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ORIGINAL PAPER

Ovarian cancer survival by tumor dominance, a surrogate for site of origin

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Abstract
Objectives Recent studies suggest that a proportion of ovarian tumors may actually originate in the distal fallopian tube. The objective of this study was to examine the relationship between dominance (a surrogate for site of origin) and survival, following a diagnosis of epithelial ovarian cancer.
Methods We classified 1,386 tumors as dominant (putatively originating in the ovary) and non-dominant (putatively originating in the fallopian tube), using parameters obtained from pathology reports. Dominant tumors were restricted to one ovary or one involved ovary that exceeded the other in dimension by at least twofold, while non-dominant tumors were identified as having a greater likelihood of a tubal origin if the disease was equally distributed across the ovaries. Cox proportional hazards models were used to estimate the hazard ratios (HRs) and 95 % confidence intervals (CIs) associated with dominance.
Results Non-dominant tumors were more likely to be serous, stage III/IV, and be associated with a *BRCA1/2* mutation, increasing parity and use of estrogen hormone replacement therapy ($p \leq 0.01$). In contrast, 46 and 26 % of the dominant tumors were serous and endometrioid, respectively, with a more even distribution of stage ($p < 0.0001$). Women with a non-dominant tumor had an increased risk of death compared to women with a

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dominant tumor (multivariate HR 1.28; 95 % CI 1.02–1.60). Findings were similar in our analysis restricted to serous only subtypes (HR 1.28; 95 % CI 1.01–1.63).
Conclusion These preliminary findings suggest significantly worse survival among women diagnosed with a tumor putatively arising from fallopian tube.

Keywords Ovarian cancer · Site of origin · Prognosis

Introduction

Despite extensive study, the etiology of epithelial ovarian cancer is not fully understood and minimal progress has been made in prevention and treatment, leading to little change in mortality and morbidity associated with this disease [1–3]. Prognosis is largely based on stage at detection, volume of disease, optimal debulking, histologic subtype, grade, and response to chemotherapy [4, 5]. Along with efforts aimed at early detection, strategies that impact morbidity and mortality are warranted.

Ovarian tumors are traditionally thought to arise from the ovarian surface epithelium or related ovarian inclusion cysts and are classified based on pathologic features such as histology, grade, and stage [2]. Recent pathology studies suggest that a proportion of high-grade serous tumors may actually originate in the fallopian tube fimbriae [6–10], which along with risk factor diversity [11] suggests that ovarian cancer is not a homogeneous disease [6, 12].

Detailed sectioning of the fallopian tube can in some cases identify tumors that are of tubal origin and have fimbrial involvement; however, this approach is labor intensive, applies essentially to localized disease, and cannot be used in cases identified after surgery [13]. Tumor "dominance" represents an alternative method for attempting to assign a greater probability of a tubal versus ovarian origin based on whether the largest tumor mass is on one of the ovaries [6]. In this model, a dominant ovarian mass would imply that the tumor has a greater likelihood of having started at that site. In contrast, absence of a dominant ovarian mass would be presumed to occur if the tumor initiated elsewhere and randomly spread throughout the peritoneal cavity. With this model, tumors that are described as originating entirely in one ovary or tumors where one ovary exceeds the other by at least twofold in size are classified as "dominant" and are more likely to have an ovarian site of origin. Tumors that are comprised of microscopic surface deposits, spread equally across peritoneal cavity, or have only tumor foci on ovaries are classified as "non-dominant" and are presumed to favor a fallopian tube origin [6]. Kotsopoulos et al. [14] recently reported differences in risk factor associations by site of origin. Specifically, they found that reproductive factors were more important for dominant versus non-dominant tumors, suggestive of potentially independent carcinogenic pathways. There are no studies, to our knowledge, that have evaluated whether tumor dominance is associated with survival. Thus, the goal of the current study was to explore the association between tumor dominance and survival, following a diagnosis of epithelial ovarian cancer.

Materials and methods

Study population

All Ontario, Canada, residents diagnosed with invasive epithelial ovarian cancer from January 1995 to December 1999 or January 2002 to December 2004 were identified through the Ontario Cancer Registry (OCR) [15, 16]. Briefly, investigators reviewed pathology records for each case, to determine subject eligibility and tumor histology. Patients were between 20 and 79 years of age at the time of diagnosis of a new primary epithelial ovarian tumor. Through a risk factor questionnaire, information on known or suspected ovarian cancer risk factors and demographic data were collected by standardized telephone script. Styrofoam-packed venipuncture kits with consent forms were mailed to subjects, who had blood samples drawn locally and, along with signed consent forms, returned to the study center by prepaid courier. All participants were offered the option to receive their genetic testing results in the context of a counseling clinic with the study team or elsewhere in the province as previously described [15]. Patient medical records were reviewed to obtain information about clinical staging, treatments received, and treatment outcomes. More information about the study design and data collection approach can be found elsewhere [15, 16].

Ovarian cancer case confirmation

Hospital medical records were requested covering a minimum of 1 year following diagnosis to ensure completion of primary surgery and chemotherapy. Information was extracted regarding clinical staging, treatments received, and response to treatment. A second chart review was undertaken 5 years after initial treatment, if necessary. The FIGO system was primarily used for staging, as this is the widely accepted practice in Ontario, but was substituted by TNM staging where the necessary information was not available.

Ascertainment of outcomes

Survival status, date of death, and cause of death were determined from death certificates linked with OCR

computerized records, as well as via chart reviews at local hospitals. The OCR contains information about cancer incidence and vital status in Ontario. More information and an evaluation of using OCR record linkage for estimates of death statistics are available [17], and the automated procedures appear to be more accurate than manual approaches.

Classification of ovarian tumors

Based on available pathology reports, 1,423 women were eligible for inclusion in the current study. Patient pathology reports were reviewed to classify all cases by tumor dominance as previously described [6]. Dominant tumors were defined as those limited to one ovary or where one involved ovary exceeded the other in dimension by at least twofold ($n = 1{,}160$) [6]. Non-dominant tumors were defined as the remainder ($n = 226$). This method of classification of site of origin was proposed by Roh et al. [6] and previously used by Kotsopoulos et al. [14]. Also, 454 tumors were classified as unknown, due to the lack of dimension information presented in the pathology reports. These subjects were excluded from our analyses, and the final study sample included data from 1,386 participants.

Statistical analysis

Differences between clinical, demographic, and other characteristics were compared by tumor dominance, using the χ^2 test or t test, as appropriate. The primary outcome was ovarian cancer-specific survival, defined as the duration of survival from time of diagnosis to date of death from ovarian cancer. Case survival was censored when death occurred from another cause, or on 30 September 2010, which was the most recent limit of available death certificate information. We performed a left-truncated analysis to reduce the extent of survivorship bias present in our study population [16, 18]. We employed Cox proportional hazards models to estimate hazard ratios (HRs) and 95 % confidence intervals (CIs) associated with tumor dominance. The reference model was adjusted for age at diagnosis (continuous). Multivariate modeling took into account both the plausibility of biological effects of each covariate as well as statistical evidence of confounding and used a 10 % change in the parameter of interest as the criterion to select covariates into the final model [19]. Multivariate model 1 was adjusted for age at diagnosis (continuous), histologic subtype [serous, mucinous, endometrioid, other (clear cell, mixed histology, and epithelial not otherwise specified)], and stage (I, II, III, IV). Although none of the variables that differed significantly by dominance and survival as outlined in Table 1 confounded the main association by more than 10 %, the authors included *BRCA1/2* mutation status (carrier/non-carrier) and estrogen hormone replacement therapy use (ever/never) into model 2 based on the association of these exposures with ovarian cancer risk and survival. The presence of a first-degree relative with a history of breast or ovarian cancer was not included in the model due to collinearity with *BRCA1/2* carrier status. The proportional hazards assumption was examined for all variables included in the final model. None of the variables, except for *BRCA1/2* mutation status, violated the proportionality assumption. Since *BRCA1/2* mutation status is not a time-dependent variable, it was allowed to remain in the proportional hazards model despite some evidence of non-proportionality. We also stratified our analyses by histology (i.e., serous, non-serous) and stage, where stage was combined into early-stage (i.e., stages I and II) and late-stage (i.e., stages III and IV) tumors. All analyses were performed using SAS version 9.2 (SAS Institute, Cary, NC, USA). All p values are two-sided.

Results

Of the 1,386 women patients included in the present analysis, we observed 1,160 (84 %) with dominant and 226 (16 %) non-dominant tumors (Table 1). The dominant tumors were primarily of serous (46 %) and endometrioid histology (26 %), while the non-dominant tumors were mostly comprised of serous subtype (87 %) ($p < 0.0001$). Approximately half of the dominant tumors (57 %) were stage III/IV versus 92 % of the non-dominant tumors ($p < 0.0001$). Compared to women with dominant tumors, those with non-dominant tumors were significantly more likely to carry *BRCA1/2* mutations (23 vs. 10 %; $p < 0.0001$), have first-degree relatives with history of ovarian or breast cancer (31 vs. 21 %; $p = 0.003$), to be parous (88 vs. 81 %; $p = 0.02$), have higher mean parity (2.8 vs. 2.4; $p = 0.008$), more likely to have ever used intrauterine devices (IUD) (21 vs. 15 %; $p = 0.03$), and more likely to have used estrogen hormone replacement therapy (30 vs. 22 %; $p = 0.01$). In our study sample, significantly more women died by the end of follow-up among women with non-dominant versus dominant tumors (66 vs. 36 %; $p < 0.0001$).

Among the entire study population, women with non-dominant tumors experienced significantly worse survival compared to women with dominant tumors ($p < 0.0001$) (Fig. 1). The findings were similar in the analyses stratified by serous ($p = 0.0002$) (Fig. 2) versus non-serous tumors ($p = 0.0001$) (Fig. 3). The HRs and 95 % CIs for ovarian cancer-specific mortality associated with tumor dominance are presented in Table 2. In the reference model (only adjusted for age at diagnosis), a non-dominant tumor was

Table 1 Selected characteristics of 1,386 epithelial ovarian cancer cases, by tumor dominance

Characteristics	Dominant $n = 1{,}160$	Non-dominant $n = 226$	p
Age at diagnosis, mean (SD)	56.84 (11.70)	56.84 (11.14)	0.99
Age at death, mean (SD)	63.55 (11.14)	62.05 (11.93)	0.19
Histology, *n* (%)			
Serous	469 (46 %)	174 (87 %)	
Mucinous	107 (10 %)	1 (0.5 %)	
Endometrioid	269 (26 %)	6 (3 %)	
Clear cell	83 (8 %)	3 (1 %)	
Other[a]	87 (9 %)	17 (8 %)	<0.0001
Stage, *n* (%)			
I	232 (23 %)	3 (2 %)	
II	206 (20 %)	11 (6 %)	
III	451 (45 %)	135 (70 %)	
IV	119 (12 %)	43 (22 %)	<0.0001
BRCA1/2 mutation (yes), *n* (%)	97 (10 %)	47 (23 %)	<0.0001
First-degree relatives with history of breast or ovarian cancer (yes), *n* (%)	216 (21 %)	60 (31 %)	0.003
Oral contraceptive use (ever), *n* (%)	608 (56 %)	129 (62 %)	0.09
Ever parous (yes), *n* (%)	891 (81 %)	183 (88 %)	0.02
Parity, mean (SD)	2.40 (1.87)	2.78 (1.92)	0.008
Duration of breastfeeding (months), mean (SD)	7.41 (20.68)	6.98 (23.49)	0.82
Age at menarche, mean (SD)	12.92 (1.53)	12.95 (1.54)	0.81
Age at (natural) menopause, mean (SD)	49.85 (5.92)	49.36 (3.85)	0.26
IUD use (ever), *n* (%)	168 (15 %)	44 (21 %)	0.03
Tubal ligation (yes), *n* (%)	237 (22 %)	57 (28 %)	0.06
Estrogen hormone replacement therapy (ever), *n* (%)	239 (22 %)	62 (30 %)	0.01
BMI 5 years prior to diagnosis, *n* (%)			
Underweight	225 (19 %)	47 (21 %)	
Normal	481 (41 %)	99 (44 %)	
Overweight	292 (25 %)	47 (21 %)	
Obese	162 (14 %)	33 (15 %)	0.58
Current smoker (yes), *n* (%)	145 (15 %)	26 (14 %)	0.77
Follow up time in years, mean (SD)	8.14 (4.31)	5.57 (3.70)	<0.0001
Died within follow-up period, *n* (%)	366 (36 %)	132 (66 %)	<0.0001

SD standard deviation

[a] Other includes the following histology types: mixed, epithelial (NOS), adenocarcinoma, other

associated with a significant increased risk of death (HR 2.41; 95 % CI 1.98–2.95) compared with non-dominant tumors. The results were similar, but attenuated, in the models additionally adjusted for histology and stage (Model 1 HR 1.29; 95 % CI 1.05–1.59) and subsequently for *BRCA1/2* mutation status and past use of estrogen hormone replacement therapy (Model 2 HR 1.28; 95 % CI 1.02–1.60).

In the analyses limited to serous subtype, non-dominant tumors were associated with increased mortality risk when compared to dominant tumors (reference model HR 1.55; 95 % CI 1.24–1.93) and again attenuated in model 1 (HR 1.28; 95 % CI 1.03–1.61) and model 2 (HR 1.28; 95 % CI 1.01–1.63) (Table 2). Among the non-serous subtypes, non-dominant tumor was also associated with increased risk of death (reference model HR 3.06; 95 % CI 1.75–5.35), although attenuated in models 1 and 2 (model 1 HR 1.49; 95 % CI 0.85–2.62 and model 2 HR 1.40; 95 % CI 0.77–2.53).

Finally, we examined mortality risks stratified by early- (i.e., stage I/II) versus late-stage (i.e., stage III/IV) tumor (Table 2). Among early-stage tumors, in the reference model, non-dominance was associated with significant increased risk of death (HR 3.93; 95 % CI 1.40–11.05) but was attenuated in model 1 (HR 2.39; 95 % CI 0.82–6.92) and model 2 (HR 0.91; 95 % CI 0.20–4.12). Among late-

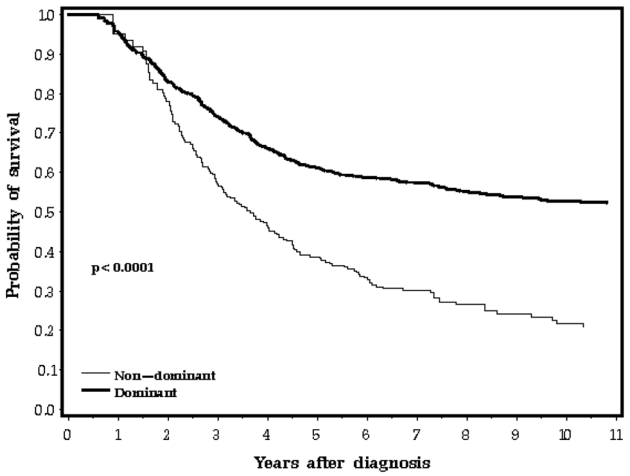

Fig. 1 Ovarian cancer-specific survival by tumor dominance, all histologic subtypes. Unadjusted estimates, left censored

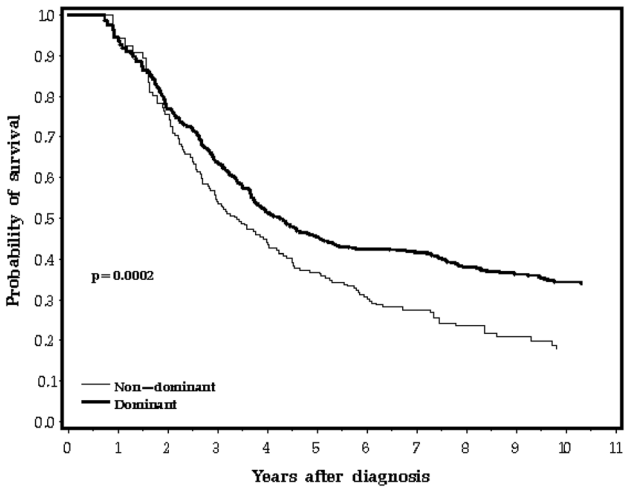

Fig. 2 Ovarian cancer-specific survival by tumor dominance, among serous tumors. Unadjusted estimates, left censored

stage tumors, women with non-dominant tumors had significant increased risk of death (reference model HR 1.45, 95 % CI 1.17–1.78), which was attenuated but still significant in model 1 (HR 1.28; 95 % CI 1.04–1.58) and model 2 (HR 1.30; 95 % CI 1.04–1.63).

Discussion

The overall goal of the current study was to evaluate whether survival following diagnosis of epithelial ovarian cancer was associated with dominance, a potential tool for assigning probable for tumor site of origin. In this study of 1,386 women, women with non-dominant tumors had significant 28 % increased mortality risks with adjustment for important covariates. These findings add to the growing

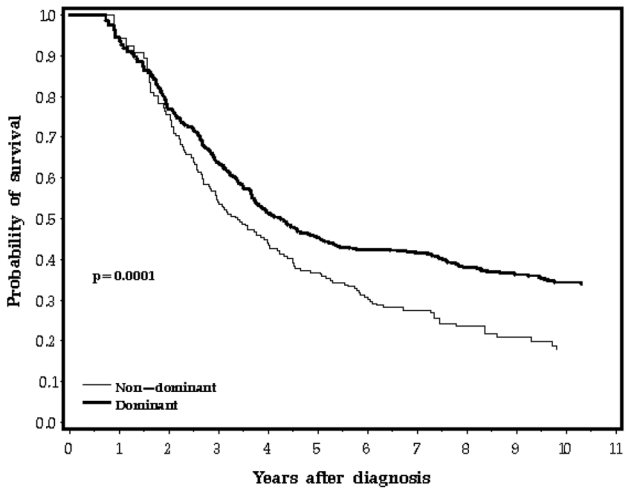

Fig. 3 Ovarian cancer-specific survival, among non-serous tumors. Unadjusted estimates, left censored

literature that ovarian cancer is not a homogenous disease and that the fallopian tube represents a potential source of serous cancers [1, 20, 21].

We observed significant differences in specific tumor and clinical characteristics by dominance. For example, non-dominant tumors were more likely to be serous, stage III/IV, occur in women with inherited *BRCA1* or *BRCA2* mutations, as well as family histories of breast or ovarian cancer, and were associated with greater parity and with use of estrogen hormone replacement therapy. In contrast, dominant tumors were more evenly split between the serous and endometrioid subtypes and had a more even distribution of stage I/II and stage III/IV tumors. This is comparable with an earlier report, which found that non-dominant tumors were more likely to be serous, higher grade, and later stage, while dominant tumors were more likely to be mucinous, endometrioid, or clear cell. Kotsopoulos et al. [14] also reported that specific factors were associated with the risk of ovarian-originating tumors (i.e., dominant tumors) but not tumors originating in the fallopian tubes (i.e., non-dominant): Tubal ligation and two or more births decreased risk, while endometriosis increased risk. Collectively, these two studies have provided preliminary evidence that risk factor profiles and survival may differ by tumor site of origin and are suggestive of different developmental pathways of ovarian tumors. Considering combinations of case characteristics may be important for understanding predictors of survival.

Evidence from pathology studies suggests that as many as half of high-grade serous tumors may originate in the distal fallopian tube [6–9, 22]. A step-wise progression to the development of invasive cancer in the fallopian tube has been supported from studies carefully examining the distal fallopian tubes of *BRCA* mutation carriers (as well as

Table 2 Site of origin as a predictor of ovarian cancer survival following diagnosis

	n	Reference model Multivariate HR[d] (95 % CI)	*p*	Model 1 Multivariate HR[e] (95 % CI)	*p*	Model 2 Multivariate HR[f] (95 % CI)	*p*
All tumors	1,386						
Dominant	1,160	1.00 (Ref.)		1.00 (Ref.)		1.00 (Ref.)	
Non-dominant	226	2.41 (1.98–2.95)	<0.0001	1.29 (1.05–1.59)	0.02	1.28 (1.02–1.60)	0.03
Serous only	643						
Dominant	469	1.00 (Ref.)		1.00 (Ref.)		1.00 (Ref.)	
Non-dominant	174	1.55 (1.24–1.93)	<0.0001	1.28 (1.03–1.61)	0.03	1.28 (1.01–1.63)	0.04
Non-serous[a]	573						
Dominant	546	1.00 (Ref.)		1.00 (Ref.)		1.00 (Ref.)	
Non-dominant	27	3.06 (1.75–5.35)	<0.0001	1.49 (0.85–2.62)	0.17	1.40 (0.77–2.53)	0.27
Early stage[b]	452						
Dominant	438	1.00 (Ref.)		1.00 (Ref.)		1.00 (Ref.)	
Non-dominant	14	3.93 (1.40–11.05)	0.009	2.39 (0.82–6.92)	0.11	0.91 (0.20–4.12)	0.90
Late stage[c]	748						
Dominant	570	1.00 (Ref.)		1.00 (Ref.)		1.00 (Ref.)	
Non-dominant	178	1.45 (1.17–1.78)	0.0005	1.28 (1.04–1.58)	0.02	1.30 (1.04–1.63)	0.02

HR hazard ratio, *CI* confidence interval

[a] Includes mucinous, endometrioid, clear cell, other

[b] Includes only stage I and II tumors

[c] Includes only stage III and IV tumors

[d] Reference model: adjusted for age at diagnosis (continuous)

[e] Model 1: adjusted for age at diagnosis (continuous), histologic subtype (serous, mucinous, endometrioid, clear cell, other) and stage (I, II, III, IV)

[f] Model 2: adjusted for covariates in Model 2 as well as *BRCA1/2* mutation carrier (yes/no) and ever estrogen hormone replacement therapy use (ever/never)

non-carriers) undergoing risk-reducing bilateral salpingo-oophorectomy [12, 13, 23]. This model includes an early or "latent" precursor lesion (i.e., p53 signature) in the fallopian tube that occurs in at least one half healthy women and yet contains conserved *p53* mutations and is located in the distal fallopian tube, similar to tubal intraepithelial carcinomas (TICs), which are considered immediate precursors to invasive or metastatic serous cancer [13, 24, 25]. The frequency of the p53 signature is similar in women with and without inherited *BRCA* mutations and appears to be an early pathogenic event in the fallopian tube that is largely independent of *BRCA* mutation status and like most precursors rarely progresses to malignancy [8, 26, 27]. We observed that a significantly higher proportion of women with non-dominant versus dominant tumors had *BRCA* mutations (23 vs. 10 %; $p < 0.0001$), which is consistent with studies indicating the distal fallopian tube as the site of origin of high-grade serous cancers among *BRCA* mutation carriers [13, 23, 25, 28, 29]. Findings were similar, although not significant likely due to small numbers, when we limited this analysis to high-grade serous cancers, raising the question of whether dominant serous cancers have different pathogenic pathways compared with their non-dominant counterparts (data not shown) [30, 31]. Further investigation of the p53 signature-to-invasive carcinoma pathway may lead to a better understanding of how to prevent and treat epithelial ovarian and fallopian tube cancers [1, 5, 20, 32, 33].

Examining ovarian cancer by putative tumor site of origin may help to obtain more precise risk estimates for survival [5]. Within our study follow-up period, 66 % of patients with non-dominant tumors had died, compared with 36 % of patients with dominant tumors, and patients with non-dominant tumors had significantly shorter total study follow-up time than those with dominant tumors (5.57 vs. 8.14 years). Accordingly, women are beginning to be offered bilateral salpingectomy at the time of pelvic surgery among those at average population risk of developing ovarian cancer, with the objective of preventing aggressive subtypes of this disease [34, 35]. Given the high lifetime risks associated with *BRCA1* and *BRCA2* mutations, such high-risk women are advised to undergo prophylactic bilateral salpingo-oophorectomy at age 35 or when childbearing is complete [23, 36]. It has been put forth that salpingectomy with oophorectomy delayed until the time of natural menopause is offered to this high-risk

population as a way to minimize the impact of early surgical menopause on overall morbidity [37]. However, this topic remains under scrutiny given the lack of evidence examining the clinical benefit of such a procedure [35, 38].

The current study has several strengths and weaknesses. The primary strength is its novelty, in which it represents, to our knowledge, the first study to investigate in greater depth the relationship between tumor site of origin and survival using tumor dominance as proxy. Furthermore, our study population was representative of all epithelial ovarian cancer cases diagnosed in Ontario during the study recruitment period, and we were able to adjust for important covariates. Finally, one study author classified tumor dominance from all of the pathology reports, which maximized consistency of the determination.

Our primary limitation was that the approach to classify tumor site of origin according to dominance has low sensitivity and low specificity. Prior studies using the classification of Roh et al. reported that 33–40 % of tumors were non-dominant [14] and 69 % in a sample that was limited to serous carcinoma cases [6]. In contrast, we found that 16 % of all of the tumors and 27 % of the serous subtypes were classified as non-dominant. One reason for this disparity may be inconsistencies in the quality of pathology reports in the current study. However, more fundamental explanations must be considered. First, the arbitrary assignment of "dominance" based on a single measurement (diameter) is highly unlikely to reliably distinguish the actual site of origin. Rather, it provides an estimate. Second, some tumors arising at the distal tube could invade directly into the adjacent ovary, creating a "dominant" mass. Another drawback is that we did not have complete information about duration and type of chemotherapy treatment received or debulking status, two factors that have previously been shown to be significant predictors of survival [39]. In fact, it is possible that non-dominant tumors may be associated with worse survival because they are more difficult to debulk optimally than dominant tumors.

In summary, we have demonstrated that the application of a tumor dominance model for site of origin, as defined by parameters of pathology reports, is associated with ovarian cancer-specific survival. Specifically, tumors putatively originating in the fallopian tubes were associated with significantly worse prognoses and support emerging evidence for a novel paradigm that classifies ovarian tumors into distinct entities based on pathologic and molecular evidence as well as site of origin [40, 41]. Based on these findings, prevention strategies including salpingectomy in women at general population risk undergoing pelvic surgery may have likelihood to decrease incidence and mortality of the more lethal subtypes of the disease. Future epidemiologic studies of ovarian cancer focusing on risk factors, treatment, and prognosis should consider tumor heterogeneity by conducting stratified analyses.

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