Human papilloma virus (HPV) testing and sentinel node biopsy both represent significant advances in the diagnosis and management of cervical cancer. In the June 2004 issue of Annals of Oncology, two papers draw attention to these techniques. Dannecker et al. [1] showed that self-testing may be a facile means of sampling in cervical cancer screening, and Barrenger et al. [2] illustrated the potential of sentinel node biopsy applied to cervical cancer. Although both of these papers contribute significantly to the current knowledge and opinion regarding the diagnostic options available for cervical cancer, I believe that both techniques will eventually be largely circumvented by DNA microarrays.

Cytology is essentially a 19th century technology. Despite refinements including the Pap stain, its overall potential has not changed vastly since the resolving power of the light microscope reached the physical limit. Cervical cytological screening has reduced the incidence and mortality of cervical cancer. However, it has a relatively low sensitivity and reproducibility [3]. The interpretation of cervical cytology is a subjective visual recognition skill rather than a specific laboratory test. It is limited by cellular sampling, human error and, most of all, by its reliance purely on the appearance of the cellular phenotype to predict diagnosis.

HPV testing may be a useful adjunct to cervical cytological screening as it has the potential to be used as an objective diagnostic assay. However, despite this, the majority of cervical HPV infections resulting in dysplasia resolve. Therefore, HPV testing cannot provide the sole solution to cervical cancer screening and diagnosis.

DNA microarrays have been shown to be capable of diagnosing a variety of cancers and to provide diagnostic and prognostic information that is unavailable from cytopathology or histopathology [4]. Beyond diagnosis of cancer, DNA microarrays have been shown to have the ability to predict metastasis. In particular, DNA microarrays have been shown to predict lymph node metastasis, for example in breast cancer [5]. Therefore, patients could have the benefit of accurate diagnosis as well as the avoidance of minimally invasive but not risk-free sentinel node biopsy. With the advent of global human genome DNA microarrays such as the Affymetrix® Hu U133 Plus 2.0 GeneChip®, it is likely that even greater diagnostic accuracy will be attained.

Limitations of DNA microarrays include the cost and the labile nature of RNA, which is subject to degradation, as well as transcriptome variations secondary to artefacts including hypoxia-induced gene induction. The answer to these limitations may be either to use defined protocols with agents such as RNAlater® combined with a cheaper, focused DNA microarray with probes for several hundred key genes. Alternatively, the solution may be to develop a protein-based diagnostic assay using a panel of protein markers developed from DNA microarray research, perhaps ultimately in the form of a protein microarray. Biomarkers have already been identified in cervical cancer using DNA microarrays [6]. I look forward to the results of further DNA microarray studies on cervical cancer in the current era of high-throughput technologies.

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Response to letter “DNA microarrays will be instrumental in the future diagnosis of cervical dysplasia and neoplasia”, by P. K. Wright

We want to thank Paul Wright for his comments. Cervical cancer is one of the leading causes of female death due to cancer world-wide. Lymph node status remains the most important prognostic factor. Pelvic lymph node dissection is therefore crucial in therapeutic decision making. Recent advances in therapeutic modalities involving surgery, radiation or chemotherapy have reduced overall cancer death rates, but treatment failure remains relatively high in locally advanced cervical cancer [1]. The major cause of failure in treating cervical cancer is probably inability to identify ‘occult’ metastatic lesions. Indeed, despite favourable prognostic features, pelvic recurrence occurs in about 10% of patients with histologically normal pelvic lymph nodes and clear surgical margins around the primary tumour [2]. Occult metastases in the lymphatic system probably account for disease recurrence as has been demonstrated in endometrial cancer by Yabushita et al. [3]. The sentinel node (SN) procedure has emerged as an alternative to systematic lymphadenectomy, reducing treatment-related morbidity without compromising patient survival. Another potential advantage is the thorough nature of SN analysis, with immunohistochemical (IHC) staining of multiple sections; this may facilitate the detection of occult metastases (such micrometastases could explain some pelvic recurrences in women with negative standard histologic findings). There are several methods to evaluate SN for occult metastatic tumour cells, including conventional histopathological evaluation (H&E), immunohistochemical staining of multiple sections and molecular biological techniques (RT–PCR).

Recently, DNA microarrays have been shown to predict axillary lymph node metastasis in breast cancer [4]. This technique is probably superior to H&E and IHC to identify occult SN metastasis. Finally, DNA microarrays in cervical cancer might contribute to predicting the development of distant metastasis (i.e. recurrence). However, this approach is slightly more costly and laborious than IHC and H&E. Further studies will be needed to compare the accuracy of conventional histological analysis (i.e. H&E and IHC) of SN with DNA microarrays to detect occult metastasis in patients with cervical cancer.

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References


Response to the letter “DNA microarrays will be instrumental in the future diagnosis of cervical dysplasia and neoplasia”, by P. K. Wright

We thank Paul Wright for his comment [1]. We are also convinced that the use of biochips will open up new dimensions...