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# Serous ovarian and primary peritoneal cancers: A comparative analysis of clinico-pathological features, molecular subtypes and treatment outcome

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## HIGHLIGHTS

- Primary peritoneal patients were older than patients with ovarian cancer.
- They were more likely treated with neoadjuvant chemotherapy and interval debulking.
- They had better debulking rates but inferior survival after neoadjuvant chemotherapy.
- Most clustered with the C1 subtype, with high stromal response and inferior survival.

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## ABSTRACT

*Objective.* Primary peritoneal cancer is rare and considered equivalent to stage III/IV ovarian cancer, but questions remain concerning its underlying biology, prognosis and optimal management.

*Methods.* Clinico-pathological and treatment details of primary peritoneal (n = 120) and ovarian cancer (n = 635) were obtained on women recruited to the Australian Ovarian Cancer Study. Log-rank test was used to compare survival and cox proportional hazards models were fitted to obtain hazard ratios and 95% confidence intervals, both unadjusted and adjusted for age, grade, FIGO stage, residual disease and treatment with neoadjuvant chemotherapy. Molecular subtype was determined by gene expression profiling using published data.

*Results.* Compared with advanced serous ovarian cancer, primary peritoneal cancer patients were older (mean age 65.5 vs. 60.2 years, $p < 0.001$), more often treated with neoadjuvant chemotherapy (38.4% vs. 11.4%, $p < 0.001$). Gene expression profiling classified a substantially higher proportion of primary peritoneal carcinomas as C1 (mesenchymal, reactive stromal infiltration) subtype (70.6% vs. 32.1%, $p = 0.029$), which was associated with lower complete surgical resection rate. Women with primary peritoneal cancer had significantly shorter progression-free (11.6 vs. 13.6 months, $p = 0.007$) and overall survival (31.7 vs. 39.8 months, $p = 0.012$). In multivariate analysis, residual disease and neoadjuvant chemotherapy were both independently associated with increased risk of progression and death.

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*Conclusions.* Primary peritoneal cancer patients were more frequently treated with neoadjuvant chemotherapy and had inferior survival. Different tumor biology characterized by activated stromal fibrosis in primary peritoneal cancer may underlie the differences in treatment and clinical outcome.



## 1. Introduction

Primary peritoneal cancer was first reported in 1959 [1]. The diagnosis denotes the diffuse involvement of abdominal peritoneal surfaces by carcinoma that is histologically identical to carcinoma of ovary, in the absence of a demonstrable primary ovarian tumor. Its incidence is considerably lower compared to epithelial ovarian cancer [2] and increased awareness may be responsible for the relative increase in its incidence. Primary peritoneal cancer has been reported not only in women with their ovaries *in situ*, but also in women carrying a germline *BRCA* mutation after prophylactic oophorectomy [3]. In some cases primary peritoneal cancer occurred decades after the procedure. Isolated cases have also been reported in males [4].

At present the origin of primary peritoneal and ovarian cancer is still debated. Increasing evidence suggests that a substantial proportion of ovarian serous cancer cases arise from precursor lesions located in the fallopian tubal epithelium (FTE) [5–7]. This view is supported by the finding of precursor lesions, namely serous tubal intraepithelial carcinoma (STIC), in fallopian tubes of both women with *BRCA* mutations after prophylactic surgery [8,9] and in patients with disseminated high-grade serous carcinoma (HGSC) [5,10]. These putative early lesions share the same morphologic, immunophenotypic features and *TP53* mutation as HGSC [11,12]. Perets *et al.* have successfully developed a genetically engineered mouse model of *de novo* HGSC that originates in fallopian tubal secretory epithelial cells [7]. This model not only recapitulated the key genetic alterations of human invasive ovarian cancer but also offered mechanistic insight into the origin and pathogenesis of HGSC. Intriguingly, removal of the ovary in this mouse model reduced peritoneal spread, suggesting that the ovary provides a permissive environment that facilitates metastasis, potentially via a mechanism involving ovarian hormone action. So while there is increasing evidence that both ovarian and primary peritoneal carcinomas may arise from a common precursor lesion in the fimbrial end of the fallopian tube, it is not clear why some would preferentially metastasize to the peritoneum and whether this represents a differing underlying biology in primary peritoneal carcinomas.

Epidemiologic risk factors appear to differ between the two diseases [13–15]. Women with peritoneal cancer have been reported to be significantly older compared to ovarian cancer patients [13,14]. While parity reduced the risk of serous ovarian cancer, it increased the risk of primary peritoneal cancer [13,14] although reports on the association have been conflicting [2,15]. Use of contraception, which also leads to anovulation, has consistently been reported to reduce the risk of both ovarian and primary peritoneal carcinoma [13].

Gene expression profiling of serous and endometrioid ovarian, primary peritoneal and fallopian tube cancer, has revealed six molecular subtypes with distinct differences in survival [16]. Subtypes C3 and C6 were predominantly low-grade/borderline serous tumors and early-stage endometrioid tumors, respectively, while the vast majority of HGSC segregated with four subtypes (C1, C2, C4, C5), first shown by Tothill et al. [16], and robustly identified in multiple independent datasets, with consistent clinical associations [17–19]. The C1 subtype (mesenchymal) is characterized by desmoplasia, extensive myofibroblast infiltration, an epithelial–mesenchymal gene expression signature, and is associated with poor survival. C2 subtype (immunoreactive) tumors are characterized by extensive intratumoral T-cell infiltration and generally have a more favorable prognosis. Patients with a C4 subtype (differentiated) have an intermediate outcome and C5 subtype (proliferative) tumors have low expression of differentiation markers, including CA125, limited inflammatory infiltration, and a similarly poor outcome to C1 subtype [16].

Studies of clinical outcome of ovarian and peritoneal cancer patients have produced conflicting results with survival times being better [20], similar [21–24] or worse compared to patients with advanced ovarian serous carcinoma [25–28]. However most of these studies were small and encompassed a wide spectrum of time periods, imaging technologies, chemotherapeutic regimens and surgical techniques.

To better understand primary peritoneal carcinoma, we conducted a large, multicenter, comparative review of clinico-pathological and treatment data of primary peritoneal and ovarian cancer cases, identified in the prospective population-based Australian Ovarian Cancer Study (AOCS).

## 2. Methods

### 2.1. Patient cohort

AOCS is an Australian-wide population-based case-control study. From January 2002 to June 2005, 1859 eligible patients were recruited through an existing network of Gynecologic Oncologists, covering >85% of the Australian population [16]. Cases recorded in the database were identified as potentially primary peritoneal carcinomas based on the initial diagnostic pathology report (n = 208). All histopathology reports were re-reviewed and the Gynecologic Oncology Group (GOG) criteria for primary peritoneal carcinoma were applied as described by Bloss et al. [23]: (i) either ovary must be normal in size (≤4.0 cm) or enlarged by a benign process; (ii) the involvement in the extra-ovarian sites was greater than the involvement on the surface of either ovary and (iii) microscopically, the ovaries were either not involved with tumor or exhibited only serosal or cortical implants <5 mm in depth. According to these criteria, the diagnosis of primary peritoneal carcinoma was confirmed in 127 cases. A complete set of diagnostic H&E stained slides of 97 (76%) cases were available for review by a Gynecological oncology pathologist (LA) and seven additional cases were excluded after the identification of cortical implants ≥5 mm in the ovaries. Of these, 85 cases had sections of fallopian tube available for review to determine the extent of involvement of the fallopian tube and the presence of serous tubal intraepithelial carcinoma (STIC). A total of 120 confirmed primary peritoneal cancer cases were included in the final analysis. Cases of primary ovarian cancer (n = 635) from AOCS, which had undergone centralized pathology review of diagnostic pathology slides by a panel of Gynecological Oncology pathologists at the time of analysis were used for comparison. A planned subset analysis on women with advanced stage (stage III/IV), serous primary peritoneal (n = 112) and ovarian carcinoma (n = 369) was performed to compare clinico-pathological characteristics and clinical outcome.

### 2.2. Clinical variables

Clinical variables were extracted from medical records and made available from the AOCS database. Histopathological grade was described using a 3-tier system, Grade 1, 2 or 3, corresponding to well, moderately and poorly differentiated tumors [29]. Surgical stage was assessed in accordance with the International Federation of Gynecology and Obstetrics (FIGO) classification. For this analysis, residual disease