Why have ovarian cancer mortality rates declined? Part III. Prospects for the future

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HIGHLIGHTS
• Up to 17% of ovarian cancers are potentially preventable through population-based genetic testing of known cancer genes.
• To improve the cure rate there must be an increase in the proportion of women with no residual disease after primary surgery.
• This may be achieved through a combination of aggressive surgery and wider application of the CA125 screening test.

ABSTRACT
Over the last 40 years, the age-adjusted ovarian cancer mortality rate in the USA declined by 23%. The decline in mortality paralleled a decline in incidence, which was largely due to changes in reproductive risk factors. There was no reduction in ovarian cancer case-fatality at 12 years, indicating that improvements in early detection or in treatment did not contribute to the decline in mortality. Here, we discuss potential strategies to further reduce ovarian cancer mortality through prevention, early detection and treatment. The first approach is to increase genetic testing, in order to identify women who are at a high risk of developing ovarian cancer and offer them preventive bilateral salpingo-oophorectomy. At present, up to 17% of ovarian cancers are potentially preventable through population-based genetic testing of known ovarian cancer susceptibility genes. The second approach is to increase the proportion of ovarian cancer patients who achieve a status of no residual disease through primary debulking surgery and subsequently receive adjuvant intraperitoneal chemotherapy. We believe that through a combination of screening to better identify low-volume advanced stage ovarian cancer, aggressive surgery to leave no residual disease and adjuvant intraperitoneal chemotherapy, the cure rate of ovarian cancer might be improved significantly.

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(18%) was between 2001 and 2011, when mortality fell from 9.0 per 100,000 per year to 7.5 per 100,000 per year. In Part I, we showed that the decline in ovarian cancer mortality to a large extent is the result of a decline in ovarian cancer incidence [1]. The decline in incidence was mainly due to the introduction of oral contraceptives in 1960 and the expansion in their use until 1990. There was no increase in the proportion of localized ovarian cancers, indicating that a stage-shift (i.e., due to early detection) did not contribute to the decline. In Part II, we showed that the decline in mortality was not due to a reduction in case-fatality; despite the introduction of chemotherapy, targeted agents and aggressive surgery, there has been no increase in the cure rate of ovarian cancer [2]. Taken together, these observations suggest that formal efforts at prevention, early detection and treatment over the past 40 years have not led to a reduction in deaths from ovarian cancer.

In the following pages, we discuss potential strategies to reduce ovarian cancer mortality through prevention (i.e., expand genetic testing and the use of preventive surgery), early detection (i.e., wider application of the CA125 screening test to identify low-volume advanced stage ovarian cancer), and treatment (i.e., aggressive surgery with the goal of no residual disease followed by intraperitoneal chemotherapy).

2. Prevention

2.1. Genetic testing: high-risk women

The most effective strategy for the prevention of ovarian cancer is bilateral salpingo-oophorectomy. The decision to undergo a prophylactic oophorectomy should be based on the (remaining) risk of developing ovarian cancer over the woman’s lifetime, relative to the side effects and morbidity associated with the surgery and the resulting hormone withdrawal. Bilateral oophorectomy is more problematic for premenopausal women than for postmenopausal women, because of the acute symptoms and long-term health consequences associated with surgical menopause [3]. From a public health perspective, the optimal threshold for oophorectomy will also depend on cost-effectiveness. There is currently no consensus on the absolute level of risk that justifies a prophylactic oophorectomy. For the purpose of this discussion, we propose that a residual lifetime risk of ovarian cancer of 5% or more may warrant a recommendation for prophylactic oophorectomy, in particular in women after menopause [4]. The average lifetime risk of ovarian cancer for women in the United States is about 1.4%, and the average age at onset of ovarian cancer is about 60 years. At present, approximately 17% of all ovarian cancers are attributable to a mutation in an ovarian cancer susceptibility gene that confers a lifetime ovarian cancer risk of 5% of more (Table 1). Mutations in BRCA1 and BRCA2 are responsible for most of these (13% of all ovarian cancers) [5]. The average lifetime risk of ovarian cancer for women with a BRCA1 mutation is about 40% and the average age at onset is about 50 years [5,6]. The lifetime risk of ovarian cancer for women with a BRCA2 mutation is about 20% and the average age at onset is about 57 years. In aggregate, mutations in the four mismatch repair genes MSH2, MLH1, MSH6 and PMS2 that cause hereditary non-polyposis colorectal cancer (Lynch syndrome) account for about 0.8% of ovarian cancers [7]. The lifetime risk of ovarian cancer for women with Lynch syndrome is about 8% [8], and the average age at onset of ovarian cancer is about 47 years [7]. Current guidelines recommend that women with a mutation in BRCA1, in BRCA2 or in a Lynch syndrome gene (MSH2, MLH1, MSH6 or PMS2) undergo a prophylactic bilateral salpingo-oophorectomy between ages 35 and 45 [9,10].

Mutations in three other genes, RAD51C, RAD51D and PPM1D also confer sufficiently high risks to warrant prophylactic oophorectomy. Mutations in RAD51C and RAD51D together account for about 1.6% of ovarian cancers and are associated with lifetime risks of about 10% [11,12]. Somatic mutations in PPM1D are found in the white blood cells of about 1.5% of ovarian cancer patients and confer a lifetime risk of ovarian cancer of about 25% [13,14]. The average age at onset of ovarian cancer is about 60 years in RAD51C mutation carriers, about 55 years in RAD51D mutation carriers and about 68 years in PPM1D mutation carriers, suggesting that for these women bilateral oophorectomy may be delayed until after natural menopause. Other genes that have been implicated in ovarian cancer susceptibility include PALB2 [15], BRIP1 [16] and TP53 [17]. Mutations in the latter genes are rare and the penetrance of mutations for ovarian cancer has not been established.

A mutation in one of these nine genes (Table 1) is present in about 17% of ovarian cancer patients. However, at present, few women who carry a mutation are identified before they develop ovarian cancer and few are given an opportunity for prevention. Despite the fact that genetic testing for BRCA1 and BRCA2 has been available since 1995, under the current testing protocol in Ontario, fewer than 4% of all ovarian cancers are potentially preventable (of a possible 13%) [18]. Realistically, only 1% of ovarian cancers are prevented [18]. Achieving maximum impact will require population-based genetic testing to identify women at high risk of ovarian cancer, followed by a recommendation for prophylactic bilateral salpingo-oophorectomy. For this approach to be feasible, the costs associated with genetic testing, with genetic counseling and with performing oophorectomies must decrease substantially.

For women without a genetic mutation, the potential for risk stratification is limited; i.e., in the absence of a mutation, few women will reach the surgical threshold of 5%. It is proposed that a high proportion of ovarian cancer heritability is due to multiple common genetic variants, each conferring modest effects [19]. To date, 17 single nucleotide polymorphisms (SNPs) have been identified in Genome Wide Association Studies that are associated with relative risks for ovarian cancer ranging from 1.1 to 1.4 [20]. The lifetime risk for a woman with multiple risk alleles is about 4%. It is estimated that fewer than 1% of women will have a lifetime risk above 4% because of multiple risk alleles [21]. Although the predictive ability of the 17 currently known SNPs is low, the discovery of common variants is still in progress, and it is possible that in the future the value of genotyping SNPs in identifying women at high-risk may improve [19]. A woman’s individual risk of ovarian cancer can also be predicted based on her age, her reproductive history and her family history. The risk to age 80 for women with exposure to each of the four reproductive risk factors (oral contraceptives, parity, breastfeeding and tubal ligation) is estimated to be about 0.35%, and the risk to age 80 for women exposed to none of the four main risk factors is estimated to be 2.8% [4]. Women with a family history of ovarian cancer are associated with an approximately two-fold increased risk of ovarian cancer [19].

Some women may exceed 5% risk threshold due to a combination of reproductive factors, single nucleotide polymorphisms and family history. In a recent study, Giannakeas et al. simulated the distribution of ovarian cancer risks to age 80 in the general population of Ontario, in a model based on reproductive factors (oral contraceptives, parity, breastfeeding and tubal ligation), family history, single nucleotide polymorphisms and BRCA1/2 mutations [4]. Only 0.7% of women in the population had a lifetime risk of ovarian cancer above 5% and 13% of all ovarian cancers developed in women with an a priori risk above 5%. The majority of women found to be at high-risk carried a BRCA1/2 mutation. When BRCA1/2 carriers were identified, but excluded, 0.2% of

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women had a risk above 5%, and 1.3% of all ovarian cancers were expected to develop in women above 5% risk. These data indicate that the majority of ovarian cancer patients at high-risk carry a mutation in BRCA1/2, and as a result, in order to prevent ovarian cancer in high-risk women, population-based genetic testing will be necessary. Furthermore, in order to prevent the majority of ovarian cancers in the population, it will be necessary to prevent ovarian cancer in women at average-risk.

2.2. Preventive surgery in average-risk women?

More than 80% of ovarian cancers occur in women with an a priori risk of less than 5%. At this level of risk, any preventive option must be safe and have few side effects. At present, prophylactic bilateral salpingo-oophorectomy is not recommended for women at average risk of developing ovarian cancer. However, elective bilateral salpingo-oophorectomy may be considered in women at average risk as an adjunct to hysterectomy [22]. Currently, about 15% of ovarian cancers are prevented each year as a result of elective bilateral oophorectomies in women undergoing hysterectomy for a benign condition (discussed in Part I). However, current guidelines recommend against elective oophorectomy in women below age 45, due to the potential adverse health effects of oophorectomy in premenopausal women in the absence of hormone replacement therapy (e.g., increased risks of cardiovascular disease, osteoporosis and cognitive impairment) [23]. In postmenopausal women, the health consequences of bilateral oophorectomy are less severe. It may be reasonable to recommend “opportunistic” oophorectomy for premenopausal women undergoing any abdominal surgery (up to 25% of all women).

An alternative surgical option for ovarian cancer prevention in premenopausal women is bilateral salpingectomy (i.e., preventive removal of the fallopian tubes) with ovariectomy preservation. Most high-grade serous carcinomas develop in the fallopian tube [24]. Removal of the fallopian tubes may thus prevent most high-grade serous ovarian cancers, while avoiding the acute symptoms and potential morbidity associated with chronic estrogen depletion. Recently, two studies have been published which evaluate ovarian cancer risk after salpingectomy in the general population. In a population-based case-control study from Denmark, bilateral salpingectomy reduced the risk of ovarian cancer by 42%, and tubal ligation reduced the risk of ovarian cancer by 12% (the risk of endometrioid carcinomas was reduced by 34% and the risk of serous carcinomas was reduced by 8%) [25]. In a population-based cohort study from Sweden, bilateral salpingectomy reduced the risk of ovarian cancer by 65%, whereas bilateral salpingo-oophorectomy reduced the risk of ovarian cancer by 94% [26]. To promote a further reduction in ovarian cancer mortality, it might be reasonable to recommend opportunistic bilateral salpingectomy for premenopausal women undergoing any abdominal surgery. No studies to date have examined the risk of ovarian cancer after salpingectomy in high-risk women [27]. At present, prophylactic bilateral salpingo-oophorectomy between age 35 and 40 should remain the standard of care for women with BRCA1/2 mutations.

3. A new approach to screening

The current approach to screening is based on the premise that ovarian cancer must be identified in stage I or stage II in order to achieve cure. Conventionally, this is done by screening asymptomatic women with CA125 at a cut-off of 35 U/ml, combined with transvaginal ultrasound. No screening protocol has yet been shown to reduce mortality from ovarian cancer [28], and current guidelines recommend against ovarian cancer screening in women in the general population [29]. In the preliminary report from the United Kingdom Collaborative Trial of Ovarian Cancer Screening, screening with CA125 (interpreted using the Risk of Ovarian Cancer Algorithm) and transvaginal ultrasound identified a greater proportion of women with stage I or stage II ovarian cancer (compared to a clinical series) [30]. The results from this trial with regard to mortality are expected in 2015.

The utility of CA125 as a screening test depends on the positive predictive value (i.e., the proportion of women with a positive screening test who have ovarian cancer). The positive predictive value of a screening test is influenced by the sensitivity (i.e., the proportion of women with ovarian cancer who have a positive test), the specificity (i.e., the proportion of women without ovarian cancer who have a negative test) and the prevalence of ovarian cancer in the population being screened.

Approximately 20% of ovarian cancers do not express the CA125 protein [31]. Thus, the maximum sensitivity that can be expected from CA125 screening is about 80%. Approximately 75% of all women with ovarian cancer have a CA125 of 35 U/ml or more at clinical presentation, 70% have a CA125 of 75 U/ml or more and 60% have a CA125 of 100 U/ml or more [32]. CA125 levels tend to correlate with tumor volume and vary by histological subtype. About 50% of women with stage I ovarian cancer present with a CA125 greater than 35 U/ml, compared to 90% of women with stage II to stage IV ovarian cancer [32]. About 85% of women with serous ovarian carcinoma present with a CA125 greater than 35 U/ml, compared to 65% of non-serous ovarian carcinomas [33,34]. About 5% of healthy women have a CA125 of 35 U/ml or more, 1% of healthy women have a CA125 of 70 U/ml or more and 0.1% of healthy women have a CA125 of 100 U/ml or more [35,36]. Due to the low prevalence of ovarian cancer in asymptomatic women at average-risk [28], the positive predictive value of a CA125 of 35 U/ml or more is only about 1% (i.e., one woman with ovarian cancer for every 100 women with a positive test).

We propose that in the future screening should focus on the detection of advanced stage ovarian cancer when the burden of disease is sufficiently low that a status of no residual disease can be achieved through surgery. The screening paradigm shifts when a cure for advanced stage serous ovarian cancer is possible (i.e., by achieving no residual disease through primary debulking surgery followed by treatment with intraperitoneal chemotherapy [2]). The majority of women with stage IIIa/IIib ovarian cancer (i.e., patients with retroperitoneal lymph node metastases or peritoneal metastases of less than 2 cm) will achieve a status of no residual disease through surgery, whereas only about 45% of patients with stage IIc/IV ovarian cancer are reduced to no residual disease [37]. By making low-volume, advanced stage ovarian cancer (stage IIIa/IIib) the target of screening, rather than stage I ovarian cancer, the threshold for CA125 can be raised from 35 U/ml to 70 U/ml. This reduces the sensitivity of CA125 for detecting all ovarian cancers from about 75% to 70%, but increases the specificity for healthy women from 95% to 99%. In asymptomatic women, the positive predictive value of a CA125 of 70 U/ml or more is about 5%. Raising the cut-off further, to 100 U/ml, reduces the sensitivity to about 60%, but increases the specificity to 99.9%, and increases the positive predictive value to 31%.

4. Treatment

Currently, there is a wide variation in ovarian cancer treatment. Although most women with advanced ovarian cancer are treated with a combination of chemotherapy and surgery, the approach to surgery, the timing of chemotherapy, and the route of administration of chemotherapy is not standard. The likelihood of a cure from advanced ovarian cancer (i.e., 12-year survival) is increased if there is complete surgical resection to no residual disease [38].

It is unclear if the survival advantage of no residual disease is the same whether it is achieved through primary debulking surgery or through neoadjuvant chemotherapy and interval debulking surgery. Two randomized trials comparing neoadjuvant chemotherapy with primary debulking surgery have been conducted [39,40]. Both trials report no difference in survival for patients randomized to neoadjuvant chemotherapy versus primary debulking surgery. In both trials,
neoadjuvant chemotherapy was associated with less treatment-related morbidity compared to primary debulking surgery, and fewer patients had any residual disease post-surgery. If survival were equivalent, neoadjuvant chemotherapy would be preferred to primary debulking surgery. However, in all studies the survival of patients with no residual disease after neoadjuvant chemotherapy is relatively poor [39,41,42]. If patients with no residual disease post-surgery have superior long-term survival rates, and if neoadjuvant chemotherapy is equivalent to primary debulking surgery in terms of survival, then increasing the proportion of patients with no residual disease post-surgery should correspond to increase in the long-term survival rate of the cohort. However, in the two trials, a much greater proportion of patients randomized to neoadjuvant chemotherapy had no residual disease after surgery compared to patients randomized to primary debulking surgery (50% versus 20% in one trial and 40% versus 17% in the other trial), yet neoadjuvant chemotherapy was not associated with increased survival [39,40].

Patients with any residual disease after primary debulking surgery derive little benefit from the procedure in terms of cure [38]. For these patients, treatment with neoadjuvant chemotherapy followed by interval debulking surgery may provide similar survival outcomes as primary debulking surgery, but with less morbidity. At present, neoadjuvant chemotherapy is commonly administered to patients with extensive disease that appears (by preoperative assessment) to be unresectable, or in patients who are considered to be poor candidates for aggressive surgery (i.e., elderly or obese women). No preoperative indices (i.e., imaging, biomarker expression or gene expression) have yet been able to accurately predict which patients cannot be expected to achieve a status of no residual disease through primary surgery (and who are therefore candidates for neoadjuvant chemotherapy) [43,44]. Recently, it has been proposed that laparoscopy can be used to reliably predict surgical resection to no residual disease [42,45]. Although this may help avoid the potential morbidity of primary surgery that results in sub-optimal residual disease, increasing the number of patients who receive neoadjuvant chemotherapy and interval debulking surgery cannot be expected to improve long-term survival rates.

Among patients who achieve a status of no residual disease through primary surgery, 12-year survival may vary depending on the initial (preoperative) disease burden. In a recent analysis of the Gynecologic Oncology Group 182 randomized trial, among stage III/IV ovarian cancer patients with no residual disease after primary debulking surgery, nine-year survival was 44% for those with low/moderate preoperative disease burden (i.e., intra-abdominal disease but sparing the upper abdomen) compared to 27% for patients with high preoperative disease burden (i.e., upper abdominal disease affecting the diaphragm, liver, spleen or pancreas). Among patients with 1–9 mm of residual disease after primary surgery, those with low/moderate disease burden had a nine-year survival of 20% compared to 15% for those with upper abdominal disease present [46]. Patients with upper abdominal disease who underwent more complex surgical procedures were less likely to have any residual disease after surgery. This suggests that patients with extensive disease may still derive a long-term survival benefit from aggressive primary surgery if a status of no residual disease can be achieved.

There may be a synergistic effect on survival if there is no residual disease and adjuvant intraperitoneal chemotherapy is administered, i.e., this combination may offer the highest chance of cure. Tewari et al. recently reported long-term survival data from two randomized trials of intraperitoneal chemotherapy versus intravenous chemotherapy [47]. Among stage III ovarian cancer patients with no residual disease after primary debulking surgery, ten-year survival was 50% for those who received intraperitoneal chemotherapy, compared to 35% for those who received intravenous chemotherapy (p < 0.001). Among patients with 1–9 mm of residual disease, ten-year survival was similar for patients in both treatment arms. The greatest potential for cure appears to be aggressive primary surgery to no residual disease followed by adjuvant intraperitoneal chemotherapy [47]. However, the use of aggressive surgery and intraperitoneal chemotherapy in clinical practice is not yet standard. Factors precluding complete surgical resection to no residual disease include the extent of disease at presentation and the skill of the surgeon. It is hoped that the proportion of women who achieve no residual disease through primary debulking surgery can be increased through broader incorporation of aggressive surgical techniques, and by wider application of the CA125 screening test (described above). Barriers to the use of intraperitoneal chemotherapy are mainly related to challenges associated with the administration of treatment (i.e., catheter-related complications, increased side effects, and low patient adherence). This can be overcome through more experience and through the standardization of intraperitoneal treatment regimens [48]. To better establish the role of intraperitoneal chemotherapy in ovarian cancer treatment, we propose a trial in which patients with stage IIIc/IV ovarian cancer who achieve no residual disease through primary debulking surgery are randomized to receive either intraperitoneal chemotherapy (in combination with intravenous chemotherapy) or conventional chemotherapy (intravenous only), and are followed for 12 years.

5. Conclusions

There are several different approaches to reduce mortality from ovarian cancer. About 17% of ovarian cancers are attributable to a mutation in a known high-risk ovarian cancer susceptibility gene. These are potentially preventable by expanding genetic testing to all women in the population, and offering preventive bilateral salpingo-oophorectomy to mutation carriers. To prevent a greater number of ovarian cancers, it may be reasonable to offer “opportunistric” bilateral oophorectomy to women undergoing any abdominal surgery. Bilateral salpingectomy is an alternative option for the prevention of high-grade serous ovarian cancers.

To improve the cure rate of ovarian cancer there must be an increase in the proportion of women with no residual disease after primary debulking surgery. This might be achieved through broader implementation of aggressive surgical techniques and wider application of the CA125 screening test. Neoadjuvant chemotherapy should be reserved for patients with medical co-morbidities who are unable to undergo aggressive surgery, until reliable predictors of surgical outcome are available. Aggressive primary surgery to no residual disease followed by intraperitoneal chemotherapy appears to hold the greatest potential for cure. Maximizing the number of patients who can undergo this treatment may require specialized facilities with appropriate surgical, medical and nursing resources. We believe that with a combination of screening to identify low-volume advanced stage ovarian cancer, aggressive surgery with the goal of no residual disease, and adjuvant intraperitoneal chemotherapy, the cure rate of ovarian cancer can be significantly improved.

Conflict of interest

The authors have nothing to disclose.

References


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