University of Groningen

Managing hereditary ovarian cancer

Mourits, M. J.; de Bock, G. H.

Published in:
Maturitas

DOI:
[10.1016/j.maturitas.2009.09.009](https://doi.org/10.1016/j.maturitas.2009.09.009)

IMPORTANT NOTE: You are advised to consult the publisher's version (publisher's PDF) if you wish to cite from it. Please check the document version below.

Document Version
Publisher's PDF, also known as Version of record

Publication date:
2009

[Link to publication in University of Groningen/UMCG research database](#)

Citation for published version (APA):

Mourits, M. J., & de Bock, G. H. (2009). Managing hereditary ovarian cancer. *Maturitas*, 64(3), 172-176.
<https://doi.org/10.1016/j.maturitas.2009.09.009>

Copyright

Other than for strictly personal use, it is not permitted to download or to forward/distribute the text or part of it without the consent of the author(s) and/or copyright holder(s), unless the work is under an open content license (like Creative Commons).

The publication may also be distributed here under the terms of Article 25fa of the Dutch Copyright Act, indicated by the "Taverne" license. More information can be found on the University of Groningen website: <https://www.rug.nl/library/open-access/self-archiving-pure/taverne-amendment>.

Take-down policy

If you believe that this document breaches copyright please contact us providing details, and we will remove access to the work immediately and investigate your claim.

Downloaded from the University of Groningen/UMCG research database (Pure): <http://www.rug.nl/research/portal>. For technical reasons the number of authors shown on this cover page is limited to 10 maximum.

Review

Managing hereditary ovarian cancer

M.J. Mourits^{a,*}, G.H. de Bock^{b,*}^a Department of Gynaecologic Oncology, University Medical Center Groningen, University of Groningen, P.O. Box 30.001, 9700RB Groningen, The Netherlands^b Department of Epidemiology, University Medical Center Groningen, University of Groningen, P.O. Box 30.001, 9700RB Groningen, The Netherlands

ARTICLE INFO

Article history:

Received 3 July 2009

Received in revised form 1 September 2009

Accepted 1 September 2009

Keywords:

Hereditary cancer syndrome

Ovarian neoplasms

BRCA1 gene

BRCA2 gene

Bilateral salpingo-oophorectomy

Reproduction

ABSTRACT

In this review we present an overview of recent developments in the management of hereditary ovarian cancer. Until recently, intensive screening of the ovaries was recommended to mutation carriers and their first-degree female relatives. However, since screening is not effective in detecting early-stage ovarian cancer, women are counselled for a prophylactic bilateral salpingo-oophorectomy (pBSO) shortly after child-bearing age (>35 years). Many mutation carriers already choose to undergo pBSO to reduce their cancer risks; however, the age of prophylactic surgery may interfere with reproductive and other important (psychosexual) issues in life. Due to the protective effect of oral contraceptives regarding ovarian cancer, we advise women at increased risk of ovarian cancer to use oral contraceptive pills for 3–5 years early in life (<25 years of age), when the absolute incidence of breast cancer is extremely low. A transient increased relative risk of breast cancer due to oral contraceptives at this age will result in a negligible increased absolute number of breast cancers, while the risk reduction of ovarian cancer remains for life. Research should aim at finding new molecular markers and screening strategies for detecting early-stage ovarian cancer in women with a hereditary ovarian cancer trait.

© 2009 Elsevier Ireland Ltd. All rights reserved.

Contents

1. Introduction	173
2. Our patient and her clinical dilemmas	173
3. How to reduce the risk of (advanced) ovarian cancer	173
3.1. Transvaginal ultrasound (TVU)	173
3.2. Serum marker CA125 and other markers	173
3.3. Combining these screening tests into screening strategies	174
3.4. Early signs and symptoms?	174
3.5. Alternative screening strategies	174
3.6. Prophylactic bilateral salpingo-oophorectomy	174
3.7. Procedure of gynecological prophylactic surgery	175
4. Reproductive issues	175
4.1. Oral contraceptive pills	175
4.2. Worries about transmitting the mutation to children	175
5. Our patient	175
6. Conclusions	175
Conflict of interest	175
Provenance	175
References	175

* Corresponding authors.

E-mail addresses: m.j.e.mourits@og.umcg.nl (M.J. Mourits), g.h.de.boock@epi.umcg.nl (G.H. de Bock).¹ Both the authors worked on the manuscript on an equal base.

1. Introduction

At least 10% of ovarian carcinomas are associated with a highly penetrant, autosomal, dominant genetic predisposition [1]. Three clinical manifestations of hereditary ovarian cancer have been identified: site-specific ovarian cancer; hereditary breast and/or ovarian cancer (HBOC) mostly due to *BRCA1* and *BRCA2* gene mutations; and Lynch syndrome, formerly known as hereditary non-polyposis colorectal cancer (HNPCC) syndrome [2]. *BRCA* germ-line mutations account for more than 90% of all hereditary ovarian carcinomas, whereas most of the remaining 10% are caused by mutations in mismatch repair genes, *MLH1*, *MSH2*, *MSH6*, *PMS2*, which are susceptibility genes for Lynch syndrome [3,4].

An accurate estimation of the risk of ovarian cancer is crucial in counselling these women, since important decisions have to be made during an often crucial phase of life, the child-bearing years. Risk assessment and counselling are based on penetrance estimates of ovarian cancer at certain ages, which have been investigated by many studies worldwide. Unfortunately, those penetrance studies show varying results, due to the choice of the population studied and hence the cancer incidence. Estimates of the average penetrance up to 70 years of age are 40% (95% CI, 35–46%) for *BRCA1* and 18% (95% CI, 13–23%) for *BRCA2* mutation carriers [5]. In *BRCA* carriers, there is no influence of birth cohort on the risk of ovarian cancer. Estimates of ovarian cancer penetrance in Lynch syndrome depend on the type of the mutation and vary between 3% and 14%, compared with a 1.4% risk in the general population. In a retrospective cohort study, Watson and Lynch found a lifetime risk of ovarian cancer of 4–6% for *MLH1* and 8–12% for *MSH2* mutation carriers, with a significant risk difference associated with year of birth [6]: women born after 1946 carried twice the risk of ovarian cancer as women born before 1946. The highest risk period for ovarian cancer in *MLH1* and *MSH2* carriers was between 40 and 55 years of age [6].

In this overview we first present a fictitious case scenario of a patient with a germ-line mutation in a *BRCA1* gene and the clinical dilemmas she encounters. We then review the clinical considerations and related current management strategies and argue which is the preferred strategy. For more clinical considerations and current management strategies related to the decision to go for genetic testing and the reduction of breast and ovarian cancer risk, we refer readers to the recently published guideline of the American College of Obstetricians and Gynecologists (ACOG) [7].

2. Our patient and her clinical dilemmas

Our case scenario concerns a woman aged 32 years. She has one son (aged 4 years). She has a family history of breast and ovarian cancer. Her mother was diagnosed with ovarian cancer at the age of 60 and died at the age of 61. Her sister (aged 37) was diagnosed with breast cancer at the age of 33 and was offered genetic testing. She appears to be a *BRCA1* mutation carrier. No other cases of breast or ovarian cancer were reported in this (small) family.

There are several clinical dilemmas our patient wants to discuss with her doctor:

- Should I go for genetic testing and what are the consequences?
- How can I reduce the risk of breast cancer? What are the pros and cons of prophylactic surgery and breast cancer screening?
- How can I reduce the risk of ovarian cancer? What are the pros and cons of prophylactic bilateral salpingo-oophorectomy and ovarian cancer screening?
- Is it safe to have another child? What are the risks for my new baby and are there possibilities to reduce this risk?

Our patient decides to undergo genetic testing. If she proves to be a carrier, given the early age of onset of breast cancer in her sister, she wants to have a prophylactic mastectomy. She has not yet decided on whether to have another pregnancy or ovarian cancer risk reduction.

Genetic testing is performed and it appears that our patient also carries the *BRCA1* mutation. She decides to have a bilateral prophylactic mastectomy and reconstructive surgery. After that she visits the family cancer clinic to discuss how to manage her increased risk of ovarian cancer and her desire to have another child.

3. How to reduce the risk of (advanced) ovarian cancer

Women diagnosed with a *BRCA1/2* mutation are given several options to reduce their risk of dying of ovarian cancer. One is to choose screening, with the main objective of identifying ovarian cancer in an early-stage, to improve the prognosis and reduce morbidity and mortality. Available screening tests for ovarian cancer include bimanual pelvic examination, transvaginal ultrasound (TVU) and measurements of serum CA125.

3.1. Transvaginal ultrasound (TVU)

There are several criteria for the definition of an abnormal TVU to predict ovarian malignancy [8]. According to the Sassone criteria, in premenopausal women only simple cysts of more than 6 cm need further investigation [9]. The main limitation to the use of TVU as a screening tool is the high false-positive rate, especially in premenopausal women [10]. Due to frequent follicle cyst formation and persistent follicles in premenopausal ovaries, criteria for further investigation need to be described carefully and have a large effect on numbers needed to operate to find one ovarian cancer [11,12].

In postmenopausal women, the specificity of TVU is higher than in premenopausal women, due to the absence of follicle cyst formation [13,14]. However, even in postmenopausal women adnexal lesions are frequently found [15]. Altered blood vessel resistance in malignant compared to benign ovarian cysts visualized by Doppler imaging was hoped to improve the identification of malignant ovarian tumors in high-risk populations [16]. However, due to considerable overlap in the measurements of benign and malignant tumors, its role in ovarian cancer screening has not been firmly established [17].

3.2. Serum marker CA125 and other markers

CA125 is expressed by coelomic and Mullerian epithelia, but the surface epithelium of normal ovaries does not express CA125 [18]. The finding that CA125 is a serum marker for ovarian cancer gave the promise of a biomarker for the monitoring of (early) ovarian cancer [19]. However, as ovarian cancer presents late and spreads early, the sensitivity of serum CA125 is very low for the early detection of ovarian cancer, since only 25–50% of the women with a stage I ovarian tumor have an elevated serum CA125 level at the time of diagnosis [20]. In addition, especially in premenopausal women, an elevated CA125 level is not very specific for the diagnosis of ovarian cancer, as it can also be found in benign and physiological conditions, including menstruation, pregnancy, endometriosis, uterine leiomyomas, infectious disease, as well as in other malignancies [21,22]. The application of algorithms for calculating the risk of ovarian cancer algorithm in healthy postmenopausal women [23,24] as well as in women at increased risk [25,26] may be useful in aiding the interpretation of CA125 and ultrasound results. However, the end-point of these studies should not be the detection of ovarian cancer but deaths attributed to ovarian cancer. Data on

mortality from ovarian cancer from the UKCTOCS study will not be available before 2014.

It is therefore of the utmost importance to develop new circulating (panels of) biomarkers which are specific for (early) ovarian cancer and specifically in mutation carriers, to improve traditional screening results. More than 30 serum markers have been evaluated alone and in combination with CA125, and mathematical techniques are being developed to analyze combinations of marker levels to improve sensitivity and specificity. Recent candidates include: HE4, mesothelin, M-CSF, osteopontin, kallikrein(s), and soluble EGF receptor [22] and the combined use of multiple markers through an artificial neural network [27]. Others have started clinical trials to assess the sensitivity and specificity of serum proteomic patterns to identify early ovarian cancer [28].

The initial results have caused a lot of interest but also much controversy regarding the reproducibility, sensitivity, and specificity of this new technology utilizing surface-enhanced laser desorption and ionization mass spectrometry (SELDI-MS) in ovarian cancer. Additional research needs to be done to find protein signalling pathways in humans, which could lead to the identification of molecular markers of early-stage ovarian cancer [29]. Although there is optimism that further developments in serum proteomic analysis will provide powerful methods for screening in ovarian cancer, current clinical screening practice will have to do without proteomics, and only prospective studies in the future will tell whether proteomics will be able to detect ovarian cancer at an early, preclinical stage [30].

3.3. Combining these screening tests into screening strategies

In 12 cohort studies, four prospective and eight retrospective, the effectiveness of conventional ovarian cancer screening in women with a *BRCA1/2* mutation and in women at high risk of hereditary breast and ovarian cancer has been determined [11,31–41]. The total sample in these studies is 5298 women, with a total of 13,979 screening contacts. Only 1435 (27.1%) women were proven *BRCA1/2* mutation carriers. The results of the screening of the subset of proven *BRCA1/2* mutation carriers in the 12 studies were as follows. A total of 43 screen-detected ovarian cancers and 9 interval cancers were found. Of the 43 screen-detected cancers, 16 cancers were found in an early-stage (FIGO stage I/II), and six of these women had been treated for breast cancer. Of these six women, it is not certain whether the tumor was a primary ovarian cancer or an ovarian metastasis from the breast cancer. The interval cancers were mostly in an advanced stage (FIGO stage II–IV). The conclusion is that annual screening, by transvaginal ultrasound and serum CA125 in women with a hereditary ovarian cancer trait, is ineffective in detecting tumors at a sufficiently early-stage to improve survival [42].

3.4. Early signs and symptoms?

Ovarian cancer has no premalignant signs or symptoms, other than non-specific complaints. For that reason, ovarian cancer is called a 'silent killer'. However, in 2007, the Gynaecologic Cancer Foundation, Society of Gynaecologic Oncologists and American Cancer Society originated an Ovarian Cancer Symptoms Consensus Statement regarding the symptoms of ovarian cancer (<http://www.sgo.org/publications/OvarianCancerSymptoms.pdf>). The symptoms that are described in this Consensus Statement are more likely to occur in women with ovarian cancer than in the general population. These symptoms include: bloating, pelvic or abdominal pain, pain in the back or legs, diarrhea, gas, nausea, constipation, indigestion, difficulty eating or feeling full quickly, urinary symptoms, pain during sex, abnormal vaginal bleeding and trouble breathing. As early diagnosis is associated with an

improved prognosis, women are advised to see their doctor once they have symptoms almost daily for more than a few weeks. However, these symptoms are not as specific as we would like them to be, and knowledge of the biology of ovarian cancer (being a surface tumor with early shedding) does not make it plausible for these signs to lead to early diagnosis and improved survival. On the other hand, they may cause an enormous amount of worry and costs, as these signs are non-specific and are frequently reported by women in the general population [43,44].

3.5. Alternative screening strategies

As the currently available screening methods, including CA125 and TVU, lack the necessary sensitivity and specificity to provide accurate and cost-efficient early-stage cancer screening for the high-risk population, other ways of screening need to be assessed. As none of the currently available screening modalities is effective in finding early-stage ovarian cancer and as the prognosis of advanced ovarian cancer is poor, it is time to stop ovarian cancer screening with the conventional tools [31]. Instead, alternative strategies need to be explored with the use of new molecular (serum) markers to detect ovarian cancer in an initial phase. In the UK, a more frequent multi-modality CA125 screening algorithm has been proposed by Jacobs et al. in healthy postmenopausal women, in which not only the absolute value but the relative value (increment) of serial CA125 values is taken into account [23,45]. Whether this algorithm is also applicable to pre- and postmenopausal women at high risk is as yet unknown.

3.6. Prophylactic bilateral salpingo-oophorectomy

As effective screening tools for detecting premalignant ovarian lesions or early-stage ovarian cancer are not yet available, and as there is currently no evidence of a mortality reduction from ovarian cancer screening, the only effective option at present for women with a hereditary susceptibility to ovarian cancer is prophylactic bilateral salpingo-oophorectomy (pBSO) [46]. In a meta-analysis of 10 studies that investigated breast or gynecologic cancer outcomes in *BRCA1/2* mutation carriers who had undergone pBSO, it was found that pBSO was associated with a statistically significant reduction in the risk of *BRCA1/2*-associated ovarian or fallopian tube cancer (HR = 0.21; 95% CI = 0.12–0.39) [46]. Data were insufficient to obtain separate estimates for ovarian and fallopian tube cancer risk reduction with pBSO in *BRCA1* or *BRCA2* mutation carriers. In addition, there is an ongoing prospective, international, two-cohort, non-randomized study of women at genetic risk of ovarian cancer, who chose to undergo either pBSO or screening at study enrollment, with the main aim of quantifying the incidence of ovarian and breast cancer in the two study groups [24]. Study accrual was completed in 2006, and we are waiting for the follow-up data.

The majority of women who have a proven *BRCA1/2* mutation are now counselled to undergo pBSO after child-bearing age [47]. In addition, pBSO before menopause has a protective effect on the incidence of breast cancer [48]. As the risk of ovarian cancer begins to rise in the late 30s and early 40s for *BRCA1* carriers and approximately 10 years later for women with a *BRCA2* mutation, the advised age for pBSO in *BRCA1* carriers is 35–40 years and in *BRCA2* carriers 40–45 years. For women who still want to opt for screening or have reasons to preserve fertility, no effective prophylactic strategy exists.

Ovarian cancers in women with Lynch syndrome are often non-serous [49]. Therefore the effectiveness of ovarian cancer surveillance in Lynch syndrome might differ from that in *BRCA1/2* mutation carriers. In a meta-analysis, ovarian tumors with mismatch repair deficiency had an earlier stage disease at presentation than did tumors without [49], although survival rates have not been

proven to be better [50]. For women with Lynch syndrome, annual screening from age 30 years followed by prophylactic surgery (hysterectomy and pBSO) from age 40 years, or 5 years before the age of the youngest affected family member, seems to be the most effective gynecologic cancer prevention strategy. However, the incremental benefit over prophylactic surgery alone was attained at substantial costs [49]. Hormone replacement therapy until the age of 50 years is indicated for women with Lynch syndrome who have to deal with early surgical menopause. After pBSO in *BRCA1/2* carriers, breast cancer screening should continue, as well as colorectal cancer screening in women with Lynch syndrome after gynecological prophylactic surgery.

3.7. Procedure of gynecological prophylactic surgery

In *BRCA1/2* mutation carriers, the minimum prophylactic procedure is a bilateral salpingo-oophorectomy. The procedure should start with peritoneal lavage and cytological examination to detect occult ovarian, peritoneal or tubal cancers, which are reported to be present in about 3% of *BRCA1/2* carriers who undergo pBSO. It is important that the ovaries and tubes are handled with care not to spread occult cancer through the abdominal cavity. For the same reason, tissue should be removed using an endo-pouch. During the histopathological examination, it is important that the entire ovaries and fallopian tubes are serially sectioned so that small and microscopic lesions are not missed. Whether hysterectomy should be part of the prophylactic surgery in *BRCA1/2* mutation carriers is debatable, because there is no evidence that a hysterectomy adds to reducing the risk of fallopian tube cancer more than a complete BSO alone [50]. For that reason, we recommend a pBSO without hysterectomy. In women with Lynch syndrome, however, risk-reducing surgery should consist of pBSO together with a total hysterectomy.

4. Reproductive issues

4.1. Oral contraceptive pills

In general, current users of oral contraceptives have a small increased relative risk of breast cancer (odds ratio: 1.24; 95% CI: 1.15–1.33) [51]. This increased risk disappears after cessation of use [51]. The use of oral contraceptive pills is controversial in women with an increased risk of breast cancer. There is an increased risk of breast cancer for *BRCA1/2* mutation carriers who ever used oral contraceptives (adjusted hazard ratio: 1.47; 95% CI, 1.16–1.87) [52]. No evidence was found among *BRCA1/2* mutation carriers that current use of oral contraceptives is associated with risk of breast cancer more strongly than is past use, as is found in the general population [52]. However, the use of oral contraceptives confers long-term protection against ovarian cancer; the use of oral contraceptive agents for as long as 5 years decreases the risk of ovarian cancer in later life by about 50% [53]. Use during the 1960s, 1970s, and 1980s was associated with similar proportional risk reductions, although typical estrogen doses in the 1960s were more than double those in the 1980s. The incidence of mucinous tumors (12% of the total) seemed little affected by oral contraceptives, but otherwise the proportional risk reduction did not vary much between different histological types [54]. Where the same effect was found for *BRCA1* mutation carriers, the number of ovarian cancer cases in *BRCA2* mutation carriers was too small to draw definitive conclusions.

4.2. Worries about transmitting the mutation to children

Women carrying a *BRCA1/2* or Lynch syndrome gene mutation have a 50% chance of conceiving a baby with the same mutation. There are a few options available to avoid having a child with the

same mutation and the availability of these options differs across countries. Besides avoiding child-bearing, options are pregnancy surrogate, and DNA analysis of tissue obtained in early pregnancy by chorionic villous biopsy or amniotic fluid assessment, with an abortion if the fetus is affected. Another option is to perform in vitro fertilization with pre-implantation genetic diagnosis (PGD) of the retrieved embryos, followed by selection of embryo(s) without a mutation and transfer of a selected embryo to the uterus [55].

5. Our patient

At the age of 34, our patient decides to become pregnant again. Before that she asked for information about PGD, to avoid the birth of an affected child. However, the demands of the procedure persuaded the couple to decline this option. She became pregnant and delivered a healthy baby girl.

Four years later, at the age of 38 years, she decides to undergo a pBSO. She is counselled about the quality of life effects of early surgical menopause and is offered hormone replacement therapy [56,57].

Her sister had decided to have a pBSO as well, but was advised not to take hormone replacement therapy because of an increased risk of breast cancer recurrence [58–60]. Hot flushes occurred and were treated with venlafaxine [61].

6. Conclusions

Until recently, intensive screening of the ovaries was recommended to mutation carriers and their first-degree female relatives. However, since conventional screening is not effective in detecting early-stage ovarian cancer and new strategies are not yet available, women should be counselled regarding a prophylactic salpingo-oophorectomy after child-bearing age (>35 years). The favourable effects in terms of a reduced risk of ovarian cancer need to be weighed against the physical and psychosexual side-effects of early surgical menopause. Counselling will help women to make informed decisions about the optimal preventive health strategy. Research should aim at finding new molecular markers and screening strategies for detecting early-stage ovarian cancer in women with a hereditary ovarian cancer trait.

Conflict of interest

The authors declare to have no competing interests.

Provenance

Commissioned and externally peer reviewed.

References

- [1] Claus EB, Schildkraut JM, Thompson WD, Risch NJ. The genetic attributable risk of breast and ovarian cancer. *Cancer* 1996;77:2318–24.
- [2] Boland CR. Evolution of the nomenclature for the hereditary colorectal cancer syndromes. *Fam Cancer* 2005;4:211–8.
- [3] Vasen HF, Wijnen JT, Menko FH, et al. Cancer risk in families with hereditary nonpolyposis colorectal cancer diagnosed by mutation analysis. *Gastroenterology* 1996;110:1020–7.
- [4] Geary J, Sasieni P, Houlston R, et al. Gene-related cancer spectrum in families with hereditary non-polyposis colorectal cancer (HNPCC). *Fam Cancer* 2008;7:163–72.
- [5] Chen S, Parmigiani G. Meta-analysis of *BRCA1* and *BRCA2* penetrance. *J Clin Oncol* 2007;25:1329–33.
- [6] Watson P, Lynch HT. Extracolonic cancer in hereditary nonpolyposis colorectal cancer. *Cancer* 1993;71:677–85.
- [7] American College of Obstetricians and Gynecologists, ACOG Committee on Practice Bulletins—Gynecology, ACOG Committee on Genetics, Society of Gynecologic Oncologists. ACOG Practice Bulletin No. 103: Hereditary breast and ovarian cancer syndrome. *Obstet Gynecol* 2009;113:957–66.

- [8] Geomini P, Kruitwagen R, Bremer GL, Cnossen J, Mol BW. The accuracy of risk scores in predicting ovarian malignancy: a systematic review. *Obstet Gynecol* 2009;113:384–94.
- [9] Sassone AM, Timor-Tritsch IE, Artner A, Wetshoff C, Warren WB. Transvaginal sonographic characterization of ovarian disease: evaluation of a new scoring system to predict ovarian malignancy. *Obstet Gynecol* 1991;78:70–6.
- [10] Muto MG, Cramer DW, Brown DL, et al. Screening for ovarian cancer: the preliminary experience of a familial ovarian cancer center. *Gynecol Oncol* 1993;51:12–20.
- [11] 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;94:814–9.
- [12] Mourits MJ, Van der Velde NM, Arts HJ, De Bock GH. High percentage of abnormal findings on TVU needs further discussion. *Br J Cancer* 2006;95:1125.
- [13] Miller JC, Horowitz NS, Thrall JH, Lee SI. Evaluating adnexal lesions: which need follow-up? *J Am Coll Radiol* 2007;4:725–9.
- [14] Healy DL, Bell R, Robertson DM, et al. Ovarian status in healthy postmenopausal women. *Menopause* 2008;15:1109–14.
- [15] Valentin L, Skoog L, Epstein E. Frequency and type of adnexal lesions in autopsy material in postmenopausal women: ultrasound study with histological correlation. *Ultrasound Obstet Gynecol* 2003;22:284–9.
- [16] Bourne TH, Campbell S, Reynolds KM, et al. Screening for early ovarian cancer with transvaginal ultrasonography and colour Doppler blood flow imaging. *Br Med J* 1993;306:1025–9.
- [17] Ueland FR, DePriest PD, Pavlik EJ, Kryscio RJ, van Nagell Jr JR. Preoperative differentiation of malignant from benign ovarian tumors: the efficacy of morphology indexing and Doppler flow sonography. *Gynecol Oncol* 2003;91:46–50.
- [18] Kabawat SE, Bast Jr RC, Bhan AK, Welch WR, Knapp RC, Colvin RB. Tissue distribution of a coelomic-epithelium-related antigen recognized by the monoclonal antibody OC125. *Int J Gynecol Pathol* 1983;2:275–85.
- [19] Bast Jr RC, Klug TL, St John E, et al. A radioimmunoassay using a monoclonal antibody to monitor the course of epithelial ovarian cancer. *N Engl J Med* 1983;309:883–7.
- [20] Mann WJ, Patsner B, Coher H, Loesch M. Preoperative serum CA-125 levels in patients with surgical stage I invasive ovarian adenocarcinoma. *J Natl Cancer Inst* 1998;90:208–13.
- [21] Jacobs IJ, Bast Jr RC. The CA 125 tumour-associated antigen: a review of the literature. *Hum Reprod* 1989;4:1–5.
- [22] Bast Jr RC, Brewer M, Zou C, et al. Prevention and early detection of ovarian cancer: mission impossible? *Recent Results Cancer Res* 2007;174:91–100.
- [23] Jacobs I. Screening for familial ovarian cancer: the need for well-designed prospective studies. *J Clin Oncol* 2005;23:5443–5.
- [24] Greene MH, Piedmonte M, Alberts D, et al. A prospective study of risk-reducing salpingo-oophorectomy and longitudinal CA-125 screening among women at increased genetic risk of ovarian cancer: design and baseline characteristics: a Gynecologic Oncology Group study. *Cancer Epidemiol Biomarkers Prev* 2008;17:594–604.
- [25] Hannemann M, Fox R, James M. Ovarian cancer death reduction for women at high risk: workload implications for gynaecology services. *J Obstet Gynaecol* 2006;26:42–4.
- [26] Zhang Z, Yu Y, Xu F, et al. Combining multiple serum tumor markers improves detection of stage I epithelial ovarian cancer. *Gynecol Oncol* 2007;107:526–31.
- [27] Petricoin EF, Ardekani AM, Hitt BA, et al. Use of proteomic patterns in serum to identify ovarian cancer. *Lancet* 2002;359:572–7.
- [28] Liu C, Shea N, Rucker S, et al. Proteomic patterns for classification of ovarian cancer and CTCL serum samples utilizing peak pairs indicative of post-translational modifications. *Proteomics* 2007;7:4045–52.
- [29] Nossov V, Amneus M, Su F, et al. The early detection of ovarian cancer: from traditional methods to proteomics. Can we really do better than serum CA-125? *Am J Obstet Gynecol* 2008;199:215–23.
- [30] Van der Velde NM, Mourits MJ, Arts HJ, et al. Time to stop ovarian cancer screening in BRCA1/2 mutation carriers? *Int J Cancer* 2009;124:919–23.
- [31] Woodward ER, Sleightholme HV, Considine AM, Williamson S, McHugo JM, Cruger DG. Annual surveillance by CA125 and transvaginal ultrasound for ovarian cancer in both high-risk and population risk women is ineffective. *BJOG* 2007;114:1500–9.
- [32] Bosse K, Rhiem K, Wappenschmidt B, et al. Screening for ovarian cancer by transvaginal ultrasound and serum CA125 measurement in women with a familial predisposition: a prospective cohort study. *Gynecol Oncol* 2006;103:1077–82.
- [33] Gaarenstroom KN, Van der Hiel B, Tollenaar RAEM, et al. Efficacy of screening at high risk of hereditary ovarian cancer: results of an 11-year cohort study. *Int J Gynecol Cancer* 2006;16:54–9.
- [34] Olivier RI, Lubsen-Brandtsma MAC, 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;100:20–6.
- [35] Vasen HFA, Tesfay E, Boonstra H, et al. Early detection of breast and ovarian cancer in families with BRCA mutations. *Eur J Cancer* 2005;41:549–54.
- [36] Meeuwissen PAM, Seynaeve C, Brekelmans CTM, Meijers-Heijboer HJ, Klijn JGM, Burger CW. Outcome of surveillance and prophylactic salpingo-oophorectomy in asymptomatic women at high risk for ovarian cancer. *Gynecol Oncol* 2005;97:476–82.
- [37] Stirling D, Evans DG, Pichert G, 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;23:5588–96.
- [38] Laframboise S, Nedelcu R, Murphy J, Cole DEC, Rosen B. Use of CA-125 and ultrasound in high-risk women. *Int J Gynecol Cancer* 2002;12:86–91.
- [39] Scheuer L, Kauff N, Robson M, et al. Outcome of preventive surgery and screening for breast and ovarian cancer in BRCA mutation carriers. *J Clin Oncol* 2002;20:1260–8.
- [40] Dørum A, Heimdal K, Løvstett K, et al. Prospectively detected cancer in familial breast/ovarian cancer screening. *Acta Obstet Gynecol Scand* 1999;78:906–11.
- [41] Evans GR, Gaarenstroom KN, Stirling D, et al. Screening for familial ovarian cancer: poor survival of BRCA1/2 related cancers. *J Med Genet* 2008 [Epub ahead of print].
- [42] Goff BA, Mandel LS, Melancon CH, Muntz HG. Frequency of symptoms of ovarian cancer in women presenting to primary care clinics. *JAMA* 2004;291:2705–12.
- [43] Lowe KA, Andersen MR, Urban N, Paley P, Dresher CW, Goff BA. The temporal stability of the Symptom Index among women at high-risk for ovarian cancer. *Gynecol Oncol* 2009 [Epub ahead of print].
- [44] Menon U, Gentry-Maharaj A, Hallett R, et al. Sensitivity and specificity of multimodal and ultrasound screening for ovarian cancer, and stage distribution of detected cancers: results of the prevalence screen of the UK Collaborative Trial of Ovarian Cancer Screening (UKCTOCS). *Lancet Oncol* 2009;10:327–40.
- [45] Jacobs IJ, Skates SJ, MacDonald N, et al. Screening for ovarian cancer: a pilot randomised controlled trial. *Lancet* 1999;353:1207–10.
- [46] Rebbeck TR, Kauff ND, Domchek SM. Meta-analysis of risk reduction estimates associated with risk-reducing salpingo-oophorectomy in BRCA1 or BRCA2 mutation carriers. *J Natl Cancer Inst* 2009;101:80–7.
- [47] Meijers-Heijboer H, Brekelmans CT, Menke-Pluymers M, et al. Use of genetic testing and prophylactic mastectomy and oophorectomy in women with breast or ovarian cancer from families with a BRCA1 or BRCA2 mutation. *J Clin Oncol* 2003;21:1675–81.
- [48] Bermejo-Pérez MJ, Márquez-Calderón S, Llanos-Méndez A. Effectiveness of preventive interventions in BRCA1/2 gene mutation carriers: a systematic review. *Int J Cancer* 2007;121:225–31.
- [49] Pal T, Permeth-Wey J, Kumar A, Sellers TA. Systematic review and meta-analysis of ovarian cancers: estimation of microsatellite-high frequency and characterisation of mismatch repair deficient tumor histology. *Clin Cancer Res* 2008;14:6847–54.
- [50] Mourits MJ, De Hullu JA, Van Der Zee AG, Hollema H. Letter commenting on "Pathologic finding in prophylactic oophorectomy specimens in high-risk women" (87:52–6) by Pamela Paley, et al. *Gynecol Oncol* 2004;93:571.
- [51] Collaborative Group on Hormonal Factors in Breast Cancer. Breast cancer and hormonal contraceptives: collaborative reanalysis of individual data on 53 297 women with breast cancer and 100 239 women without breast cancer from 54 epidemiological studies. *Lancet* 1996;347:1713–27.
- [52] Brohet RM, Goldgar DE, Easton DF, et al. Oral contraceptives and breast cancer risk in the international BRCA1/2 carrier cohort study: a report from EMBRACE, GENEPSO, GEO-HEBON and the IBCCS Collaboration Group. *J Clin Oncol* 2007;25:3831–6.
- [53] Collaborative Group on Epidemiological Studies of Ovarian Cancer Beral V, Doll R, Hermon C, Peto R, Reeves G. Ovarian cancer and oral contraceptives: collaborative reanalysis of data from 45 epidemiological studies including 23,257 women with ovarian cancer and 87,303 controls. *Lancet* 2008;371:303–14.
- [54] Antoniou AC, Rookus M, Andrieu N, et al. Reproductive and hormonal factors, and ovarian cancer risk for BRCA1 and BRCA2 mutation carriers: results from the International BRCA1/2 Carriers Cohort Study. *Cancer Epidemiol Biomarkers Prev* 2009;18:601–10.
- [55] Kuliev A, Verlinsky Y. Place of preimplantation diagnosis in genetic practice. *Am J Med Genet A* 2005;134A:105–10.
- [56] Madalinska JB, Hollenstein J, Bleiker E, et al. Quality-of-life effects of prophylactic salpingo-oophorectomy versus gynecologic screening among women at increased risk of hereditary ovarian cancer. *J Clin Oncol* 2005;23:6890–8.
- [57] Madalinska JB, van Beurden M, Bleiker EM, et al. The impact of hormone replacement therapy on menopausal symptoms in younger high-risk women after prophylactic salpingo-oophorectomy. *J Clin Oncol* 2006;24:3576–82.
- [58] Holmberg L, Iversen OE, Rudenstam CM, et al. Increased risk of recurrence after hormone replacement therapy in breast cancer survivors. *J Natl Cancer Inst* 2008;100:475–82.
- [59] Kenemans P, Bundred NJ, Foidart JM, et al. Safety and efficacy of tibolone in breast-cancer patients with vasomotor symptoms: a double-blind, randomised, non-inferiority trial. *Lancet Oncol* 2009;10:135–46.
- [60] Von Schoultz E, Rutqvist LE. Menopausal hormone therapy after breast cancer: the Stockholm randomized trial. *J Natl Cancer Inst* 2005;97:533–5.
- [61] Buijs C, Mom CH, Willems PH, et al. Venlafaxine versus clonidine for the treatment of hot flashes in breast cancer patients: a double-blind, randomized cross-over study. *Breast Cancer Res Treat* 2009;115:573–80.