Commentary

The feasibility for screening for ovarian cancer

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Abstract

Introduction

The majority of the high-grade serous ovarian cancer (HGSOC) cases are diagnosed late, preventing effective treatment and therapy. We examine the feasibility of using EVA (Early oVArian cancer), a new molecular test for early HGSOC detection.

Methods

Comparison of the advantages and disadvantages of EVA with previously reported ovarian cancer tests, including CA125, was made, and the positive and negative predictive values of the tests were calculated as a measure of usefulness in the clinic.

Results

The positive predictive value of EVA and CA125 was 8.6% and 6.8% respectively, which was calculated based on the disease prevalence of 0.5%. The negative predictive value was 99.9% in both cases.

Conclusions

EVA and CA125 are unlikely to provide a meaningful population screening method for HGSOC in women at risk, since the predictive values would drive women not to perform these tests.

Introduction

In a recent issue of the journal Science Translational Medicine, Paracchini and colleagues described a new approach to the early detection of high-grade serous ovarian cancer (HGSOC), which is based on the assessment of genomic instability patterns of DNA extracted from cervical Papanicolaou (Pap) smears [1]. In this commentary, the usefulness of screening for ovarian cancer will be summarized, the plethora of biomarkers that have already been used for HGSOC diagnosis and management will be mentioned, the new test (EVA, Early oVArian cancer) will be described and attention will be drawn to the importance of the positive predictive value (PPV) of a screening test, an issue that was not covered in the aforementioned paper [1].

Ovarian cancer

Ovarian cancer is one of the most lethal gynecological malignancies, and despite its relatively low prevalence, is responsible for more deaths of middle-aged women than the approximately 10-fold more prevalent breast cancer. Part of the reason for the increased patient mortality is that the majority of HGSOCs are diagnosed late (stages III, VI) which prevents curative therapy by surgery and chemotherapy. There is convincing data demonstrating that detection of many cancers at an early stage, including ovarian cancer, leads to superior clinical outcomes (disease-free and overall survival) [2,3]. Motivated by this knowledge, the National Cancer Institute created the organization named EDRN (Early Detection Research Network), which supports discovery and validation of new biomarkers, in collaboration with researchers, charity organizations and industry [4]. EDRN has already spent more than $100 million for this task. One landmark study sponsored by EDRN on ovarian cancer screening will be briefly commented upon below, and the data will be contrasted with those of Paracchini and colleagues [1,5]. Large, prospective clinical trials of ovarian cancer screening were conducted, such as the UK Collaborative Trial of Ovarian Cancer Screening (UKCTOCS) [5], using either a biochemical serum test (marker CA125), transvaginal ultrasound or combination of the two tests (multimodal screening) and the Prostate, Lung, Colorectal and Ovarian (PLCO) trial in the US [6]. These trials, conducted among average-risk, asymptomatic women of ages 50-74 and 55-74 respectively, found that ovarian cancer mortality did not significantly differ between screened and unscreened women [5-7]. The U.S. Preventive Services Task Force (USPSTF) recommends population screening for only four cancer sites (colorectal, lung, breast and cervical) and ovarian cancer is not included. Thus, ovarian cancer screening with currently available methods appears to have no net benefit [8].

Biomarkers for ovarian cancer

Hundreds of potential blood-based biomarkers for ovarian cancer detection and management have been evaluated. The latest advance is multi-cancer detection by "liquid biopsy" which involves molecular analysis of circulating tumor DNA [9,10]. These tests have not yet been validated for clinical use, and prospective trials are ongoing [9,11]. An ambitious project sponsored by EDRN [7] examined 49 of the most promising serum HGSOC biomarkers for which a reliable assay was available, for their potential to diagnose asymptomatic/preclinical ovarian cancer by using the PLCO blood collection. Specimens were collected at diagnosis, within 6 months after the time of diagnosis and >6 months after diagnosis (up to 18 months). Top performing markers included CA125, human epididymis protein 4 (HE4), transthyretin, CA15.3, and CA72.4, with sensitivity at 95% specificity ranging from 0.73 to 0.40, which declined when drawing of blood occurred >6 months after diagnosis [7]. In the study, CA125 remained the single-best biomarker for specimens collected at any time, despite the relatively low sensitivity and specificity of CA125 in pre-diagnostic samples still being problematic for screening (see below).

The EVA test and its performance for ovarian cancer screening

Malignant HGSOC cells that originate from tumors, mostly in the fallopian tube and ovarian epithelium [11], are shed into the tubes and end up at the uterine cervix, intermixed with non-cancerous cells and other debris, where they can be harvested with a Pap smear collection method and isolated DNA. This process is reminiscent of the liquid biopsy [9,10], whereby tumor cells and circulating free DNA are shed into the systemic circulation. The isolated DNA can be analysed for ovarian cancer-related mutations, such as mutations of the gene p53 and other genes. The authors chose instead to analyze genomic instability by profiling copy number variation through low-pass whole-genome sequencing, which supports a more specific assay than by profiling tumor-associated mutations. As a measure of the overall genomic instability, they used the copy number profile abnormality score (CPA), defined in their paper [1]. The CPA reflects a comprehensive quantification of unbalanced genomic traits (gains and losses), and the higher the CPA value, the greater the genomic instability. In this setting, at a specificity of 96%, the sensitivity was 75.4% [1]. These reported numbers are almost identical to the best blood-based ovarian cancer biomarker, CA125 (sensitivity of 73% at 95% specificity) [12]. An important limitation of the EVA test is that the test is equivocal in about 14% of the patients [1]. An advantage of EVA, however, is that it is claimed to detect cancer up to 9 years before diagnosis, although two patients changed status (one from positive to equivocal and one from equivocal to positive) in longitudinal samples [1].

Positive predictive value and negative predictive value (PPV, NPV)

The authors do not mention the positive and negative predictive value (PPV, NPV) of their test [1]. These performance parameters are the most important for screening tests for any disease. In addition to a well-performing test, the criteria for screening for any disease has been defined by Wilson and Jungner in 1968 [13]. Below, we will only focus on the screening test.

The asymptomatic patient who undergoes screening for a disease does not understand terms like sensitivity and specificity, which describe the effectiveness of the test in groups of diseased and non-diseased subjects (but not for the testing individual). The individual being tested is interested to know what their chance is to have or not have the disease if their test is positive or negative. PPV represents the chance of having the disease if the individual is test-positive. NPV represents the chance of not having the disease if their test is negative. Below, the PPV and NPV of the EVA and CA125 tests will be calculated for comparison, under a hypothetical but realistic scenario whereby women are between the ages of 50-74 in a population, and the prevalence of ovarian cancer is 0.5% (as described in reference [5]). Please refer to Table 1 for numerical values.

Table 1: PPV and NPV of EVA test, CA125 and 3 hypothetical tests with fixed sensitivity and variable specificity, as shown.

Test name	EVA Test	CA125	Hypothetical test #1	Hypothetical test #2	Hypothetical test #3	EVA Test modified*
Sensitivity, %	75%	73%	90%	90%	90%	75%
Specificity, %	96%	95%	98%	99%	99.50%	96%
Population	100,000	100,000	100,000	100,000	100,000	100,000
Ovarian cancer prevalence #1	0.50%	0.50%	0.50%	0.50%	0.50%	5%
Diseased women	500	500	500	500	500	5,000
Non-diseased women	99,500	99,500	99,500	99,500	99,500	95,000
Test positive diseased women (true positives, TP)	375	365	450	450	450	4,500
Test negative non-diseased women (true negative, TN)	95,520	94,525	97,510	98,505	99,002	91,200
Test positive non-diseased women (false positives, FP)	3,980	4,975	1,990	995	498	3,800
Test negative diseased women (before false negatives , FN)	125	135	50	50	50	500
Positive predictive value(TP)/ (TP+FP)x100, %	8.6	6.8	18	31	47	54
Negative predictive value(TN)/ (TN+FN)x100, %	99.9%	99.9%	99.9%	99.9%	99.9%	99.4%

#1,2,3.For women of ages 50-74 as per [5]
*Altered numbers of the EVA test based on a hypothetical scenario

In a population of women ages 50-74 old, the prevalence of ovarian cancer is about 0.5% [5]. The screening test EVA has a sensitivity of 75% at a specificity of 96%. Among 100,000 women in the screened population, there are 500 women with ovarian cancer and 99,500 women with no cancer. The test will identify 375 women who have cancer (true positive, TP) (500 x 0.75) and it will miss 125 diseased women (false negative, FN) (500 x 0.25). The test will also be negative for 95,520 women (true negative, TN) (99,500 x 0.95) and 3,980 women will be positive (false positive, FP) (99,500 x0.04). The PPV of the EVA test will then be (375(TP)/(375(TP) + 3,980 (FP))) x100=8.6%. By using similar calculations for the classical and best ovarian cancer biomarker (CA125) with sensitivity of 73% and a specificity of 95%, the PPV of CA125 is 6.8%. The NPV of the EVA and CA125 tests, using the formula NPV=(TN)/(TN+FN) x100, the NPV is 99.9%. For discussion purposes, it is also useful to calculate the PPV and NPV of a test with a fixed hypothetical sensitivity of 90% (which is acceptable for a good screening test) and hypothetical specificities higher than the EVA and CA125 tests, such as 98%, 99% and 99.5% (Table 1). The PPV and NPV of the EVA test was calculated with a modified disease prevalence of the screened population from 0.5% to 5%. The latter scenario could fit with women who are at higher risk of ovarian cancer such as family predisposition, symptoms, or presence of abdominal masses of unknown pathologies or with more prevalent cancers such as breast cancer. As mentioned, screened individuals for ovarian cancer or any other disease are interested about their own risk, and not parameter/risks that are associated with groups of patients (such as sensitivity and specificity). The PPV and NPV are the most informative indicators that explain the generated results of testing. Importantly, the risk of a woman having ovarian cancer before the test is done is equal to the disease prevalence, in this case 0.5%. Before screening, these women also have a high chance (99.5%) of not having the disease. When the test is performed, the risk is elevated from 0.5 % to about 8% for EVA and to about 7% for CA125 if the test is positive. When the test is negative, the chances of not having the disease is decreased

from 96 or 95% to 99.9% (Table 1). With such low PPV of EVA and CA125 tests (7-8%) there is doubt that many women will choose invasive laparoscopic or other surgical interventions to confirm or exclude presence of HGSOC. In Table 1, the PPV is calculated for a hypothetical, more specific test (specificities of 98%, 99% and 99.5%) at a fixed sensitivity of 90%. In this case, the PPVs increase to 18%, 31% and 47%, respectively, and laparoscopic verification is likely acceptable to these women. The EVA test could have a PPV of >50% in a screened population with prevalence of 5% (Table 1).

Conclusion

The conclusion from the aforementioned discussion is that the EVA and CA125 tests are not effective and likely not acceptable for population screening of average risk women of 50-74 years old for HGSOC. Despite their similar performance for screening, the CA125 test, invented 40 years ago [12], has important advantages over the EVA test. It is known that the performance of diagnostic tests is reduced when they migrate from the discovery lab to the clinic. This notion remains to be verified for EVA. While the CA125 test is a simple ELISA-type assay in serum, EVA is more technically demanding, slower and likely much more expensive. EVA gives equivocal results in about 14% of patients and predictably it will be less precise and less reproducible than a well-established ELISA assay for CA125. This raises concerns regarding its clinical applicability, with results requiring sufficient management in a clinical setting, including using potential follow-up tests or protocols that have been discussed elsewhere [14]. Furthermore, the implementation of EVA-like tests in clinical practice will require appropriate equipment, personnel training, direct and indirect costs of running the test and time, which, taken with the previously mentioned caveats, may prove unfeasible for widespread adoption. There is a light at the end of the tunnel, however. A potential distinct advantage of EVA is its hypothesized ability to diagnose ovarian cancer 9-11 years before clinical diagnosis. If this is confirmed, it could facilitate cures of the disease with early interventions, despite its low PPV.

Author's Disclosure statement

MKC and EPD have no conflicts to report.

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