Gynecologic Oncology 139 (2015) 253–260

Contents lists available at ScienceDirect

Gynecologic Oncology

journal homepage: www.elsevier.com/locate/ygyno

Identifying post-menopausal women at elevated risk for epithelial ovarian cancer

Nicole Urban [a,*], Sarah Hawley [a], Holly Janes [a], Beth Y. Karlan [b], Christine D. Berg [c], Charles W. Drescher [a], JoAnn E. Manson [d], Melanie R. Palomares [e], Mary B. Daly [f], Jean Wactawski-Wende [g], Mary J. O'Sullivan [h], Jason Thorpe [a], Randal D. Robinson [i], Dorothy Lane [j], Christopher I. Li [a], Garnet L. Anderson [a]

[a] Fred Hutchinson Cancer Research Center, Seattle, WA, United States
[b] Cedars-Sinai Medical Center, Los Angeles, CA, United States
[c] Johns Hopkins Medicine, Baltimore, MD, United States
[d] Brigham and Women's Hospital, Harvard Medical School, Boston, MA, United States
[e] Cancer Prevention, Inc., Las Vegas NV and Keck School of Medicine, University of Southern California, Los Angeles, CA, United States
[f] Fox Chase Cancer Center, Philadelphia PA, United States
[g] University at Buffalo, SUNY, Buffalo, NY, United States
[h] University of Miami, Miami, FL, United States
[i] University of Texas Health Science Center, San Antonio TX, United States
[j] Stony Brook University, Stony Brook, NY, United States

HIGHLIGHTS

- Risk for ovarian cancer was predicted using data from the Women's Health Initiative.
- Predictors include serum markers as well as epidemiologic risk factors.
- At-risk post-menopausal women were identified, independent of deleterious mutations.
- 8% of women were classified as elevated risk, and 31% of cancers were identified.
- A125 and HE4 contributed significantly to risk prediction.

ARTICLE INFO

Article history:
Received 5 June 2015
Received in revised form 26 August 2015
Accepted 29 August 2015
Available online 3 September 2015

Keywords:
Ovarian cancer
Risk prediction
CA125
HE4

ABSTRACT

Objective. We developed and validated a hybrid risk classifier combining serum markers and epidemiologic risk factors to identify post-menopausal women at elevated risk for invasive fallopian tube, primary peritoneal, and ovarian epithelial carcinoma.

Methods. To select epidemiologic risk factors for use in the classifier, Cox proportional hazards analyses were conducted using 74,786 Women's Health Initiative (WHI) Observational Study (OS) participants. To construct a combination classifier, 210 WHI OS cases and 536 matched controls with serum marker measurements were analyzed; validation employed 143 cases and 725 matched controls from the WHI Clinical Trial (CT) with similar data.

Results. Analyses identified a combination risk classifier composed of two elevated-risk groups: 1) women with CA125 or HE4 exceeding a 98% specificity threshold; and 2) women with intact fallopian tubes, prior use of menopausal hormone therapy for at least two years, and either a first degree relative with breast or ovarian cancer or a personal history of breast cancer. In the WHI OS population, it classified 13% of women as elevated risk, identifying 30% of ovarian cancers diagnosed up to 7.8 years post-enrollment (Hazard Ratio [HR] = 2.6, $p < 0.001$). In the WHI CT validation population, it classified 8% of women as elevated risk, identifying 31% of cancers diagnosed within 7 years of enrollment (HR = 4.6, $p < 0.001$).

Conclusion. CA125 and HE4 contributed significantly to a risk prediction classifier combining serum markers with epidemiologic risk factors. The hybrid risk classifier may be useful to identify post-menopausal women who would benefit from timely surgical intervention to prevent epithelial ovarian cancer.

1. Introduction

We describe a hybrid risk classifier combining serum markers with epidemiologic risk factors, designed to identify post-menopausal

* Corresponding author at: Fred Hutchinson Cancer Research Center, 1100 Fairview Ave N. M5-C800, Seattle, WA 98109, United States.
E-mail address: nurban@fhcrc.org (N. Urban).

http://dx.doi.org/10.1016/j.ygyno.2015.08.024
0090-8258/

women at elevated risk for epithelial ovarian cancer (EOC) independent of the risk associated with known mutations. The classifier could aid decision-making in post-menopausal women regarding opportunistic bilateral salpingo-oophorectomy (BSO), follow-up for EOC in symptomatic women [1], and periodic screening in asymptomatic women. We were interested in defining a clinically accessible way to identify subgroups of women for whom these interventions might be considered. Statistical models were used to help identify important predictors but the actual classifier is based on a simple assessment of presence or absence of selected risk factors.

In a meta-analysis of 22 studies [3], the average cumulative risks for EOC by age 70 years were 39% (18%–54%) and 11% (2.4%–19%) for *BRCA1* and *BRCA2* mutation carriers respectively. In a meta-analysis of 10 studies, risk-reducing salpingo-oophorectomy (RRSO) reduced future risk of EOC in these women by >80% [4]. Among women with a significant family history (FH), including those with deleterious mutations in high penetrance cancer susceptibility genes such as *BRCA1* and *BRCA2*, RRSO reduces risk of EOC by at least 69%, as well as risk of breast cancer by at least 37% [5].

Opportunistic BSO might similarly prevent EOC in women without deleterious mutations; this is important because over 75% of EOC cases occur in these women. Many women elect BSO at the time of surgery for benign gynecologic conditions such as hysterectomy, but many others do not due to a reluctance to lose natural hormonal function. Post-menopausal women below the age of 65 may avoid BSO because of its potential association with cardiovascular disease, hip fracture, dementia and Parkinson's disease [7].

Recent evidence suggests that bilateral salpingectomy with ovarian retention (BSOR) may be an alternative to BSO for women who wish to retain ovarian function [8]. The fallopian tubes, especially the native serous epithelium at the fimbria, are increasingly recognized as a site of origin of high grade serous EOC [9,10], suggesting that bilateral salpingectomy may be both necessary and sufficient for EOC risk reduction. The addition of BSOR to hysterectomy in women who do not carry *BRCA1/2* mutations was recently reported to show no negative effects on ovarian function or perioperative complications [8,11]. Efficacy of this approach remains to be demonstrated [12].

Post-menopausal women having hysterectomy for benign conditions must choose among prophylactic BSO, prophylactic BSOR, or retention of both ovaries and fallopian tubes. Recent recommendations state that women at high risk for EOC undergo BSO at hysterectomy [13], but criteria for identifying high-risk women are not well defined. A woman with a significant FH suggesting inherited susceptibility may be considered high risk [13] in the absence of a negative mutation test in the proband from her high-risk family EOC [14,15].

A reliable tool to assess EOC risk associated with factors other than deleterious mutations in cancer susceptibility genes, in addition to FH, is needed to inform a post-menopausal woman's decision-making regarding EOC prevention and early detection. The use of serum markers in a risk classifier is novel but is strongly supported by the literature [16] including some evidence that CA125 levels signal EOC precursor lesions [17]. The serum marker component of our combination classifier relies on CA125 and human epididymis 4 (HE4) protein. CA125 is a predictive marker for EOC that becomes increasingly sensitive with proximity to diagnosis [16]. HE4 similarly predicts EOC and is used clinically in women with a pelvic mass [18]; it is more specific than CA125 in women with benign tumors [19]. Both CA125 and HE4 show promise as risk and early detection markers [16,20–23].

2. Material and methods

2.1. Overview

Using data from participants in the Women's Health Initiative (WHI) Observational Study (OS) and Clinical Trial (CT), we defined and validated a risk prediction classifier based on a combination of epidemiologic risk factors and serum markers. Our goal was to achieve the best sensitivity for acceptable specificity. Traditional epidemiologic risk factors [24] for which WHI data were available were considered for inclusion in the epidemiologic component of the classifier, in addition to FH based on its widespread use clinically, and use of menopausal hormone therapy (HT) based on recent reports of its association with increased risk of EOC in post-menopausal women [25–27].

We first assessed epidemiologic risk factors in univariate and multivariate Cox proportional hazards models in the WHI OS population, selecting the risk factors most associated with risk of EOC for inclusion in candidate classifiers. Serum markers CA125 and HE4 were selected for inclusion based on predictive performance reported previously [16]. For ease of clinical application, each risk factor was defined as present or absent; candidate classifiers were defined using simple "and/or" combinations of the risk factors. The performance of each candidate risk classifier was evaluated in the WHI OS study populations, and subsequently validated in the WHI CT study populations in terms of [1] the percent of women later diagnosed with EOC that the classifier correctly identified as elevated risk (sensitivity); and [2] the percent of the unaffected population it erroneously classified as elevated risk (specificity). We determined statistical significance for each classifier by coding it as a yes/no, time-dependent variable and fitting a univariate Cox proportional hazards model. We report the hazard ratios and p-values from these models.

2.2. Study population

The WHI was a national prospective study of post-menopausal women's health. In total, over 161,000 women aged 50–79 were enrolled between 1993 and 1998, including 93,676 in the WHI Observational Study (OS) and 68,132 in the Clinical Trial (CT). After excluding participants reporting prior BSO at baseline, 74,786 women were eligible for these analyses from the OS and similarly 55,467 participants were eligible from the CT. Mean (maximum) follow-up at the time of these analyses was 12.3 (17.5) years for the OS and 13.2 (17.0) years for the CT; these analyses were based on a mean 12.3 years of follow-up (maximum 17.5 years). Details of the WHI design and implementation have been published [28,29]. Women in the WHI OS and CT can be assumed to be from the same reference population because they met very similar eligibility criteria, had similar data collected, and lived in the same communities; their assays were conducted with the same methods, and their blood samples were stored for similar periods.

2.3. Cancer outcomes

We define EOC as invasive ovarian, fallopian tube and primary peritoneal cancer. All incident ovarian cancers were documented and centrally reviewed at the WHI Clinical Coordinating Center according to SEER guidelines [29], including 461 cases of invasive EOC in the OS and 334 cases of invasive EOC in the CT; unconfirmed cases of EOC ($n = 68$ in the OS, $n = 31$ in the CT) and diagnoses of LMP or non-epithelial tumors of the ovary ($n = 53$ in the OS and $n = 80$ in the CT) were censored at time of event. Due to low mortality rates, LMP tumors are not considered invasive EOC [30–33]. We excluded stromal and germ cell tumors because they have a different biology and are seldom diagnosed in post-menopausal women; they are generally excluded in validation studies of CA125 and HE4 for early detection of EOC [21,22].

2.4. Data collection

Information on epidemiologic risk factors was obtained from baseline self-administered questionnaires. Most items were collected in parallel in the two cohorts. Because information was limited regarding age of personal history of breast cancer and FH of breast cancer, cancer in aunts, Ashkenazi ethnicity, and lineage, significant FH was defined as any of the following conditions: Personal history of breast cancer