East African Medical Journal Vol. 94 No. 5 May 2017
SCREENING AND PREVENTION OF OVARIAN CANCER
J. J. Chesang, MBChB, MMED, PhD

SCREENING AND PREVENTION OF OVARIAN CANCER

J. J. Chesang

ABSTRACT

Objective: **To present a review of screening methods for ovarian cancer and preventive strategies.**

Data source: **Relevant literature was identified through a search of the MEDLINE, EMBASE and CINAHL databases.**

Study Selection: **Recent Studies assessing methods used in prevention of and screening for ovarian cancer were selected.**

Data Extraction: **Data from selected studies were extracted as reported in the studies. They were then grouped into respective subtopics.**

Data Synthesis: **Data were grouped into two broad groups: screening and prevention. They were further refined into subtopics. The findings of this study are: currently, there are no screening tests recommended for women at average risk of ovarian cancer. Surveillance tests employed in high risk women include monitoring of cancer antigen (CA)-125 serum levels, transvaginal ultrasound, and pelvic examination. None, either individually or in combination, has consistently been shown to detect ovarian cancer at an early stage or to reduce mortality from ovarian cancer. Furthermore, the high false-positive rates associated with these tests, result in anxiety and unnecessary surgical interventions. Oral contraceptives, which have been shown to decrease the risk of ovarian cancer by up to 50%, have been proposed for use as a chemopreventive agent. The most effective ovarian cancer preventive strategy in women at high risk is risk-reducing salpingo-oophorectomy after the completion of child bearing, although this has the disadvantage of inducing early menopause.**

Conclusion: **Lack of effective screening methods for ovarian cancer has contributed to the low survival rate. An understanding of the pathogenesis of ovarian cancer may help in the development of effective preventive and screening methods.**

INTRODUCTION

An effective screening method has to be able to detect disease at an earlier stage at diagnosis such that treatment would result in better outcome (1-3), and reduce disease-specific morbidity and mortality (2, 3). It also has to have high levels of sensitivity and specificity with acceptable levels of negative and positive predictive values (NPV and PPV) (1). NPV and PPV are affected by disease prevalence and the specificity and sensitivity of the screening test. Ovarian cancer is a rare disease (prevalence of about 1 in 2,500 in postmenopausal women), which means that an ovarian cancer screening test has to have very high specificity and sensitivity in order

to achieve acceptable levels of NPV and PPV. A high false-positive rate in the screening of ovarian cancer is costly as it may lead to unnecessary anxiety and to surgical intervention with its associated morbidity (1). A high false-negative value, of course, completely negates the value of a screening programme for each individual with a missed diagnosis.

Ovarian cancer could potentially benefit from screening because diagnosis at an early stage (stage 1) is associated with a high 5-year survival rate (95%). Development of effective screening strategies for ovarian cancer has been hampered by the low prevalence of ovarian cancer, and lack of evidence of efficacy; therefore, screening for ovarian cancer does not meet criteria for population screening, but possibly may benefit those women who are known to be at high-risk of ovarian cancer (3-5).

Lack of understanding of the pathogenesis of ovarian cancer has also hampered the development of an effective preventive strategy. Understanding the natural history of disease helps in the identification of a point at which intervention is most effective in preventing disease occurrence (1). This paper explores current screening methods and preventive strategies employed in women at high risk of ovarian cancer.

METHODS

Relevant studies were identified through a search of the MEDLINE, EMBASE and CINAHL databases. Additional papers were found by checking reference lists. Recent Studies assessing methods used in prevention of and screening for ovarian cancer were selected. Data from selected studies were extracted as reported in the studies. They were then grouped into screening and prevention. Screening included clinical detection, pelvic ultrasound and biomarkers. Prevention included chemoprevention and surgical prevention. The data were then integrated to give a coherent view. Merits and demerits of each method of screening and prevention are discussed, and studies on the same presented.

SCREENING

Clinical detection: Use of symptoms has been proposed for the early detection of ovarian cancer (6-8). Urinary frequency, urinary urgency, abdominal bloating, early satiety, difficulty eating, and pelvic or abdominal pain have been proposed as symptoms that suggest the presence of ovarian cancer, which should therefore be considered as a possible diagnosis in subsequent investigations (6-8). A positive symptom index, defined as the occurrence of any one of the above 6 symptoms >12 times in a month for less than a year, was found to have a sensitivity of 56.7% for early stage, 79.5% for advanced disease, and 80% for unstaged disease. The sensitivity and specificity were both 86.7% for women who were <50 years, whereas for women who were ≥50 years the sensitivity and specificity were 66.7% and 90% respectively (8). There is the possibility that such use of symptom indices aids in earlier detection of advanced disease and not detection of disease at an early stage. Early detection of advanced disease may be beneficial because there is better success at optimal surgical debulking and early intervention may also improve quality of life of the patients (9).

In a population-based case-control study in California, only 16% of women diagnosed with ovarian cancer were asymptomatic at the time of diagnosis. In addition, asymptomatic women were at an early stage compared to the symptomatic women (65% versus 51%; P = 0.01). Relative to other tumour types (mucinous-10%; endometrioid-19%; and clear cell-14%), the majority (55%) of asymptomatic women

diagnosed with serous tumours had advanced disease (P = 0.01). The short duration of symptoms and advanced disease at diagnosis of serous tumours may point to rapid disease progression as opposed to a delay in diagnosis. Diagnosis by symptoms may therefore fail to detect a high proportion of early serous tumours. In addition, symptoms were found to differ by histological subtype of epithelial ovarian cancer (EOC). Abdominal distension was a common presentation in women diagnosed with mucinous tumours (60%), followed by serous tumours (43%), and endometrioid tumours (26%). History of abnormal vaginal bleeding was more common in women with endometrioid tumours (19%) than in those with serous tumours (7%), whereas bowel symptoms were more commonly reported by women with serous tumours (47%) compared to non-serous (19-32%). There were also differences in symptom presentation according to tumour grade, stage, and age, but not with ethnicity. However, it is important to note that stage and grade were influenced by the histological type of tumour. The majority of serous tumours (69%) were diagnosed at an advanced stage compared to 13-38% of non-serous tumours. The majority of serous (75%) and clear cell (72%) tumours were high-grade compared to endometrioid (38%) and mucinous (13%).There was also a positive relationship between tumour grade and stage at diagnosis, with high-grade tumours being diagnosed at an advanced stage (61%) relative to low-grade tumours (27%), although even here, influence of histological subtype was observed, with most of the non-serous high-grade tumours still being diagnosed at an early stage (10). Pelvic examination can be used to detect adnexal masses; however, it has low sensitivity (7, 11). Pelvic examination detects about 1 in 10,000 ovarian cancers in asymptomatic women (7), and fails to detect 10% of adnexal masses of 10 cm in size (11).

Ultrasound: Ultrasound has limited value in detecting early-stage ovarian cancer (7). However, in a study in which surveillance of asymptomatic women using annual transvaginal ultrasound (TVS) was done, the 5-year survival rate of screened women after a diagnosis of invasive EOC was significantly better than that of unscreened women (76% +/-6.6% Versus 53.7% +/-2.3%; P <0.001). Use of TVS as a screening test had a sensitivity of 86.4% and a specificity of 98.8%. Ovarian cancer was also detected at an early stage (47% in stage I and 23% in stage II); the improved survival observed in this study was due to detection at an early stage (which may have been partly due to lead-time bias). Follow-up began at 25 years of age for women with a strong family history of breast or ovarian cancer (genetic testing was not routinely done in this study) and at 50 years of age for women at average risk. The mean follow-up period was 5.8 years. Patients underwent standard treatment with surgery followed by 6 cycles of platinum-based chemotherapy (carboplatin plus taxanes) (3).

Use of TVS as a screening test is limited by its low PPV (2, 3), which is more marked in premenopausal women due to frequent formation of functional cysts (2). In the above study, the NPV of a normal ultrasound was 99.97%, and the PPV was 14.5% (6.9 surgical operations per ovarian cancer detected) (3).

Biomarkers: Cancer antigen (CA)-125, a large transmembrane glycoprotein, was first identified in human ovarian cancer cell lines in 1981 by Bast and colleagues (1, 12). In 2001, the gene encoding CA-125 (MUC16) was cloned (1, 12). Currently, CA-125 is used in detection as well as monitoring of treatment and follow-up among patients with ovarian cancer (12, 13). The biologic function of CA-125 is unclear (1, 12); however, it is thought to promote ovarian cancer tumourigenesis (12). The normal cut-

point for CA-125 plasma level is 35 IU/ml (12, 13).

A cut-point of 35 IU/ml is associated with a high false-positive rate in pre-menopausal women, which may be of concern particularly in high-risk women (13). CA-125 is produced by many tissues including epithelia of female reproductive tract, pleura, pericardium, peritoneum, lung, pancreas, breast, stomach, and gall bladder. In addition, CA-125 is elevated in certain benign conditions such as endometriosis, fibroids, pregnancy, pelvic inflammatory disease, pericarditis, pleurisy, pancreatitis, liver disease, tuberculosis, and peritonitis, and also in malignancies of other sites such as breast and gastrointestinal cancers (12). It is elevated in women with EOC (7, 11), but varies according to histological subtype (highest in serous and lowest in mucinous) (7). In addition, use of CA-125 as a screening test for women with Lynch syndrome may not be as effective as in BRCA1/2 mutation carriers because tumours in this group of women are usually non-serous (14). The sensitivity of CA-125 for the detection of stage I ovarian cancer is low (25-50%) (2).

Normal levels of CA-125 are also affected by certain clinical and demographic factors and are higher in premenopausal than postmenopausal women (12, 13). In a prospective study in the US in which levels of CA-125 were measured in high-risk women (women with a strong family history of breast or ovarian cancer), premenopausal women had a significantly higher 98th percentile cut-point of CA-125 than postmenopausal women (52 IU/ml versus 36 IU/ml; P<0.001). In pre-menopausal women, use of oral contraceptives was associated with a significant reduction in the cut-point (98th percentile) of CA-125 (reduced to 39 IU/ml; P <0.001) (13).

Other factors that were associated with lower CA-125 levels in pre-menopausal women included smoking, irregular periods, BRCA1/2 mutation, Ashkenazi Jewish heritage, and a family history of ovarian cancer. Factors that were associated with lower CA-125 levels in post-menopausal women included history of bilateral oophorectomy, hysterectomy, black race, and history of use of fertility treatment. Factors that were associated with levels of CA-125 (in both pre-and post-menopausal women) had an additive effect. The authors concluded that in order to have equivalent false-positive rates between pre-and post-menopausal women, a cut-point of 35 IU/ ml should be used for post-menopausal women, 50 IU/ml for pre-menopausal women, and 40 IU/ml for premenopausal women on oral contraceptives (13). However, this may decrease the sensitivity of CA-125 as a screening test and therefore result in failure to detect ovarian cancer at an early stage (12). Individualisation of CA-125 levels is further complicated by the effect of more than one factor (12). The Risk of Ovarian Cancer Algorithm (ROCA) takes into account the variations in CA-125 levels. Women with CA-125 levels within the normal range but rising are considered at high risk, whereas those with CA -125 levels above the normal range but static are deemed to be at low risk. In estimating an individual's risk of ovarian cancer, ROCA utilizes an algorithm that includes a woman's age-specific risk of ovarian cancer and CA-125 dynamic profile. Using ROCA the sensitivity of CA-125 is 86% and the specificity is 98% (12).

The risk of malignancy index (RMI) first proposed by Jacob et al. (15) has also been used for the pre-operative diagnosis of ovarian cancer. The scoring is derived from the product of the absolute level of plasma CA-125 levels, menopausal status (a score of 1 for pre-menopause and 3 for post-menopause), and ultrasound features (scores of 0, 1, and 3) (15, 16). Using a cut-point of 200 to indicate malignancy a sensitivity of 90% and a specificity of 89% in discriminating between benign and

malignant disease has been reported. A high PPV (96%) and NPV (78%) were also observed. Furthermore, RMI was more accurate in detecting cancer at an early stage than any of its individual components. RMI can be used in less-specialised units and helps avoid unnecessary surgery (16).

The findings of the UK Collaborative Trial of Ovarian Cancer Screening (UKTOCS), a randomised controlled trial involving 202,638 post-menopausal women (50-74 years of age), suggest that use of CA-125 in combination with pelvic ultrasound may reduce mortality from ovarian cancer in this group of women. In that study, participants were randomised into 3 groups: no screening, ultrasound screening (USS), and CA-125 with ultrasound as a secondary test (multimodal screening (MMS)). Over years 0-14, a reduction in mortality from ovarian cancer of 15% (95% CI -3 to 30) was observed in the MMS group and 11% (95% CI -7 to 27) in the USS group, which were not statistically significant. However, for years 7-14, there was a reduction in mortality of 23% (95% CI = 1-46) in the MMS group and 21% (-2 to 42) in the USS group. MMS had a sensitivity of 84% (95% CI = 79-88) and USS 73% (66-79). There was a false-positive rate of 1% in the MMS group and 3.2% in the USS group; 14 and 50 unnecessary surgeries per 10,000 screens respectively. There was no difference in the incidence of ovarian cancer in the three groups (17).

Biomarkers other than CA-125 have also been evaluated for use as screening tests for ovarian cancer (1, 2). Biomarkers have been shown to differ according to epithelial ovarian cancer histological subtype, which may be one of the reasons why it is difficult to establish a single biomarker for ovarian-cancer detection (18). Despite the presence of other biomarkers, CA-125 is still the best available and has been described as "the best of a bad lot" (1).

PREVENTION

Chemoprevention: Oral contraceptives have been shown to be associated with about a 50% reduction in the risk of ovarian cancer (2, 19) and the inverse association lasts up to 20 years after cessation of use (14). However, there are concerns about increased risk of breast cancer with use of oral contraceptives as a chemopreventive agent in premenopausal women (2, 14, 19). This has led to the suggestion that women at high-risk of ovarian cancer should use oral contraceptives for 3-5 years when they are <25 years of age (at this age, the incidence of breast cancer is low) (2). Use of oral contraceptives solely for the prevention of ovarian cancer has the disadvantage of also preventing pregnancy (19).

Surgical prevention: The most effective preventive strategy for women with BRCA1/2 mutations is prophylactic bilateral salpingo-oophorectomy (PBSO), also known as risk-reducing salpingo-oophorectomy (RRSO) (2, 13, 19). Ovarian cancer is diagnosed, on average, at an earlier age in BRCA1/2-mutation carriers than in the general population (14). A diagnosis of ovarian cancer is made in about 3% of BRCA1-mutation carriers aged £40 years and this rises to 21% at £50 years (20). The recommended age for PBSO is 35-40 years in BRCA1-mutation carriers and 40-45 years in BRCA2-mutation carriers. Oophorectomy done in premenopausal women has the added advantage of decreasing the incidence of breast cancer (2).

PBSO has been shown to decrease the risk of tubal/ovarian cancer by 85-95% and that of breast cancer by ≥50%. It also lowers disease-specific mortality from ovarian or breast cancer (19). Occult ovarian, peritoneal, or tubal cancers have been reported in 2-18% of cases at the time of surgery (2, 19, 20). Therefore, care is recommended and needed at the time of surgery in order to minimise the risk of

spread. In addition, peritoneal washing for cytological examination and careful sectioning of ovaries and tubes during histological examination is recommended (2, 20). In BRCA1/2-mutation carriers bilateral salpingo-oophorectomy may be sufficient; however, in women with Lynch syndrome, hysterectomy is required due to the elevated risk of endometrial cancer (2).

The risk of peritoneal cancers is not totally eliminated by PBSO (14, 19, 20). A residual risk of 1-4% is present (19, 20) and is more common in BRCA1-than in BRCA2-mutation carriers (19). This is thought to arise as a result of malignant transformation of peritoneal tissue or from occult cancer that is not detected at the time of surgery and therefore left untreated (20). Despite this, surveillance with CA-125 after surgery is not recommended (20). Overall, the incidence of ovarian, tubal, or peritoneal cancer is decreased from 1% to 0.2% per year (20).

Prophylactic total hysterectomy and bilateral salpingo-oophorectomy (THBSO) after the age of 40 is a preventive option for women with Lynch syndrome. The timing is recommended on the basis of the risk of ovarian and endometrial cancers up to this age: £2% for endometrial cancer and £1% for ovarian cancer. Due to the possibility of occult endometrial cancer, endometrial biopsy is recommended prior to surgery (21, 22). Women with Lynch syndrome undergoing colon surgery benefit from THBSO done at the same time. There is the possibility of peritoneal cancer after risk-reducing THBSO (22). In addition, THBSO does not eliminate the risk of other malignancies associated with Lynch syndrome (21); therefore, screening for colorectal cancer should continue (2).

The downside to oophorectomy prior to menopause is that it leads to surgical menopause, which results in hormonal deprivation with its attendant complications (23). To mitigate the complications associated with premature menopause induced by RRSO, women may use post-menopausal hormone (PMH) for 2-3 years (19, 21). Use of PMH in women with no prior history of breast cancer does not negate the reduction of risk of breast cancer accorded by oophorectomy (19, 21, 23). Use of PMH is contraindicated in women with prior history of breast cancer (20). PMH should only be used up to the age of 50 years (approximate age at menopause); beyond this it has been shown to reduce life expectancy even in women with history of mastectomy (21).

In a prospective study in Toronto, women with BRCA1/2 mutations who underwent PBSO completed questionnaires before and after surgery; surgery prior to menopause was shown to affect quality of life. Increase in vasomotor symptoms and a fall in sexual function were observed. This was substantially, but not fully, alleviated by use of PMH. However, satisfaction with the decision to undergo surgery was high (mean 4.55 out of 5), with no difference in the level of satisfaction between pre-and post-menopausal women (4.53 vs 4.61, P = 0.63) (23). Women with surgical menopause are also at higher risk of cardiovascular disease, and loss of bone density; the latter, may be improved by PMH (20).

With the recent proposal that the most aggressive histological type, serous tumours, arise from the fimbrial end of the fallopian tubes (24), bilateral salpingectomy without oophorectomy has been suggested for women who desire to conserve their ovaries (20, 25). However, the effect of this on decreasing the risk of ovarian cancer risk is unknown. In addition, it does not decrease the risk of breast cancer (20).

CONCLUSION

Ovarian cancer is associated with a high mortality rate and most (>70%) are diagnosed at an advanced stage (14). The

primary reasons are lack of early-detection methods and lack of an understanding of its pathobiology. In addition, ovarian cancer seems to be a heterogeneous disease that requires screening and management methods specific to its histological subtypes. There is no screening test currently recommended for the general population (7, 14). Screening methods employed for women with BRCA1/2 mutations include bimanual pelvic examination, transvaginal ultrasound, and monitoring of CA-125 levels (2, 7). Screening with TVS and CA-125 are inefficient (high false-positive rate) and ineffective (detects disease at an advanced stage) (19). Despite these limitations, bi-annual TVS and CA-125 levels measurement have been recommended from the age of 35 years until oophorectomy is done (19). The most effective preventive strategy is PBSO (19).

The appropriate measure of an effective screening method is its ability to decrease disease- specific mortality (1, 2). CA-125 measurements and annual TVS have failed to detect ovarian cancer at an early stage and failed to decrease mortality attributed to ovarian cancer (2, 12). Our current lack of effective screening results in the diagnosis of ovarian cancer at an advanced stage, at which time the cost of treatment is high and the survival rate is low (3).

REFERENCES

1. Mai, P.L., N. Wentzensen, and M.H. Greene, Challenges Related to Developing Serum-Based Biomarkers for Early Ovarian Cancer Detection. Cancer Prevention Research, 2011. 4: p. 303-306.
2. Mourits, M.J. and G.H. de Bock, Managing hereditary ovarian cancer. Maturitas, 2009. 64: p. 172-176.
3. Van Nagell, J.R., R.W. Miller, C.P. DeSimone, F.R. Ueland, I. Podzielinski, S.T. Goodrich, et al., Long-Term Survival of Women With Epithelial Ovarian Cancer Detected by Ultrasonographic Screening. Obstetrics and Gynecology, 2011. 118: p. 1212-1221.
4. National Health Committee, Screening to improve health in New Zealand: criteria to assess screening programmes. 2003, National Advisory Committee on Health and Disability: Wellington.
5. Wilson, J.M.G. and G. Jungner, Principles and practice of screening for disease. World Health Organization, 1968.
6. Argento, M., P. Hoffman, and A.-S. Gauchez, Ovarian cancer detection and treatment: current situation and future prospects. Anticancer Research, 2008. 28(5B): p. 3135-8.
7. Jelovac, D. and D.K. Armstrong, Recent progress in the diagnosis and treatment of ovarian cancer. CA Cancer Journal for Clinicians, 2011. 61: p. 183-203.
8. Goff, B.A., L.S. Mandel, C.W. Drescher, N. Urban, S. Gough, K.M. Schurman, et al., Development of an ovarian cancer symptom index. Cancer, 2007. 109: p.221-227.
9. Markman, M., Development of an ovarian cancer symptom index: possibilities for earlier detection. Cancer, 2007. 110: p. 226-227.
10. Lurie, G., L.R. Wilkens, P.J. Thompson, R.K. Matsuno, M.E. Carney, and M.T. Goodman, Symptom presentation in invasive ovarian carcinoma by tumor histological type and grade in a multiethnic population: a case analysis. Gynecologic Oncology, 2010. 119: p. 278-84.
11. DeCherney, A.H., L. Nathan, T.M. Goodwin, and N. Laufer, Current diagnosis and treatment obstetrics and gynaecology. 10th ed, ed. Anne M. Sydor and K. Edmonson. 2007, New York: McGraw-Hill.
12. Dorigo, O. and J.S. Berek, Personalizing CA125 levels for ovarian cancer screening. Cancer Prevention Research, 2011. 4: p. 1356-9.
13. Skates, S.J., P. Mai, N.K. Horick, M. Piedmonte, C.W. Drescher, C. Isaacs, et al., Large prospective study of ovarian cancer screening in high-risk women: CA125 cut-point defined by menopausal status. Cancer Prevention Research, 2011. 4: p. 1401-8.
14. Rice, L.W., Hormone prevention strategies for breast, endometrial and ovarian cancers. Gynecologic Oncology, 2010. 118: p. 202-7.

15. Jacobs, I., D. Oram, J. Fairbanks, J. Turner, C. Frost, and J.G. Grudzinskas, A risk of malignancy index incorporating CA 125, ultrasound and menopausal status for the accurate preoperative diagnosis of ovarian cancer. BJOG: An International Journal of Obstetrics and Gynaecology, 1990. 97: p. 922-929.
16. Obeidat, B.R., Z.O. Amarin, J.A. Latimer, and R.A. Crawford, Risk of malignancy index in the preoperative evaluation of pelvic masses. International Journal of Gynecology and Obstetrics, 2004. 85: p. 255-258.
17. Jacobs, I.J., U. Menon, A. Ryan, A. Gentry-Maharaj, M. Burnell, J.K. Kalsi, et al., Ovarian cancer screening and mortality in the UK Collaborative Trial of Ovarian Cancer Screening (UKCTOCS): a randomised controlled trial. The Lancet, 2015.
18. Kalloger, S.E., M. Kobel, S. Leung, E. Mehl, D.X. Gao, K.M. Marcon, et al., Calculator for ovarian carcinoma subtype prediction. Modern Pathology, 2011. 24: p. 512-521.
19. Gulati, A.P. and S.M. Domchek, The clinical management of BRCA1 and BRCA2 mutation carriers. Current Oncology Reports, 2008. 10: p. 47-53.
20. Finch, A., G. Evans, and S.A. Narod, BRCA carriers, prophylactic salpingo-oophorectomy and menopause: Clinical management considerations and recommendations. Women's Health, 2012. 8: p. 543-555.
21. Hanson, H. and S. Hodgson, Cancer genetics and reproduction. Best Practice & Research: Clinical Obstetrics and Gynaecology, 2010. 24: p. 3-18.
22. Lu, K.H. and M. Daniels, Endometrial and ovarian cancer in women with Lynch syndrome: update in screening and prevention. Familial Cancer, 2013. 12: p. 273-277.
23. Finch, A., K.A. Metcalfe, J.K. Chiang, L. Elit, J. McLaughlin, C. Springate, et al., The impact of prophylactic salpingo-oophorectomy on menopausal symptoms and sexual function in women who carry a BRCA mutation. Gynecologic Oncology, 2011. 121: p.163-168.
24. Nezhat, F.R., R. Apostol, C. Nezhat, and T. Pejovic, New insights in the pathophysiology of ovarian cancer and implications for screening and prevention. American Journal of Obstetrics and Gynecology, 2015. 213: p. 262-267.
25. Vitonis, A.F., L. Titus-Ernstoff, and D.W. Cramer, Assessing ovarian cancer risk when considering elective oophorectomy at the time of hysterectomy. Obstetrics and Gynecology, 2011. 117: p. 1042-50