International Journal of Gynecology and Obstetrics 124 (2014) 189–192

Contents lists available at ScienceDirect

International Journal of Gynecology and Obstetrics

journal homepage: www.elsevier.com/locate/ijgo

FIGO GUIDELINES

Hereditary gynecologic cancers ☆

David Mutch *, Lynette Denny, Michael Quinn; for the FIGO Committee on Gynecologic Oncology [1]

ARTICLE INFO

Keywords:
BRCA1 and *BRCA2*
Breast cancer
Genetic risk assessment
Germline mutations
Intensified early cancer detection
Ovarian cancer
Prophylactic surgery
Screening and prevention

1. Introduction

The present document has been developed by the FIGO Committee on Gynecologic Oncology to aid in the recognition of, and counseling and testing for inherited gynecologic cancers. Extensive consultation was conducted with the Committee and the FIGO Executive Board. This represents a consensus statement.

In the early 1990s, the molecular etiology of several hereditary cancers was established. The identification of specific genes associated with some cancers has allowed clinicians to more accurately assess hereditary cancer risk and establish screening and preventive interventions. Two of the best examples of this scientific discovery and increased awareness regarding gynecologic cancers are the discovery of the *BRCA1* and *BRCA2* genes and the identification of the molecular basis of the Lynch family cancer syndrome. The following paragraphs address the diagnostic, screening, and treatment issues associated with these syndromes.

2. Hereditary breast and ovarian cancer syndrome

Germline mutations in *BRCA1* and *BRCA2* account for the majority of families with hereditary breast and ovarian cancer syndrome. Although the reported incidence varies widely, approximately 10% of cases of ovarian cancer and 3%–5% of cases of breast cancer are due to mutations in the *BRCA1* or *BRCA2* genes [1–6]. However, a recent Australian study reported an overall incidence of 14% in over 1000 ovarian cancers screened and an incidence of almost 23% in high-grade serous cancers in the patient population [7]. In the general population, it is estimated that approximately 1 in 300 to 1 in 800 individuals carry a mutation in *BRCA1* or *BRCA2* [8]. A woman with a *BRCA1* mutation has a 39%–46% risk of developing ovarian cancer, while a woman with a *BRCA2* mutation has a 12%–27% risk. Furthermore, the estimated lifetime risk of breast cancer with a *BRCA1* or *BRCA2* mutation can be as high as 65%–74% [9–12]. For women with breast cancer, the 10-year actuarial risk of developing a subsequent ovarian cancer is 12.7% for *BRCA1* mutation carriers and 6.8% for *BRCA2* mutation carriers [13].

Ovarian cancers associated with *BRCA1* and *BRCA2* mutations have a distinct histologic phenotype. This type of cancer is predominantly of serous or endometrioid histology and is high grade. Mucinous and borderline ovarian cancers do not appear to be part of the tumor spectrum [14,15]. Primary fallopian tube cancer and primary peritoneal cancer are also part of the spectrum of disease associated with mutations in these genes [16,17].

Tailored screening and prevention strategies can reduce morbidity and mortality from breast and ovarian cancer, making it important to identify individuals at risk. Clinical criteria have been developed to assess patients with at least a 20%–25% chance of having an inherited predisposition to breast or ovarian cancer (Box 1). It is these patients for whom genetic risk assessment is strongly recommended. A second set of criteria is designed for those patients with greater than a 5%–10% chance of having an inherited predisposition to breast and ovarian cancer and for whom genetic risk assessment may be helpful [18] (Box 2). It should be noted, however, that these recommendations are not universal and this distinction is not made in a number of settings—in particular, in Germany and Australia.

More recent data indicate that, in the setting of a diagnosis of high-grade serous ovarian cancer, primary peritoneal cancer, or fallopian tube cancer, between 16% and 22% of unselected patients with a family history of these diseases will have a *BRCA1* or *BRCA2* mutation, while only 9% of patients without a family history of either breast or ovarian cancer will have a germline *BRCA1* or *BRCA2* mutation [7,19]. Given this prevalence of mutations, it is reasonable to consider hereditary risk assessment in any patient with high-grade serous ovarian cancer, primary peritoneal cancer, or fallopian tube cancer, especially if the results of such assessment could potentially have an impact on other family members. Testing for *BRCA1* mutations should also include women with triple-negative breast cancer. A recent meta-analysis of 12 studies found that the relative risk of *BRCA1* mutation in women with triple-negative breast cancer was 5.65 (95% confidence interval

☆ These guidelines were approved by the FIGO Executive Board on November 11, 2013.

* Corresponding author at: Division of Gynecologic Oncology, 4911 Barnes Jewish Hospital Plaza, Washington University School of Medicine, St Louis, MO 63110, USA. Tel.: +1 314 362 3181; fax: +1 314 362 2893.
E-mail address: mutchd@wudosis.wustl.edu (D. Mutch).

[1] Committee members: H. Belhadj (Switzerland), J. Berek (USA), A. Bermudez (Argentina), N. Bhatla (India), J. Cain (USA), L. Denny (Chair; South Africa), K. Fujiwara (Japan), N. Hacker (Australia), E. Åvall-Lundqvist (Sweden), D. Mutch (USA), F. Odicino (Italy), S. Pecorelli (Italy), J. Prat (Spain), M. Quinn (Co-chair; Australia), M.A-F. Seoud (Lebanon), S.K. Shrivastava (India).

http://dx.doi.org/10.1016/j.ijgo.2013.12.001

Box 1
Criteria for genetic risk assessment for hereditary breast and ovarian cancer (>20%–25% chance of inherited predisposition).

Patients with greater than a 20%–25% chance of having an inherited predisposition to breast and ovarian cancer and for whom genetic risk assessment is recommended:

- Women with a personal history of both breast cancer and ovarian cancer [a].
- Women with ovarian cancer and a first-degree relative with ovarian cancer or premenopausal breast cancer, or both.
- Women with breast cancer at age 50 years or younger and a close relative with ovarian cancer [a] or male breast cancer at any age.
- Women of Ashkenazi Jewish ancestry with ovarian cancer.
- Women of Ashkenazi Jewish ancestry in whom breast cancer was diagnosed at age 40 years or younger.
- Any woman with high-grade serous ovarian, primary peritoneal, or fallopian tube cancer.
- Women with a close relative with a known *BRCA1* or *BRCA2* mutation.
- Women with a family history indicative of Lynch syndrome (hereditary nonpolyposis colon cancer) such as colon cancer—particularly if diagnosed before the age of 50 years—or endometrial, ovarian, gastric, or renal tract cancers.

[a]Cancer of the peritoneum and fallopian tubes should be considered as part of the spectrum of hereditary breast and ovarian cancer syndrome.

[CI], 4.15–7.69), which was significantly higher than in women without triple-negative breast cancer [20]. Other criteria for testing are shown in Boxes 1 and 2.

Box 2
Criteria for genetic risk assessment for hereditary breast and ovarian cancer (>5%–10% chance of inherited predisposition).

Patients with greater than a 5%–10% chance of having an inherited predisposition to breast and ovarian cancer and for whom genetic risk assessment should be strongly considered:

- Women with breast cancer at age 40 years or younger.
- Women with ovarian cancer, primary peritoneal cancer, or fallopian tube cancer of high-grade serous histology at any age.
- Women with bilateral breast cancer (particularly if the first case of breast cancer was diagnosed at age 50 years or younger).
- Women with breast cancer at age 50 years or younger and a close relative with breast cancer at age 50 years or younger.
- Women of Ashkenazi Jewish ancestry with breast cancer at age 50 years or younger.
- Women with breast cancer at any age and 2 or more close relatives with breast cancer at any age (particularly if at least 1 case of breast cancer was diagnosed at age 50 years or younger).
- Unaffected women with a close relative who meets one of the previous criteria.
- Women with triple-negative breast cancer (ER/PR negative, HER2 negative).

Women with *BRCA1* or *BRCA2* mutations should be offered risk-reducing salpingo-oophorectomy (RRSO) by age 35 years or when childbearing is complete [21,22]. Some countries recommend surgery at age 40 years or at an age 5 years younger than the youngest affected family member [23]. For bilateral RRSO, all tissue from the ovaries and fallopian tubes should be removed. Thorough visualization of the peritoneal surfaces with pelvic washings should be performed. Complete pathologic assessment that includes serial sectioning of the ovaries and fallopian tubes—at no more than 3-mm intervals—is necessary, with microscopic examination for occult cancer. Patients should also be counseled that they have a 2%–5% chance of having an occult cancer and a small residual risk of primary peritoneal cancer following RRSO.

2.1. Other risk reduction strategies

Combined oral contraceptives (COCs) may reduce the risk of ovarian cancer in women averse to risk-reduction surgery. In a case–control study of 670 women with *BRCA1* mutations and 128 with *BRCA2* mutations (including 1 patient with both), COC use reduced the risk of ovarian cancer in carriers of *BRCA1* mutations (odds ratio [OR] 0.56 [95% CI, 0.45–0.71]; $P < 0.0001$) and carriers of *BRCA2* mutations (OR 0.39 [95% CI, 0.23–0.66]; $P = 0.0004$) [24]. Similar findings were reported by Cibula et al. [25], who performed a meta-analysis on 3 case–control studies and showed a significant risk reduction for ovarian cancer in *BRCA1* and *BRCA2* mutation carriers with any past COC use and a significant trend by duration of COC use. For women with *BRCA* mutations, other strategies include CA-125 surveillance and transvaginal ultrasound; however, this approach does not enable detection of cancer at an early, curable stage and is not recommended [26–28]. Tamoxifen use in mutation carriers with breast cancer has been shown to reduce the risk of cancer in the contralateral breast by up to 53% but there are no published data on tamoxifen use and reduction in the incidence of ovarian cancer.

In 2007, Crum et al. [29] suggested that a subset of high-grade serous ovarian cancers arises from the distal fallopian tube, and coined the term tubal intraepithelial neoplasia (TIC). However, the etiologic significance of TIC in pelvic serous carcinoma is not yet known. Defining this is important because it may provide an additional means for risk-reducing surgery for pelvic serous carcinomas, particularly in women who carry *BRCA* mutations [30,31]. In fact, some have suggested routine removal of fallopian tubes during hysterectomy, even for benign disease, when childbearing is complete. Until more data become available, this approach should not be recommended as a routine.

3. Lynch syndrome

Lynch syndrome (or hereditary nonpolyposis colorectal cancer [HNPCC]) is caused by mutations in DNA mismatch repair genes (*MLH1*, *MSH2*, *PMS2*, or *MSH6*) [32]. For patients with HNPCC, the risks of developing endometrial and ovarian cancer by age 70 years are approximately 42%–60% and 9%–12%, respectively [33,34]. Women with HNPCC also have a 40%–60% lifetime risk of colorectal cancer. Genetic risk assessment for these hereditary cancer syndromes enables physicians to provide individualized and quantified assessment of risk, as well as options for tailored screening and prevention strategies that may reduce morbidity from these hereditary processes (Box 3). Strategies that may improve outcomes in individuals at inherited risk include colorectal cancer screening with colonoscopy [35] and risk-reducing surgery [36–40].

Hysterectomy with removal of both fallopian tubes and ovaries in women considered to be at high risk for ovarian cancer due to confirmed Lynch syndrome is associated with a decreased risk of developing endometrial and ovarian cancer and should be strongly considered when childbearing is complete.

Box 3
Recommendations regarding counseling and testing for Lynch syndrome (HNPCC).

Patients with greater than a 20%–25% chance of having an inherited predisposition to endometrial, colorectal, and related cancers and for whom genetic risk assessment is recommended:

- Patients with endometrial or colorectal cancer who meet the revised Amsterdam criteria, as listed below:
  - At least 3 relatives with a Lynch/HNPCC-associated cancer (colorectal cancer or cancer of the endometrium, small bowel, ureter, or renal pelvis) in 1 lineage.
  - One affected individual should be a first-degree relative of the other 2.
  - At least 2 successive generations should be affected.
  - At least 1 HNPCC-associated cancer should be diagnosed before age 50 years.
- Patients with synchronous or metachronous endometrial and colorectal cancer, with the first cancer diagnosed prior to age 50 years.
- Patients with synchronous or metachronous ovarian and colorectal cancer, with the first cancer diagnosed prior to age 50 years.
- Patients with colorectal or endometrial cancer with evidence of a mismatch repair defect (i.e. MSI or immunohistochemical loss of expression of *MLH1*, *MSH2*, *MSH6*, or *PMS2*).
- Patients with a first- or second-degree relative with a known mismatch repair defect.

Abbreviations: HNPCC, hereditary nonpolyposis colorectal cancer; MSI, microsatellite instability.

4. General testing and counseling guidelines

It is important to emphasize that hereditary cancer risk assessment is a process that:

- Includes risk assessment, education, and counseling;
- Is conducted by a physician, genetic counselor, or other provider with expertise in cancer genetics;
- May include genetic testing if desired after appropriate counseling and after consent has been obtained.

Genetic testing for cancer predisposition requires informed consent that should include pre-test education and counseling concerning the risks, benefits, and limitations of testing, including the implications of both positive and negative genetic test results. Pre-test counseling should also include education on the limitations of current genetic testing technology, including the risks of false-negative results, as well as the uncertainties associated with genetic variants of unknown clinical significance. Individuals considering genetic testing should be aware that the potential risks of such testing include psychological stress and changes to family dynamics.

Risks may also include the potential for discrimination in health insurance or employment but there is little evidence that this has actually occurred to date [41,42].

Other factors that should be taken into account when counseling women include discussion regarding the management of menopausal symptoms and the use of hormone replacement therapy (HRT). Surgically induced menopause is often associated with more significant vasomotor symptoms compared with natural menopause. Hormone replacement therapy appears to be effective in managing the symptoms of surgically induced menopause. In addition, there does not seem to be an increased risk of breast cancer in women who carry a *BRCA* mutation and who use HRT after RRSO performed before the age of 50 years compared with those who do not take HRT [43]. Women with a previous history of ER-positive breast cancer due to *BRCA* mutation should generally not be offered HRT after RRSO. Primary peritoneal cancer may still occur in women who have undergone risk-reducing surgery.

Other inherited mutations can affect cancer risk in the female genital tract:

- Peutz–Jeghers syndrome, which is characterized by pigmented lesions on the lips/buccal mucosa and multiple gastrointestinal polyps due to *STK11* mutation. Peutz–Jeghers syndrome is associated with ovarian sex cord-stromal tumors, adenoma malignum (minimal deviation adenocarcinoma), and lobular endocervical glandular hyperplasia.
- Cowden syndrome is characterized by the development of multiple hamartomas, distinctive dermatopathologic manifestations, and a predisposition toward various malignancies due to *PTEN* mutation, particularly endometrial cancer.
- Li–Fraumeni syndrome is characterized by a high frequency of multiple primary tumors, especially soft-tissue sarcoma. The syndrome is linked to germline mutations of the *TP53* tumor suppressor gene and also increases the risk of breast cancer.

5. Summary points

- Cancer is a genetic disease that is either inherited or somatic.
- Mutations in *BRCA1*, *BRCA2*, and mismatch repair genes (Lynch syndrome) can be identified by genetic testing [18] (Boxes 1 and 2).
- Genetic counseling is important for patients with suspected inherited risk and should be recommended before testing.
- Once a mutation is identified, the patient should be counseled regarding risk-reducing surgery, other risk-reduction strategies, and altered screening.
- Inherited cancer risk affects other family members, and counseling with testing should be recommended for other family members who are at risk.

Conflict of interest

L.D. and N.B. have received honoraria for appearing on various speaker forums about HPV vaccination and have received research support from GlaxoSmithKline and MSD/Merck for HPV-related research. The other Committee members have no conflicts of interest.

References

[1] Robson ME, Boyd J, Borgen PI, Cody III HS. Hereditary breast cancer. Curr Probl Surg 2001;38(6):387–480.
[2] Risch HA, McLaughlin JR, Cole DE, Rosen B, Bradley L, Fan I, et al. Population BRCA1 and BRCA2 mutation frequencies and cancer penetrances: a kin-cohort study in Ontario, Canada. J Natl Cancer Inst 2006;98(23):1694–706.
[3] Rubin SC, Blackwood MA, Bandera C, Behbakht K, Benjamin I, Rebbeck TR, et al. BRCA1, BRCA2, and hereditary nonpolyposis colorectal cancer gene mutations in an unselected ovarian cancer population: relationship to family history and implications for genetic testing. Am J Obstet Gynecol 1998;178(4):670–7.
[4] Garber JE, Offit K. Hereditary cancer predisposition syndromes. J Clin Oncol 2005;23(2):276–92.
[5] Karlan BY, Berchuck A, Mutch D. The role of genetic testing for cancer susceptibility in gynecologic practice. Obstet Gynecol 2007;110(1):155–67.
[6] Wooster R, Weber BL. Breast and ovarian cancer. N Engl J Med 2003;348(23):2339–47.
[7] Alsop K, Fereday S, Meldrum C, deFazio A, Emmanuel C, George J, et al. BRCA mutation frequency and patterns of treatment response in BRCA mutation-positive women with ovarian cancer: a report from the Australian Ovarian Cancer Study Group. J Clin Oncol 2012;30(21):2654–63.
[8] Whittemore AS, Gong G, Itnyre J. Prevalence and contribution of BRCA1 mutations in breast cancer and ovarian cancer: results from three U.S. population-based case-control studies of ovarian cancer. Am J Hum Genet 1997;60(3):496–504.
[9] Struewing JP, Hartge P, Wacholder S, Baker SM, Berlin M, McAdams M, et al. The risk of cancer associated with specific mutations of BRCA1 and BRCA2 among Ashkenazi Jews. N Engl J Med 1997;336(20):1401–8.
[10] Roa BB, Boyd AA, Volcik K, Richards CS. Ashkenazi Jewish population frequencies for common mutations in BRCA1 and BRCA2. Nat Genet 1996;14(2):185–7.
[11] Antoniou A, Pharoah PD, Narod S, Risch HA, Eyfjord JE, Hopper JL, et al. Average risks of breast and ovarian cancer associated with BRCA1 or BRCA2 mutations detected in

case Series unselected for family history: a combined analysis of 22 studies. Am J Hum Genet 2003;72(5):1117–30.
[12] King MC, Marks JH, Mandell JB. New York Breast Cancer Study Group. Breast and ovarian cancer risks due to inherited mutations in BRCA1 and BRCA2. Science 2003;302(5645):643–6.
[13] Metcalfe KA, Lynch HT, Ghadirian P, Tung N, Olivotto IA, Foulkes WD, et al. The risk of ovarian cancer after breast cancer in BRCA1 and BRCA2 carriers. Gynecol Oncol 2005;96(1):222–6.
[14] Boyd J, Sonoda Y, Federici MG, Bogomolniy F, Rhei E, Maresco DL, et al. Clinicopathologic features of BRCA-linked and sporadic ovarian cancer. JAMA 2000;283(17):2260–5.
[15] Lakhani SR, Manek S, Penault-Llorca F, Flanagan A, Arnout L, Merrett S, et al. Pathology of ovarian cancers in BRCA1 and BRCA2 carriers. Clin Cancer Res 2004;10(7):2473–81.
[16] Berchuck A, Heron KA, Carney ME, Lancaster JM, Fraser EG, Vinson VL, et al. Frequency of germline and somatic BRCA1 mutations in ovarian cancer. Clin Cancer Res 1998;4(10):2433–7.
[17] Levine DA, Argenta PA, Yee CJ, Marshall DS, Olvera N, Bogomolniy F, et al. Fallopian tube and primary peritoneal carcinomas associated with BRCA mutations. J Clin Oncol 2003;21(22):4222–7.
[18] Comprehensive Cancer Network National. Genetic/familial high-risk assessment: breast and ovarian. NCCN Clinical Practice Guidelines in Oncology. V.4.2013. http://www.nccn.org/professionals/physician_gls/PDF/genetics_screening.pdf . Published 2013. Retrieved April 2013.
[19] Risch HA, McLaughlin JR, Cole DE, Rosen B, Bradley L, Kwan E, et al. Prevalence and penetrance of germline BRCA1 and BRCA2 mutations in a population series of 649 women with ovarian cancer. Am J Hum Genet 2001;68(3):700–10.
[20] Tun N, Villani G, Ong K, Yoe L, Bo Z. Risk of having BRCA1 mutation in high-risk women with triple-negative breast cancer: a meta-analysis. Clin Genet 2013 (in press).
[21] Finch A, Beiner M, Lubinski J, Lynch HT, Moller P, Rosen B, et al. Salpingo-oophorectomy and the risk of ovarian, fallopian tube, and peritoneal cancers in women with a BRCA1 or BRCA2 Mutation. JAMA 2006;296(2):185–92.
[22] Domchek SM, Friebel TM, Singer CF, Evans DG, Lynch HT, Isaacs C, et al. Association of risk-reducing surgery in BRCA1 or BRCA2 mutation carriers with cancer risk and mortality. JAMA 2010;304(9):967–75.
[23] Meindl A, Ditsch N, Kast K, Rhiem K, Schmutzler RK. Hereditary breast and ovarian cancer: new genes, new treatments, new concepts. Dtsch Arztebl Int 2011;108(19):323–30.
[24] McLaughlin JR, Risch HA, Lubinski J, Moller P, Ghadirian P, Lynch H, et al. Reproductive risk factors for ovarian cancer in carriers of BRCA1 or BRCA2 mutations: a case-control study. Lancet Oncol 2007;8(1):26–34.
[25] Cibula D, Zikan M, Dusek L, Majek O. Oral contraceptives and risk of ovarian and breast cancers in BRCA mutation carriers: a meta-analysis. Expert Rev Anticancer Ther 2011;11(8):1197–207.
[26] Stirling D, Evans DG, Pichert G, Shenton A, Kirk EN, Rimmer S, et al. Screening for familial ovarian cancer: failure of current protocols to detect ovarian cancer at an early stage according to the International Federation of Gynecology and Obstetrics system. J Clin Oncol 2005;23(24):5588–96.
[27] Oei AL, Massuger LF, Bulten J, Ligtenberg MJ, Hoogerbrugge N, de Hullu JA. Surveillance of women at high risk for hereditary ovarian cancer is inefficient. Br J Cancer 2006;94(6):814–9.
[28] Olivier RI, Lubsen-Brandsma MA, Verhoef S, van Beurden M. CA125 and transvaginal ultrasound monitoring in high-risk women cannot prevent the diagnosis of advanced ovarian cancer. Gynecol Oncol 2006;100(1):20–6.
[29] Crum CP, Drapkin R, Miron A, Ince TA, Muto M, Kindelberger DW, et al. The distal fallopian tube: a new model for pelvic serous carcinogenesis. Curr Opin Obstet Gynecol 2007;19(1):3–9.
[30] Kurman RJ, Shih IeM. The origin and pathogenesis of epithelial ovarian cancer: a proposed unifying theory. Am J Surg Pathol 2010;34(3):433–43.
[31] Levanon K, Crum C, Drapkin R. New insights into the pathogenesis of serous ovarian cancer and its clinical impact. J Clin Oncol 2008;26(32):5284–93.
[32] Vasen HF, Watson P, Mecklin JP, Lynch HT. New clinical criteria for hereditary nonpolyposis colorectal cancer (HNPCC, Lynch syndrome) proposed by the International Collaborative group on HNPCC. Gastroenterology 1999;116(6):1453–6.
[33] Win AK, Young JP, Lindor NM, Tucker KM, Ahnen DJ, Young GP, et al. Colorectal and other cancer risks for carriers and noncarriers from families with a DNA mismatch repair gene mutation: a prospective cohort study. J Clin Oncol 2012;30(9):958–64.
[34] Aarnio M, Sankila R, Pukkala E, Salovaara R, Aaltonen LA, de la Chapelle A, et al. Cancer risk in mutation carriers of DNA-mismatch-repair genes. Int J Cancer 1999;81(2):214–8.
[35] Järvinen HJ, Aarnio M, Mustonen H, Aktan-Collan K, Aaltonen LA, Peltomäki P, et al. Controlled 15-year trial on screening for colorectal cancer in families with hereditary nonpolyposis colorectal cancer. Gastroenterology 2000;118(5):829–34.
[36] Kwon JS, Tinker A, Pansegrau G, McAlpine J, Housty M, McCullum M, et al. Prophylactic salpingectomy and delayed oophorectomy as an alternative for BRCA mutation carriers. Obstet Gynecol 2013;121(1):14–24.
[37] Kauff ND, Satagopan JM, Robson ME, Scheuer L, Hensley M, Hudis CA, et al. Risk-reducing salpingo-oophorectomy in women with a BRCA1 or BRCA2 mutation. N Engl J Med 2002;346(21):1609–15.
[38] Rebbeck TR, Lynch HT, Neuhausen SL, Narod SA, Van't Veer L, Garber JE, et al. Prophylactic oophorectomy in carriers of BRCA1 or BRCA2 mutations. N Engl J Med 2002;346(21):1616–22.
[39] Schmeler KM, Lynch HT, Chen LM, Munsell MF, Soliman PT, Clark MB, et al. Prophylactic surgery to reduce the risk of gynecologic cancers in the Lynch syndrome. N Engl J Med 2006;354(3):261–9.
[40] Schmeler KM, Lu KH. Gynecologic cancers associated with Lynch syndrome/HNPCC. Clin Transl Oncol 2008;10(6):313–7.
[41] Hall MA, Rich SS. Laws restricting health insurers' use of genetic information: impact on genetic discrimination. Am J Hum Genet 2000;66(1):293–307.
[42] Armstrong K, Weber B, FitzGerald G, Hershey JC, Pauly MV, Lemaire J, et al. Life insurance and breast cancer risk assessment: adverse selection, genetic testing decisions, and discrimination. Am J Med Genet A 2003;120A(3):359–64.
[43] Rebbeck TR, Friebel T, Wagner T, Lynch HT, Garber JE, Daly MB, et al. Effect of short-term hormone replacement therapy on breast cancer risk reduction after bilateral prophylactic oophorectomy in BRCA1 and BRCA2 mutation carriers: the PROSE Study Group. J Clin Oncol 2005;23(31):7804–10.