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Commentary

Commentary on changing the risk threshold for surgical prevention of ovarian cancer

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Introduction

Ovarian cancer (OC) remains a lethal disease and a major cause of gynaecological cancer deaths, particularly in western countries. Despite advances in treatment, there have been only marginal improvements in survival rates over the last 30 years. Additionally, the number of OC cases in the UK is estimated to increase by 27–45%, which translates to a 15% rise in the incidence rate by 2035.[1] A national OC screening programme is unavailable as this has not yet shown a conclusive mortality benefit.[2] Hence, primary prevention continues to be the cornerstone in reducing the burden of OC and improving health outcomes. This is essential to achieve long term transformational change and cost-efficiencies in our health-system. Its importance is amplified by current economic restraints, with a ~2.4% funding shortfall reported in the UK National Health Service (NHS).

Risk-reducing salpingo-oophorectomy (RRSO) is the most effective method of preventing OC. It is usually feasible as a laparoscopic day-case procedure, though an overnight stay may at times be needed. This option of surgical prevention has traditionally been offered to high-risk women with *BRCA1/BRCA2* mutations or those with Lynch syndrome, in whom the lifetime OC risk ranges from 10 to 40%. The procedure has been shown to be cost-effective in this patient population.[3] In *BRCA1/BRCA2* carriers, RRSO is associated with a 79% reduction in OC risk (HR = 0.21, CI:0.12,0.39)[4] and a reduction in OC and all-cause mortality.[5] There is a small (2–4%) residual risk of primary peritoneal cancer over 20 years follow-up.

Among average-risk women, RRSO is associated with a 94% reduced risk of OC (HR = 0.06, CI:0.02,0.17)[6] and is also a potentially cost-effective option for this group of women. This had not previously been explored. We recently estimated the OC-risk thresholds at which RRSO would be cost-effective in premenopausal[7] and postmenopausal[8] women. To do this, we used a decision-analytic modelling framework. Our decision-analytic modelling shows that premenopausal RRSO is cost-effective at >4% lifetime OC absolute risk, with an incremental cost-effectiveness ratio (ICER) of UK£19,536/quality-adjusted life-year (QALY), leading to an averaged >42.7 days' gain in life-expectancy if hormone-replacement-therapy (HRT) compliance is high.[7] In postmenopausal women >50 years, RRSO is cost-effective at ≥5% lifetime OC-risk levels, with an ICER of UK£15,247/QALY and life-expectancy increased by an average of >29.2 days.[8] At values above these risk levels, RRSO saves more life-years and QALYs and is highly cost-effective at the National Institute for Health and Care Excellence (NICE) £20,000–30,000/QALY willingness-to-pay threshold. While the number of days gained in life-expectancy appear small, it is important to highlight that these values are averaged across the population, and hence, for the individual woman in whom OC is prevented, this number is many-fold higher. As a comparator, undergoing cervical cancer screening leads to an average gain in life-expectancy of 11.6–32.4 days,[9] and colorectal cancer screening to a gain of 55–91 days.[10] These analyses fulfil NICE requirements for health-economic decision-making and are necessary for assessing the balance of costs and consequences before recommending policy changes

related to new interventions such as new thresholds for surgical prevention.

It is estimated that around 9% of the UK population has an OC risk ≥5%, and this group accounts for 53% of OC cases, while 13.4% of the population is at >4% risk and accounts for 62.8% of OC cases.[11] The availability of data supporting surgical prevention at intermediate (5–10%) levels of OC-risk provides a significant opportunity to reduce OC incidence and make a much greater impact on the burden of this fatal disease. Genetic testing for more recently identified moderate-risk OC genes *RAD51C, RAD51D,* and *BRIP1* is now clinically available. Mutations in these genes are associated with lifetime risks in the range 5.8 to 11%, although confidence intervals are wide. As more data accumulate, the precision of these estimates will improve and CIs narrow. We feel that, following proper counselling, RRSO should be made available to unaffected women with these moderate penetrance mutations who have completed their families. Data on OC has not yet been reported for *RAD51C* and *RAD51D* carriers under 40 years of age or for *BRIP1* carriers under age 50. Hence, surgical prevention in these women is best delayed until after age 40 or 50, respectively. First-degree relatives of women with OC and *BRCA1/BRCA2*-negative women with no known pathogenic mutations in the family but a strong family history of OC or OC and breast cancer (BC) are also at intermediate risk and could qualify for surgical prevention. For intermediate-risk women with no gene mutation, we would suggest RRSO after age 50 or the menopause.

We recently published OC-risk models that can identify women at these intermediate-risk thresholds.[11,12] Incorporating SNPs/common genetic variants into models permits more accurate risk prediction. Three-quarters of the familial-relative risk for OC is not accounted for by *BRCA* mutations, and using a SNP-based polygenic risk score in combination with family history can identify women above the 5% risk threshold and improve risk prediction in *BRCA*-negative women.[11] Using a combination of known OC risk factors — endometriosis, tubal ligation, parity, contraceptive pill, and family history (first-degree-relative with OC) — along with SNP profile, it is possible to identify eight categories with a ≥5% life time OC risk.[12] The authors estimated that 2% of women in the USA would be at ≥5% lifetime OC risk.[12]

More-sophisticated models incorporating epidemiological data, next-generation-sequencing driven panel-testing, moderate-penetrance genes, and an increasing number of OC SNPs are under development within the PROMISE (Predicting Risk of Ovarian Malignancies, Improved Screening and Early detection) programme and OCAC (Ovarian Cancer Action Consortium). As these models get validated and are made available, the capability to predict risk will increase and its clinical application will expand even more in the near future. Going forward, it could provide a potential opportunity for population-based risk stratification for OC for targeted surgical prevention. A pilot study to assess feasibility of such an approach will commence in summer of 2017.

Limitations

While acceptability of RRSO for high-penetrance gene mutations is well established, with uptake rates of up to 70% reported, the acceptability and uptake at intermediate-risk thresholds is unknown as RRSO was not previously available at these levels. The risk of surgical complications from RRSO is around 3% and needs to be an important part of informed decision-making on whether to undergo the procedure. Another important issue for women undergoing premenopausal oophorectomy is the detrimental consequences of premature surgical menopause. It is associated with osteoporosis, vasomotor symptoms, increased risk of cardiovascular disease, and detrimental impact on sexual-function. An absolute increase in cardiovascular mortality of 3.03% has been described in women who do not take HRT.[6] The harmful side effects can be ameliorated by HRT and are seen predominantly in women <45 years who decline or are unable to receive it. Studies suggest that some of the protective neurocognitive effects may not be fully addressed by HRT, however. Short-term HRT from premature surgical menopause until age 50 has not been shown to increase BC-risk. The importance of these issues in decision making is well documented in high-risk women such as *BRCA1/BRCA2* carriers, as a number of them delay RRSO till after menopause. Despite the downsides, high satisfaction rates of >85% are reported with RRSO in *BRCA1/BRCA2* carriers. Corresponding data for intermediate-risk women are not available.

Role of hysterectomy

The utility of concomitant hysterectomy as part of the surgical procedure with RRSO to prevent OC has been debated. Practice varies in different parts of the world, with hysterectomy more prevalent in some countries like the USA and Australia. In a number of these countries, a significant proportion of medical practice is private and insurance-driven, which may also influence differences in approach. Proponents of a concurrent hysterectomy cite the benefits of HRT with estrogen alone and avoidance of cervical smears. Hysterectomy is a major operation with significantly higher morbidity, longer operating time, hospital stay, and recovery than bilateral salpingo-oophorectomy. We, and most UK centres, don't routinely undertake hysterectomy for OC prevention in high-risk women for a

number of reasons. Hysterectomy is not routinely offered as an alternate to the progesterone component of HRT in gynaecological practice. The large numbers of women on HRT who attend routine gynaecological menopause clinics are not offered this. Short-term HRT given in this context until the average age of menopause (51 years) does not increase BC risk.[13] The Mirena® intrauterine system (intrauterine progestogen coil) with minimal systemic absorption can be used for the progestogenic component of HRT. While one recent report suggests the relative risk of serous endometrial cancer (EC) may be increased in *BRCA1* women,[14] corroborating studies are awaited. Additionally, the serous subtype comprises a very small proportion (~6.5%) of ECs, and the overall EC risk is not significantly increased in *BRCA1* women. Hence, it is not currently our practice to offer this routinely. Premenopausal *BRCA*/high-risk women with ER+ BC on tamoxifen have a ~2–3-fold increased risk of endometrioid EC. However, the absolute EC-risk is still very low (2.3 cases/1000 women/year of use),[15] with a favourable risk profile in premenopausal women and increased EC risk reported in women ≥50 years.[15] We do not feel this risk justifies routine hysterectomy, but any unscheduled/abnormal bleeding is promptly investigated. This is consistent with ACOG and RCOG guidelines for tamoxifen. One clear exception is women with Lynch syndrome (lifetime EC risk ~40%), in whom hysterectomy is undertaken for surgical prevention.

Salpingectomy in high-risk women

The increasing acceptance of the tubal origin of OC has led to premenopausal early salpingectomy (ES) followed by delayed oophorectomy (DO) at menopause being proposed as a two-step OC prevention strategy for high-risk women. This enables women to obtain some OC-risk reduction while averting detrimental consequences of premature menopause. However, prospective data are lacking for (a) long-term endocrine function and menopause onset, (b) precise level of OC-risk reduction obtained, (c) quality of life, and (d) psychosocial impact. Concerns have also been expressed regarding long-term follow-up and attrition from DO. Some DO patients may develop OC, and this procedure will have been a failure.[16] While 70% occult *in situ*/invasive lesions identified at RRSO in *BRCA1/BRCA2* women are tubal, 30% are not.[17] Our understanding of the roles and interactions of the tube and ovary in OC etiopathogenesis is still incomplete and evolving. Not all STIC (serous tubal intraepithelial carcinomas) are precursors of OC, and some may be metastatic.[18] Only up to 61% of OCs have STICs associated with them. Salpingectomy will therefore not prevent all OC. Surgico-pathological protocols for undertaking ES and managing occult lesions need standardisation, and utility scores required for health-economic analysis need developing. Given the limitations highlighted above, there remains significant uncertainty around the cost-effectiveness of an ES strategy. It is best that ES-and-DO is evaluated/undertaken within the safe environment of a clinical trial, not routine practice. Salpingectomy studies are underway in France (Radical Fimbriectomy study NCT01608074), USA (MD Anderson: NCT01907789), The Netherlands (TUBA study NCT02321228). A UK study (PROTECTOR) will commence later this year.

The contraceptive pill

There is good evidence to show that oral contraceptive pill (OCP) use significantly reduces OC risk in average-risk women.[19] The level of risk-reduction increases with duration of use, and benefits persist for 30 years after stopping the pill. The risk-reduction obtained is 22% with 1–4 years use, 35% after 5–9 years use, 45% with 10–14 years, and 58% with ≥15 years use.[19] Data from high-risk populations suggest similar benefits are found in *BRCA1/BRCA2* carriers, with 5-years' OCP use halving the OC risk (risk-reduction ranges from 33%–80% in *BRCA1,* 58%–63% in *BRCA2).*[20] Although specific data for intermediate-risk women are lacking, OCP use is likely to provide similar benefits to them. A disadvantage is an increased BC risk in average-risk women (RR = 1.24, CI:1.15,1.33) for up to 10 years after stopping the pill. However, the absolute increase in BC-risk is small. OCP is contraindicated in women who have had BC, but not in those with a family history of BC. Studies evaluating the impact of OCP on BC risk in *BRCA1/BRCA2* carriers show conflicting results. Meta-analysis from case-control data shows no increase in BC risk (*BRCA1* ES = 0.78, CI:0.59–1.04; *BRCA2* ES = 1.04, CI:0.81–1.32),[20] but, cohort data report an increased BC risk (*BRCA1* ES = 1.59, CI:1.32–1.92; *BRCA2* ES = 1.85, CI:1.30–2.64).[20] The absolute increase in risk is probably small if the pill is taken at a young age. A progesterone-only pill, implants, and injectable contraception may be safer options.

The OC-risk threshold for surgical prevention has previously been set too high. We call for a review of this threshold. Changing this to around the 5% lifetime risk level provides an important cost-effective strategy for OC prevention. Widening access to RRSO will also require health professionals to ensure that women who undergo premenopausal oophorectomy appreciate the importance and need for HRT until the age of natural menopause. A mechanism will be needed to ensure compliance that includes sustained access to prescriptions and long-term monitoring. Health-service capacity issues will need to be addressed, including expansion in downstream management pathways. The rising costs of OC drugs and treatment, persistent poor survival outcomes, lack of an effective screening programme, and a predicted increase in burden of disease emphasise the need for

shifting focus towards better-targeted cost-effective prevention. It is important we seize this opportunity to maximise prevention of this devastating disease.

Disclosure of interests

None declared. Completed disclosure of interests form available to view online as supporting information.

Ethical approval

This commentary is not new research and did not require ethical approval.

Contribution to authorship

RM prepared an initial draft that was critically contributed to by all authors UM, AA, LP, RL. All authors approved the final version of the manuscript.

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