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A model for estimating ovarian cancer risk: Application for preventive oophorectomy

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HIGHLIGHTS

- 13% of all ovarian cancers in Ontario occur in the 0.7% of women above 5% risk.
- BRCA1/2 mutations account for 89% of ovarian cancer patients at high risk.
- Achieving maximum impact will require population-based genetic testing of BRCA1/2.

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ABSTRACT

Objective. It is important to identify women in the population who have a high risk of ovarian cancer and who might benefit from prophylactic bilateral salpingo-oophorectomy. The probability that a woman will develop ovarian cancer depends on her current age, her reproductive history and her genetic status.

Methods. We simulated the distribution of ovarian cancer risk for the 2011 Ontario female population. We generated (at random) individual risks of ovarian cancer to age 80 for 6,301,340 women, based on the published risk factors, mutation frequencies and population age-specific incidence rates (SEER database). Risk factors included parity, breastfeeding, oral contraceptives, tubal ligation and family history. Genetic factors included 11 single nucleotide polymorphisms (SNPs) and BRCA1/2 mutations.

Results. Of the 6,301,340 women simulated as the general population of Ontario, the (complete) model predicts that 65,805 women (1.0%) will develop ovarian cancer by age 80. There were 46,069 women (0.7%) with a risk of ovarian cancer above 5%. BRCA1/2 mutation carriers accounted for 67.4% of the women at greater than 5% risk (31,028 women). Among ovarian cancer patients at greater than 5% risk, a BRCA1/2 mutation was present in 89.2%. In contrast, SNPs contribute to a very small proportion of the ovarian cancer patients who were at greater than 5% risk.

Conclusions. Approximately 12.9% of all ovarian cancers in Ontario occur in the 0.7% of women in the general population who have a lifetime ovarian cancer risk in excess of 5%, the majority of whom carry a mutation in BRCA1 or BRCA2.

1. Introduction

The average lifetime risk of ovarian cancer for a woman born in Ontario is about 1.4% [1]. A woman's risk of ovarian cancer depends on her age and her past exposure to the relevant risk factors; parity, oral contraceptive use, breastfeeding and tubal ligation all reduce the risk of ovarian cancer [2]. Women with a mutation in BRCA1 or BRCA2 have a particularly high risk of ovarian cancer [3]. Women with a strong family history [4] or with a mutation in another ovarian cancer susceptibility gene, such as RAD51C, RAD51D or a Lynch syndrome gene [5–7], are also at increased risk. Several common low-penetrance genetic variants (single nucleotide polymorphisms) have also been identified that are associated with ovarian cancer, with relative risks ranging from 0.8 to 1.4 [8]. In the model described by Pearce et al., 11 low-penetrance single nucleotide polymorphisms (hereafter referred to as SNPs) were used to stratify women into genetic risk score quintiles, and these authors propose that information derived from SNP genotyping may be used to identify women at increased risk of ovarian cancer, who might benefit from increased surveillance. Screening for ovarian cancer has not been proven to be effective – the most effective means of cancer

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prevention is through bilateral salpingo-oophorectomy – but this is reserved for women at moderate to high risk. In women with BRCA1 and BRCA2 mutations, prophylactic bilateral salpingo-oophorectomy reduces the risk of ovarian cancer by 80% [9]. The residual risk is attributable to the subsequent development of primary peritoneal cancer. In non-carriers, peritoneal cancer is rare and bilateral salpingo-oophorectomy is generally assumed to offer complete protection [10]. To warrant a prophylactic oophorectomy, a woman's risk of ovarian cancer should be sufficiently high that the benefits of surgery outweigh the risks, although currently there is no consensus on the absolute risk level to justify an oophorectomy.

Preventing ovarian cancer in the population through prophylactic oophorectomy requires a means of identifying high risk women as well as the capacity to perform oophorectomies in large numbers. Risk assessment may be based on family history and other risk factors and/or genetic testing for BRCA mutations and for SNPs. Depending on the risk of ovarian cancer before and after age 50, prophylactic oophorectomy may be recommended prior to menopause or after menopause. Bilateral oophorectomy prior to menopause is more problematic than post-menopausal oophorectomy because of the acute symptoms and the potential morbidity associated with surgical menopause [10].

We wished to evaluate the potential impact of using prophylactic oophorectomy in high risk women as a cancer prevention strategy in the Ontario population. We modeled the distribution of ovarian cancer risks to age 80 for the entire Ontario population. For the purposes of this study, we consider a residual lifetime risk of developing invasive ovarian cancer of 5% sufficiently high to justify a preventive oophorectomy. We consider the effect on a provincial level of testing for BRCA1 and BRCA2, and of SNPs, alone and in combination.

2. Methods

We simulated the distribution of ovarian cancer risk for the 2011 Ontario female population. We created a theoretical cohort of 6,301,340 women and generated at random individual risks of ovarian cancer to age 80 for each woman, based on the distribution of risk factors and population incidence rates. First, each women was assigned at random a current age between 1 and 80, based on the age distribution of the Ontario population in 2011. Then, each woman was assigned a personal risk factor profile at random, according to the distribution of risk factors for her birth cohort and her age group (data available on request). We included eight risk factors in the model: parity (0, 1, 2, 3, 4, 5, 6+ live births), breastfeeding (0, 1–5, 6–11, 12–23, 24+ cumulative months), oral contraceptive use (0, <1, 1–1.99, 2–4, 5–9, 10–14, 15+ years of use), oophorectomy (yes/no), tubal ligation (yes/no), family history (yes/no), BRCA1/2 mutation status (BRCA1, BRCA2, both, neither) and 11 single nucleotide polymorphisms (SNPs). We obtained information on the prevalence of reproductive risk factors (parity, breastfeeding, oral contraceptive use and tubal ligation) from questionnaires that were completed by 2000 North American women without ovarian cancer who attended a clinic appointment for BRCA genetic testing at our research laboratory and were found to be negative for mutations in BRCA1/2. Relative risk estimates for the reproductive risk factors were obtained from Whittemore et al. [2]. We used published data from the National Health Discharge Survey to estimate the prevalence of elective bilateral oophorectomies [11]. We obtained prevalence estimates for the 11 SNPs associated with ovarian cancer from the 1000 Genome Project [12] and relative risk estimates from Pearce et al. (Table 1) [13]. We used prevalence and relative risk estimates for BRCA1/2 mutations from Zhang et al. [3]. With the exception of the hazard ratio for BRCA1/2 status, hazard ratios were assumed to be constant with age (Table 1). For BRCA1 and BRCA2, age-specific relative risks were derived from Zhang et al. [3] and were used to generate age-specific hazard ratios. We obtained age-specific ovarian cancer incidence rates for the 2011 United States population from the SEER registry database (Table S1) [14].

Table 1
Effect measures of ovarian cancer risk factors.

	Prevalence[a] (%)	Relative risk
Parity[b] (number of live births)		
0	22.5	1
1	14.0	0.60
2	37.0	0.53
3	20.0	0.48
4	5.0	0.36
5	0	0.33
≥6	1.5	0.29
Breastfeeding[b] (cumulative months)		
Never	37.7	1
1–5.99	13.9	0.87
6–11.99	14.4	0.74
12–23.99	20.1	0.69
≥24	13.9	0.69
Oral contraceptive use[c] (cumulative years)		
<1	24.2	1
1–4.99	25.3	0.78
5–9.99	24.7	0.64
10–14.99	12.9	0.56
≥15	12.9	0.42
Tubal ligation[d]		
No	79.2	1
Yes	20.8	0.74
Bilateral oophorectomy[e]		
No	86.4	1
Yes	13.6	0.00
Family history[d]		
No	96.0	1
Yes	4.0	2.09
BRCA1 mutation[f]		
No	99.7	1
Yes	0.2	
<30		1
30–39		68
40–49		110.4
50–59		47.8
60–69		19.6
70–80		19.6
BRCA2 mutation[f]		
No	99.7	1
Yes	0.3	
<30		1
30–39		1
40–49		30.0
50–59		25.5
60–69		26.1
7 0–80		26.1
Low-penetrance alleles[g]		
rs7725218	34.3	1.08
rs2363956	46.5	1.10
rs2072590	34.8	1.16
rs10088218	11.6	0.84
rs129426666	16.2	1.11
rs7651446	6.1	1.44
rs11782652	9.1	1.19
rs1243180	31.3	1.10
rs9303542	28.8	1.12
rs3744763	41.4	1.06
rs3814113	33.3	0.82

[a] Prevalence of exposure (by age 50) in the general population.
[b] Relative risk estimated from Whittemore et al. [2].
[c] Relative risk estimated from [21].
[d] Relative risk estimated from Pearce et al. [4].
[e] Prevalence estimated from the National Health Discharge Survey [11]. For this analysis we assume oophorectomy is 100% protective.
[f] Age-specific risks approximated from Zhang et al. [2].
[g] Population frequencies obtained from 1000 Genome project (Utah residents from Northern and Western Europe ancestry) [12], relative risks obtained from Pearce et al. [13].

Next, we calculated annual risks of ovarian cancer for each woman, from her current age (in 2011) to age 80, by multiplying the hazard ratios in her risk profile by the population age-specific ovarian cancer