Published in final edited form as:
Int J Gynecol Cancer. 2012 May ; 22(Suppl 1): S24–S26. doi:10.1097/IGC.0b013e318256488a.

OCS: Development of the Risk of Ovarian Cancer Algorithm (ROCA) and ROCA screening trials

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Abstract

Ovarian cancer is most often detected in late stage when prognosis is poor; in contrast, prognosis is excellent when detection occurs in early stage. Early detection with regular biomarker tests may reduce disease specific mortality. Two screening trials with annual CA125>35U/mL demonstrated promise. Before undertaking larger trials, statistical analyses of serial CA125 levels showed each woman has her own baseline level, and in ovarian cancer cases, CA125 rose rapidly from her baseline following a change-point. Improved early detection of ovarian cancer may result if each woman were tested for the presence of a change-point CA125 profile. Using the serial CA125 from the completed trials, a statistical method was developed to measure the probability a change-point had occurred. Subsequent screening trials implemented the risk of ovarian cancer algorithm (ROCA) in which screening decisions are made on the basis of the risk of having a change-point. Development of ROCA is described and ROCA trials are listed.

Introduction

In 80% of cases, ovarian cancer is detected in late stage when prognosis is poor with five-year survival rates less than 20%. In contrast, when detected in early stage, either serendipitously when oophorectomy accompanies hysterectomy, or the rare cases where the disease remains confined to the ovaries but is sufficiently large to cause symptoms, five-year survival often exceeds 85%. The high rate of late stage detection under standard care with the vast contrast in survival between early and late stages, leads to the hypothesis that early detection through regular tests may reduce disease specific mortality.

Following publication of the successful use of serum CA125 as a blood test for second look surgeries, two screening trials of CA125 for early detection of ovarian cancer were initiated. The first was in the UK where 22,000 women age>45 had a prevalence screen,[1] and the second in Sweden where 5,550 women age>40 had two annual screens.[2] The workup for a positive CA125 test was an ultrasound scan of the ovaries. Since ovarian cancer has a relatively low annual incidence of 50 per 100,000 in postmenopausal women, screening might have led to too many surgeries on women without ovarian cancer for each case of ovarian cancer as surgery provides the only definitive diagnosis. The literature has suggested an ovarian cancer screening program lead to no more than ten surgeries to identify one screen detected ovarian cancer.[3] The serial combination of a blood test, followed by an imaging test for women with a positive blood test, provided a combined false positive rate of 0.1 – 0.2%, a specificity in excess of 99.8%. The number of false positive surgeries per true positive surgery was less than five in the UK trial and two in the Swedish trial.

The often-raised concern that ovarian cancer had too low an incidence for screening to be sufficiently specific was clearly countered by the excellent specificity and acceptable positive predictive value (PPV) in both trials. Nonetheless there remained concern over the assumed low sensitivity for early stage disease, particularly as CA125 was regarded as a

marker of late stage, with only 50% of early stage cases having elevated levels compared to 90% of late stage cases. Standard care results in 20% of cases detected in early stage. The two studies provided promising results of 40% and 50% sensitivity for early stage ovarian cancer. Yet the small number of cases was not sufficient to remove the concern over CA125's purported lack of sensitivity for early stage disease.

To this end, statistical analysis of the two trials demonstrated longitudinal features of CA125 that may contribute to addressing these concerns. Graphs of serial CA125 levels for each women classified by disease status indicated that for most women without ovarian cancer the CA125 profile was relatively flat. Some women had initial levels above 100 that remained above 100 throughout the trial with no subsequent diagnosis of ovarian cancer. For women with ovarian cancer however, the CA125 profile showed rapidly increasing levels above each woman's baseline prior to diagnosis. An increase in screen sensitivity might be obtained through utilizing this contrast in CA125 profile while maintaining the very high specificity previously established. A woman with a low baseline followed by a change-point where CA125 levels increase significantly above the baseline, may be detected earlier than when a fixed reference level of 35U/mL is applied. Conversely, a woman with a high yet steady CA125 would yield in an appropriately negative test result, in contrast to a fixed reference level.

Risk of Ovarian Cancer Calculation

To maximize the value of this insight on the differential longitudinal behavior of CA125, formal statistical modeling was applied to the serial CA125 data. As standard statistical assumptions such as a Gaussian distribution were more closely followed on the log(CA125) scale, modeling proceeded on the log scale. Separate statistical models were developed for ovarian cancer cases and for all other women. In women without ovarian cancer, an individual baseline and variation about the baseline was estimated for each woman, as well as estimating the distribution of baseline levels and variations across the population. Modeling the population level with a hierarchical model conferred improved estimates for individual baselines and variations given the few data points per woman; the hierarchy being the baselines between women at the population level and the CA125 values within a woman at the individual level. In women with ovarian cancer, the expected CA125 levels followed a change-point model for each woman, comprising the baseline level, the time of ovarian cancer CA125 production following tumor inception, and the rate of rise following the change-point. A hierarchical model again conferred improved estimation for each woman of her baseline, change-point, rate of rise, and variation about the expected level. The statistical analysis results in a hierarchical change-point model describing the behavior of CA125 over time in ovarian cancer cases, and a hierarchical flat profile model describing the behavior of CA125 over time in all other women.[4,5]

Estimates from the model for women without cancer clearly showed substantially less variation within a woman with an average CV about a woman's CA125 baseline of 25% compared to the variation of CA125 baselines between women with a CV of 50%. The significantly lower within woman CV compared to the between women CV confirmed the graphical observation that each woman has her own CA125 baseline.[5]

The systematic and objective calculation of the risk of having undetected ovarian cancer is built on the two statistical models above, one estimated from the ovarian cancer cases, and the other from all other women. To calculate the risk for a new woman with a series of CA125 values, the average distance between her CA125 profile and the change-point profiles is calculated and compared to the average distance between her CA125 profile and the flat profiles. The more her profile looks like the profiles from previously identified

ovarian cancer cases the greater is her estimated risk of having ovarian cancer. The ratio of the two distances provides the odds ratio for the woman having a change point. The initial odds for having ovarian cancer is given by the risk based on the woman's age as derived from population tumor registries multiplied by two years, the estimated average duration of pre-clinical ovarian cancer.[5] For a woman of 50 years of age, the initial risk is 1 in 2,000, while for a woman of 75 years of age the initial risk is 1 in 1,000. The final odds is the product of the initial odds and the odds ratio calculated from her serial CA125 values, which is readily converted to a probability, or risk, of having a change-point, interpreted as the risk of having undetected ovarian cancer. If a woman aged 50 has a sequence of CA125 values that is 10 times as close to a change-point profile as to a flat profile, then her odds of having ovarian cancer are estimated to be 10 times 1 in 2,000, that is 1 in 200.

Risk of Ovarian Cancer Algorithm (ROCA)

Having developed the machinery for calculating a risk of having a change-point based on a woman's age and CA125 profile, the calculation is implemented in a screening program by prescribing decisions for each level of risk. The implementation defines a screening algorithm, termed the risk of ovarian cancer algorithm (ROCA). Within ROCA, intermediate and elevated levels of risk are defined, the first indicating a low level screening intervention, and the second a high level intervention. In trials of women at normal risk where CA125 is tested annually, an intermediate ROCA risk triggers a CA125 test in three months and the risk is recalculated. Elevated ROCA risk triggers referral to a trans-vaginal scan (TVS). In women at high risk due to a multiple family history of ovarian or breast cancers, an intermediate ROCA risk triggers referral to TVS, while an elevated ROCA risk results in a referral for TVS and a consult from a gynecological oncologist. Following each new CA125, the risk is recalculated and the woman re-triaged. Thus ROCA efficiently distributes screening resources on a dynamic basis and rapidly triages women with significantly rising CA125 levels to TVS, while assigning normal testing frequency to women with high but stable CA125 levels.

Screening trials implementing ROCA

Following the first two ovarian cancer screening trials, six subsequent multicenter trials have implemented ROCA wherein decisions are made on the basis of the risk of having a change-point, a surrogate for a woman's risk of having undetected ovarian cancer. The trials are:

1. The first ROCA trial (1995-2001) screened 14,000 postmenopausal normal risk UK women[6]. Intermediate endpoints of sensitivity, specificity, and PPV provided justification for funding and conducting the next trial.
2. UKCTOCS (UK Collaborative Trial of Ovarian Cancer Screening – 2001-2015) is a screening trial of 200,000 postmenopausal women age>50 randomized equally to a screening arm or a standard care arm, with ROCA applied to half the screening arm and ultrasound as a primary screen to the other half, with definitive endpoint of ovarian cancer mortality.[7]
3. ROCA trial in the high-risk women, initiated in 2001 under the NCI's Cancer Genetics Network, the Early Detection Research Network (EDRN), and the ovarian SPORE program, is a single arm trial of 2,400 high-risk women age≥30 where CA125 tests are scheduled every three months. Results expected in 2012.[8]
4. GOG0199 is a two arm prospective study begun in 2003 of women at high risk who chose between immediate risk reducing salpingo-oophorectomy (RRSO) and screening with ROCA. Almost 1,600 women chose ROCA, although during the

course of the study almost 400 screening patients switched to RRSO. Results expected in 2013.[9]

5. UKFOCSS is the UK Familial Ovarian Cancer Screening Study with two phases. The first phase, initiated in 2002 on 3,500 high risk women, screened with an annual CA125>35U/mL, and a second phase on 4,500 women begun in 2007 with four monthly CA125 tests interpreted with ROCA. Phase 1 results expected in 2012.

6. NROSS, the Normal Risk Ovarian Screening Study, a US trial initiated in 2001 of 3,200 normal risk postmenopausal women implements ROCA analogously to the UKCTOCS ROCA arm. Results expected in 2013.

Acknowledgments

Dr. Skates was supported by the NCI's Early Detection Research Network grant U01–CA152990, and the Julie Fund at the Massachusetts General Hospital.

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