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Brief Communications

A framework for assessing interactions for risk stratification models: the example of ovarian cancer

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Abstract

Generally, risk stratification models for cancer use effect estimates from risk/protective factor analyses that have not assessed potential interactions between these exposures. We have developed a 4-criterion framework for assessing interactions that includes statistical, qualitative, biological, and practical approaches. We present the application of this framework in an ovarian cancer setting because this is an important step in developing more accurate risk stratification models. Using data from 9 case-control studies in the Ovarian Cancer Association Consortium, we conducted a comprehensive analysis of interactions among 15 unequivocal risk and protective factors for ovarian cancer (including 14 non-genetic factors and a 36-variant polygenic score) with age and menopausal status. Pairwise interactions

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between the risk/protective factors were also assessed. We found that menopausal status modifies the association among endometriosis, first-degree family history of ovarian cancer, breastfeeding, and depot-medroxyprogesterone acetate use and disease risk, highlighting the importance of understanding multiplicative interactions when developing risk prediction models.

The development of risk stratification approaches to identify individuals who would most benefit from primary prevention strategies has become increasingly important. Risk stratification models use the effect estimates for the risk/protective factors considered to be unequivocal in their association with the disease under study. Generally, the effect estimates come from analyses in which multiplicative relationships were assumed among risk and protective factors. Using invasive epithelial ovarian cancer (ovarian cancer), we offer a strategy for the initial steps needed to develop accurate risk stratification models, including a 4-criterion framework for assessing whether potential interactions should be included. Interaction analyses are notoriously underpowered, so using this framework ensures that important differences that may indicate departures from multiplicativity are not missed.

- **Criterion A (statistical approach):** A likelihood ratio test comparing a logistic model with the interaction term vs the same model without the interaction term (a 2-sided $P < .05$ for interaction was considered statistically significant was used here, but other statistical approaches could be used);
- **Criterion B (qualitative approach):** Comparing the consistency and magnitude of the odds ratios (ORs) of a factor across the levels of the other factor (visualization from stratified analysis);
- **Criterion C (biological approach):** Considering biological plausibility; and
- **Criterion D (practical approach):** Assessing the prevalence of the risk/protective factors to determine whether an interaction would have a meaningful impact on the risk stratification model.

Ovarian cancer is an ideal example for refining risk stratification approaches because primary prevention strategies are available for women at both average and high risk, including risk-reducing salpingo-oophorectomy, opportunistic salpingectomy, tubal ligation, and possibly hormonal contraceptives (1-4). Unequivocal ovarian cancer risk and protective factors include 14 non-genetic factors (4-14) and a 36-variant polygenic score for ovarian cancer (15) (15 factors are shown in Supplementary Table 1, available online). Importantly for ovarian and many other cancers affecting women, the effects of age and menopausal status on the risk/protective factors must first be disentangled to determine whether one, both, or neither modifies the associations (16).

We applied the framework to questionnaire data from 9 Ovarian Cancer Association Consortium case-control studies from Australia (17), Germany (18), and the United States (19-25). Institutional review board approval was obtained by the original studies, and all participants had provided written informed consent. To determine whether there was an age interaction, a menopausal status interaction, or both, the initial ovarian cancer and risk and protective factor analyses were conducted among participants in the following strata (Table 1):

- **Stratum 1:** Younger than 45 years of age and premenopausal
- **Stratum 2:** Aged 45 to 54 years and premenopausal
- **Stratum 3:** Aged 45 to 54 years and postmenopausal
- **Stratum 4:** Aged 55 to 64 years and postmenopausal
- **Stratum 5:** Aged 65 to 84 years and postmenopausal

We found differences in the associations between the risk/protective factors for ovarian cancer by menopausal status but not by age (particularly informed by comparing results between strata 2 and 3; Supplementary Table 2, A-D, available online) based on the 4-criterion interaction evaluation framework described earlier.

Menopausal status appeared to modify the associations between ovarian cancer risk and endometriosis, first-degree family history of ovarian cancer, breastfeeding, and depot-medroxyprogesterone acetate use (Table 2). For example, a self-reported history of endometriosis was associated with a greater increase in risk of ovarian cancer among premenopausal women than among postmenopausal participants ($P = .04$ for interaction; criterion A). Moreover, although no standardized definitions exist on how different the 2 stratum-specific associations should be for a factor to be an effect modifier, it is widely accepted that an OR less than 1.5 is considered a small effect size, while an OR between 1.5-2.0 is considered medium (26). Thus, the magnitude of the difference in the endometriosis association between premenopausal (OR = 1.94) and postmenopausal (OR = 1.33) women is qualitatively meaningful (criterion B). Further, the endometriosis-menopausal status interaction is biologically plausible (criterion C) because during the premenopausal period, endometriosis is active (ovulatory proinflammatory and proliferative processes) (27-30), whereas endometriosis is generally quiescent in the postmenopausal period (31). Finally, endometriosis is estimated to have a prevalence of up to 10% in the general population (32); thus, it is sufficiently common to warrant fitting separate risk stratification models for pre- and postmenopausal women to be able to incorporate different effect estimates for endometriosis (criterion D).

Given that 4 risk and protective factors suggest an interaction with menopausal status based on our framework, including one that met all 4 criteria, we further evaluated pairwise interactions between the risk and protective factors separately for pre- and postmenopausal women. Ultimately, our application of the framework led to the decision that there were no meaningful interactions among the 14 environmental factors or the polygenic score within the pre- or postmenopausal groups. As an example, among premenopausal women, the pairwise interaction between family history and parity was statistically significant ($P = .022$ for interaction; criterion A; Supplementary Table 2, O, available online). Parity also appeared to be more protective among women with a family history of ovarian cancer (OR = 0.25 for 3+ parity compared with nulliparity) vs women without a family history (OR = 0.52) (criterion B); this interaction may also be biologically plausible (criterion C). Elevated progesterone levels during pregnancy may clear genetically abnormal cells in the Fallopian tube fimbriae (33), which may preferentially benefit genetically driven ovarian cancers (34). Although this potential pairwise interaction may be useful for individual-level precision prevention, it would have minor impacts on ovarian cancer risk stratification because of the low proportion of people with a positive family history of ovarian cancer [approximately 2% (35)] as well as the low absolute risk of ovarian cancer among premenopausal women (36) (criterion D). Thus, we concluded that it is not necessary to

Table 1. Characteristics of participants with (cases) and without (controls) ovarian cancer included in the analysis, by age and menopausal status group

	Premenopausal women younger than 45 years		Premenopausal women aged 45-54 years		Postmenopausal women aged 45-54 years		Postmenopausal women aged 55-64 years		Postmenopausal women aged 65-84 years	
	Case participants (n = 965)	Control participants (n = 2111)	Case participants (n = 1269)	Control participants (n = 2109)	Case participants (n = 903)	Control participants (n = 1214)	Case participants (n = 2493)	Control participantss (n = 3502)	Case participants (n = 2226)	Control participants (n = 3148)
Ovarian Cancer Association Consortium study, No. (%)										
AUS 2001-2005Australia	114 (11.8)	266 (12.6)	183 (14.4)	226 (10.7)	134 (14.8)	146 (12.0)	479 (19.2)	454 (13.0)	435 (19.5)	390 (12.4)
DOV 2002-2009Washington, USA	116 (12.0)	182 (8.6)	209 (16.5)	311 (14.7)	99 (11.0)	122 (10.0)	425 (17.0)	660 (18.8)	224 (10.1)	414 (13.2)
GER 1993-1998Germany	26 (2.7)	90 (4.3)	25 (2.0)	66 (3.1)	15 (1.7)	53 (4.4)	72 (2.9)	175 (5.0)	42 (1.9)	125 (4.0)
HAW1993-2008Hawaii, USA	105 (10.9)	246 (11.7)	89 (7.0)	174 (8.3)	111 (12.3)	127 (10.5)	175 (7.0)	240 (6.9)	203 (9.1)	290 (9.2)
HOP 2003-2009Western Pennsylvania, northeast Ohio, western New York, USA	64 (6.6)	176 (8.3)	120 (9.5)	354 (16.8)	34 (3.8)	125 (10.3)	208 (8.3)	489 (14.0)	252 (11.3)	534 (17.0)
NEC 1992-2008New Hampshire, eastern Massachusetts, USA	235 (24.4)	496 (23.5)	249 (19.6)	354 (16.8)	187 (20.7)	214 (17.6)	422 (16.9)	542 (15.5)	347 (15.6)	452 (14.4)
NJO 2002-2009New Jersey, USA	22 (2.3)	19 (0.9)	50 (3.9)	43 (2.0)	20 (2.2)	21 (1.7)	77 (3.1)	154 (4.4)	45 (2.0)	205 (6.5)
UCI 1994-2005Southern California, USA	41 (4.2)	132 (6.3)	74 (5.8)	99 (4.7)	33 (3.7)	74 (6.1)	101 (4.1)	150 (4.3)	117 (5.3)	140 (4.4)
USC 1993-2010Los Angeles, California, USA	242 (25.1)	504 (23.9)	270 (21.3)	482 (22.9)	270 (29.9)	332 (27.3)	534 (21.4)	638 (18.2)	561 (25.2)	598 (19.0)
Age at diagnosis for cases/reference age for controls, year										
Mean (SD)	38.3 (5.28)	36.9 (5.92)	48.9 (2.63)	48.7 (2.63)	51.4 (2.31)	51.4 (2.34)	59.6 (2.77)	59.5 (2.78)	70.8 (4.46)	70.9 (4.49)
Median (Min, Max)	40.0 (20.0, 44.0)	38.0 (18.0, 44.0)	49.0 (45.0, 54.0)	49.0 (45.0, 54.0)	52.0 (45.0, 54.0)	52.0 (45.0, 54.0)	60.0 (55.0, 64.0)	59.0 (55.0, 64.0)	70.0 (65.0, 84.0)	70.0 (65.0, 84.0)
Race/ethnicity, No. (%)										
Asian	111 (11.5)	148 (7.0)	108 (8.5)	121 (5.7)	69 (7.6)	61 (5.0)	100 (4.0)	99 (2.8)	130 (5.8)	158 (5.0)
Black	30 (3.1)	54 (2.6)	24 (1.9)	45 (2.1)	28 (3.1)	24 (2.0)	57 (2.3)	53 (1.5)	35 (1.6)	52 (1.7)
Hispanic White	67 (6.9)	135 (6.4)	49 (3.9)	92 (4.4)	59 (6.5)	67 (5.5)	120 (4.8)	110 (3.1)	70 (3.1)	56 (1.8)
Non-Hispanic White	691 (71.6)	1603 (75.9)	1044 (82.3)	1749 (82.9)	688 (76.2)	1005 (82.8)	2121 (85.1)	3116 (89.0)	1927 (86.6)	2778 (88.2)
Other[a]	62 (6.4)	157 (7.4)	41 (3.2)	97 (4.6)	54 (6.0)	55 (4.5)	84 (3.4)	119 (3.4)	58 (2.6)	99 (3.1)
Missing	4 (0.4)	14 (0.7)	3 (0.2)	5 (0.2)	5 (0.6)	2 (0.2)	11 (0.4)	5 (0.1)	6 (0.3)	5 (0.2)
Education level, No. (%)										
Less than high school	55 (5.7)	95 (4.5)	87 (6.9)	105 (5.0)	86 (9.5)	89 (7.3)	352 (14.1)	348 (9.9)	467 (21.0)	439 (13.9)
High school	205 (21.2)	389 (18.4)	261 (20.6)	374 (17.7)	172 (19.0)	251 (20.7)	585 (23.5)	805 (23.0)	634 (28.5)	932 (29.6)
Some college	297 (30.8)	605 (28.7)	376 (29.6)	644 (30.5)	275 (30.5)	374 (30.8)	742 (29.8)	1021 (29.2)	593 (26.6)	869 (27.6)
College graduate or above	396 (41.0)	959 (45.4)	529 (41.7)	935 (44.3)	346 (38.3)	461 (38.0)	742 (29.8)	1237 (35.3)	441 (19.8)	810 (25.7)
Missing	12 (1.2)	63 (3.0)	16 (1.3)	51 (2.4)	24 (2.7)	39 (3.2)	72 (2.9)	91 (2.6)	91 (4.1)	98 (3.1)

[a] Other includes mixed race and those that do not belong in one of the specified racial/ethnic groups. AUS = Australian Ovarian Cancer Study; DOV = Diseases of the Ovary and their Evaluation; GER = German Ovarian Cancer Study; HAW = Hawaii Ovarian Cancer Case-Control Study; HOP = Hormones and Ovarian Cancer Prediction; NEC = New England Case Control Study; NJO = New Jersey Ovarian Cancer Study; SD = Standard deviation; USA = United States of America; UCI = University California Irvine Ovarian Study; USC = Study of Lifestyle and Women's Health.

Table 2. Associations between risk/protective factors and ovarian cancer that differed by menopausal status among women aged 45-54 years

Risk/protective factor	All women aged 45-54 years (pre- and postmenopausal combined)			Premenopausal women aged 45-54 years			Postmenopausal women aged 45-54 years				
	Case participants,[a] No.	Control participants,[a] No.	OR[b] (95% CI)	Case participants,[a] No.	Control participants,[a] No.	OR[b] (95% CI)	Case participants,[a] No.	Control participants,[a] No.	OR[b] (95% CI)	P-interaction[c]	Interaction criteria met[d]
Breastfeeding											
Never	1212	1278	1.0	693	763	1.0	519	515	1.0		
<12 months	551	978	0.76 (0.64 to 0.89)	327	595	0.78 (0.62 to 0.98)	224	383	0.71 (0.55 to 0.92)		
≥12 months	397	998	0.59 (0.49 to 0.72)	240	706	0.53 (0.42 to 0.68)	157	292	0.69 (0.51 to 0.94)	.064	(b), (c), (d)
Depot-medroxyprogesterone acetate use											
No	1886	2793	1.0	1109	1793	1.0	777	1000	1.0		
Yes	21	76	0.61 (0.36 to 1.02)	10	52	0.51 (0.26 to 1.00)	11	24	0.80 (0.38 to 1.69)	.35	(b), (c), (d)
First-degree family history of ovarian cancer											
No	1610	2548	1.0	943	1633	1.0	667	915	1.0		
Yes	119	87	2.15 (1.56 to 2.97)	69	48	2.43 (1.58 to 3.73)	50	39	1.83 (1.15 to 2.91)	.39	(b), (c), (d)
Endometriosis											
No	1889	3058	1.0	1128	1981	1.0	761	1077	1.0		
Yes	269	255	1.60 (1.32 to 1.95)	135	123	1.94 (1.47 to 2.57)	134	132	1.33 (1.00 to 1.76)	.041	(a), (b), (c), (d)

[a] Numbers may not sum to total because of missing values. CI = confidence interval; OR = odds ratio.
[b] Pooled estimates from logistic regression models in the 50 imputed datasets, adjusted for age at diagnosis for cases/reference age for controls (45-49 years vs 50-54 years), race/ethnicity, education level, and Ovarian Cancer Association Consortium study.
[c] P value for interaction between risk or protective factor and menopausal status using the likelihood ratio test.
[d] Criteria to assess interactions: (a) $P < .05$ for interaction; (b) odds ratios of a factor across the levels of the other factor are consistent, and the differences in magnitude are large; (c) the interaction is biologically plausible; and (d) the prevalence of the risk factors is large enough so that the interaction would have a meaningful impact on the risk stratification model.

include an interaction term for family history and parity in a risk stratification model.

Our proposed framework has some level of subjectivity. The risk associations for 3 of the 4 risk factors that drove our conclusion that associations differ by menopausal status were not statistically significantly different in the 2 strata (criterion A) but met the other 3 criteria used for evaluation. Some investigators, however, may want to prioritize statistical significance (either using the interaction test presented here or using the Bayes false-positive probability) over the other 3 criteria and only use criteria B through D to decide against there being an interaction. Operationally, we decided that criterion A or B must be met before criteria C and D are considered. When criteria conflict with each other, however, we considered all criteria to inform our decision-making process (see the examples earlier). Another example is the age-parity interaction among postmenopausal women. The interaction was statistically significant ($P = .009$ for interaction; criterion A) and the prevalence of ever having given birth [85% (37)] is sufficient for this potential interaction to have a meaningful impact on risk stratification (criterion D). There was no pattern in the odds ratios for parity across the age groups (Supplementary Table 2, C, available online; criterion B), suggesting that this is a chance finding. We therefore determined, based on applying our framework, that this was not an interaction that should be incorporated into a risk stratification model.

In conclusion, the application of our 4-criterion interaction evaluation framework (Supplementary Tables 2, A-F, available online) demonstrates that menopausal status modifies the association of at least one ovarian cancer risk/protective factor and the disease risk, supporting the use of separate models by menopausal status in risk stratification. The menopausal status–risk factors interactions are likely not influenced by histotype because the distributions are similar between pre- and postmenopausal women aged 45 to 54 years (Supplementary Table 3, available online). The finding of no age–risk factor interactions could in part be due to the differences in histotype distributions across age groups. Interaction analyses stratified by histotype, however, would not be meaningful because of the small sample size of the rare histotypes. Additional research in prospective cohorts is needed to estimate absolute risk incorporating interactions to assess their impact on risk stratification.

To develop meaningful risk stratification models, it is critical first to comprehensively assess interactions using statistical, qualitative, biological, and practical approaches (criteria A-D). Many published cancer risk stratification models either do not consider interactions or are based solely on *P* values (criterion A) to assess interactions (38-44). This approach has limitations because *P* values vary according to sample size, and there are issues related to multiple comparison. As such, we propose a framework that co-emphasizes the statistical (criterion A) and qualitative (criterion B) approaches and also includes the biological approach (criterion C) and practical approach (criterion D). Comprehensive interaction analysis for risk stratification can most effectively be done within consortia with large sample sizes. Continued collaboration in the field is necessary, and using the data fully must be a priority to move closer to realizing the goals of precision cancer prevention.

Data availability

The data generated in this study are not publicly available because of limitations imposed by the original studies in which these data were collected. The corresponding author will

facilitate access through existing data request processes for the Ovarian Cancer Association Consortium.

Author contributions

Minh Tung Phung, PhD, MPH (Conceptualization; Formal analysis; Methodology; Writing—original draft; Writing—review & editing), Malcolm C. Pike, PhD (Funding acquisition; Writing—review & editing), Bhramar Mukherjee, PhD (Writing—review & editing), Rafael Meza, PhD (Writing—review & editing), Gillian E. Hanley, PhD (Writing—review & editing), Kathleen R. Cho, MD (Writing—review & editing), Andrew Berchuck, MD (Funding acquisition; Writing—review & editing), Argyrios Ziogas, PhD (Funding acquisition; Writing—review & editing), Nur Zeinomar, PhD (Funding acquisition; Writing—review & editing), Anna H. Wu, PhD (Funding acquisition; Writing—review & editing), Penelope M. Webb, PhD (Funding acquisition; Writing—review & editing), Linda J. Titus, PhD (Funding acquisition; Writing—review & editing), Kathryn L. Terry, ScD (Funding acquisition; Writing—review & editing), Bo Qin, PhD (Funding acquisition; Writing—review & editing), Celeste Leigh Pearce, PhD, MPH (Conceptualization; Funding acquisition; Methodology; Resources; Supervision; Writing—original draft; Writing—review & editing), Paul D. P. Pharoah, PhD (Funding acquisition; Writing—review & editing), Francesmary Modugno, PhD, MPH (Funding acquisition; Writing—review & editing), Allan Jensen, PhD (Funding acquisition; Writing—review & editing), Holly R. Harris, ScD, MPH (Funding acquisition; Writing—review & editing), Marc T. Goodman, PhD (Funding acquisition; Writing—review & editing), Renee T. Fortner, PhD (Funding acquisition; Writing—review & editing), Jennifer Anne Doherty, MS, PhD (Funding acquisition; Writing—review & editing), Daniel W. Cramer, MD, ScD (Funding acquisition; Writing—review & editing), Jenny Chang-Claude, PhD (Funding acquisition; Writing—review & editing), Michael E. Carney, MD (Funding acquisition; Writing—review & editing), Elisa V. Bandera, MD, PhD (Funding acquisition; Writing—review & editing), Hoda Anton-Culver, PhD (Funding acquisition; Writing—review & editing), Karen McLean, MD, PhD (Writing—review & editing), Alice W. Lee, PhD, MPH (Writing—review & editing), Kirsten B. Moysich, MS, PhD (Funding acquisition; Writing—review & editing), Britton Trabert, PhD (Conceptualization; Funding acquisition; Methodology; Supervision; Writing—original draft; Writing—review & editing).

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Conflicts of interest

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