Pre-Invasive Disease: Pathogenesis and Clinical Management
Cover illustration: Biopsy of Barrett’s oesophagus (metaplastic oesophageal epithelium which predisposes to adenocarcinoma) stained with Alexa 555-labelled lectin called wheat germ agglutinin (WGA). Non-dysplastic areas within the biopsy demonstrate strong WGA staining of both the apical epithelial membrane and the superficial epithelial mucous globules. The superficial epithelial mucous globule staining is lost in areas of low grade dysplasia and in high grade dysplasia, this as well as the apical membrane staining is almost entirely lost. (Picture provided by Dr. Elizabeth Bird-Lieberman)
On a weekly basis, as we discuss new oesophago-gastric cancer cases within a multidisciplinary team, I am reminded of how dismal cancer is for the majority of patients. The lucky ones in whom we can achieve a cure are, generally speaking, those who present with early-stage disease.

It has been recognized for almost two centuries that pre-cancerous conditions exist, and indeed it is now known that most cancers develop over a period of years through a series of pre-invasive stages. This being the case there should be ample opportunity to intervene early in the natural history of cancer in order to improve outcomes. To do this effectively requires an understanding of the molecular and cellular basis for the disease.

Whilst the concept of early detection and prevention of cancer is an attractive one there are many questions which remain unanswered. For example, what are the causes of pre-invasive lesions, are they as a result of inherited genetic susceptibility or environmental factors, and how then can we use this information to minimize risk? At a population level, one could intervene through promotion of a healthier diet or smoking cessation programmes; at an individual level, one could implement screening programmes to identify individuals at increased risk due to pre-invasive lesions. Screening is already widely adopted for colon, cervix, and breast cancers but remains a controversial subject. It is hotly debated whether the magnitude of the risk justifies screening interventions which incur individual and societal costs, both fiscal and psychological. Once pre-invasive lesions are identified the clinician is faced with complex management decisions which might entail monitoring (surveillance), chemoprevention, or removal through endoscopic or surgical means.

There are currently exciting opportunities to revolutionise our approach to pre-invasive disease with an explosion of technological advances for understanding the cancer genome at an increasing level of detail. Clinical modalities have also progressed rapidly with the advent of new imaging and therapeutic options which incorporate knowledge of the molecular characteristics of the disease. Surgery is becoming less and less invasive and minimally invasive approaches using endoscopy and laparoscopy are ideally placed to treat small, early lesions.

Whilst cancer is widely studied and written about, pre-invasive disease has lagged behind. In addition, discourse on basic biology and clinical approaches to
pre-invasive disease are seldom brought together. The purpose of this monograph is to bring together expert knowledge on this area in one volume. It has been a pleasure to bring this book to fruition, and I hope that it will be a valuable resource for all those interested in this fascinating area of research and clinical practice. Most of all I hope that it spurs us all on, as there are many unanswered questions still to be addressed.

Cambridge, UK

Rebecca Fitzgerald
Foreword

Questions in the Study of Epithelial Preneoplasia

Bruce Ponder

The practical interest in preneoplasia is because it offers the possibility of diagnosis of cancer at an early, pre-invasive stage, and of successful intervention by local (endoscopy, surgery, irradiation) or systemic therapies. The preneoplastic lesion can potentially be the means to recognition of the developing cancer, to insights into mechanism and hence strategies for treatment and prevention, and to early read-out of response.

This however raises several questions, many of them still awaiting a complete answer.

The yield: what proportion of cancers with lethal potential at different sites evolve through an identifiable pre-invasive stage and so in principle could be detected and dealt with early?

The answer must be defined in terms of the methods at hand. Estimates are hard to find even though they would presumably be part of the public health decisions that underlie screening policy. For colorectal cancer, it seems that 90% or more of potentially lethal cancers are detectable at a curable stage by endoscopy; for breast cancer and mammography maybe 25% of deaths are prevented; for prostate cancer and PSA screening possibly 50%; for adenocarcinoma of the oesophagus by detection and follow-up of the Barrett’s lesion, maybe 50% or fewer [1]. This is with current detection methods: can we make any estimate of which cancers have the best potential for improvement, if methods could be improved?

More sensitive detection raises a second question, the reverse side of the coin:

The trade-off: what is the potential cost of early detection in terms of over-diagnosis and over-treatment?

The prevalence, in all of us, of multiple lesions in different tissues that have morphological features of early cancer but which have very low or uncertain
probability of progression to clinically significant disease, has been recognised for many years. In the context of PSA screening for early diagnosis of prostate cancer, it has been estimated that 48 men must undergo radical treatment to save one prostate cancer death [2]. CT scan-based screening for lung cancer detects many peripheral lung nodules with the morphological appearances of cancer; but the screening studies show no shift in the stage distribution of lung cancers away from the more advanced stages [3]. It was shown in the 1970s that 30% of moderate or severe dysplasia detected in cervical cancer screening regressed without treatment [4]; more recent studies show that even in patients with recognised pre-invasive lesions such as dysplasia of the bronchial epithelium or Barrett’s oesophagus, the annual probability of invasive cancer is of the order of 1 in 100 or less. This implies prolonged surveillance of large groups of individuals and possibly quite significant interventions, for small yield and the possibility of inadvertent harm.

There is thus a balance to be struck between the potential costs and benefits of programmes of early detection and surveillance, which demands attention. To resolve this balance in each case requires better information about risk and to predict behaviour of each lesion. Will the new technologies of genetic analysis, applied to either lesion or normal tissue of the host, allow us to achieve this? For discussion this question can be split into three overlapping parts. The first relates to predicting the behaviour of a specific lesion, the second to the risks and behaviour of future lesions and thus to issues of intervention and surveillance, and the third to overall estimates of individual risk and thus to stratification of the population into groups at different risk and hence different potential to benefit from programmes of early detection.

Predicting the behaviour of a specific lesion and the need for intervention.

If we knew which screen-detected lesions were of clinical significance, we could match the treatment appropriately and avoid over-treatment – as for example in PSA-detected prostate cancer, described above. Pathologists have for many years used morphological criteria on tissue sections to do this: but the examples of localised breast cancer, PSA-detected prostate cancer and of Barrett’s oesophagus show that, as detection methods become more sensitive and the prevalence of pre-invasive and early invasive lesions increases, these criteria are no longer sufficient. Gene expression profiling of the primary lesion has the potential to do better, as for example in breast cancer, where the subset of apparently localised cancers that have metastasised can be identified with useful sensitivity and specificity by gene expression profiling of the primary tumour. This provides optimism that molecular analysis can predict the behaviour of a single lesion. The next question is whether it can also be predictive for other lesions in the same tissue:

*Can analysis of a single lesion predict the risks and behaviour of subsequent lesions within the same epithelium?*

If this were so, the prediction would be useful for the design of programmes of surveillance, and of possible tissue-wide efforts at prevention. The underlying question is one of biology. The development of a cancer is thought of as the accumulation
of successive stochastic genetic or epigenetic events. Are these events truly independent in multiple cancers within a single tissue, or are they to some extent determined or constrained by host factors – genetic background or exposure? If the latter, then depending upon the strength of the constraints, different lesions within an individual will tend to be similar, and the characteristics of one lesion will to some degree be predictive for others.

Evidence that such constraints exist comes from studies of inherited susceptibility. In familial breast cancer, the gene expression profiles (and estrogen receptor (ER) status) of tumours from women who carry a mutation in BRCA1, in BRCA2, or in neither gene, are different [5]. BRCA mutations are strongly predisposing, so this might be discounted as an extreme case: but characteristic molecular subtypes and ER status are also seen in the associations between common, weakly predisposing gene variants such as FGFR2 and breast cancer [6]. Specific exposures may also drive characteristic patterns of altered gene expression: for example the changes in the airway epithelium in response to cigarette smoke [7].

In principle, then, multiple lesions within a single epithelium are likely to be more similar, because of host factors, than lesions from different individuals. This similarity may be even greater if the lesions have arisen from within the same extended mutant clone, and so share some of the initial events. Whether and in what circumstances these effects are strong enough to provide clinically useful predictors is for empirical test. Formal data are hard to find, but current clinical practice suggests that these circumstances are few.

If such constraints exist, they will presumably be mediated through, or reflected in, the molecular and cellular phenotype of the cognate normal epithelium – the “soil” in which the malignancies arise. This leads to the final question:

*Can analysis of the apparently normal tissue from which the cancer will arise provide a prediction of future cancer risk (and possibly behaviour)?*

If this were so the prediction would have important applications in stratification of the population in terms of risk, and thus in terms of the cost/benefit balance of entry into programmes of early detection. If the prediction were not just of risk of cancer, but of risk of clinically significant cancer, the application would be even greater.

*The factors that will differ between individuals and which can be expected to influence risks of cancer and cancer type are, broadly, individual genetic make-up and exposure. What is the potential size of these effects and how can they be measured?*

The majority of strongly predisposing genes for cancer have been identified, but these account for under 5% of overall cancer incidence. For most of the common cancers (e.g. breast, prostate, lung) some 70% of the estimated inherited cancer risk is still unexplained. This 70% is thought to be made up of probably hundreds of common and rare genetic variants, each of small effect, but in combination these may be potentially very significant in terms of distribution of risk in the population, and hence in terms of application to the stratification of risk. Imagine these normal
genetic variants dealt out at conception like a hand of cards: it has been estimated that for breast cancer the 20% of women with the “worst” hand will have on average a 30–40-fold greater risk than the 20% with the “best” hand [8]. This means that half of all breast cancers will occur in the 12% of women at greatest [genetic] risk. As noted above, some of these variants increase the risk of different molecular subtypes of breast cancer more than others; and it is possible that they may also influence aggressiveness and outcome.

Most environmental exposures are difficult to quantify. Smoking is relatively easy because it is a well-defined behaviour that can be measured in pack-years of exposure reaching back many years, and so is UV damage resulting in sunburn; but accurate dietary history is notoriously difficult to obtain even in the present, let alone after the lapse of many years. Even if data on exposures and genetics were available, the multiple interactions between the hundreds of components would present a daunting problem.

An interesting possibility, so far not widely explored, is that the history of these genetic effects and exposure and their many interactions, in so far as it impinges on cancer risk and behaviour, should be written in an integrated form in the tissue from which the cancers will arise. (This is not to exclude direct effects on the emerging cancer: but many of these, for example differences in DNA repair, or immune or paracrine effects may also be written in the uninvolved tissue).

Following this idea, cancer – and other diseases such as diabetes – can be thought of as “an emergent property of a regulatory network” [9]: a gene regulatory network which can be perturbed by inherited or somatic mutation, normal genetic variation, or causes external to the tissue (for example hormones, or external exposures and the damage resulting from them). If this is correct, gene expression profiles of uninvolved tissue would be expected to differ between individuals, and it might be possible using the training set/validation set approach that has been extensively applied to cancer tissues to define subsets of those cancers, also to define patterns in the uninvolved tissue that are predictive of the risk of cancer. There are obvious pitfalls to be avoided, for example the possibility of sampling emergent altered clones that are not representative: but there are already several reports suggesting that this approach might work. They include a series of papers (e.g. 10) by Spira and colleagues on the patterns of gene expression in bronchial and upper airway epithelium, showing a similar signature of smoking, but different signatures in smokers with and without lung cancer; and publications reporting on a variety of phenotypic measures in colorectal mucosa and their association with the presence of polyps [11, 12]. Further prospective validation of these potential predictors is however required.

Schadt and others [13] have taken the analysis a step further to the definition of specific gene regulatory networks, and putative functional molecules within them. Others have defined gene expression profiles in terms of signatures of the activities of different signalling pathways [14]. Kopelovich [15] pointed out a decade ago the potential of using accessible tissues as surrogates for tissues difficult to access (for example, oral or nasal epithelium for bronchus), an important concept that also requires further validation.
Setting aside practical issues of access to certain tissues, the challenges that currently threaten to limit the use of preneoplasias as a route to cancer prevention, are about the balance of cost and benefit. The costs are in terms of resources and false positive diagnosis, when screening for preneoplasias at the population level; and in terms of over-treatment by interventions for lesions only a minority of which will progress to clinically significant disease. The commonly used multi-stage process of screening, combining sensitivity with increasing levels of specificity, recognises this. Careful phenotyping of the epithelium from which the lesions arise, as well as analysis of the lesions themselves, may allow us to refine and improve this process.

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