How family doctors can help prevent Ovarian Cancer

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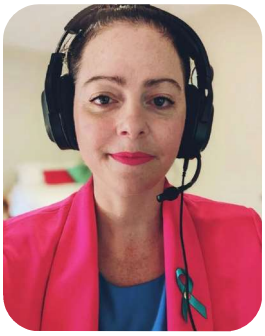
Why prevention is key to changing outcomes for ovarian cancer



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Ovarian cancer (OC) is the fifth most common cause of cancer deaths in Canadian women. Approximately 3,000 Canadians will be diagnosed in 2023; more than half will die within 5 years of diagnosis. While many individuals with OC are living longer and better with advances in treatment and supportive care, 75% of patients continue to be diagnosed at a late stage (stage III or IV) and long-term survival rates have not changed in 50 years.[1,2,3]

So why is OC so hard to detect at an earlier, potentially curable, stage? To understand this, it is important to appreciate that OC is not one disease; rather, the term "ovarian cancer" refers to a group of diseases that originate at or near the ovaries. Each type of OC is associated with a distinct tissue and/or cell of origin, risk factors, precursor lesions, molecular alterations, response to treatment and prognosis.[4] This complexity has resulted in a lack of reliable screening methods that can detect the different types of OC at an early enough stage to impact mortality.[5] While most individuals with OC report experiencing symptoms prior to their diagnosis (e.g., persistent bloating, difficulty eating, abdominal pain/discomfort, changes in urinary habits).[6] symptoms are typically non-specific and attributed to other causes. Furthermore, the most common and lethal type of OC, high-grade serous carcinoma, typically starts in the fallopian tubes and can spread when the primary tumour is still very small and before symptoms appear. While the scientific community is searching for new solutions for early detection and precision oncology, **prevention is our most effective tool for decreasing the incidence of, and mortality from, OC now.**

Ovarian cancer prevention: one size does not fit all

In order to determine the best prevention strategy, you must first understand an individual's estimated lifetime risk for OC.

Anyone born with ovaries is at some risk for OC; in the absence of other risk factors, the lifetime chance of developing OC is around 1.5% (1 in 70). For individuals in this "average risk" population, opportunistic salpingectomy (OS) – surgical removal of the fallopian tubes (but not ovaries) in individuals planning to undergo gynecologic surgery (e.g., tubal sterilization, hysterectomy) for reasons unrelated to OC – is the best option for decreasing OC risk.[7,8] The role of OS in OC prevention has previously been covered in the Spring 2022 Journal found at http://www.bccancer.bc.ca/family-oncology-network-site/Documents/2022%20Spring%20FPONjournal%20WebMay5.pdf

A simplified pathway for preventing OC in the "high-risk" population is shown in Figure 1; the importance of genetic testing in this pathway cannot be understated. Clinical recommendations for management of previvors (individuals confirmed to be at high genetic risk for OC) are shown in Table 1.[9,10] In contrast to individuals at average risk for OC, those at high risk are recommended to undergo surgical removal of ovaries and fallopian tubes (risk-reducing salpingo-oophorectomy, RRSO). While surgical menopause resulting from RRSO can be life-altering, this procedure can also be lifesaving: OC risk is reduced by up to 98% if surgery is performed in accordance with age recommendations, and breast cancer risk in *BRCA1/2* mutation carriers is cut in half if RRSO is performed prior to natural menopause.[10,11,12,13]

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Figure 1. Prevention in individuals at high risk for OC: a simplified view.

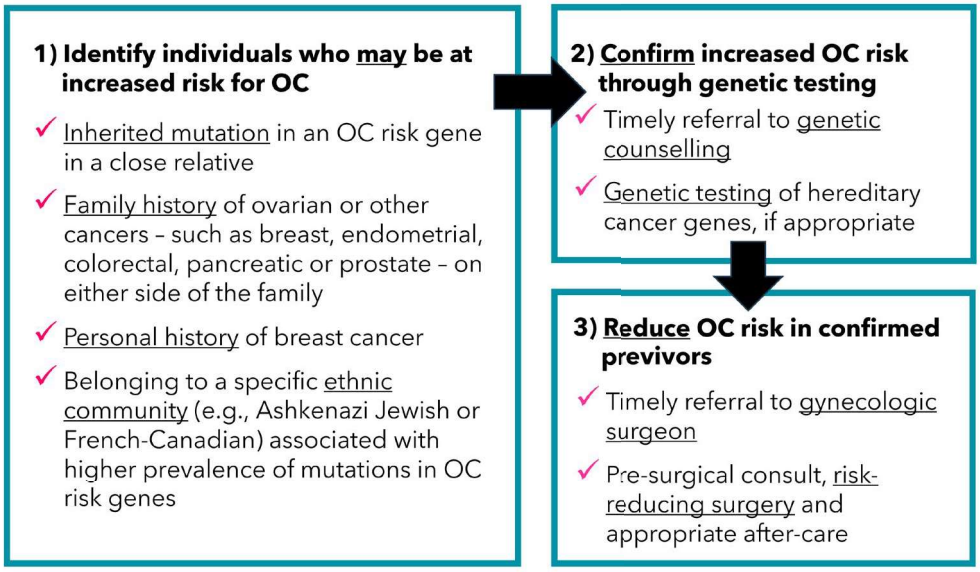

Table 1. Lifetime risk and recommendations for risk reduction in individuals with inherited mutations in OC risk genes.

Gene/s	Estimated risk for OC*	Recommended age for risk-reducing salpingo-oophorectomy**
BRCA1	39-44% by age 70	35-40 years
BRCA2	11-18% by age 70	40-45 years
MSH2, MLH1, MSH6, PMS2, EPCAM ("Lynch Syndrome")	~10-20% by age 70	Timing individualized
RAD51C, RAD51D	~11-13% by age 80	Consider at 45-50 years
BRIP1	~6% by age 80	Consider at 45-50 years
PALB2	~5% by age 80	Based on family history or >45 years

*Mutation carriers are also at increased risk for other cancers, depending on the affected gene.
**Family history will also be considered when determining optimal timing for an individual patient.

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Ovarian Cancer Canada's work with previvors, genetics clinics and gynecologic surgeons from across Canada has revealed many gaps and inequities that must be addressed in order to maximize the opportunity for OC prevention in Canada.[14,15] Of note, a lack of discussion on family cancer history with primary care physicians is likely contributing to missed opportunities from the outset: of 60+ previvors we spoke with 61% denied discussing their family's cancer history with their family doctor prior to genetic testing, and only 11% reported that it was their family doctor who recommend that they pursue genetic testing.

How can family doctors help?

Understanding an individual's estimated lifetime risk of OC is the necessary first step to knowing how best to support them in their journey to prevention. Table 2 outlines concrete steps that you can take to help your patient navigate the pathway to OC prevention, depending on their personal/family circumstances. The resources listed below may also be helpful for both primary care physicians and their patients.

- Ovarian Cancer Canada website ovariancanada.org
  - Prevention information and resources https://ovariancanada.org/?s=prevention This section of the Ovarian Cancer Canada website includes information on the role of genetics in OC, genetic counselling and testing, and surgical and non-surgical risk reduction strategies. It also contains links to relevant webinars and patient tools.
  - Talking to your family doctor about ovarian cancer. https://ovariancanada.org/resources/talking-to-your-family-doctor-about-ovarian-cancer includes a printable worksheet that is designed to help facilitate effective conversations on OC risk.
- BC Cancer Hereditary Program www.bccancer.bc.ca/health-professionals/clinical-resources/hereditary-cancer includes a referral form that outlines detailed criteria for genetic counselling/testing for hereditary cancer genes in BC.
- Canadian Association of Genetic Counsellors (CAGC) website. This website www.cagc-accg.ca includes a list of all genetics clinics in Canada, for patients outside of British Columbia.
- Gynecologic Cancer Survivorship Clinic https://brcainbc.ca/gynecologic-oncology-survivorship-clinic This clinic is led by Dr. Lesa Dawson MD FRCSC in Vancouver and specializes in the care of individuals at high risk for OC. For questions on specialized clinics outside of British Columbia, contact atone@ovariancanada.org
- SOGC Clinical Practice Guideline: Gynaecologic Management of Hereditary Breast and Ovarian Cancer www.jogc.com/article/S1701-2163(18)30522-X/fulltext
- Commercially available genetic testing. The following companies offer clinical-grade

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Table 2. Steps that family doctors can take to prevent OC.

To help identify and manage individuals/families at high risk for OC	
If your patient:	**Then you should:**
✓ Has a family history (on either the maternal or paternal side) of ovarian, breast, pancreatic, prostate, colorectal and/or endometrial cancer; AND/OR ✓ Has a personal history of breast cancer; AND/OR ✓ Is a member of a high-risk ethnic community	✓ Send a referral for genetic counselling*
✓ Has been found to have an inherited mutation in an OC risk gene; AND ✓ Has not been personally diagnosed with OC	✓ Discuss risks and benefits of RRSO (risk-reducing salpingo-oophorectomy) ✓ Send a referral to a high-risk clinic or gynecologic surgeon who has experience performing RRSO
✓ Has been found to have an inherited mutation in an OC risk gene; AND ✓ Has been diagnosed with OC	✓ Encourage them to discuss their genetic result with their family members, and the importance of cascade genetic testing to understand their own risks
✓ Has been diagnosed with OC; AND ✓ Has not had genetic testing	✓ Reinforce** the potential benefits of genetic testing for both the patient themselves (treatment, prevention of other cancers) and their family members (prevention)
To help prevent OC in individuals at average risk	
If your patient:	**Then you should:**
✓ Does not have a relevant personal or family history of cancer, or ethnicity AND ✓ Is considering tubal ligation for permanent contraception	✓ Discuss opportunistic salpingectomy as a safe and effective contraceptive choice that also prevents OC
✓ Does not have a relevant personal or family history of cancer, or ethnicity AND ✓ Is undergoing a hysterectomy for reasons unrelated to OC	✓ Discuss benefit of opportunistic salpingectomy for OC prevention

*These genetics experts will then determine whether your patient should consider genetic testing of hereditary cancer genes. A listing of all genetic clinics can be found at the CAGC (Canadian Association of Genetic Counsellors) website.

**Your patient should be offered genetic testing as part of their ovarian cancer care

Systemic therapies for advanced lung cancers continued from page 26

nivolumab are available in the second-line setting after chemotherapy.

For advanced or extensive-stage small cell lung cancers (SCLC), atezolizumab and durvalumab are funded options used in combination with chemotherapy irrespective of PD-L1 expression. Immunotherapy in SCLC has demonstrated modest improvements in survival which may related to the different biology of this cancer compared to NSCLC.

4. Tailored systemic therapies confer clinically meaningful survival benefits.

Figure 3 summarizes median overall survival (OS) data from Phase 3 clinical trials conducted in the specific molecular alteration population. Data for entrectinib, larotrectinib, and selpercatinib are based on Phase 1-2 trials because these mutations are rare.

5. Side effects are manageable.

While side effects are a significant challenge for patients' quality of life, early recognition and prompt management can help avoid serious toxicities. Rates of toxicity-related discontinuations are generally low, in the order of <10%. Further guidance can be found online in the BC Cancer: Cancer Drug Manual www.bccancer.bc.ca/health-professionals/clinical-resources/cancer-drug-manual for individual drug mongraphs (click "Go to the Drug Index") and algorithms for classifying and managing immune-mediated adverse events (click "Go to Immunotherapy").

References

1. Siegel, R.L., Miller, K.D., Wagle, N.S., and Jemal, A. (2023). Cancer statistics, 2023. CA Cancer J Clin 73, 17–48. 10.3322/caac.21763.
2. Wu, F.T.H., Diab, M., Myers, R., Ho, C., Lam, S., and McGuire, A. (2023). Update on lung cancer. Canadian Journal of Respiratory, Critical Care, and Sleep Medicine, 1–5. 10.1080/24745332.2023.2226410.
3. Singal, G., Miller, P.G., Agarwala, V., Li, G., Kaushik, G., Backenroth, D., Gossai, A., Frampton, G.M., Torres, A.Z., Lehnert, E.M., et al. (2019). Association of Patient Characteristics and Tumor Genomics With Clinical Outcomes Among Patients With Non-Small Cell Lung Cancer Using a Clinicogenomic Database Supplemental content. JAMA 321, 1391–1399. 10.1001/jama.2019.3241.
4. Thai, A.A., Solomon, B.J., Sequist, L. V, Gainor, J.F., and Heist, R.S. (2021). Lung cancer. Lancet 398, 535–554. 10.1016/S0140-6736(21)00312-3.

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genetic testing for individuals who do not meet provincial testing criteria. Tests are ordered through a healthcare provider, with genetic counselling services available.

- Invitae: Breast and Gyn Cancers Panel (link)
- LifeLabs Genetics: Hereditary Breast and Ovarian Cancer Test (link)
- GeneDx: Breast/Gyn Cancer Panel (link)

References

1. Brenner DR, Poirier A, Woods RR, Ellison LF, Billette JM, Demers AA, et al. Projected estimates of cancer in Canada in 2022. CMAJ. 2022;194(17):E601-E7.
2. Society AC. Survival Rates for Ovarian Cancer 2022 [Available from: www.cancer.org/cancer/ovarian-cancer/detection-diagnosis-staging/survival-rates.html
3. Lheureux S, Braunstein M, Oza AM. Epithelial ovarian cancer: Evolution of management in the era of precision medicine. CA Cancer J Clin. 2019;69(4):280-304.
4. Karnezis AN, Cho KR, Gilks CB, Pearce CL, Huntsman DG. The disparate origins of ovarian cancers: pathogenesis and prevention strategies. Nat Rev Cancer. 2017;17(1):65-74.
5. Menon U, Gentry-Maharaj A, Burnell M, Singh N, Ryan A, Karpinskyj C, et al. Ovarian cancer population screening and mortality after long-term follow-up in the UK Collaborative Trial of Ovarian Cancer Screening (UKCTOCS): a randomised controlled trial. Lancet. 2021;397(10290):2182-93.
6. Tone A, Boghosian T, Ross A, Baugh E, Altman AD, Dawson L, et al. Understanding the Experience of Canadian Women Living with Ovarian Cancer through the Every Woman Study (TM). Curr Oncol. 2022;29(5):3318-40.
7. ACOG Committee Opinion No. 774: Opportunistic Salpingectomy as a Strategy for Epithelial Ovarian Cancer Prevention. Obstet Gynecol. 2019;133(4):e279-e84.
8. Hanley GE, Pearce CL, Talhouk A, Kwon JS, Finlayson SJ, McAlpine JN, et al. Outcomes From Opportunistic Salpingectomy for Ovarian Cancer Prevention. JAMA Netw Open. 2022;5(2):e2147343.
9. Daly MB, Pal T, Berry MP, Buys SS, Dickson P, Domchek SM, et al. Genetic/Familial High-Risk Assessment: Breast, Ovarian, and Pancreatic, Version 2.2021, NCCN Clinical Practice Guidelines in Oncology. J Natl Compr Canc Netw. 2021;19(1):77-102.
10. Jacobson M, Bernardini M, Sobel ML, Kim RH, McCuaig J, Allen L. No. 366-Gynaecologic Management of Hereditary Breast and Ovarian Cancer. J Obstet Gynaecol Can. 2018;40(11):1497-510.
11. Finch AP, Lubinski J, Moller P, Singer CF, Karlan B, Senter L, et al. Impact of oophorectomy on cancer incidence and mortality in women with a BRCA1 or BRCA2 mutation. J Clin Oncol. 2014;32(15):1547-53.
12. Finch A, Evans G, Narod SA. BRCA carriers, prophylactic salpingo-oophorectomy and menopause: clinical management considerations and recommendations. Womens Health (Lond). 2012;8(5):543-55.
13. Kotsopoulos J, Hall E, Finch A, Hu H, Murphy J, Rosen B, et al. Changes in Bone Mineral Density After Prophylactic Bilateral Salpingo-Oophorectomy in Carriers of a BRCA Mutation. JAMA Netw Open. 2019;2(8):e198420.
14. Tone A. Ovarian cancer prevention in high-risk population: the patient & previvor perspective 2023 [Available from: www.bccancer.bc.ca/family-oncology-network-site/Documents/Tone.pdf
15. Tone A. Ovarian cancer prevention: understanding the Canadian landscape & the previvor experience 2021 [cited Gynecologic Cancer Initiative Research Rounds. Available from: www.youtube.com/watch?v=XSNgU5IAFkg