruff TK.

Author information:
(1)Division of Reproductive Biology, Department of Obstetrics and Gynecology, Northwestern University, Chicago, IL, USA.

OBJECTIVE: To quantify the number of follicles in patients with ovarian pathologies, benign and malignant, in pregnant and nonpregnant states and to determine how the presence of ovarian masses and BRCA status affects follicular counts.
MATERIALS AND METHODS: Slides from 134 reproductive-aged women undergoing oophorectomy were examined using light microscopy by 3 independent counters blinded to the diagnosis. In all, 20 patients had cancer, 69 had benign conditions, and 35 patients were BRCA+ or had a strong family history of breast and/or ovarian cancer. In all, 10 women were either pregnant or immediately postpartum.

RESULTS: Patients undergoing risk-reducing surgery had significantly decreased follicle count compared to physiologic control. Patients with cancer had significantly decreased counts compared to all other groups. There were no differences within the benign cohort.

CONCLUSIONS: When compared to benign masses, the cortex surrounding an ovarian malignancy has decreased follicle density. The stretch impact may minimize any impact on total follicle numbers. Furthermore, there may be a proliferation of ovarian stroma, with the same number of follicles spread over a larger surface area. This information is important when counseling women with ovarian masses regarding the use of ovarian tissue cryopreservation.

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PMID: 24096576  [PubMed - indexed for MEDLINE]

Long-term satisfaction and quality of life following risk reducing surgery in BRCA1/2 mutation carriers.


Author information:
(1)Department of Oncology, Jess and Mildred Fisher Center for Familial Cancer Research, Lombardi Comprehensive Cancer Center, Georgetown University, Washington, DC 20057, USA. schwartm@georgetown.edu.

BACKGROUND: As BRCA1/2 testing becomes more routine, questions remain about long-term satisfaction and quality of life following testing. Previously, we described long term distress and risk management outcomes among women with BRCA1/2 mutations. This study addresses positive psychological outcomes in BRCA1/2 carriers, describing decision satisfaction and quality of life in the years following testing.

METHODS: We evaluated satisfaction with testing and management decisions among 144 BRCA1/2 carriers. Prior to genetic testing, we assessed family history, sociodemographics and distress. At a mean of 5.3 years post-testing, we assessed management decisions, satisfaction with decisions and, among women with cancer, quality of life.

RESULTS: Overall, satisfaction with decision making was high. Women who had risk reducing mastectomy or oophorectomy were more satisfied with management decisions. Participants who obtained a risk reducing oophorectomy were more satisfied with their genetic testing decision. Among affected carriers, high pretest anxiety was associated with poorer quality of life and having had risk reducing mastectomy prior to testing was associated with better quality of life. The negative impact of pre-test anxiety was diminished among women who had mastectomies before testing.

CONCLUSIONS: BRCA1/2 carriers are satisfied with their testing and risk management decisions and report good quality of life years after testing. Having risk reducing surgery predicts increased satisfaction and improved quality of life.
The frequency and outcome of breast cancer risk-reducing surgery in Finnish BRCA1 and BRCA2 mutation carriers.

Koskenvuo L(1), Svarvar C, Suominen S, Aittomäki K, Jahkola T.

Author information:
(1)Department of Plastic Surgery, Helsinki University Central Hospital, Helsinki, Finland.

BACKGROUND AND AIMS: Risk-reducing mastectomy of BRCA1 and BRCA2 gene mutation carriers is known to significantly reduce lifetime risk of breast cancer. Our aim was to study the frequency and outcome of risk-reducing mastectomies performed in Helsinki University Central Hospital during 1997-2010.

MATERIAL AND METHODS: In testing for mutations in BRCA1 and BRCA2, 136 female carriers had been identified and followed up in Helsinki University Central Hospital.

RESULTS: A total of 69 breasts in 52 women were operated on for risk-reduction, including 28 (54%) bilateral mastectomies at mean age of 43 years. Autologous tissue was used for reconstruction in 40 (50%) and implants in 31 (39%) of the breasts, respectively. In all, 8 patients (15%) chose to have no reconstruction. Minor or major complications were recorded in 21 (40%) patients. Five reconstructions failed and were corrected with re-reconstruction.

CONCLUSIONS: In this series of Finnish BRCA1 and BRCA2 mutation carriers, a high percentage 52 (41%) chose risk-reducing breast surgery. Autologous tissue was favored in breast reconstructions. Immediate breast reconstructions were associated with a relatively high risk of complications in free flaps and in implant reconstructions, but not in latissimus dorsi reconstructions. It is mandatory that patients are informed about the risks associated with risk-reducing operations.

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Moyer VA; U.S. Preventive Services Task Force.


Summary for patients in

DESCRIPTION: Update of the 2005 U.S. Preventive Services Task Force (USPSTF)
recommendation on genetic risk assessment and BRCA mutation testing for breast and ovarian cancer susceptibility.

METHODS: The USPSTF reviewed the evidence on risk assessment, genetic counseling, and genetic testing for potentially harmful BRCA mutations in asymptomatic women with a family history of breast or ovarian cancer but no personal history of cancer or known potentially harmful BRCA mutations in the family. The USPSTF also reviewed interventions aimed at reducing the risk for BRCA-related cancer in women with potentially harmful BRCA mutations, including intensive cancer screening, medications, and risk-reducing surgery.

POPULATION: This recommendation applies to asymptomatic women who have not been diagnosed with BRCA-related cancer.

RECOMMENDATION: The USPSTF recommends that primary care providers screen women who have family members with breast, ovarian, tubal, or peritoneal cancer with 1 of several screening tools designed to identify a family history that may be associated with an increased risk for potentially harmful mutations in breast cancer susceptibility genes (BRCA1 or BRCA2). Women with positive screening results should receive genetic counseling and, if indicated after counseling, BRCA testing. (B recommendation)

The USPSTF recommends against routine genetic counseling or BRCA testing for women whose family history is not associated with an increased risk for potentially harmful mutations in the BRCA1 or BRCA2 genes. (D recommendation).

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Prevalence of occult gynecologic malignancy at the time of risk reducing and nonprophylactic surgery in patients with Lynch syndrome.

Lachiewicz MP(1), Kravochuck SE(2), O'Malley MM(2), Heald B(2), Church JM(3), Kalady MF(3), Drake RD(4).

Author information:
(1)Women's Health Institute; Cleveland Clinic, Cleveland, OH, USA. Electronic address: mlachiewicz@gmail.com. (2)Sanford R. Weiss, MD, Center for Hereditary Colorectal Neoplasia; Cleveland Clinic, Cleveland, OH, USA. (3)Sanford R. Weiss, MD, Center for Hereditary Colorectal Neoplasia; Department of Colorectal Surgery, Digestive Disease Institute; Cleveland Clinic, Cleveland, OH, USA. (4)Women's Health Institute; Cleveland Clinic, Cleveland, OH, USA.

OBJECTIVE: The primary aim of this study was to determine the prevalence of occult gynecologic malignancy at the time of risk reducing surgery in patients with Lynch Syndrome. A secondary aim was to determine the prevalence of occult gynecologic malignancy at the time of surgery for non-prophylactic indications in patients with Lynch Syndrome.

METHODS: A retrospective review of an Inherited Colorectal Cancer Registry found 76 patients with Lynch syndrome (defined by a germline mutation in a DNA mismatch repair gene) or hereditary nonpolyposis colorectal cancer (HNPCC) (defined by Amsterdam criteria) who had undergone hysterectomy and/or salpingo-oophorectomy for a prophylactic or non-prophylactic indication. Indications for surgery and the prevalence of cancer at the time of each operation were reviewed.

RESULTS: 24 of 76 patients underwent prophylactic hysterectomy and/or bilateral salpingo-oophorectomy for Lynch syndrome or HNPCC. In 9 of these patients, a benign indication for surgery was also noted. 4 of 24 patients (17%, 95% CI =
5-38%) were noted to have cancer on final pathology. 20 of 76 patients (26%) undergoing operative management for any indication were noted to have occult malignancy on final pathology. CONCLUSIONS: Patients should be counseled about the risks of finding gynecologic cancer at the time of prophylactic or non-prophylactic surgery for Lynch syndrome and HNPCC, and the potential need for additional surgery.

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Rates of risk-reducing surgery in Israeli BRCA1 and BRCA2 mutation carriers.


Author information:
(1)Susanne Levy Gertner Oncogenetics Unit.

The frequency of BRCA1 and BRCA2 mutations is higher in Israel than in almost all other countries. One strategy to reduce the burden of hereditary breast and ovarian cancers is to offer genetic testing followed by risk-reducing surgery (mastectomy and salpingo-oophorectomy) for mutation carriers. The extent to which Israeli women who carry mutations undergo these surgeries is not well characterized. Israeli women who are BRCA1 or BRCA2 mutation carriers and followed at a single high-risk clinic were asked to complete a questionnaire detailing their clinical histories at the time of genetic results disclosure and a follow-up questionnaire was completed 18 or more months thereafter. A total of 205 mutation carriers completed the questionnaires. Of 170 women with no cancer history, 84 (49%) had a risk-reducing bilateral salpingo-oophorectomy and 22 (13%) had a risk-reducing mastectomy. Five of 35 (14.3%) women with breast cancer opted for contralateral mastectomy. Approximately one half of Israeli women with a BRCA1 or BRCA2 mutation opt for risk-reducing oophorectomy, but the rate of risk-reducing mastectomy is only 13%.

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Advances in tumor screening, imaging, and avatar technologies for high-grade serous ovarian cancer.

Ohman AW(1), Hasan N(1), Dinulescu DM(1).

Author information:
(1)Division of Women's and Perinatal Pathology, Department of Pathology, Eugene Braunwald Research Center, Brigham and Women's Hospital, Harvard Medical School, Boston, MA, USA.

The majority of high-grade serous ovarian carcinoma cases are detected in advanced stages when treatment options are limited. Surgery is less effective at
eradicating the disease when it is widespread, resulting in high rates of disease relapse and chemoresistance. Current screening techniques are ineffective for early tumor detection and consequently, BRCA mutations carriers, with an increased risk for developing high-grade serous ovarian cancer, elect to undergo risk-reducing surgery. While prophylactic surgery is associated with a significant reduction in the risk of cancer development, it also results in surgical menopause and significant adverse side effects. The development of efficient early-stage screening protocols and imaging technologies is critical to improving the outcome and quality of life for current patients and women at increased risk. In addition, more accurate animal models are necessary in order to provide relevant in vivo testing systems and advance our understanding of the disease origin and progression. Moreover, both genetically engineered and tumor xenograft animal models enable the preclinical testing of novel imaging techniques and molecularly targeted therapies as they become available. Recent advances in xenograft technologies have made possible the creation of avatar mice, personalized tumorgrafts, which can be used as therapy testing surrogates for individual patients prior to or during treatment. High-grade serous ovarian cancer may be an ideal candidate for use with avatar models based on key characteristics of the tumorgraft platform. This review explores multiple strategies, including novel imaging and screening technologies in both patients and animal models, aimed at detecting cancer in the early-stages and improving the disease prognosis.

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PMID: 25478323  [PubMed]


Risk-reducing surgery increases survival in BRCA1/2 mutation carriers unaffected at time of family referral.


Author information:
(1)Centre for Health Informatics, Institute of Population Health, The University of Manchester, Jean McFarlane Building, Oxford Road, Manchester, M13 9PL, UK.

The aim of this study was to establish if risk-reducing surgery (RRS) increases survival among BRCA1/2 carriers without breast/ovarian cancer at the time of family referral. Female BRCA1/2 carriers were identified from the Manchester Genetic Medicine Database. Those patients alive and unaffected at the date of first family ascertainment were included in this study. Female first-degree relatives (FDRs) without predictive genetic testing who otherwise met eligibility criteria were also included. The effect of breast and ovarian RRS on survival was analysed. The survival experiences of RRS and non-RRS patients, stratified by BRCA status, were examined with Kaplan-Meier curves and contrasted using log-rank tests and Cox models. 691 female BRCA1/2 mutation carriers without breast or ovarian cancer at time of family ascertainment were identified; 346 BRCA1 and 345 BRCA2. 105 BRCA1 carriers and 122 BRCA2 carriers developed breast cancer during follow-up. The hazard of death was statistically significantly lower (P < 0.001) following RRS versus no RRS. 10-year survival for women having RRS was 98.9 % (92.4-99.8 %) among BRCA1 and 98.0 % (92.2-99.5 %) among BRCA2 carriers. This survival benefit with RRS remained significant after FDRs were added. Women who had any form of RRS had increased survival compared to those who did not have
RRS; a further increase in survival was seen among women who had both types of surgery. However, formal evidence for a survival advantage from bilateral mastectomy alone requires further research.

PMID: 24249359 [PubMed - indexed for MEDLINE]


Multidisciplinary one-stage risk-reducing gynaecological and breast surgery with immediate reconstruction in BRCA-gene carrier women.


Author information:
(1)Department of Plastic Surgery, Belfast City Hospital, Belfast, Northern Ireland BT16 1QN, United Kingdom. Electronic address: drfaheemk2002@yahoo.com.

Familial breast cancer accounts for 5-10% of all breast cancers. Due to BRCA1/2 tumour suppressor gene mutation, hereditary breast and ovarian syndrome is the most common form. Risk-reducing gynaecological and breast surgery is offered to such patients in ever-increasing numbers. Hence, the development of a multi-specialty combined treatment approach is called for. Twenty-two BRCA gene-mutation carrier women underwent one-stage gynaecological and breast risk-reducing surgery and immediate reconstruction between January 2005 and December 2011 at the Belfast City Hospital. Their mean age was 41.2 years (median 41 years). Nearly half of the patients were BRCA2 and a quarter were BRCA1 carriers. The rest were positive for both genes. Hormone-replacement therapy was initiated in 14 women. Average theatre time and stay in the hospital were three hours and two and a half days, respectively. Two patients developed complications unrelated to combining the procedures. Both were treated conservatively and recovered. The one-stage approach logically proves economical by limiting the time the patients are in the hospital and away from work. We describe our multidisciplinary team service that is offering safe and economical one-stage risk-reducing surgery and reconstruction to young BRCA gene-mutation carrier women in Northern Ireland.

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Preventing breast and ovarian cancers in high-risk BRCA1 and BRCA2 mutation carriers.


Author information:
(1)Peter MacCallum Cancer Centre, Melbourne, VIC, Australia. Kelly.Phillips@petermac.org.
OBJECTIVE: To estimate the prevalence of the use of cancer risk-reducing measures among Australian BRCA1 and BRCA2 mutation carriers.

DESIGN, SETTING AND PARTICIPANTS: Prospective follow-up of female carriers of BRCA1 or BRCA2 mutations who had no personal history of cancer and were enrolled in a multiple-case breast cancer family cohort study (kConFab). Data, including cancer events and uptake of risk-reducing surgery and medication were collected by self-report at cohort entry and 3 yearly thereafter. Surgery was confirmed from pathology and medical records. Women were followed up from enrolment until cancer diagnosis, date of last follow-up, or death. Data were collected from 3 November 1997 to 21 May 2012.

MAIN OUTCOME MEASURES: Uptake of risk-reducing surgery and/or medication.

RESULTS: Of 175 BRCA1 and 150 BRCA2 mutation carriers (median age, 37 years at cohort enrolment), 69 (21%) underwent risk-reducing mastectomy, 125 (38%) underwent risk-reducing bilateral salpingo-oophorectomy and nine (3%) participated in a clinical trial of risk-reducing medication, during 2447 person-years of follow-up (median follow-up, 9 years). Sixty-eight women (21%) reported incident cancers, including 52 breast cancers and nine ovarian cancers (defined in this article as high-grade serous cancers of the ovary, fallopian tube or peritoneum).

CONCLUSIONS: There is considerable scope to increase the uptake of cancer risk-reducing measures in Australian BRCA1 and BRCA2 mutation carriers. These findings should drive (i) future research into the factors contributing to low uptake in Australia and (ii) changes to policy and practice to help better translate genetic knowledge into reductions in cancer incidence.

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Alternatives to risk-reducing surgery for ovarian cancer.

Gadducci A(1), Sergiampietri C, Tana R.

Author information:
(1)Department of Clinical and Experimental Medicine, Division of Gynecology and Obstetrics, University of Pisa, Pisa, Italy.

BRCA1 and BRCA2 mutation carriers have an 18%-60% and 11%-27% lifetime risk of developing ovarian carcinoma, respectively. Prophylactic bilateral salpingo-oophorectomy reduces the risk of this malignancy by up to 96%. Gynecological screening programs with periodical trans-vaginal ultrasound and serum CA125 assay have been widely used in women at hereditary high risk of ovarian carcinoma, but clinical results have been conflicting. These surveillance protocols have often fallen short of expectations because of the advanced stage of ovarian carcinoma in the identified screened women. Several investigations have been addressed to the detection of additional tumor markers able to generate more reliable screening tools. The combined serum assay of leptin, prolactin, osteopontin, CA125, macrophage inhibiting factor and insulin-like growth factor-II appears to have a significant better diagnostic reliability compared with serum CA125 alone in discriminating healthy individuals from ovarian carcinoma patients, and therefore, it could have a role in the screening of women at high risk for this malignancy. As far as chemoprevention is concerned, oral contraceptives significantly reduce the ovarian carcinoma risk also in BRCA mutation carriers, whereas the efficacy of fenretinide is still under investigation.

Young adult daughters of BRCA1/2 positive mothers: what do they know about hereditary cancer and how much do they worry?

Patenaude AF(1), Tung N, Ryan PD, Ellisen LW, Hewitt L, Schneider KA, Tercyak KP, Aldridge J, Garber JE.

Author information:
(1)Dana-Farber Cancer Institute, Boston, MA 02215, USA. andrea_patenaude@dfci.harvard.edu

OBJECTIVE: The objectives of this study are to determine (i) what daughters, ages 18-24 years, of BRCA1/2 mutation carriers understand about their 50% chance of carrying a BRCA1/2 mutation and about risk reduction or management options for mutation carriers, (ii) the extent and nature of daughters' cancer-related distress, and (iii) the effects of knowing mother's mutation status on daughters' future plans.

METHODS: A total of 40 daughters, currently aged 18-24 years, of mothers who tested positive for a mutation in BRCA1/2 were invited by mail to participate (with contact information supplied by their mothers). Daughters participated in a qualitative telephone interview about the impact of learning their mother's mutation status on their understanding of their own cancer risks and their cancer-related distress, and their knowledge of screening strategies, risk-reducing surgery, current health status, and future plans. Participants also completed study-specific demographic and family history questionnaires, the Brief Symptom Inventory-18, Impact of Event Scale (with hereditary predisposition to breast/ovarian cancer as the event), and the Breast Cancer Genetic Counseling Knowledge Questionnaire.

RESULTS: Daughters' genetic knowledge is suboptimal; gaps and misconceptions were common. Over 1/3 of the daughters reported high cancer-related distress, despite normal levels of general distress. Disclosed genetic information raised future concerns, especially regarding childbearing.

CONCLUSION: Targeted professional attention to this high-risk cohort of young women is critical to inform the next generation of daughters of BRCA1/2 mutation carriers and encourage recommended screening by age 25 years. Improved uptake of screening and risk reduction options could improve survival, and psychoeducation could reduce cancer-related distress.

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Lynch syndrome is one of the most common hereditary cancer syndromes. Although Lynch syndrome is associated with increased risk for developing colorectal, endometrial, and other cancers specialized screening, risk-reducing surgery, and chemoprevention offer promise for reducing morbidity and mortality. Frequent colonoscopic surveillance has proven effective for early detection and prevention of Lynch syndrome-associated colorectal cancer; however, the optimal strategy for managing endometrial cancer risks in women with germline mutations in DNA mismatch repair genes has yet to be determined. In this issue of Cancer Prevention Research, Lu and colleagues report their findings of a phase II prospective, multicenter randomized trial comparing the effects of oral contraceptive pills and Depo-Provera on endometrial proliferation in women with Lynch syndrome. Although short-term hormonal treatment with either modality altered endometrial proliferation indices, it remains unknown whether hormonal suppression actually reduces endometrial cancer risk in women with Lynch syndrome. This trial represents the first of its kind in evaluating agents which might offer protection against Lynch syndrome-associated endometrial cancer and provides preliminary data regarding potential biomarkers for early detection of endometrial neoplasia. The investigators' experience with this trial also offers insights regarding the various technical and scientific challenges inherent in chemoprevention research.

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Impact of family history on choosing risk-reducing surgery among BRCA mutation carriers.

Singh K(1), Lester J, Karlan B, Bresee C, Geva T, Gordon O.

Author information:
(1)Cedars-Sinai Medical Genetics Institute, Cedars-Sinai Medical Center, Los Angeles, CA 90048, USA. krishna.singh@cshs.org

OBJECTIVE: Despite substantial survival benefits of risk-reducing mastectomy (RRM) and risk-reducing bilateral salpingo-oophorectomy (RRBSO) among BRCA mutation carriers, only a minority elect to undergo these procedures. This study investigates factors that might influence decision making regarding prophylactic surgeries among women with BRCA mutations.

STUDY DESIGN: Unaffected BRCA mutation carriers who were counseled at our center and either underwent prophylactic surgery or participated in a high-risk surveillance program at our institution from 1998 through 2010 were included in the study. Medical records were reviewed and data collected included age, family history, parity, mutation type, history of breast biopsy or cosmetic surgery, and uptake of prophylactic surgeries.

RESULTS: Among 136 unaffected women with BRCA mutations, uptake of RRM was 42% and uptake of RRBSO was 52%. Family history of first- and second-degree relatives being deceased from breast cancer was predictive of uptake of RRM and of RRBSO (odds ratio [OR], 11.0; P = .005; and OR, 15.8; P = .023, respectively), and history of a mother lost to pelvic cancer was predictive of uptake of RRBSO (OR, 7.9; P = .001). Parity also predicted both RRM and RRBSO uptake (OR, 4.2; P = .001; and OR, 5.4; P = .003, respectively). Age at the time of genetic testing
and history of breast biopsy or cosmetic surgery were not predictive of RRM uptake.

CONCLUSION: Perceptions of cancer risk are heavily influenced by particular features of an individual's family history and may be motivators in preventive surgery more than actual cancer risk estimations themselves. Awareness of subtle factors beyond the statistical risk for cancers is relevant when counseling at-risk women.

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Serial sectioning of the fallopian tube allows for improved identification of primary fallopian tube carcinoma.

Lengyel E(1), Fleming S, McEwen KA, Montag A, Temkin SM.

Author information:
(1)Department of Obstetrics and Gynecology, Section of Gynecologic Oncology, The University of Chicago Medical Center, Chicago, IL, USA.

OBJECTIVE: Serial sectioning of the fallopian tube in women undergoing risk reducing surgery has been shown to increase the detection rate of occult malignancy in BRCA mutation carriers. We undertook this study to determine whether this protocol at the time of surgery for ovarian cancer (OV) or primary peritoneal malignancies (PP) changes the detection rate of fallopian tube carcinoma (FT). We secondarily investigated where this difference affects patient outcomes.

METHODS: A retrospective review of 130 patients treated at the University of Chicago Medical Center for ovarian, peritoneal or fallopian tube carcinoma was conducted. Sixty five patients diagnosed with OV, PP or FT who had serial sectioning of the fallopian tubes at the time of diagnoses (SS) were compared to 65 patients whose fallopian tubes were sectioned in a standard fashion (PSS).

RESULTS: Serial sectioning of the fallopian tube at the time of pathologic examination in women with presumed OV or PP led to an increase in the number of women diagnosed with FT as the primary site of origin (p<0.001). Clinical or pathologic risk factors leading to an increased risk of FT were not identified. Survival between the two groups was similar.

CONCLUSION: In women with presumed OV or PP, serial sectioning identifies women with FT. FT may be more common than previously noted; however distinct biologic or clinical behavior to differentiate it from OV or PP could not be identified. Clinical management of FT should continue to be the same as that of OV or PP.

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Reproductive decision-making in young female carriers of a BRCA mutation.


Author information:
(1)Nightingale Centre and Genesis Prevention Centre, University Hospital of South Manchester, Manchester, UK.

STUDY QUESTION: How do young women, who were identified as carrying a BRCA gene mutation before they had children, approach reproductive decision-making and what are their attitudes towards reproductive genetic testing?

SUMMARY ANSWER: Reproductive decision-making within the context of cancer risk is complex and influenced by personal experiences of cancer. Younger women were not concerned with reproductive decision-making at the time of their genetic test; however, the impact on subsequent reproductive decision-making was considerable and left them with unanticipated dilemmas, such as having children who would be at risk of inheriting cancer predisposition, timing risk-reducing surgery and changing perceptions of responsibility.

WHAT ISKNOWN ALREADY: Individuals carrying gene mutations predisposing to hereditary breast/ovarian cancer have concerns about passing on the gene mutation to children.

STUDY DESIGN, SIZE, DURATION: Qualitative methodology and thematic analysis.

PARTICIPANTS/MATERIALS, SETTING, METHODS: Data were collected through semi-structured interviews with 25 women aged 18-45 who had received a positive result for a BRCA1 or BRCA2 gene mutation while childless.

MAIN RESULTS AND THE ROLE OF CHANCE: Analysis revealed four central themes: (i) the impact of cancer on reproductive decision-making; (ii) motivation for genetic testing; (iii) risk management and timing of planning children; and (iv) optimism for future medical advancements.

LIMITATIONS, REASONS FOR CAUTION: This study explores the views of female BRCA carriers. Further research should explore the views of couples, men, and include samples with greater ethnic and social diversity.

WIDER IMPLICATIONS OF THE FINDINGS: This evidence highlights the need for reproductive decision-making to be addressed at the time of pretest genetic counselling. More information should be provided on reproductive options as well as counselling/support to guide women's reproductive decision-making and prenatal testing options at the time they undertake genetic testing.

STUDY FUNDING/COMPETING INTEREST(S): This research was supported by Cancer Research UK (Number C1226 A7920) and NIHR support to the Biomedical Research Centre at The Institute of Cancer Research and RMH. The authors have no conflicts of interest to declare.

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Management of genetic syndromes predisposing to gynecologic cancers.

Miesfeldt S(1), Lamb A, Duarte C.

Author information:
(1)Cancer Risk and Prevention Program, Maine Medical Center Cancer Institute, Scarborough, ME 04074, USA. miesfs@mmc.org
Women with personal and family histories consistent with gynecologic cancer-associated hereditary cancer susceptibility disorders should be referred for genetic risk assessment and counseling. Genetic counseling facilitates informed medical decision making regarding genetic testing, screening, and treatment, including chemoprevention and risk-reducing surgery. Because of limitations of ovarian cancer screening, hereditary breast and ovarian cancer-affected women are offered risk-reducing bilateral salpingo-oophorectomy (BSO) between ages 35 and 40 years, or when childbearing is complete. Women with documented Lynch syndrome, associated with mutations in mismatch repair genes, should be screened at a young age and provided prevention options, including consideration of risk-reducing total abdominal hysterectomy and BSO, as well as intensive gastrointestinal screening. Clinicians caring for high-risk women must consider the potential adverse ethical, legal, and social issues associated with hereditary cancer risk assessment and testing. Additionally, at-risk family members should be alerted to their cancer risks, as well as the availability of risk assessment, counseling, and treatment services.

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The physical consequences of gynecologic cancer surgery and their impact on sexual, emotional, and quality of life issues.

Carter J(1), Stabile C, Gunn A, Sonoda Y.

Author information:
(1)Gynecology Service, Department of Surgery, Memorial Sloan-Kettering Cancer Center, New York, NY 10065, USA. carterj@mskcc.org

INTRODUCTION: Surgical management of gynecologic cancer can cause short- and long-term effects on sexuality, reproductive function, and overall quality of life (QOL) (e.g., sexual dysfunction, infertility, lymphedema). However, innovative approaches developed over the past several decades have improved oncologic outcomes and reduced treatment sequelae.

AIM: To provide an overview of the standards of care and major advancements in gynecologic cancer surgery, with a focus on their direct physical impact, as well as emotional, sexual, and QOL issues. This overview will aid researchers and clinicians in the conceptualization of future clinical care strategies and interventions to improve sexual/vaginal/reproductive health and QOL in gynecologic cancer patients.

MAIN OUTCOME MEASURES: Comprehensive overview of the literature on gynecologic oncology surgery.

METHODS: Conceptual framework for this overview follows the current standards of care and recent surgical approaches to treat gynecologic cancer, with a brief overview describing primary management objectives and the physical, sexual, and emotional impact on patients. Extensive literature support is provided.

RESULTS: The type and radicality of surgical treatment for gynecologic cancer can influence sexual function and play a significant role in QOL. Psychological, sexual, and QOL outcomes improve as surgical procedures continue to evolve. Procedures for fertility preservation, laparoscopy, sentinel lymph node mapping, and robotic and risk-reducing surgery have advanced the field while reducing treatment sequelae. Nevertheless, interventions that address sexual and vaginal health issues are limited.

CONCLUSIONS: It is imperative to consider QOL and sexuality during the treatment decision-making process. New advances in detection and treatment exist; however,
psycho-educational interventions and greater patient-physician communication to address sexual and vaginal health concerns are warranted. Large, prospective clinical trials including patient-reported outcomes are needed in gynecologic oncology populations to identify subgroups at risk. Future study designs need clearly defined samples to gain insight about sexual morbidity and foster the development of targeted interventions.

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The role of the fallopian tube in ovarian cancer.


Author information:
(1)University of British Columbia, Vancouver, British Columbia, Canada.

High-grade serous carcinoma (HGSC) is the most common and lethal subtype of ovarian cancer. Research over the past decade has strongly suggested that "ovarian" HGSC arises in the epithelium of the distal fallopian tube, with serous tubal intraepithelial carcinomas (STICs) being detected in 5-10% of BRCA1/2 mutation carriers undergoing risk-reducing surgery and up to 60% of unselected women with pelvic HGSC. The natural history, clinical significance, and prevalence of STICs in the general population (ie, women without cancer and not at an increased genetic risk) are incompletely understood, but anecdotal evidence suggests that these lesions have the ability to shed cells with metastatic potential into the peritoneal cavity very early on. Removal of the fallopian tube (salpingectomy) in both the average and high-risk populations could therefore prevent HGSC, by eliminating the site of initiation and interrupting spread of potentially cancerous cells to the ovarian/peritoneal surfaces. Salpingectomy may also reduce the incidence of the 2 next most common subtypes, endometrioid and clear cell carcinoma, by blocking the passageway linking the lower genital tract to the peritoneal cavity that enables ascension of endometrium and factors that induce local inflammation. The implementation of salpingectomy therefore promises to significantly impact ovarian cancer incidence and outcomes.

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Long-term psychosocial outcomes of BRCA1/BRCA2 testing: differences across affected status and risk-reducing surgery choice.


Author information:
(1)Department of Oncology, Cancer Control Program, Breast Cancer Program, Jess and Mildred Fisher Center for Familial Cancer Research, Lombardi Comprehensive
BACKGROUND: Numerous studies have documented the short-term impact of BRCA1/BRCA2 (BRCA1/2) testing; however, little research has examined the long-term impact of testing. We conducted the first long-term prospective study of psychosocial outcomes in a U.S. sample of women who had BRCA1/2 testing.

METHODS: Participants were 464 women who underwent genetic testing for BRCA1/2 mutations. Prior to testing, we measured sociodemographics, clinical variables, and cancer specific and general distress. At long-term follow-up (Median = 5.0 years; Range = 3.4-9.1 years), we assessed cancer-specific and genetic testing distress, perceived stress, and perceived cancer risk. We evaluated the impact of BRCA1/2 test result and risk-reducing surgery on long-term psychosocial outcomes.

RESULTS: Among participants who had been affected with breast or ovarian cancer, BRCA1/2 carriers reported higher genetic testing distress ($\beta = 0.41, P < 0.0001$), uncertainty ($\beta = 0.18, P < 0.0001$), and perceived stress ($\beta = 0.17, P = 0.005$) compared with women who received negative (i.e., uninformative) results. Among women unaffected with breast/ovarian cancer, BRCA1/2 carriers reported higher genetic testing distress ($\beta = 0.39, P < 0.0001$) and lower positive testing experiences ($\beta = 0.25, P = 0.008$) than women with negative results. Receipt of risk-reducing surgery was associated with lower perceived cancer risk ($P < 0.0001$).

CONCLUSIONS: In this first prospective long-term study in a U.S. sample, we found modestly increased distress in BRCA1/2 carriers compared with women who received uninformative or negative test results. Despite this modest increase in distress, we found no evidence of clinically significant dysfunction.

IMPACT: Although a positive BRCA1/2 result remains salient among carriers years after testing, testing does not seem to impact long-term psychologic dysfunction.

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Prospective study of breast cancer risk for mutation negative women from BRCA1 or BRCA2 mutation positive families.

Harvey SL(1), Milne RL, McLachlan SA, Friedlander ML, Birch KE, Weideman P; kConFab Investigators, Goldgar D, Hopper JL, Phillips KA.

Author information:
(1)Division of Cancer Medicine, Peter MacCallum Cancer Centre, Locked Bag 1, A'Beckett St, Melbourne, VIC 8006, Australia.

Published studies have reached contradictory conclusions regarding breast cancer risk for women from families segregating a BRCA1 or BRCA2 mutation who do not carry the family-specific mutation. Accurate estimation of breast cancer risk is crucial for appropriate counselling regarding risk management. The aim of this study is to prospectively assess whether breast cancer risk for mutation negative women from families segregating BRCA1 or BRCA2 mutations is greater than for women in the general population. Eligible women were 722 first-, second- and third-degree relatives of a BRCA1 or BRCA2 mutation carrier from 224 mutation positive (128 BRCA1, 96 BRCA2) families, had no personal cancer history at
baseline, and had been tested and found not to carry the family-specific mutation. Self-reported family history of cancer, preventive interventions and verified cancer diagnoses were collected at baseline, and every 3 years thereafter. Median follow-up was 6.1 years (range 0.1-12.4 years). Time at risk of breast cancer was censored at cancer diagnosis or risk-reducing surgery. Standardised incidence ratios (SIR) were estimated by comparing observed to population incidences of invasive breast cancer using Australian Cancer Incidence and Mortality Books. Six cases of invasive breast cancer were observed. The estimated SIRs were 1.14 (95% CI: 0.51-2.53) overall (n = 722), 1.29 (95% CI: 0.58-2.88) when restricted to first- and second-degree relatives of an affected mutation carrier (n = 442) and 0.48 (95% CI: 0.12-1.93) when restricted to those with no family history of breast cancer in the non-mutation carrying parental lineage (n = 424). There was no evidence that mutation negative women from families segregating BRCA1 or BRCA2 mutations are at increased risk of breast cancer. Despite this being the largest prospective cohort to assess this issue, moderately increased breast cancer risk (2-fold) cannot be ruled out.

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Psychometric testing of the decisional conflict scale: genetic testing hereditary breast and ovarian cancer.

Katapodi MC(1), Munro ML, Pierce PF, Williams RA.

Author information:
(1)School of Nursing, University of Michigan, Ann Arbor, USA. mcatapo@umich.edu

BACKGROUND: Hereditary breast and ovarian cancer (HBOC) syndrome is attributed mostly to mutations in the Breast Cancer 1 and Breast Cancer 2 genes (BRCA1/2). Mutation carriers of BRCA1/2 genes have significantly higher risk for developing breast cancer compared with the general population (55%-85% vs. 12%) and for developing ovarian cancer (20%-60% vs. 1.5%). The availability of genetic testing enables mutation carriers to make informed decisions about managing their cancer risk (e.g., risk-reducing surgery). However, uptake of testing for HBOC among high-risk individuals is low, indicating the need to better understand and measure the decisional conflict associated with this process.

OBJECTIVE: The aim of this study was to evaluate the reliability and validity of the modified Decisional Conflict Scale for use in decisions associated with genetic testing for HBOC.

METHODS: This cross-sectional cohort study, recruited women who pursued genetic testing for HBOC in two genetic risk assessment clinics affiliated with a large comprehensive cancer center and one of their female relatives who did not pursue testing. The final sample consisted of 342 women who completed all 16 items of the Decisional Conflict Scale. The psychometric properties of the scale were assessed using tests of reliability and validity, including face, content, construct, contrast, convergent, divergent, and predictive validity.

RESULTS: Factor analysis using principal axis factoring with oblimin rotation elicited a three-factor structure: (a) Lack of Knowledge About the Decision (α = .97), (b) Lack of Autonomy in Decision Making (α = .94), and (c) Lack of Confidence in Decision Making (α = .87). These factors explained 82% of the variance in decisional conflict about genetic testing. Cronbach's alpha coefficient was .96.

DISCUSSION: The instrument is an important tool for researchers and healthcare providers working with women at risk for HBOC who are deciding whether genetic
testing is the right choice for them.

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Nipple-sparing mastectomy for breast cancer and risk-reducing surgery: the Memorial Sloan-Kettering Cancer Center experience.

de Alcantara Filho P(1), Capko D, Barry JM, Morrow M, Pusic A, Sacchini VS.

Author information:
(1)Breast Service, Department of Surgery, Memorial Sloan-Kettering Cancer Center, New York, NY, USA.

BACKGROUND: Nipple-sparing mastectomy (NSM) has been gathering increased recognition as an alternative to more traditional mastectomy approaches. Initially, questions concerning its oncologic safety limited the use of NSM. Nevertheless, mounting evidence supporting the practice of NSM for both prophylactic and oncologic purposes is leading to its more widespread use and broadened indications.

METHODS: Using a prospectively maintained database, we reviewed our experience of 353 NSM procedures performed in 200 patients over the past 10 years.

RESULTS: The indications for surgery were: 196 prophylactic risk-reduction (55.5%), 74 ductal carcinoma in situ (DCIS) (20.8%), 82 invasive cancer (23.2%), and 1 phyllodes tumor (0.5%). The nipple areolar complex (NAC) was entirely preserved in 341 mastectomies (96.7%). There were 11 patients (3.1%) who were found to have cancer at the nipple margin, warranting further excision. A total of 69 breasts (19.5%) had some degree of skin desquamation or necrosis, but only 12 (3.3%) required operative debridement, of which 3 breasts (1%) necessitated removal of a breast implant. Also, 6 patients (2%) were treated for infection. Of the 196 prophylactic NSMs, 11 specimens (5.6%) were found to harbor occult cancer (8 DCIS and 3 invasive cancers). One patient who underwent NSM for invasive ductal carcinoma in 2006 developed metastatic disease to her brain. No other recurrences are attributable to the 353 NSMs.

CONCLUSIONS: The trends demonstrate the increasing acceptance of NSM as a prophylactic procedure as well as for therapeutic purposes. Although NSM is not standard, our experience supports the selective use of NSM in both prophylactic and malignant settings.

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Preoperative risk assessment among women undergoing bilateral prophylactic mastectomy for cancer risk reduction.

Rueth NM(1), McMahon M, Arrington AK, Swenson K, Leach J, Tuttle TM.

Author information:
(1)Department of Surgery, Division of Surgical Oncology, University of Minnesota,
BACKGROUND: Cancer risk assessment is an important decision-making tool for women considering irreversible risk-reducing surgery. Our objective was to determine the prevalence of BRCA testing among women undergoing bilateral prophylactic mastectomy (BPM) and to review the characteristics of women who choose BPM within a metropolitan setting.

METHODS: We retrospectively reviewed records of women who underwent BPM in the absence of cancer within 2 health care systems that included 5 metropolitan hospitals. Women with invasive carcinoma or ductal carcinoma in situ (DCIS) were excluded; neither lobular carcinoma in situ (LCIS) nor atypical hyperplasia (AH) were exclusion criteria. We collected demographic information and preoperative screening and risk assessment, BRCA testing, reconstruction, and associated cancer risk-reducing surgery data. We compared women who underwent BRCA testing to those not tested.

RESULTS: From January 2002 to July 2009, a total of 71 BPMs were performed. Only 25 women (35.2%) had preoperative BRCA testing; 88% had a BRCA mutation. Compared with tested women, BRCA nontested women were significantly older (39.1 vs. 49.2 years, P < 0.001), had significantly more preoperative biopsies and mammograms and had fewer previous or simultaneous cancer risk-reducing surgery (oophorectomy). Among BRCA nontested women, common indications for BPM were family history of breast cancer (n = 21, 45.6%) or LCIS or AH (n = 16, 34.8%); 9 nontested women (19.6%) chose BPM based on exclusively on cancer-risk anxiety or personal preference.

CONCLUSION: Most women who underwent BPM did not receive preoperative genetic testing. Further studies are needed to corroborate our findings in other geographic regions and practice settings.

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A cost-effectiveness analysis of prophylactic surgery versus gynecologic surveillance for women from hereditary non-polyposis colorectal cancer (HNPCC) Families.

Yang KY(1), Caughey AB, Little SE, Cheung MK, Chen LM.

Author information:
(1)Department of Obstetrics, Gynecology, and Reproductive Sciences, University of California, 1600 Divisadero St. 4th Floor, San Francisco, CA 94115-1702, USA. Kathleen.Yang@usoncology.com

Women at risk for Lynch Syndrome/HNPCC have an increased lifetime risk of endometrial and ovarian cancer. This study investigates the cost-effectiveness of prophylactic surgery versus surveillance in women with Lynch Syndrome. A decision analytic model was designed incorporating key clinical decisions and existing probabilities, costs, and outcomes from the literature. Clinical forum where risk-reducing surgery and surveillance were considered. A theoretical population of women with Lynch Syndrome at age 30 was used for the analysis. A decision analytic model was designed comparing the health outcomes of prophylactic hysterectomy with bilateral salpingo-oophorectomy at age 30 versus annual gynecologic screening versus annual gynecologic exam. The literature was searched for probabilities of different health outcomes, results of screening modalities, and costs of cancer diagnosis and treatment. Cost-effectiveness expressed in dollars per discounted life-years. Risk-reducing surgery is the least expensive
option, costing $23,422 per patient for 25.71 quality-adjusted life-years (QALYs). Annual screening costs $68,392 for 25.17 QALYs; and annual examination without screening costs $100,484 for 24.60 QALYs. Further, because risk-reducing surgery leads to both the lowest costs and the highest number of QALYs, it is a dominant strategy. Risk-reducing surgery is the most cost-effective option from a societal healthcare cost perspective.

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Oral contraceptives and risk of ovarian and breast cancers in BRCA mutation carriers: a meta-analysis.

Cibula D(1), Zikan M, Dusek L, Majek O.

Author information:
(1)Gynecological Oncologic Centre, First Faculty of Medicine and General University Hospital, Charles University, Apolinarska 18, Prague 2, Czech Republic. david.cibula@iol.cz

Prophylactic salpingo-oophorectomy is currently the only effective strategy available for decreasing ovarian cancer risk in BRCA1/2 mutation carriers. Significantly decreased risk of ovarian cancer associated with the use of combined oral contraceptives (COCs) was shown in the general population, which could be an alternative approach for those who do not accept risk-reducing surgery. Cohort, case-control and case-case studies published in English up to December 2009 reporting the association of ovarian or breast cancer risk with the use of COCs and presenting BRCA status were selected for meta-analysis. Meta-analysis of three case-control studies showed a significant risk reduction of ovarian cancer in BRCA1/2 mutation carriers who were associated with any past COC use (odds ratio [OR]: 0.57; 95% CI: 0.47-0.70; p < 0.001) and significant trend by duration of COC use (OR: 0.95; 95% CI: 0.93-0.97; p < 0.001). No significant increase in breast cancer risk associated with COC use has been found in case-control studies in BRCA1 (OR: 1.08; p = 0.250), in BRCA2 (OR: 1.03; p = 0.788) mutation carriers or in case-case studies in BRCA1/2 carriers (OR: 0.80; p = 0.147). Significantly increased risk of breast cancer was only shown on a subset of cohort studies in BRCA1 mutation carriers (OR: 1.48; 95% CI: 1.14-1.92). In conclusion, meta-analysis confirmed significantly decreased ovarian cancer risk in BRCA1/2 mutation carriers associated with the use of COCs comparable to the relative extent shown in the general population. Data on the risk of breast cancer associated with COC use in BRCA mutation carriers are heterogeneous and results are inconsistent. COCs can be considered as an alternative strategy in the chemoprevention of ovarian cancer in BRCA1 mutation carriers who do not accept prophylactic salpingo-oophorectomy above the age of 30 years.

PMID: 21916573  [PubMed - indexed for MEDLINE]


BACKGROUND: Testing has been advocated for all persons with newly diagnosed colorectal cancer to identify families with the Lynch syndrome, an autosomal dominant cancer-predisposition syndrome that is a paradigm for personalized medicine.

OBJECTIVE: To estimate the effectiveness and cost-effectiveness of strategies to identify the Lynch syndrome, with attention to sex, age at screening, and differential effects for probands and relatives.

DESIGN: Markov model that incorporated risk for colorectal, endometrial, and ovarian cancers.

DATA SOURCES: Published literature.

TARGET POPULATION: All persons with newly diagnosed colorectal cancer and their relatives.

TIME HORIZON: Lifetime.

PERSPECTIVE: Third-party payer.

INTERVENTION: Strategies based on clinical criteria, prediction algorithms, tumor testing, or up-front germline mutation testing, followed by tailored screening and risk-reducing surgery.

OUTCOME MEASURES: Life-years, cancer cases and deaths, costs, and incremental cost-effectiveness ratios.

RESULTS OF BASE-CASE ANALYSIS: The benefit of all strategies accrued primarily to relatives with a mutation associated with the Lynch syndrome, particularly women, whose life expectancy could increase by approximately 4 years with hysterectomy and salpingo-oophorectomy and adherence to colorectal cancer screening recommendations. At current rates of germline testing, screening, and prophylactic surgery, the strategies reduced deaths from colorectal cancer by 7% to 42% and deaths from endometrial and ovarian cancer by 1% to 6%. Among tumor-testing strategies, immunohistochemistry followed by BRAF mutation testing was preferred, with an incremental cost-effectiveness ratio of $36,200 per life-year gained.

RESULTS OF SENSITIVITY ANALYSIS: The number of relatives tested per proband was a critical determinant of both effectiveness and cost-effectiveness, with testing of 3 to 4 relatives required for most strategies to meet a threshold of $50,000 per life-year gained. Immunohistochemistry followed by BRAF mutation testing was preferred in 59% of iterations in probabilistic sensitivity analysis at a threshold of $100,000 per life-year gained. Screening for the Lynch syndrome with immunohistochemistry followed by BRAF mutation testing only up to age 70 years cost $44,000 per incremental life-year gained compared with screening only up to age 60 years, and screening without an upper age limit cost $88,700 per incremental life-year gained compared with screening only up to age 70 years.

LIMITATION: Other types of cancer, uncertain family pedigrees, and genetic variants of unknown significance were not considered.

CONCLUSION: Widespread colorectal tumor testing to identify families with the Lynch syndrome could yield substantial benefits at acceptable costs, particularly for women with a mutation associated with the Lynch syndrome who begin regular
screening and have risk-reducing surgery. The cost-effectiveness of such testing depends on the participation rate among relatives at risk for the Lynch syndrome.

PRIMARY FUNDING SOURCE: National Institutes of Health.

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Outcome of risk-reducing salpingo-oophorectomy in BRCA carriers and women of unknown mutation status.


Author information:
(1)Department of Gynaecological Oncology, EGA Institute for Women's Health, UCL, London, UK.

OBJECTIVE: To compare surgical outcomes and occult cancer rates at risk-reducing salpingo-oophorectomy in BRCA carriers and high-risk women who had not undergone genetic testing.

DESIGN: Prospective cohort study.

SETTING: Tertiary high-risk familial gynaecological cancer clinic.


METHODS: Women at high-risk of ovarian/tubal cancer were identified on the basis of the inclusion criteria for the UK Familial Ovarian Cancer Screening Study. Risk management options discussed with 1456 high-risk women included risk-reducing salpingo-oophorectomy. A strict histopathological protocol with serial slicing was used to assess tubes and ovaries.

RESULTS: In total, 308 high-risk women (191 with unknown mutation status; 117 known BRCA1/BRCA2 carriers) chose risk-reducing surgery; 94.5% of procedures were performed laparoscopically. The surgical complication rate was 3.9% (95% CI 2.0-6.7). Four ovarian and ten tubal occult invasive/in situ cancers were found. The overall occult invasive cancer rate was 5.1% (95% CI 1.9-10.83) in BRCA1/BRCA2 carriers and 1.05% (95% CI 0.13-3.73) in untested women. When tubal in situ cancers were included, the overall rate was 4.55% (95% CI 2.5-7.5). Two untested women with tubal carcinoma in situ were subsequently found to be BRCA carriers. The median ages of BRCA carriers (58 years; IQR 13.4 years) and untested women (49.5 years; IQR 20.6 years) with occult invasive/in situ cancer were not significantly different (P = 0.454).

CONCLUSIONS: Both high-risk women of unknown mutation status and BRCA carriers have a significant (although higher in the latter group) rate of occult invasive/in situ tubal/ovarian cancer, with a similar age distribution at detection. The data has important implications for counselling high-risk women on the likelihood of occult malignancy and perioperative complications at risk-reducing salpingo-oophorectomy. Women with occult disease should be offered genetic testing.

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Lynch syndrome.

Backes FJ(1), Cohn DE.

Author information:
(1)Division of Gynecologic Oncology, Department of Obstetrics and Gynecology, The Ohio State University College of Medicine, Columbus, Ohio 43204, USA.

Almost 100 years ago Lynch syndrome was discovered by Dr Aldred Warthin. Initially, the syndrome was named Hereditary Nonpolyposis Colorectal Cancer as colorectal cancer seemed most prevalent. Over time uterine cancer and several other malignancies were recognized as part of the spectrum. This autosomal-dominant inherited cancer syndrome is characterized by a defect in mismatch repair genes and puts patients at a significantly increased risk for colorectal and uterine cancer. Recognition and diagnosis of Lynch syndrome is extremely important so that appropriate screening programs and/or risk-reducing surgery can be initiated to prevent development or promote early detection of cancers.

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Radical fimbriectomy: a reasonable temporary risk-reducing surgery for selected women with a germ line mutation of BRCA 1 or 2 genes? Rationale and preliminary development.

Leblanc E(1), Narducci F, Farre I, Peyrat JP, Taieb S, Adenis C, Vennin P.

Author information:
(1)Department of Gynecologic Oncology, Centre Oscar Lambret, Lille, France. e-leblanc@o-lambret.fr

OBJECTIVE: Bilateral salpingo-oophorectomy (BSO) is the gold standard prophylactic surgery for BRCA1 or 2 mutation carriers. However, due to the resulting early menopause and fertility desires, young women are reluctant to undergo this procedure. In view of the recent literature on ovarian carcinogenesis, we wish to report a novel conceptual surgical procedure we called "radical fimbriectomy." This procedure is aimed to protect this subset of high-risk women from high-grade serous pelvic carcinoma, while preserving their ovarian function.

METHODS: Women with BRCA mutation, who were scheduled for BSO, were informed of the procedure approved by our local review board. Radical fimbriectomy consists of removing all the tube and the fimbrio-ovarian junction, step immediately followed in this developmental phase by completion oophorectomy. Four methods of partial ovarian transsection were prospectively compared: sharp division, stapler, bipolar division and harmonic scalpel. Surgical safety and pathological alterations were assessed. All specimens underwent extensive pathological evaluation using both SEE-FIM protocol and serial sections.

RESULTS: Fourteen women were enrolled in the study. Sharp and EndoGIA® appeared to be the safest methods of ovarian resection providing the best specimen quality for pathological examination.
CONCLUSION: We believe this technique could be suggested to young mutation carriers reluctant to undergo BSO. This approach is preferable to no prophylactic surgery at all. However, until the safety and validity of this procedure is confirmed by a multi-institutional study, women who undergo radical fimbriectomy should continue to receive regular multimodal evaluation and be advised of the risks involved until they finally accept secondary castration.

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Preserving the self: the process of decision making about hereditary breast cancer and ovarian cancer risk reduction.

Howard AF(1), Balneaves LG, Bottorff JL, Rodney P.

Author information:
(1)School of Population and Public Health, University of British Columbia, Vancouver, Canada. fuchsiahoward@mac.com

Women who carry BRCA1 or BRCA2 (BRCA1/2) gene mutations have up to an 88% lifetime risk of breast cancer and up to a 65% lifetime risk of ovarian cancer. Strategies to address these risks include cancer screening and risk-reducing surgery (i.e., mastectomy and salpingo-oophorectomy). We conducted a grounded theory study with 22 BRCA1/2 mutation-carrier women to understand how women make decisions about these risk-reducing strategies. Preserving the self was the overarching decision-making process evident in the participants' descriptions. This process was shaped by contextual conditions including the characteristics of health services, the nature of hereditary breast and ovarian cancer risk-reduction decisions, gendered roles, and the women's perceived proximity to cancer. The women engaged in five decision-making styles, and these were characterized by the use of specific decision-making approaches. These findings provide theoretical insights that could inform the provision of decisional support to BRCA1/2 carriers.

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Does bilateral salpingectomy with ovarian retention warrant consideration as a temporary bridge to risk-reducing bilateral oophorectomy in BRCA1/2 mutation carriers?

Greene MH(1), Mai PL, Schwartz PE.

Author information:
(1)Division of Cancer Epidemiology and Genetics, Clinical Genetics Branch, National Cancer Institute, Rockville, MD, USA.

Risk-reducing salpingo-oophorectomy (RRSO) is the most definitive surgical
intervention for ovarian cancer risk reduction among BRCA1/2 mutation carriers. For women who have completed child-bearing but who are not ready for RRSO, bilateral salpingectomy with ovarian retention (BSOR) might serve as a temporary measure while definitive risk-reducing surgery is being contemplated. Here we summarize recent insights into the pathogenesis of hereditary ovarian cancer that might provide a basis for consideration of the proposed BSOR management strategy and outline the evidence for and against this potential risk-reducing intervention. Based on the evidence, we suggest that there may be sufficient merit in this proposed intervention to consider evaluating it formally, perhaps through an intergroup-based clinical trial. In the meanwhile, we believe that BSOR should be considered an investigational risk management option of unproven clinical usefulness, particularly because delay in bilateral oophorectomy theoretically could reduce the protective effect against breast cancer that has been documented in women who have undergone RRSO.

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Association of risk-reducing surgery with cancer risks and mortality in BRCA mutation carriers.

Heemskerk-Gerritsen BA, Kriege M, Seynaeve C.

Comment on

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Uptake of breast cancer prevention and screening trials.

Evans DG(1), Harvie M, Bundred N, Howell A.

Author information:

(1)Genesis Prevention Centre, University Hospital of South Manchester NHS Trust, Manchester, UK. gareth.evans@cmft.nhs.uk

BACKGROUND: Uptake of cancer trials and in particular prevention trials has been disappointing globally.

METHODS: Uptake to three randomised chemotherapy breast cancer prevention trials and two dietary prevention trials in women at increased familial risk were assessed and compared with uptake of screening trials across a range of risk categories.

RESULTS: Uptake of drug prevention trials remains low at 5.3-13.6%, but is significantly higher in the high (12%) compared to very high risk group (8.4%) for IBIS1 and IBIS2 combined (p=0.004). Recruitment to two dietary prevention studies via mail shot was also disappointingly low at 6.2% and 12.5%. In contrast, uptake to two mammography screening trials was >90% in all risk categories.
CONCLUSIONS: More work must be done to improve recruitment to prevention trials if they are to be seen as viable alternatives to risk reducing surgery. IMPACT: Trial designs and decision aids need to be developed to improve recruitment.

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Risk-reducing strategies for women carrying BRCA1/2 mutations with a focus on prophylactic surgery.

Salhab M(1), Bismohun S, Mokbel K.

Author information:
(1)London Breast Institute, The Princess Grace Hospital, 45 Nottingham Place, London W1U 5NY, UK.

BACKGROUND: Women who have inherited mutations in the BRCA1 or BRCA2 genes have substantially elevated risks of breast and ovarian cancer. Mutation carriers have various options, including extensive and regular surveillance, chemoprevention and risk-reducing surgery. The aim of this review is to provide an up-to-date analysis and to subsequently summarise the available literature in relation to risk-reducing strategies, with a keen focus on prophylactic surgery.

METHODS: The literature review is facilitated by Medline and PubMed databases. The cross-referencing of the obtained articles was used to identify other relevant studies.

RESULTS: Prophylactic surgery (bilateral mastectomy, bilateral salpingo-oophorectomy or a combination of both procedures) has proved to be the most effective risk-reducing strategy. There are no randomised controlled trials able to demonstrate the potential benefits or harms of prophylactic surgery; therefore, the evidence has been derived from retrospective and short follow-up prospective studies, in addition to hypothetical mathematical models. Based on the current knowledge, it is reasonable to recommend prophylactic oophorectomy for BRCA1 or BRCA2 mutation carriers when childbearing is completed in order to reduce the risk of developing breast and ovarian cancer. In addition, women should be offered the options of rigorous breast surveillance, chemoprevention with anti-oestrogens—especially for carriers of BRCA2—or bilateral prophylactic mastectomy.

CONCLUSION: The selection of the most appropriate risk-reducing strategy is not a straightforward task. The impact of risk-reducing strategies on cancer risk, survival, and overall quality of life are the key criteria considered for decision-making. Notably, various other factors should be taken into consideration when evaluating individual mutation carriers' individual circumstances, namely woman's age, morbidity, type of mutation, and individual preferences and expectations. Although prospective randomised controlled trials concerned with examining the various interventions in relation to the woman's age and type of mutation are needed, randomisation is extremely difficult and rather deemed unethical given the current available evidence from retrospective studies.

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