Qualitative Age Interactions between Low-grade and High-grade Serous Ovarian Carcinomas

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Abstract

Purpose: **Ovarian epithelial carcinomas, including the predominant serous ovarian carcinoma (SOC) type, are heterogeneous malignancies. Even though invasive SOCs of low and high grade can be distinguished by morphology and molecular or immunohistochemical profiles, age-specific risks relevant to their separate carcinogenic pathways and clinical features have not been fully explored.**

Methods: **In search of further clues to the etiology/pathogenesis of low-grade and high-grade SOCs, we analyzed incidence rate patterns. Case and age-adjusted population data were obtained from the National Cancer Institute's Surveillance, Epidemiology, and End Results (SEER) program for years 1990 through 2005. Descriptive epidemiology for $n = 19,899$ cases was supplemented with age-period-cohort models fitted by grade.**

Results: **SOC age-adjusted incidence rate ratios (IRR) of high to low grade ($IRR^{H/L}$) were <1.0 before age 40, and >1.0 thereafter. Accordingly, SOC age-specific incidence rates were also greater for low grade before age 40 years, and then greater for high grade. The reversals of $IRR^{H/L}$, with crossings of the age-specific incidence rate near age 40 years occurred irrespective of early or late SOC stage. These results were reproducible and reliable in age-period-cohort models that were adjusted for period and cohort effects ($P \approx 0$ for age interactions by grade).**

Conclusions: **Robust qualitative age interactions between low-grade and high-grade SOC showed that grade is an age-specific effect modifier in these malignancies. With increasing research interest in identifying the genomic determinants of SOC risk, therapeutic response, and outcome, future analytic studies and clinical trials should be powered to account for age-dependent grade interactions.** (Cancer Epidemiol Biomarkers Prev 2009;18(8):2256–61)

Introduction

The heterogeneity of ovarian epithelial cancers, including the predominant histologic type of serous ovarian carcinoma (SOC), is well-recognized (1-5). Indeed, contemporary molecular-based models implicate two major carcinogenic pathways (2, 6-8). High-grade SOCs represent the majority of invasive ovarian cancers (9-11), and typically show molecular signatures or DNA amplification associated with genetic instability (12-16). Low-grade SOCs, which can also spread progressively (17, 18), have been associated with stable oncogenic mutations (*KRAS* or *BRAF*) that influence cell proliferation (2, 19).

There is growing interest in defining the molecular determinants of ovarian cancer risk, including cancer genomic patterns, epigenetic modifications, and molecular signatures (3, 13, 15, 16, 20-23). Although a major grade-based dichotomy in SOC molecular biology is now widely acknowledged, the age-specific risks relevant to heterogeneity in the carcinogenic pathways have not been fully explored. A number of recent population studies have shown that robust analyses of cancer incidence rate patterns can unmask qualitative (crossing or reversing) age interactions relevant to pathogenesis, histogenesis (grade), progression (stage), or outcome (24-26). Such findings can influence the design of clinical trials and guide subgroup analyses (27).

We aimed to gain further information relevant to ovarian cancer pathobiology by analysis of age-adjusted and age-specific incidence rate patterns of SOC using comprehensive data available through the internet from the National Cancer Institute's Surveillance, Epidemiology, and End Results (SEER) program. We supplemented standard descriptive epidemiology with a structured mathematical framework for rigorous analysis of age interactions by cancer grade.

Materials and Methods

Data Source. All cases with a primary diagnosis of invasive ovarian cancer during the years 1990 to 2005, and related population data, including all identified racial groups, were obtained from the SEER program. Incidence and mortality data were merged from three major registry

groupings encompassing 17 regional tumor registries.[6] Specifically, the registries included 10% (SEER 9; 1990-1991), 14% (SEER 13; 1992-1999), and 26% (SEER 17; 2000-2005) of the U.S. population.

Tumor Characterization. Histologic types of ovarian cancer specified in the SEER Program Coding and Staging Manual[7] are designated by the WHO International Classification of Diseases for Oncology, 3rd edition (ICD-O-3); and relevant morphologic criteria for diagnosis have been amply described (see refs. 5, 10, 28). Microscopic patterns of SOC recognized in SEER include serous cystadenocarcinoma (ICD-O-3, code 8441), papillary serous cystadenocarcinoma (code 8460), and serous surface papillary carcinoma (code 8461). In pilot testing, each of these SOC subtypes showed comparable age-adjusted stage and grade distributions and parallel patterns of age-specific incidence rates. As designated by the WHO (29), SOC was thus analyzed as a single entity. The staging of ovarian cancer recorded in SEER accords to standards developed by the International Federation of Gynecology and Obstetrics (11) or equivalent standards of the American Joint Committee on Cancer. For the present study, data were collapsed into sets of early stage (stage I or II) and late stage (stage III or IV). The diagnostic grades transcribed in SEER accord with American Joint Committee on Cancer and International Federation of Gynecology and Obstetrics guidelines: G_1, well differentiated; G_2, moderately differentiated; G_3, poorly differentiated, and G_4, undifferentiated. The American Joint Committee on Cancer pairs G_3-G_4. For the present study, we tested each grade individually or in collapsed sets of low grade (G_1, G_2) and high grade (G_3, G_4). This "two-tiered" division followed expert recommendations for diagnostic practice (5, 30) and matched to reports of molecular and immunohistochemical profiling (2, 14).

Statistical Methods. The rate data extracted from SEER were all age-adjusted to the 2000 U.S. Standard Population. Relative risks were expressed as incidence rate ratios (IRR), in which a given characteristic was compared with a reference characteristic with an assigned IRR = 1.0. Incidence rate trends were plotted by a succession of four 4-year calendar periods (years 1990-1993, 1994-1997, 1998-2001, and 2002-2005). Cross-sectional age-specific incidence rates were stratified by high or low grade and plotted by 17 4-year age groups (ages 17-20, 21-24, …, and 81-84). Poisson regression models were used to examine trend and age interactions between low and high grade (31). Quantitative interactions exhibit changes in magnitude but not direction; i.e., IRR of high versus low grade ($IRR^{H/L}$) remain either <1.0 or >1.0. Qualitative interactions showed changes in magnitude and direction with a relative rate reversal and age line "crossover"; i.e., corresponding to an $IRR^{H/L}$ reversal between <1.0 and >1.0.

Age-Period-Cohort Analysis. Our 17 4-year age groups and 4 4-year calendar periods spanned 20 4-year birth cohorts (i.e., 1909 to 1985, designated by mid-year of birth). As previously detailed, we used the age-period-cohort (APC) "fitted" age-at-onset curve to provide an estimate of the age-specific incidence rate, coordinately adjusted for both calendar-period and birth cohort effects (26, 31).

We fitted the age-at-onset curves separately by grade because high-grade and low-grade SOC subgroups could be subject to different calendar period or birth cohort effects. For example, period effects such as case ascertainment or grade classification might vary by grade, and cohort or generational effects such as risk factor prevalence and/or exposures might also vary by grade.

Survival Analysis. Cumulative survival by grade and stage for the present data set of SOC was calculated using the Kaplan-Meier estimator (32), and curves were drawn with 95% confidence intervals (95% CI). The log rank test (33) was used to assess actuarial survival differences. The survival function defined the cumulative percentage of survival from the date of SOC diagnosis to the date of ovarian cancer death; all other events were censored.

Results

Descriptive Statistics. The merged SEER data sets yielded n = 19,899 cases of invasive SOCs among women ages 17 to 84 years (mean age, 61.5 years) with more than 299×10^6 woman-years follow-up (Table 1). Low-grade cases (mean age, 59.4 years) accounted for 23% of the total SOC; high-grade cases (mean age, 62.2 years) accounted for 58%; the remaining 19% (3,848 SOC) had not been graded. The overall age-adjusted incidence rate for SOC was 6.65 per 100,000 woman-years; the age-adjusted $IRR^{H/L}$ was 2.50 (95% CI, 2.42-2.59). Prior to age 40 years, the $IRR^{H/L}$ was <1.0 (0.68; 95% CI, 0.25-1.82) after which the $IRR^{H/L}$ was >1.0 (range, 2.10-2.56). For SOC detected at early stage onset (stages I-II), the $IRR^{H/L}$ was 1.16 (95% CI, 1.09-1.23). At late stage onset (stages III-IV), it was 3.05 (95% CI, 2.92-3.17); i.e., the $IRR^{H/L}$ increased 2.6-fold.

Incidence Rates. The cross-sectional, age-specific incidence rate of SOC increased earlier in life (after age 15 years), and at a slower rate for low grade than for high grade (Fig. 1A). In contrast, age-specific incidence rate increased later in life, and at a faster rate for high grade than low grade. Slower increasing rates for low grade and faster increasing rates for high grade eventually crossed near age 40 years. Exclusion of well differentiated SOC (G_1 = 22% of low-grade cases) and/or undifferentiated SOC (G_4 = 19% of high-grade cases) did not obscure the relative slope differences and incidence rate crossings. A quantitative (non-crossover) interaction became evident when the age-adjusted rates of high-grade versus low-grade SOC were followed at periodic intervals of 4 calendar years between 1990 and 2005 (Fig. 1B; $P < 0.001$ for trend interaction between low and high grade). At corresponding intervals, the age-adjusted incidence rate for high-grade SOC increased from 3.16 per 100,000 woman-years during 1990 to 1993 to 4.06 per 100,000 woman-years in the latest calendar period of 2002 to 2005. During this same interval, the incidence rate for low-grade SOC decreased from 1.60 to 1.32 per 100,000 woman-years.

APC Models. Given the age and trend interactions shown in Fig. 1, we examined APC fitted age-at-onset curves that were adjusted for period and cohort effects (Fig. 2). As in Fig. 1, the APC fitted age-specific incidence rate for low and high grade crossed near age 40 years; and this crossing occurred irrespective of stage (Fig. 2B and C; $P \approx 0$ for age interaction by grade). For all stages combined, the APC fitted $IRR^{H/L}$ reversed from 0.26 (95% CI,

Table 1. Invasive SOCs registered in SEER, newly diagnosed during the years 1990 to 2005

Mean age (SE)	All cases				Low grade				High grade				High/low grade ratio
	61.5 (0.09) y				59.4 (0.20) y				62.2 (0.11) y				
Variables	n^*	Rate	SE	IRR[†]	n	Rate	SE	IRR	n	Rate	SE	IRR	IRR[H/L] (95% CI)
	19,899	6.65	0.05	—	4,580	1.53	0.02	—	11,471	3.83	0.04	—	2.50 (2.42-2.59)
Age group													
<40	905	0.67	0.02	1.00	382	0.28	0.14	1.00	259	0.19	0.01	1.00	0.68 (0.25-1.82)
40-49	2,803	4.69	0.09	7.00	738	1.24	0.05	4.41	1,556	2.60	0.07	13.68	2.10 (1.91-2.31)
50-59	4,785	11.1	0.16	16.61	1,102	2.56	0.08	9.11	2,939	6.84	0.13	36.00	2.67 (2.49-2.87)
60-69	5,332	18.3	0.25	27.24	1,135	3.89	0.12	13.84	3,192	10.9	0.19	57.53	2.81 (2.62-3.01)
70-79	4,767	20.4	0.30	30.45	947	4.05	0.13	14.41	2,820	12.1	0.23	63.68	2.99 (2.77-3.21)
80+	1,307	16.3	0.45	24.39	276	3.45	0.21	12.28	705	8.82	0.33	46.42	2.56 (2.22-2.94)
Race													
White	17,607	7.56	0.06	1.00	4,081	1.75	0.03	1.00	10,149	4.36	0.04	1.00	2.49 (2.40-2.59)
Black	1,066	3.24	0.10	0.43	235	0.71	0.05	0.41	572	1.74	0.07	0.40	2.45 (2.09-2.87)
Other or unknown	1,226	3.65	0.10	0.48	264	0.79	0.05	0.45	750	2.23	0.08	0.51	2.82 (2.45-3.26)
Laterality													
Not paired	7,721	2.58	0.03	1.00	1,967	0.66	0.01	1.00	4,281	1.43	0.02	1.00	2.17 (2.08-2.26)
Bilateral	10,954	3.66	0.03	1.42	2,456	0.82	0.02	1.24	6,751	2.26	0.03	1.58	2.76 (2.61-2.91)
Other or unknown	1,224	0.41	0.01	0.16	157	0.05	0.00	0.08	439	0.15	0.01	0.10	3.00 (2.48-3.62)
Stages combined[‡]													
Early (I-II)	3,579	1.20	0.02	1.00	1,279	0.43	0.01	1.00	1,505	0.50	0.01	1.00	1.16 (1.09-1.23)
Late (III-IV)	15,807	5.28	0.04	4.40	3,208	1.07	0.02	2.49	9,762	3.26	0.03	6.52	3.05 (2.92-3.17)
Unknown	513	0.17	0.01	0.14	93	0.03	0.00	0.07	204	0.07	0.00	0.14	2.33 (2.82-2.99)

NOTE: National Cancer Institute's SEER Registry groups 9 + 13 + 17.
Rate, age-adjusted incidence rate per 100,000 woman-years (2000 U.S. standard population).
*Number (includes grade unknown).
†The reference rate is assigned an IRR = 1.0, and nonstatistically significant IRR ($\alpha = 0.05$) is in boldface.
‡International Federation of Gynecology and Obstetrics and American Joint Committee on Cancer equivalent.

0.12-0.56) in women ages 25 to 28 to 3.08 (95% CI, 2.47-3.84) in women ages 77 to 80.

Cancer-Specific Survival. Cumulative ovarian cancer–specific survival for women with SOC showed a dissocia-

tion that accorded with the diagnostic grades assigned in SEER (Fig. 3), irrespective of stage. Estimated cumulative survival was optimal for women with early stage diagnosis of invasive low-grade SOC (Fig. 3B). The survival advantage of low grade diminished in late stages (Fig. 3C).
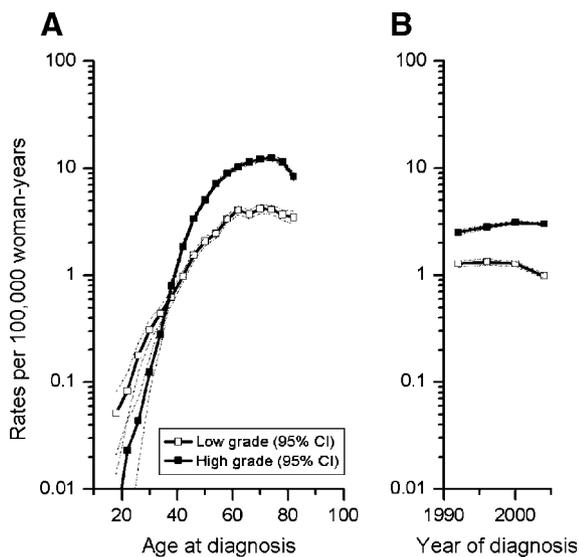
Discussion

Essential differences in the incidence rate patterns (qualitative interactions), and estimated cumulative survival of low-grade and high-grade SOC emerged from SEER data representing a substantial fraction of women from the United States. The general SEER catchment offered an advantageous distribution of ovarian cancers across a broad swath of the U.S. population with socioeconomic diversity. Stratification of the age-specific incidence rate, both by grade and stage, thus was powered by exceptionally large numbers of SOC cases with pertinent descriptive data. Overall results showed a qualitative age interaction by low and high grade. This population evidence of SOC heterogeneity was concordant with respective molecular constructs of type I and type II oncogenic pathways (2, 6); and further showed that age had a nonuniform biological effect on the incidence rates. Crossings of the age-specific incidence rates occurred near age 40 years, and fitting of data in recently improved APC models (26, 31) was crucial in demonstrating that the age-dependent rate differences by grade were not driven solely by secular cohort or calendar period factors during the 16-year span examined (1990-2005).

Compared with the age of incidence rate crossovers shown here for SOCs near age 40, low-grade and high-grade incidence rate crossovers for breast cancers were reported to occur nearly 10 years of age later (34); and this data has lately been confirmed by fitting for APC effects.[8]

Figure 1.   A. age-specific incidence rates for SOCs stratified by grade and stage (SEER, 1990-2005). Log rates (at 17 4-year intervals) per 100,000 woman-years are plotted on the *Y*-axis, age-at-diagnosis on the *X*-axis; 95% CI (*dotted lines*). $P < 0.001$ ($\alpha = 0.05$) for age-interaction by grade. **B.** age-adjusted (standardized) incidence rates of SOCs stratified by grade and calendar year (SEER, 1990-2005). Rates per 100,000 woman-years (at 4-year intervals) are plotted on the *Y*-axis, age-at-diagnosis on the *X*-axis; 95% CI (*dotted lines*).

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[8] Matsuno RK, Grimley PM, Anderson WF. Unpublished data analysis.

Figure 2. Fitted age-specific incidence rate curves (adjusted for period-cohort effects), and corresponding incidence rate ratios (IRR) for SOCs stratified by grade and stage (based on SEER, 1990-2005). Log rates per 100,000 woman-years are plotted on the *Y*-axis, age-at-diagnosis on the *X*-axis; 95% CI (*dotted lines*). **A.** all stages. **B.** early stage (III). **C.** late stage (III-IV).
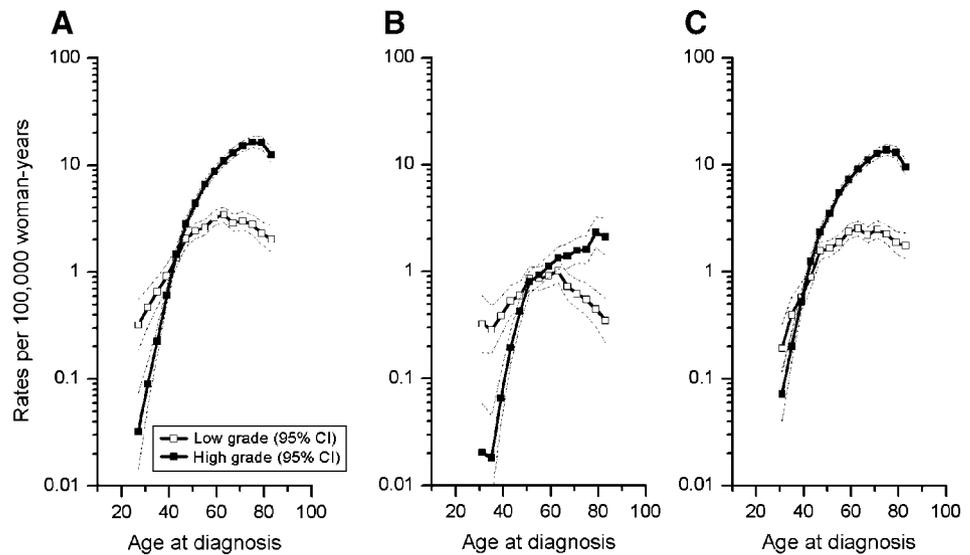
Because ovarian and breast cancers develop within a common context of reproductive risk factors, one explanation for the crossing age variances might be a difference in sensitivities or exposures to hormonal influences on carcinogenesis (see refs. 23, 35, 36). Of possible relevance is an apparent discordance in the effect of racial-ethnic background on the crossovers of age-specific incidence rate for the ovarian and breast cancers. In an initial study of Black and White women with SOC, no difference in the ages for incidence rate crossovers of low and high grade was detected.[9] In contrast, recent studies of breast cancer identified crossovers of incidence rate for Black and White women when tumors were stratified by hormone receptor status or grade (31, 37).

The clinicopathologic stage and tumor burden at presentation, or after surgical cytoreduction, are especially reliable indicators of ovarian cancer clinical behavior (11, 38, 39). The present distinction of fitted age-specific rates for low-grade and high-grade SOCs, irrespective of early and late clinicopathologic stages (see Fig. 2), substantiates morphologic grade as an age-specific effect modifier. The results also affirm clinical impressions that invasive low-grade SOC typically are detected at a younger age than high-grade SOC (17, 18). Even so, comparisons of Fig. 2B and C and Table 1 showed an absolute increase in the detection of low-grade SOC during late stage versus early stage. As noted by other investigators (2, 13, 17, 40), this epidemiologic observation would not conform to the classic paradigm of a linear age-grade-stage progression. Indeed, present survival estimates (see Fig. 3) indicate that the prognosis for low-grade SOC detected in late stage was only marginally better than for high-grade SOC. This could reflect observations that low-grade SOC are less responsive to conventional genotoxic therapies than high-grade SOC (18). The interactions between aging and oncogenetic factors

driving low-grade versus high-grade cancer cell migration and stage progression probably deserve further investigation (40).

Despite the apparent parallel of our descriptive findings and the molecular heterogeneity of SOC, we recognized that SEER data has potential shortcomings based on primary diagnoses from multiple contributors without independent slide reviews. Misclassifications, diagnostic bias, or random error could blunt evidence of real differences within the cancer population. Bias in diagnostic classification of noninvasive SOC (borderline tumors), which are typically well differentiated (G_1), was excluded in a sensitivity test which censored all of the G_1 cases. In fact, the observed qualitative age interactions occurred even when only G_2 and G_3 case data were tested.[10] Bias in grading due to inconsistent weightings of cytologic atypia and mitotic index by individual observers could not be directly excluded. Nevertheless, the reliability of study comparisons can be increased with the use of two-tier grading (30, 41), so that the collapse of the SEER grades into two tiers for the present study convincingly partitioned the age-specific incidence rates. Robust age-specific differences were evident between the cross-sectional incidence rates of low and high grades (compared in Figs. 1 and 2), as well as between the cumulative ovarian cancer–specific survival of SOC estimated by grade and by stage (compared in Fig. 3). Grade/stage proportions determined from SEER and the sensitivities of the survival estimates were comparable to findings reported in expertly refereed case series (4, 7, 30); whereas the statistical power was magnified by the extraordinary $n = 19,899$ compared with most previously reported SOC case series with n at least 10-fold lower.

In summary, qualitative age interactions between low-grade and high-grade SOCs, irrespective of stage, showed that grade is an age-specific effect modifier in this predominant histologic type of ovarian malignancy. Our results offer an age dimension of SOC risk that supplements the molecular-genetic and immunohistochemical tissue

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[10] Matsuno RK, Grimley PM, Rosenberg PS, Anderson WF. Unpublished data.
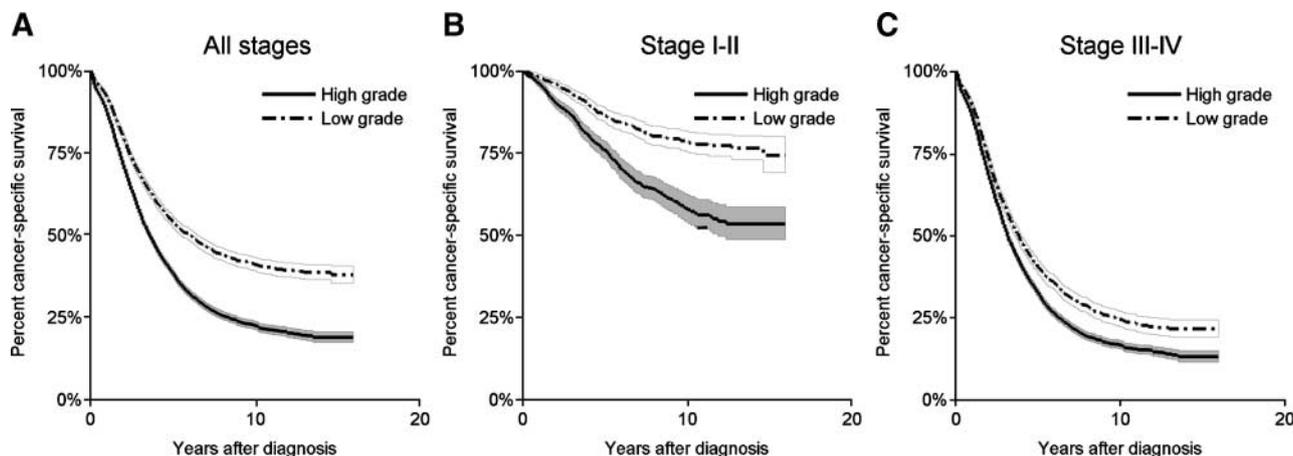
Figure 3. Estimated cumulative survival (Kaplan-Meier) for women with SOC stratified by grade and stage (SEER, 1990-2005). Percentage of ovarian cancer–specific survival is plotted on the *Y*-axis, time up to 15 years after diagnosis on the *X*-axis; 95% CI (shaded), with a separation of high/low grades ($P < 0.0001$). **A.** All stages. **B.** Early stage (I-II). **C.** Late stage (III-IV).

analyses which have implicated two grade-based pathways of carcinogenesis (type I and type II; refs. 2, 7, 14, 19). Considering the burgeoning interest in identifying genomic determinants or markers of ovarian cancer risks, progression, therapeutic response, and outcome (6-8, 20-23, 42-44), future analytic studies and clinical trials of SOC should be powered to anticipate the nonuniform age-dependent interaction (effect modification) delineated by low and high grade.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

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Correction

Correction: Article on Aging in Serous Ovarian Carcinomas

In the article (1) on aging in serous ovarian carcinomas in the August 2009 issue, there were minor errors in the legends for Figs. 1 and 2. The correct legends follow.

Figure 1. **A.** age-specific incidence rates for SOC stratified by grade (SEER, 1990-2005). Log rates (at 17 4-year intervals) per 100,000 woman-years are plotted on the _Y_-axis, age-at-diagnosis on the _X_-axis; 95% CI (_dotted lines_). $P < 0.001$ ($\alpha = 0.05$) for age-interaction by grade. **B.** age-adjusted (standardized) incidence rates of SOC stratified by grade (SEER, 1990-2005). Rates per 100,000 woman-years (at 4 4-year time intervals) are plotted on the _Y_-axis, year of diagnosis on the _X_-axis; 95% CI (_dotted lines_).

Figure 2. Fitted age-specific incidence rate curves (adjusted for period and cohort effects) for SOC stratified by grade and stage (SEER, 1990-2005). Log rates per 100,000 woman-years are plotted on the _Y_-axis, age-at-diagnosis on the _X_-axis; 95% CI (_dotted lines_). **A.** all stages. **B.** early stage (I-II). **C.** late stage (III-IV).

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Qualitative Age Interactions between Low-grade and High-grade Serous Ovarian Carcinomas

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