Primary Peritoneal Carcinoma Can Have Multifocal Origins: Implications for Prophylactic Oophorectomy

Andrea Eisen, Barbara L. Weber*

The clinical entity of primary peritoneal carcinoma has had many different names, including papillary serous carcinoma of the peritoneum (PSCP). First reported in 1959 (1), PSCP refers to the diffuse involvement of peritoneal surfaces with a neoplasm appearing identical to papillary serous carcinoma of the ovary, in the absence of a demonstrable primary ovarian tumor. It can occur in women after oophorectomy for prophylaxis or benign disease or in women with intact ovaries. Clinically, it is indistinguishable from stage III epithelial ovarian cancer (2,3). Historically, there have been two theories about the origin of this cancer. The first is that the tumor develops in the ovarian surface epithelium and subsequently spreads throughout the peritoneal cavity. The primary tumor is postulated to be microscopic, and therefore not detectable, or to have regressed completely. The second theory is that the disease starts de novo in the peritoneal mesothelium, which is of müllerian origin. This theory seems plausible because the cell of origin of epithelial ovarian cancer is the peritoneal reflection on the surface of the ovary, not the underlying stromal or germ cell components. PSCP may be particularly relevant in women with inherited susceptibility to ovarian cancer, where germline mutations create a field defect. In this setting, the entire peritoneal surface, not just that covering the ovary, is at risk for malignant transformation. However, the peritoneal reflection on the surface of the ovary may be particularly vulnerable to malignant transformation as a result of repeated injury following ovulation and/or high levels of local estrogen exposure.

The report by Schorge et al. (4) appearing in this issue of the Journal provides evidence for the latter hypothesis. Schorge et al. identified 22 women with PSCP and intact ovaries, 20 of whom were heterozygous at the androgen receptor (AR) locus on the X chromosome and thus informative for their analysis. These investigators demonstrated that, in five of the 20 cases, tumor DNA from multiple sites showed different patterns of loss of heterozygosity (LOH) at the AR locus. These data could be interpreted as evidence for the development of multiple, independent tumor clones or as evidence of tumor heterogeneity. However, two of these five tumors had different patterns of X-chromosome inactivation, a finding that strongly supports a multifocal origin, at least in these two cases. These results support the results obtained in a previous study (5) by the same group, in which they found a different pattern of 17p LOH and p53 gene mutation in four of six women with PSCP. Together, these results suggest that, in at least some cases, PSCP is polyclonal, arising in multiple primary peritoneal sites. Conversely, other investigators (6), using analysis of p53 gene mutations, have provided some evidence for monoclonal disease origin. In that series, nine of 10 patients with stage III ovarian cancer and two patients with PSCP had identical molecular changes at all tumor sites analyzed.

While rare, PSCP has attracted attention lately as a cancer that may occur with increased frequency in women who carry inherited mutations in BRCA1 and BRCA2. It is well known that women with germline mutations in BRCA1 and BRCA2 have a markedly increased risk of developing ovarian cancer, with lifetime risk estimates ranging from 16% to 44%, depending on the populations being studied (7,8). The incidence of PSCP, before or after oophorectomy, is not known in these high-risk women. Of course, a major goal in the clinical management of these women is the reduction of cancer risk and related mortality. Strategies to this end have included increased cancer surveillance, risk factor modification, consideration of chemoprevention, and prophylactic surgery. Unfortunately, data from prospective trials of ovarian cancer risk alteration in known BRCA1 and BRCA2 mutation carriers are lacking. However, many women with BRCA1 and BRCA2 mutations are being advised to undergo prophylactic oophorectomy because of the lack of proven means of effective surveillance for ovarian cancer. A subset of these women goes on to develop PSCP, sometimes decades after oophorectomy.

For ovarian cancer, secondary prevention efforts within the general population, including clinical examination, transvaginal ultrasound, and determination of CA125 serum levels, have not been shown to improve survival rates. Some investigators (10,11) have shown that intensive surveillance by use of transvaginal ultrasound in women with a family history of ovarian cancer can detect early stage disease with increased frequency, but this has not been confirmed in women with known BRCA1 and BRCA2 mutations. Unfortunately, the modification of life-
style factors known to be associated with an increased risk of ovarian cancer is not always practical or feasible. Finally, chemoprevention of ovarian cancer in this group is still experimental; although oral contraceptives are known to reduce the incidence of ovarian cancer in the general population (12), their potential benefit in carriers must be balanced against a possible increase in the risk of breast cancer associated with prolonged use (13).

As noted above, the limitations of ovarian cancer risk reduction strategies have contributed to an interest in prophylactic surgery among BRCA1 and BRCA2 mutation carriers. Guidelines for the management of these high-risk individuals, based largely on expert opinion, have been developed (9,14). These consensus statements have recommended that female mutation carriers be counseled to consider prophylactic oophorectomy after childbearing is complete or by the age of 35 years. However, surgical prophylaxis in individuals with a hereditary predisposition to cancer remains controversial, partly because of the incomplete protection conferred against subsequent cancer. Indeed, numerous reports (15–19) in the literature have documented the occurrence of PSCP after prophylactic oophorectomy. With the exception of one case report, all of the women described in these series had a family history of ovarian cancer. In this setting, various investigators have reported rates of peri-
toneal cancer ranging from 1.9% to 10.7%. Despite this recognized risk, a decision analysis that incorporated a prophylactic oophorectomy efficacy rate of only 50% in the model still showed a modest survival benefit in a theoretical cohort of BRCA1 mutation carriers undergoing this procedure (20).

Schorge et al. (4) also attempt to address the question of PSCP origin in BRCA1 mutation carriers. Of the 22 PSCP pa-
tients analyzed in their study, 17 have been tested for BRCA1 mutations by single-strand conformation polymorphism (SSCP) analysis. Only three patients were found to have deleterious BRCA1 mutations. All three of these patients had molecular evidence of multifocal disease based on analysis of the AR locus, an apparently statistically significant result when compared with the two out of 14 patients without BRCA1 mutations whose tumors also showed evidence of multifocality. The generalizability of this finding to all BRCA1 mutation carriers is limited, given the small size of this study. However, it is possible that more of the patients did in fact have hereditary disease. Schorge et al. did not test for BRCA2 muta-
tions in their patients, and SSCP as a mutation-screening tech-
nique has limited sensitivity. In addition, all the women in their study had intact ovaries—no case of PSCP described in this study occurred after prophylactic oophorectomy, the scenario that is most common among BRCA1 and BRCA2 mutation car-
riers. Whether the development and/or biology of these cancers are different in women with and without intact ovaries is unknown.

If PSCP is at least sometimes a multifocal disease, what are the implications for the use of prophylactic oophorectomy in known BRCA1 mutation carriers? The results of the study by Schorge et al. (4) provide important information about the pathogenesis of the disease as well as evidence refuting the hypothesis that PSCP always originates from occult malignant cells in the ovarian surface epithelium. These findings re-emphasize the fact that preventive surgery will never completely protect against the development of intra-abdominal cancer in these high-risk women, although the occurrence of this cancer may be substantially reduced. Finally, these findings remind us that novel approaches are needed to eliminate the increased cancer morbidity and mortality risks faced by these women. Such approaches may even require a combination of surgical prophylaxis, to remove the formidable ovarian cancer risk faced by women with BRCA1 and BRCA2 mutations, followed by a chemopreventive agent to address the problem of PSCP. The identification of genetically defined, high-risk women and the molecular character-
ization of the tumors that arise in these women represent the essential first steps in the right direction.

References

(10) Bourne TH, Campbell S, Reynolds KM, Whitehead ML, Hampson J, Roys-
(11) Dorum A, Kristensen GB, Abeler VM, Trope CG, Moller P. Early detect-
(12) The reduction in risk of ovarian cancer associated with oral-contraceptive use. The Cancer and Steroid Hormone Study of the Centers for Disease Control and the National Institute of Child Health and Human Develop-
(14) Burke W, Daly M, Garber J, Botkin J, Kahn MJ, Lynch P, et al. Recommen-
dations for follow-up care of individuals with an inherited predisposition to cancer. II. BRCA1 and BRCA2. Cancer Genetics Studies Consor-
(16) White CD. Papillary intraperitoneal neoplasia resembling ovarian carcino-
Prognostic Applications of the Epidermal Growth Factor Receptor and Its Ligand, Transforming Growth Factor-α

Carol J. Wikstrand, Darell D. Bigner*

Because growth factors and their receptors have a central role in regulating developmental and neoplastic processes, the expression and action of various growth factor receptors and their ligands in human neoplasia have been extensively investigated. During the past two decades, several investigators have described the amplification of the epidermal growth factor receptor (EGFRe) at the genotypic level and overexpression of the EGFRe protein at the phenotypic level in many tumors (1–16). However, great heterogeneity in the incidence of overexpression, in the intensity and localization of receptor deposition, and of prognostic significance has been observed both within and between various tumor types. EGFRe protein overexpression has been reported to occur and to be of prognostic value for predicting either shorter disease-free survival or shorter overall survival in endometrial carcinoma [49% incidence (1)], esophageal carcinoma [43% incidence (2)], bladder carcinoma [35% incidence (3)], and prostatic carcinoma (4). In several other tumor types where multiple studies have been reported, the results have been mixed. Overexpression of EGFRe has been frequently reported in non-small-cell lung carcinoma (5–8); however, the incidence of EGFRe overexpression ranges from 12% (21 of 169 cases) to 37.5% (12 of 32 cases), with no demonstrated association between disease-free or overall survival. Similar heterogeneity has been reported in ovarian cancer with observed incidences of 19% (9) to 50% (10); both studies claimed an association of EGFRe with either advanced stage (10) or poorer prognosis (9). Verbeek et al. (11) reported overexpression of EGFRe in 20%–30% of breast cancer cases investigated by immunostaining and claimed an association with poorer prognosis; however, by use of either conventional (12) or quantitative (13) radioimmunohistochemistry, two studies have suggested that the expression level of EGFRe is significantly lower in malignant breast tissue than in benign and normal breast epithelium. Although Iwase et al. (14) reported a 38.8% incidence of EGFRe positivity among tumor tissue samples in 80 breast carcinoma cases, EGFRe expression was inferior to lymph node involvement or tumor size as a prognostic indicator. Similarly, conflicting reports of quantitative analysis of lower than normal tissue levels of EGFRe in cervical carcinoma (15) versus increased levels in patients with invasive cervical carcinoma (16) without prognostic significance have been reported. As summarized by Robertson et al. (13), a great deal of this heterogeneity may be attributable to a general lack of standardization between laboratories for EGFRe assay procedures. Quantitative methodologies, whether by labeled ligand or by messenger RNA (mRNA) or DNA analyses, are performed on preparations derived from tumor biopsy specimens containing malignant cells and non-tumor-cell populations and thus do not necessarily represent the neoplastic cell population; immunohistochemical analysis, while subjectively capable of discriminating between normal and neoplastic elements, is not readily quantifiable. Conflicting series observations will need to be clarified by carefully controlled studies comparing quantitative and qualitative determinations of frequency and identity of EGFRe-expressing cells and examination of sufficiently large patient cohorts to determine potential prognostic significance.

In this issue of the Journal, Rubin Grandis et al. (17) present the fifth paper in a series of studies of EGFRe protein expression in head and neck carcinomas and report on the potential of these marker levels for predicting disease-free and overall survival. Previous studies of EGFRe expression in head and neck cancer (18–20) have generally concurred that EGFRe overexpression was associated with shorter relapse-free intervals and overall survival; a single study in 68 patients with laryngeal carcinoma (21), while identifying a 42.6% incidence of EGFRe protein overexpression, found no association of EGFRe overexpression with survival or recurrence rates. The study by Rubin Grandis et al. (17) is itself noteworthy for the strength of the demonstrated association between EGFRe and transforming growth factor-α