Profilining Cytochrome P450 Expression in Ovarian Cancer: Identification of Prognostic Markers
Diane Downie,1 Morag C.E. McFadyen,1 Patrick H. Rooney,1,3 Margaret E. Cruickshank,2 David E. Parkin,2 Iain D. Miller,1 Colin Telfer,3 William T. Melvin,3 and Graeme I. Murray1

Abstract Purpose: The cytochromes P450 are a multigene family of enzymes with a central role in the oxidative metabolism of a wide range of xenobiotics, including anticancer drugs and biologically active endogenous compounds. The purpose of this study was to define the cytochrome P450 profile of ovarian cancer and identify novel therapeutic targets and establish the prognostic significance of expression of individual cytochrome P450s in this type of cancer.

Experimental Design: Immunohistochemistry for a panel of 23 cytochrome P450s and cytochrome P450 reductase was done on an ovarian cancer tissue microarray consisting of 99 primary epithelial ovarian cancers, 22 peritoneal metastasis, and 13 normal ovarian samples. The intensity of immunoreactivity in each sample was established by light microscopy.

Results: In primary ovarian cancer, several P450s (CYP1B1, CYP2A2/2B, CYP2F1, CYP2R1, CYP2U1, CYP3A5, CYP3A7, CYP3A43, CYP4Z1, CYP26A1, and CYP51) were present at a significantly higher level of intensity compared with normal ovary. P450 expression was also detected in ovarian cancer metastasis and CYP2S1 and P450 reductase both showed significantly increased expression in metastasis compared with primary ovarian cancer. The presence of low/negative CYP2A/2B (log rank = 7.06, P = 0.008) or positive CYP4Z1 (log rank = 6.19, P = 0.01) immunoreactivity in primary ovarian cancer were each associated with poor prognosis. Both CYP2A/2B and CYP4Z1 were also independent markers of prognosis.

Conclusions: The expression profile of individual P450s has been established in ovarian cancer. Several P450s show increased expression in ovarian cancer and this provides the basis for developing P450-based therapeutics in ovarian cancer. Expression of CYP2A/2B or CYP4Z1 in primary ovarian cancer were independent markers of prognosis.

Ovarian cancer is the most common gynecological malignancy worldwide; yet, the 5-year survival rate for this disease has remained low at ~30% for the last 20 years and with relatively little recent improvement (1, 2). Poor prognosis is generally considered to be the result of late presentation when ovarian cancer is of advanced stage and the unpredictable and generally very limited response of this type of cancer to current cancer therapies (3, 4). Improved survival in ovarian cancer is, therefore, dependent on the development of new paradigms in treatment.

The cytochrome P450 (P450) enzymes are a large family of constitutive and inducible mono-oxygenase enzymes that metabolize many lipophilic, biologically active endogenous and xenobiotic substrates, including a large number of therapeutic drugs and toxic environmental chemicals (5–8). Currently, the human P450 superfamily is classified into 18 distinct families based on nucleic acid homology (5). Some P450s, especially the major xenobiotic metabolizing forms of P450, have been very well characterized, whereas very little is known about the biology of some of the more recently identified P450s. Individual P450s show characteristic cell type – and tissue-specific patterns of expression. The primary site of expression for the major xenobiotic-metabolizing P450s in normal tissues is the liver, although specific P450s are expressed in many extrahepatic tissues (9).

Several P450s, most notably CYP1B1, are overexpressed in tumors whereas individual P450s have been detected in a range of tumor types (10–16). The identification of P450s, especially those P450s that show enhanced expression in tumor tissue, provides potential targets from which chemotherapeutic strategies can be developed (17, 18). Several therapeutic approaches based on the expression and/or overexpression of P450s in tumors are beginning to be developed. These therapeutic strategies include P450 vaccines, P450-mediated prodrug activation, and P450 inhibitors (15, 16).

Several P450s are involved in the metabolism of a range of anticancer drugs and recent studies have shown that individual forms of P450 play a role in anticancer drug resistance.
CYP1B1 has been shown to be potentially involved in resistance to a range of anticancer drugs, particularly the taxane docetaxel (19). However, the outcome of P450-mediated anticancer drug metabolism in terms of activation or resistance in tumor cells is dependent on both the relative amount and activity of individual P450s present (18).

In this study, the P450 expression profile has been defined in primary and metastatic ovarian cancer and established those P450s that are overexpressed in ovarian cancer and markers of prognosis. This study provides the basis for the development of new treatment strategies based on the expression of P450s in ovarian cancer.

### Materials and Methods

**Tumor samples.** Samples of ovarian cancer that had been submitted to the Department of Pathology, University of Aberdeen, over a 5-year period (1993-1998) for histopathologic diagnosis were used in this study. All the specimens had been fixed in formalin and selected tissue blocks embedded in wax. In total, samples from 115 patients were studied comprising 99 primary epithelial ovarian cancer samples, 22 metastases (all peritoneal metastases), and 13 normal ovarian tissue samples (all obtained from postmenopausal women undergoing surgery for ovarian cancer in the contralateral ovary). Information regarding age, tumor histopathology (the histopathology of all cases was reviewed by an expert in gynecologic histopathology—I.D. Miller), Fesddration Internationale des Gynaecologistes et Obstetristes stage of disease, and survival was available for each case and is summarized in Table 1. The median survival of the patients was 40 months (mean 60) with the survival range between 1 and >126 months. At the time of the most recent follow-up, 62.5% of patients had died. The study had the approval of the Grampian Research Ethics Committee.

**Cytochrome P450 antibodies.** A panel of 23 P450 antibodies and cytochrome P450 reductase were used in this study. Polyclonal antibodies to CYP2F1, CYP2J2, CYP2R1, CYP2S1, CYP2U1, CYP3A43, Table 2. Cytochrome P450 antibodies used in this study and their conditions for use in immunohistochemistry

<table>
<thead>
<tr>
<th>Antibody</th>
<th>Source (reference)</th>
<th>Type</th>
<th>Requirement for antigen retrieval*</th>
<th>Antibody dilution for immunohistochemistry</th>
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<tr>
<td>CYP1A1</td>
<td>Chemicon</td>
<td>Polyclonal</td>
<td>Yes</td>
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<tr>
<td>CYP1B1</td>
<td>Own laboratory (21)</td>
<td>Monoclonal</td>
<td>Yes</td>
<td>Undiluted tissue culture supernatant</td>
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<td>CYP2A/2B</td>
<td>Own laboratory (20)</td>
<td>Monoclonal</td>
<td>Yes</td>
<td>Undiluted tissue culture supernatant</td>
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<tr>
<td>CYP2C8/9/19</td>
<td>Chemicon</td>
<td>Polyclonal</td>
<td>No</td>
<td>1/500</td>
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<tr>
<td>CYP2D6</td>
<td>BD Bioscience</td>
<td>Monoclonal</td>
<td>No</td>
<td>1/20</td>
</tr>
<tr>
<td>CYP2E1</td>
<td>Oxford Biomedical Research</td>
<td>Polyclonal</td>
<td>Yes</td>
<td>1/2,000</td>
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<tr>
<td>CYP2F1</td>
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<td>Polyclonal</td>
<td>Yes</td>
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<td>1/1,000</td>
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<td>Polyclonal</td>
<td>Yes</td>
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<tr>
<td>CYP3A4</td>
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<td>Monoclonal</td>
<td>Yes</td>
<td>Undiluted tissue culture supernatant</td>
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<td>CYP3A5</td>
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<td>CYP26A1</td>
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<tr>
<td>CYP39A1</td>
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<td>Yes</td>
<td>1/1,000</td>
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<tr>
<td>CYP5A1</td>
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<td>Yes</td>
<td>1/1,000</td>
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<td>P450 reductase</td>
<td>Chemicon</td>
<td>Polyclonal</td>
<td>No</td>
<td>1/1,000</td>
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*The antigen retrieval step consisted of microwaving the sections in 0.01 mol/L citrate buffer (pH 6) for 20 minutes in an 800 W microwave oven operated at full power.

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Table 1. Clinicopathologic characteristics of the patients in the study

<table>
<thead>
<tr>
<th>Age mean (range)</th>
<th>62 y (30-89)</th>
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<tr>
<td>≤70</td>
<td>74% (85)</td>
</tr>
<tr>
<td>&gt;70</td>
<td>26% (30)</td>
</tr>
<tr>
<td>Tumor histopathology</td>
<td></td>
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<tr>
<td>Serous adenocarcinoma</td>
<td>61.7% (71)</td>
</tr>
<tr>
<td>Endometrioid adenocarcinoma</td>
<td>26.1% (30)</td>
</tr>
<tr>
<td>Mucinous adenocarcinoma</td>
<td>12.2% (14)</td>
</tr>
<tr>
<td>FIGO stage</td>
<td></td>
</tr>
<tr>
<td>I</td>
<td>26.1% (30)</td>
</tr>
<tr>
<td>II</td>
<td>10.4% (12)</td>
</tr>
<tr>
<td>III</td>
<td>59.1% (68)</td>
</tr>
<tr>
<td>IV</td>
<td>4.3% (5)</td>
</tr>
</tbody>
</table>

Abbreviation: FIGO, Fesddration Internationale des Gynaecologistes et Obstetristes.
CYP4A2, CYP4X1, CYP4Z1, CYP24, CYP39A1, and CYP51A1 were raised to the COOH-terminal peptide of the relevant human P450 as previously described (20). These antibodies are all available from Auvation, Ltd. (Aberdeen, United Kingdom). Polyclonal antibodies to CYP1A1, CYP2C, and cytochrome P450 reductase were bought from Chemicon Europe (Chadders Ford, United Kingdom), whereas a polyclonal antibody to CYP2E1 was obtained from Oxford Biomedical Research (Oxford, MI). Monoclonal antibodies to CYP1B1, CYP2A/2B (This antibody, which was raised to the COOH-terminal peptide of CYP2A6, recognized both CYP2A6 and CYP2B6, reflecting the very close sequence similarity of these two P450s and in particular the almost identical COOH-terminal amino acid sequences of these P450s. Therefore, this antibody has been designated CYP2A/CYP2B.), CYP3A4, CYP3A5, CYP3A7, CYP4F11, and CYP26A1 were developed as previously described (20–22). These antibodies are all available from Auvation. Each monoclonal antibody, with the exception of CYP1B1 and CYP3A4, were produced by the immunization of mice to the appropriate COOH-terminal peptide conjugated to ovalbumin of the relevant human P450. A monoclonal antibody to CYP2D6 was bought from BD Biosciences (Oxford, United Kingdom).

**Ovarian cancer tissue microarray.** A three-block ovarian cancer tissue microarray was constructed using a procedure that we have previously described (20, 23). A single representative 1.6 mm core of tissue was taken from each donor block using a steel Menghini needle and arrayed into the recipient wax block. One section from each microarray was stained with H&E to confirm the histopathologic findings and the adequacy of tissue sampling.

**Immunohistochemistry.** The tissue microarray blocks were cut (5 μm) onto silane-coated glass slides. Slides were dewaxed in xylene, rehydrated in alcohol, and antigen retrieval when required was carried out for 20 minutes in citrate buffer [0.01 mol/L (pH 6)] in an 800 W microwave oven. The immunohistochemical characterization of the antibodies with formalin-fixed, wax-embedded sections, including the requirement for antigen retrieval, positive and negative controls, and the determination of optimum antibody dilutions has been previously described (20–22). Of the antibodies studied, only antibodies to CYP2C, CYP2D6, and CYP2J2 did not require an antigen retrieval step. Primary antibody appropriately diluted (Table 2) in antibody diluent (DakoCytomation, Ely, United Kingdom) was applied for 60 minutes at room temperature, then washed with buffer (DakoCytomation) followed by peroxidase blocking (DakoCytomation) for 5 minutes. The sections were then subject to a single 2-minute buffer wash. Prediluted peroxidase-polymer labeled goat anti-mouse/rabbit secondary antibody (Envision, DakoCytomation) was then applied for 30 minutes at room temperature, followed by further washing with wash buffer to remove unbound antibody. Sites of peroxidase activity were then shown with diaminobenzidine as the chromogen applied for three successive 5-minute periods. Finally, sections were washed in water, lightly counterstained with hematoxylin, dehydrated, and mounted in DPX. Tissues known to express the relevant P450 were used as positive controls. Omitting the primary antibody from the immunohistochemical procedure and replacing it with antibody diluent or nonimmune rabbit serum acted as negative controls. The sections were evaluated by light microscopic examination and the intensity of immunostaining in each section assessed independently by two observers (D. Downie and G.I. Murray) using a scoring system that we have previously described (20, 23). In this system, the intensity of immunostaining in each core is assessed semiquantitatively and scored using the following scale; negative (absence of immunostaining = 0, weak immunoreactivity = 1, moderate immunoreactivity = 2, and strong immunoreactivity = 3). There were very few discrepancies (<5% of cases) in the assessment of the cases and these were resolved by simultaneous reevaluation by both observers. A core loss of up to 15% was accepted in accordance with previous reports (23, 24).

**Statistical analysis.** Statistical analyses including Kaplan-Meier survival analysis and Cox multivariate regression analysis were done using SPSS v12.0.1 for Windows XP (SPSS UK Ltd., Woking, United Kingdom). The log-rank test was used to determine survival differences between individual groups. We regarded $P < 0.05$ as significant.

**Results**

**P450s in normal ovary.** All of the P450s, with the exception of CYP1B1, showed immunoreactivity in normal ovary (Figs. 1–3). CYP2U1 and CYP3A4 were the P450s that were most frequently expressed and at the highest level of intensity, whereas most of the other P450s displayed weak to moderate immunoreactivity in normal ovary. Within the ovary, it was stromal cells that showed positive immunoreactivity for individual P450s.

**P450s in ovarian cancer.** All the P450s displayed some immunoreactivity in ovarian cancer (Figs. 1–3). There was a higher frequency and greater intensity of immunohistochemical staining for all P450s, with the exception of CYP1A1, CYP4F11, CYP24, and CYP39, in ovarian cancer compared with normal ovary. The highest percentage of strong staining was observed for CYP2U1 and CYP3A7 with 73.6% and 70.8% of the tumors showing strong immunohistochemical staining.
respectively, whereas for CYP1A1, CYP4X1, and CYP24 >60% of the cores were negative. There was a significantly greater intensity of immunohistochemical staining for CYP1B1 ($P = 0.001$), CYP2A2B ($P = 0.002$), CYP2R1 ($P = 0.006$), CYP2U1 ($P < 0.001$), CYP3A5 ($P < 0.001$), CYP3A43 ($P = 0.004$), CYP4Z1 ($P = 0.005$), CYP26A1 ($P < 0.001$), and CYP51A1 ($P = 0.01$) in ovarian cancer compared with normal ovary (Fig. 1). $P450$ immunoreactivity was localized to the cytoplasm of tumor cells (Fig. 3) and there was diffuse immunoreactivity with no evidence of heterogeneity of immunohistochemical staining within individual tumor cores.

$P450$s in metastatic ovarian tissue. All of the $P450$s studied showed some degree of immunoreactivity in the ovarian metastasis (Figs. 1–3). The highest frequency of strong immunoreactivity was observed for CYP2A2B, CYP2S1, and CYP3A7 with ≥50% of all cases showing strong immunoreactivity. The intensity of immunoreactivity in ovarian metastasis was significantly higher for CYP2S1 ($P = 0.007$) and $P450$

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**Fig. 2.** The frequency distribution (percentage) of the intensity of individual $P450$s in normal ovary (A), primary ovarian cancer (B), and metastatic ovarian cancer (C).
reductase ($P = 0.02$) compared with primary ovarian cancer (Fig. 1).

**P450 expression and survival in ovarian cancer.** There was poorer survival in those patients whose tumors showed no CYP2A/2B immunoreactivity compared with those patients whose tumors showed strong immunoreactivity (log rank = 7.06; $P = 0.008$; Fig. 4). In the poor survival group ($n = 48$), there were 35 deaths and the median survival was 25 months [95% confidence interval (95% CI), 16-34; mean 40 months, 95% CI, 30-50]. In the good survival group ($n = 43$), there were 22 deaths and the median survival in this group was 74 months (95% CI, 6-142; mean 74 months, 95% CI, 60-115). In the good survival group ($n = 48$), there were 35 deaths and the median survival was 25 months (95% CI, 16-34; mean 40 months, 95% CI, 30-50). In the poor survival group ($n = 43$), there were 22 deaths and the median survival in this group was 74 months (95% CI, 6-142; mean 74 months, 95% CI, 60-115). Tumor stage (stage I versus stages II, III and IV, log rank = 17.6, $P < 0.001$) and serous histology type (log rank = 12.65, $P = 0.002$) were both prognostically significant in univariate survival analysis. Cox multivariate regression analysis showed that tumor stage (hazard ratio, 5.82; 95% CI, 1.94-17.49; $P = 0.002$), CYP2A2B (hazard ratio, 2.31; 95% CI, 1.25-4.28; $P = 0.003$), and CYP4Z1 (hazard ratio, 3.3; 95% CI, 1.29-8.45; $P = 0.02$) remained independently prognostically significant, whereas tumor histopathology was not an independent prognostic factor ($P = 0.78$).

**Discussion**

In this study, we have analyzed by immunohistochemistry P450 expression in primary ovarian cancer, metastatic ovarian cancer, and normal ovary and defined the expression profile for individual P450s in epithelial ovarian cancer. We have also established the prognostic significance of individual P450 expression in this type of tumor and found that low or negative expression of CYP2A2B and high expression CYP4Z1 were both associated with poor survival and each of these P450s was an independent prognostic factor. However, the biological functions, including effects on cell growth and survival, of both CYP2A2B and CYP4Z1 in ovarian cancer cells still require to be defined. Although xenobiotic substrates for CYP2A2B are well characterized, endogenous substrates for this P450 are poorly described. Substrates (either xenobiotic or endogenous) for CYP4Z1 have yet to be characterized, although other members of the CYP4 family are predominantly involved in the metabolism of biologically active endogenous compounds, including fatty acids, prostaglandins, and other eicosanoids (9, 10).

It is still not sufficiently widely recognized that individual forms of P450 are overexpressed in specific types of cancer (10, 11, 18, 25) and that individual P450s represent particularly versatile therapeutic targets (17, 18), which can be exploited by a range of therapeutic strategies, including prodrug activation, immunotherapy, and inhibitors (17, 18). Furthermore, the increased expression of individual forms of P450 in specific types of tumors may also be readily exploited as diagnostic biomarkers. The development of P450-based vaccines offers a direct route to the clinical exploitation of the expression of these molecules in tumors. However, a P450-based prodrug activation strategy, utilizing P450 overexpression in tumors, has the greatest potential to offer significant therapeutic benefits while overcoming the problems of dose-limiting toxicity that limit the use of many of the current
generation of anticancer drugs. In developing strategies to produce such P450-activated prodrugs, knowledge of the relative expression of individual P450s in other tissues may also be necessary to ensure that especially in the early stages of the drug development process the most suitable candidate compounds are identified and evaluated. Expression of P450s in tumors can be exploited both as a consequence of their overexpression in tumor cells and because of the distinct microenvironment in which tumors exists even when a P450 is present but not necessarily overexpressed. Hypoxia is one of the main features of the tumor microenvironment that is currently being exploited by P450-targeted therapy. AQ4N is a CYP3A-activated prodrug, which, in hypoxic conditions, is activated to a highly potent topoisomerase inhibitor and is currently being evaluated in early stage-clinical trials (26, 27). This P450 is present in some types of tumor (11) and is also present in normal tissues, particularly liver; however, AQ4N is not associated with hepatotoxicity (26, 27).

Fig. 4. A, comparison of survival in patients whose tumors showed strong CYP2A/2B immunoreactivity and those tumors that have moderate, low, or negative immunoreactivity. There is poorer survival in those patients whose tumors expressed low CYP2A/2B immunoreactivity (log rank test = 7.06, \( P = 0.008 \)). B, comparison of survival in patients whose tumors showed strong, moderate, or weak CYP4Z1 immunoreactivity and those that have no immunoreactivity. There is poorer survival in those patients whose tumors expressed CYP4Z1 (log-rank test = 6.19, \( P = 0.01 \)).
It is, therefore, important to define the expression profile of P450 in ovarian cancer and identify those P450s that are overexpressed, and hence most likely to be therapeutic targets or diagnostic biomarkers, and also establish their prognostic significance. The most frequently expressed P450s in normal ovary were CYP2U1 and CYP3A4, whereas CYP1B1 was the only P450 not to be detected in normal ovarian tissue, a finding consistent with our previous studies that have shown the presence of CYP1B1 in ovarian cancer cells with an absence of expression in normal ovarian tissue (15, 25).

Several P450s, in particular CYP1B1, CYP2U1, CYP3A5, and CYP26A1, showed a very significantly enhanced expression in the primary ovarian cancers compared with normal ovary. This further supports the concept of overexpression of individual forms of P450 in tumors (10) and also indicates that there is tumor type–specific expression of individual P450s (10, 11, 28).

For example, the cytochrome P450 expression profile of ovarian cancer seems to be distinct from the profile of colorectal cancer where the most significantly overexpressed P450s are CYP2U1 and CYP51A1 (20). CYP1B1 showed a highly significant overexpression in ovarian cancer, and of the P450s that are overexpressed in tumors its exploitation as a therapeutic target is the most advanced with an anticytotoxic P450 vaccine about to enter phase 2 clinical trials having completed a successful phase 1 trial (29). Although the P450s are located intracellularly, proteolytic processing of the P450s results in peptides being presented on the cell surface that are available to be recognized as tumor antigens (30, 31).

Because most chemotherapy is targeted at metastatic tumors, it is important to have knowledge of the expression profile of P450s in the metastases and how this relates to the expression pattern in the corresponding primary tumors. This is important because it cannot necessarily be assumed that the pattern of expression in the primary tumors will be reflected in the metastases. The expression pattern of P450s of ovarian cancer metastasis has not previously been studied. In this study, we found that CYP2S1 and cytochrome P450 reductase both showed significantly increased expression in metastases compared with primary ovarian cancer, whereas for all the other P450s there were no significant differences between the level of expression in primary tumors and metastases.

In conclusion, we have defined the P450 profile of ovarian cancer, peritoneal metastasis, and normal ovary. We have identified overexpression of several P450s in ovarian cancer, most notably CYP2A28 and CYP421. Both of these enzymes show independent prognostic significance.

Acknowledgments

We thank Joan Aitken and Nicky Fyfe for technical assistance.

References

4. Park TW, Kuhn WC. Neoadjuvant chemotherapy in primary ovarian cancers compared with normal ovary. This finding consistent with our previous studies that have shown the presence of CYP1B1 in ovarian cancer cells with an absence of expression in normal ovarian tissue (15, 25).

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