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Gynecologic Oncology 96 (2005) 520–530

Gynecologic Oncology

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Histologic types of epithelial ovarian cancer: have they different risk factors?

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Received 1 September 2004
Available online 13 December 2004

Abstract

Objectives. The histologic types of epithelial ovarian cancer differ in clinical behavior, descriptive epidemiology, and genetic origins. The goals of the current study were to characterize further the relation of histologic-specific ovarian cancer risks to reproductive and lifestyle attributes.

Methods. The authors conducted a pooled analysis of 10 case-control studies of ovarian cancer in US White women, involving 1834 patients with invasive epithelial ovarian cancer (1067 serous, 254 mucinous, 373 endometrioid, and 140 clear cell) and 7484 control women.

Results. Risks of all four histological types were inversely associated with parity and oral contraceptive use, but the histologic types showed different associations with nonreproductive factors. Unique associations include an inverse relation of serous cancer risk to body mass index, a positive relation of mucinous cancer risk to cigarette smoking, and a weakly positive relation of endometrioid cancer risk to body mass index. Risk of all histologic types was unassociated with age at menarche, age at menopause, a history of infertility, noncontraceptive estrogen use, and alcohol consumption.

Conclusions. The most important modifiers of ovarian cancer risk (parity and oral contraceptive use) showed similar associations across the histologies. Nevertheless, the unique associations seen for other modifiers support the conjecture that the histologic types of epithelial ovarian cancer have different etiologies, which should be addressed in future investigations of the molecular basis of ovarian cancers and their responses to therapies.

Keywords: Ovarian cancer; Histology; Serous; Mucinous; Endometrioid; Clear cell; Risk factors; Case-control study

In many epidemiological and clinical investigations, including those confirming established risk factors such as nulliparity and absence of oral contraceptive use, epithelial ovarian cancer has been treated as a single disease, without distinguishing among its histologic types [1–10]. Differences in risk factors for epithelial ovarian cancer by histologic type were first reported by Risch et al. [11] and subsequently confirmed by others [12–14]; these authors have found a protective role for reproductive factors such as parity, multiple births, and oral contraceptive use against nonmucinous, but not mucinous tumors. However, other authors have not observed such differences [15,16].

Recently, genetic differences between the histologic types of ovarian cancer have been reported, which lend support to the hypothesis that risk factors differ. Three such observations include (1) ovarian cancers in patients with germline mutations of the tumor suppressor genes BRCA1 and BRCA2 are more likely to be serous (or endometrioid) than mucinous [17–20]; (2) among patients without these germline mutations, the gene expression patterns of serous (and some endometrioid) cancers are similar to those of BRCA1- and BRCA2-related cancers

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doi:10.1016/j.ygyno.2004.10.037

[21]; and (3) serous cancers have a higher prevalence of BRCA1 and BRCA2 dysfunction than do mucinous cancers, including loss of heterozygosity and promoter methylation of the BRCA1 gene, and deletions of the BRCA1 region on chromosome 17q [22–24]. It has also been reported that mucinous cancers have a higher percentage of abnormal K-ras expression than do other histologies [25].

Differences have also been noted in the clinical behavior of the different histologic types of ovarian cancer. Some investigators have found mucinous cancers to have lower grade and stage, and to be associated with better survival than other types [26,27]; one series reported that serous cancers are associated with a higher mortality rate than other histologic subtypes [28]. However, other authors have found both mucinous and clear cell cancers to be associated with poorer survival than serous cancers [29–34]. Patients with mucinous (and perhaps clear cell) cancers appear less responsive to cisplatin-based therapy than do patients with serous (and perhaps endometrioid) cancers [35–37]. Shimizu [38] classified the histologies into a cisplatin-sensitive group (serous, endometrioid, transitional cell, and undifferentiated) with 80–90% response (i.e., complete or partial tumor disappearance) and a cisplatin-resistant group (mucinous and clear cell) with less than 5% response. Similar patterns in response have been noted for carboplatin and paclitaxel, with response rates of 71–81% among serous and endometrioid histologies, and of 14–22% among mucinous and clear cell histologies [36]. Some explanation of these observations may be found in reports of better survival in patients with cancers, usually of serous histology, related to germline mutations in BRCA1 or BRCA2; this finding has been attributed to their greater responsiveness to platinum-based chemotherapy [39,40]. In vitro experiments have shown that BRCA1-dysfunctional cells are particularly vulnerable to cisplatin, which is thought to reflect the cells' loss of BRCA1-mediated ability to repair cisplatin-induced DNA damage [41].

Further support for histologic-specific ovarian cancer etiology arises from differences in the descriptive epidemiology of the histologic types. Age-adjusted incidence rates among United States White women during the period 1995–1998 for serous, mucinous, endometrioid, and clear cell cancers were, respectively, 4.85, 1.05, 1.62, and 0.56 cases per 10^5 person-years. Serous cancers are most common among patients of all ages; however, the relative ranking of other histologies varies with age, with mucinous cancer the most common nonserous type among women aged less than 45 years but not in older women [42]. Racial and ethnic differences also exist in the incidence of cancers of different histologies, with a recent report finding mucinous tumors more common in Asian than Caucasian women [12]. Moreover, the different histologic types exhibit different temporal trends. Incidence rates of serous cancers increased among United States Whites during the period 1978–1998, while the rates of mucinous cancers decreased [42]. Such findings lead to consideration of whether differences in etiology underlie these trends.

Motivated by the cumulative evidence for differences among the histologic types in their biological and epidemiological features, we examined differences in risk factors for serous, mucinous, endometrioid, and clear cell ovarian cancers using pooled data from 10 case-control studies. The large numbers of patients (1067 with serous cancers, 254 with mucinous cancers, 373 with endometrioid cancers, and 140 with clear cell cancers) afford an opportunity to evaluate differences in odds-ratios (OR) associated with menstrual and reproductive factors, exogenous hormone use, total years of ovulation, pelvic surgeries, family history of breast and ovarian cancer, and consumption of alcohol and tobacco.

Methods

Study subjects

Data on reproductive and lifestyle characteristics of White women with invasive epithelial ovarian cancers of serous, mucinous, endometrioid, and clear cell types, and of White control women, were obtained from 10 case-control studies conducted in the United States during the period 1973–2001. Nine of the studies are those with available histology data in the combined analysis of the Collaborative Ovarian Cancer Group (COCG) [1–10]. The 10th study was conducted in the San Francisco Bay Area during the period March 1, 1997 to July 31, 2001 as part of the Familial Registry of Ovarian Cancer (FROC), a population-based ovarian cancer registry funded by the United States National Cancer Institute [43]. Table 1 describes the studies, numbers, origins, and age range of cases by histology, the numbers and origins of controls, and the matching criteria.

Attributes considered in the present analysis include age, educational level, marital status, number of term pregnancies (those of at least 20 weeks gestation), age at first term pregnancy, use of oral contraceptives and noncontraceptive estrogens, history of tubal ligation, family history (mother or sister with breast or ovarian cancer), body mass index (weight in kilograms divided by the square of height in meters), age at menarche, physician-diagnosed infertility not attributed to the male partner, cigarette smoking, mean duration of breast-feeding per term pregnancy, total years of ovulation, age at natural menopause, and alcohol consumption. Additional details concerning the study protocols, response rates, and measures to insure uniformity of data and variable coding can be found in the publications cited in Table 1 and in the description of methods used by the COCG [10].