This leaves us with the larger question of what kind of change is occurring in the transformed cells. Given the level of molecular complexity of cells and the immense number of reactions all running near reversibility, it has been argued that biological phenomena like cancer and differentiation are inherently irreducible to a complete chain of molecular causality [14]. This conclusion is reinforced by the great variety of degrees and types of transformation in tumours. It has been proposed that the appropriate level of description and understanding is that of the intact living cell and above [11]. The concept of progressive state selection has been introduced to represent the process of change. This concept assumes that physiological constraints can select among the ever-fluctuating physiological states in cells, and that repeated state selections result in heritability of those states. These considerations focus attention on the living cell and its neighbours which provide the immediate environment for selection, and ultimately on the whole organism. Constraints include the multifarious physiological effects of aging. It is noteworthy that this dynamic epigenetic or adaptive view of cancer development provides us with more rational approaches to the prevention of cancer than does the genetic view, and may suggest some new ideas about cure.

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1. Murray M, Shilo B, Shih C, Cowing D, Hsu HW, Weinberg RA. Three different human tumor cell lines contain different oncogenes. *Cell* 1981, **25**, 355–361.
2. Krontiris TG, Cooper GM. Transforming activity of human tumor DNAs. *Proc Natl Acad Sci USA* 1981, **78**, 1181–1184.
3. Perucho M, Goldfarb M, Shimizu K, Lama C, Fogh J, Wigler M. Human-tumor-derived cell lines contain common and different transforming genes. *Cell* 1981, **27**, 467–476.
4. Varmus HE. The molecular genetics of cellular oncogenes. *Annu Rev Genet* 1984, **18**, 553–612.
5. Rubin H, Xu K. Evidence for the progressive and adaptive nature of spontaneous transformation in the NIH 3T3 cell line. *Proc Natl Acad Sci USA* 1989, **86**, 1860–1864.
6. Kennedy AR, Fox M, Murphy G, Little JB. Relationship between X-ray exposure and malignant transformation in C3H 10T1/2 cells. *Proc Natl Acad Sci USA* 1980, **77**, 7262–7266.
7. Mondal S, Heidelberger C. *In vitro* malignant transformation by methylcholanthrene of the progeny of single cells derived from C3H mouse prostate. *Proc Natl Acad Sci USA* 1970, **65**, 219–229.
8. Brouty-Boyé D, Gresser I, Baldwin C. Reversion of the transformed phenotype to the parental phenotype by subcultivation of X-ray-transformed C3H/10T1/2 cells at low cell density. *Int J Cancer* 1979, **24**, 253–260.
9. Rubin AL, Yao A, Rubin H. Relation of spontaneous transformation in cell culture to adaptive growth and clonal heterogeneity. *Proc Natl Acad Sci USA* 1990, **87**, 482–486.
10. Rubin AL, Arnstein P, Rubin H. Physiological induction and reversal of focus formation and tumorigenicity in NIH-3T3 cells. *Proc Natl Acad Sci USA* 1990, **87**, 10005–10009.
11. Farber E, Rubin H. Cellular adaptation in the origin and development of cancer. *Cancer Res* 1991, **51**, 2751–2761.
12. Clark WH. Tumor progression and the nature of cancer. *Br J Cancer* 1991, **64**, 631–644.
13. Mintz B, Illmensee K. Normal genetically mosaic mice produced from malignant teratocarcinoma cells. *Proc Natl Acad Sci USA* 1975, **72**, 3585–3589.
14. Elsasser WM. *Reflections on a Theory of Organisms*. Frelighsburg, Quebec, Canada, Éditions Orbis, 1987.

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Tumour Markers for Ovarian Cancer

THE SITE AND PATTERN of spread of ovarian cancer make it so difficult to detect and monitor that a circulating serum or urine marker is potentially very valuable. Great interest was generated by the discovery of the serum marker CA-125 in the early 1980s [1], but we are only now appreciating to what extent the measurement of serum CA-125 affects patient management. This marker for ovarian cancer is far less sensitive or specific than human chorionic gonadotropin (HCG) is for trophoblastic tumours, yet has become the benchmark for comparison of other markers. The advent of commercial assay kits for CA-125 has made it a widely available, though expensive test, and several quality control schemes have now been set up to monitor the accuracy of the different laboratories and kits.

The observation that serum CA-125 is only elevated in about 50% of patients with stage I ovarian cancer immediately suggests that about half of all these potentially curable tumours will not be detected by CA-125-based screening. A study at the Royal London Hospital measured serum CA-125 in 20 000 postmenopausal women attending a screening clinic [2]. By performing an ultrasound in all those with CA-125 levels over 30 U/ml, they obtained an overall specificity of almost 100% and detected 11 ovarian carcinomas. Only three of these screen detected cancers were stage I. We do not know yet whether stage I ovarian carcinomas detected by an elevated CA-125 level are cured by surgery and only time will tell how many tumours develop in women who are negative on screening. This led the UK Co-ordinating Committee on Cancer Research in 1989 to recommend that screening for ovarian cancer should not yet be offered to women outside a clinical trial.

When using serum CA-125 to help in the diagnosis of ovarian carcinoma, it should be remembered that its level is above 35 U/ml in a number of conditions. These include 1% of healthy controls, the first trimester of pregnancy, endometriosis, cirrhosis especially if ascites is present, a variety of other benign conditions and over 40% of patients with advanced intra-abdominal (non-ovarian) malignancy [1, 3]. In a patient suspected of having ovarian cancer, an elevated CA-125 level increases the likelihood of finding cancer and should prompt the surgeon either to refer the patient to a gynaecological

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oncologist or at least perform the operation through a more extensive midline incision. Attempts have been made to refine decision making by the use of a risk of malignancy index. Such an index, which used CA-125 levels, ultrasound criteria and menopausal status, gave a sensitivity for malignancy of 85.4% and specificity of 98% among 143 women with a pelvic mass [4].

A persistently elevated CA-125 level after oophorectomy for suspected stage I tumour is definite evidence of residual tumour. This information has an impact on management as patients with persistently elevated tumour marker levels following surgery are candidates for chemotherapy rather than surveillance. Very high CA-125 levels prior to surgery are associated with a worse prognosis, but knowledge of this is unlikely to lead to any alteration in the therapy. Similarly, knowing that a patient with a CA 125 level over 250 U/ml prior to starting chemotherapy has a worse prognosis [5] is unlikely to prevent a trial of chemotherapy. However, information after one or two courses of chemotherapy that indicated the patient had a poor prognosis or was not responding could influence the clinician to stop or change therapy. Several groups have shown that the CA-125 level after one, two or three courses of chemotherapy is the most important prognostic variable for survival [6, 7]. A long half-life and a less than 7-fold fall in CA-125 levels over the first month of chemotherapy have also been shown to be adverse prognostic factors [8, 9].

It is important to know how accurately CA-125 measurements predict lack of tumour response before using them to change therapy. To obtain this information requires definitions according to serial CA-125 levels that have been tested in a large number of patients. Among 127 women with a greater than 50% decrease in CA-125 levels 9 (7%) had progressive disease [6, 10]. A tighter definition as used to define response according to WHO criteria would require a CA-125 response to be maintained for 1 month and is likely to give a lower error rate. Such a definition has been proposed and would be useful for assessing response to new agents or drug combinations in phase II trials [11].

A serial rise of CA-125 levels of >25% has been shown in several studies to predict progression with almost 100% specificity [6, 10, 12, 13]. Although Van der Berg *et al.* [13] have reported that 73% of ovarian cancer patients will have elevated CA-125 levels at or before clinical progression, fewer than 50% of those progressing on initial therapy were found to exhibit a higher than 25% increase [12]. These patients and those with persistently high levels (>100 U/ml) could be saved unnecessary chemotherapy if CA-125 levels were acted upon. Furthermore if progression is accurately predicted by serial CA-125 levels and no additional surgery is contemplated, ultrasound and computed tomography are not required.

There is no evidence at present that early reintroduction of chemotherapy is of any survival benefit, or that searching for the site of relapse will result in surgery that can improve survival. Therefore serial CA-125 measurements during follow up off therapy cannot be recommended. However, once there is any suspicion of relapse, serial CA-125 levels at that point are likely to be the best indicator of recurrent tumour.

A number of other markers have been found to be elevated in a proportion of patients with ovarian carcinomas. These include the polymorphic epithelial mucins, placental alkaline phosphatase, tumour-associated trypsin inhibitor, tissue polypeptide antigen, CA-19.9, amino-terminal propeptide of type III procollagen, the fibrin derivative D-dimer, galactosyltransferase and lipid associated sialic acid. Dependent on the availability of a commercial assay, one of the most promising of these additional markers is urinary gonadotropin fragment [14]. None of these markers have yet been shown to be as clinically useful as CA-125. Although combining these markers with CA-125 may lead to a higher percentage of patients with advanced cancer having elevated marker levels, we do not yet know whether the sensitivity for small tumours is increased sufficiently to have an impact on screening.

We have become used to measuring alpha fetoprotein, HCG, lactate dehydrogenase and now CA-125 levels in patients with germ cell tumours. We should also become used to measuring inhibin in patients with granulosa cell tumours [15]. Often only one marker is elevated and worth following. As many patients, especially those with non-serous epithelial tumours, have normal CA-125 levels following cytoreductive surgery, screening a preoperative sample against a panel of markers might indicate which one to follow. However, unless tumour marker assays become non-isotopic and cheap, they will only be performed in certain laboratories that receive sufficient samples to perform frequent cost-effective assays.

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1. Bast RC Jr, Klug TL, St John E, *et al.* A radioimmunoassay using a monoclonal antibody to monitor the course of epithelial ovarian cancer. *N Engl J Med* 1983, **309**, 883–887.
2. Oram DH, Jacobs IJ, Brady JL, Prys-Davies MR. Early diagnosis of ovarian cancer. *Br J Hosp Med* 1990, **44**, 320–324.
3. Jacobs I, Bast RC, Jr. The CA 125 tumour-associated antigen: a review of the literature. *Human Reprod* 1989, **4**, 1–12.
4. Jacobs J, Oram D, Fairbanks J, *et al.* A risk of malignancy index incorporating CA 125, ultrasound and menopausal status for the accurate preoperative diagnosis of ovarian cancer. *Br J Obstet Gynaecol* 1990, **97**, 922–929.
5. Parker D, Patel K, Alred EJ, *et al.* CA 125 and survival in ovarian cancer: preliminary communication. *J Soc Med* 1988, **81**, 2.
6. Vergote IB, Bormer OP, Abeler VM. Evaluation of serum CA 125 levels in the monitoring of ovarian cancer. *Am J Obstet Gynecol* 1987, **157**, 88–92.
7. Lavin PT, Knapp RC, Malkasian G, *et al.* CA 125 for the monitoring of ovarian carcinoma during primary therapy. *Obstet Gynecol* 1987, **69**, 223–227.
8. van der Burg MEL, Lammes FB, van Putten WLJ, *et al.* Ovarian cancer: the prognostic value of the serum half-life of CA 125 during induction chemotherapy. *Gynecol Oncol* 1988, **30**, 307–312.
9. Rustin GJS, Gennings JN, Nelstrop AE, *et al.* Use of CA 125 to predict survival of patients with ovarian carcinoma. *J Clin Oncol* 1989, **7**, 1667–1671.
10. Alvarez RD, To A, Boots LR, *et al.* CA 125 as a serum marker for poor prognosis in ovarian malignancies. *Gynecol Oncol* 1987, **26**, 284–289.
11. Rustin GJS, Neijt J, Piccart M, *et al.* Defining response and progression of ovarian carcinoma according to serum CA-125 levels. *Proc Int Gynaecol Cancer Soc* (in press).
12. Rustin GJS, Nelstrop A, Stilwell MA, *et al.* Savings obtained by CA 125 measurements during therapy for ovarian carcinoma. *Eur J Cancer* 1992, **28**, 79–82.
13. van der Burg MEL, Lammes FB, Verweij J. The role of CA 125 in the early diagnosis of progressive disease in ovarian cancer. *Ann Oncol* 1990, **1**, 301–302.
14. Cole LA, Joo-Hyun N, Chambers T, *et al.* Urinary gonadotrophin fragment, a new tumour marker II. Differentiating a benign from a malignant pelvic mass. *Gynecol Oncol* 1990, **36**, 391–394.
15. Lappohn RE, Burger HG, Bouma J, *et al.* Inhibin as a marker for granulosa-cell tumors. *N Engl J Med* 1989, **321**, 790–793.