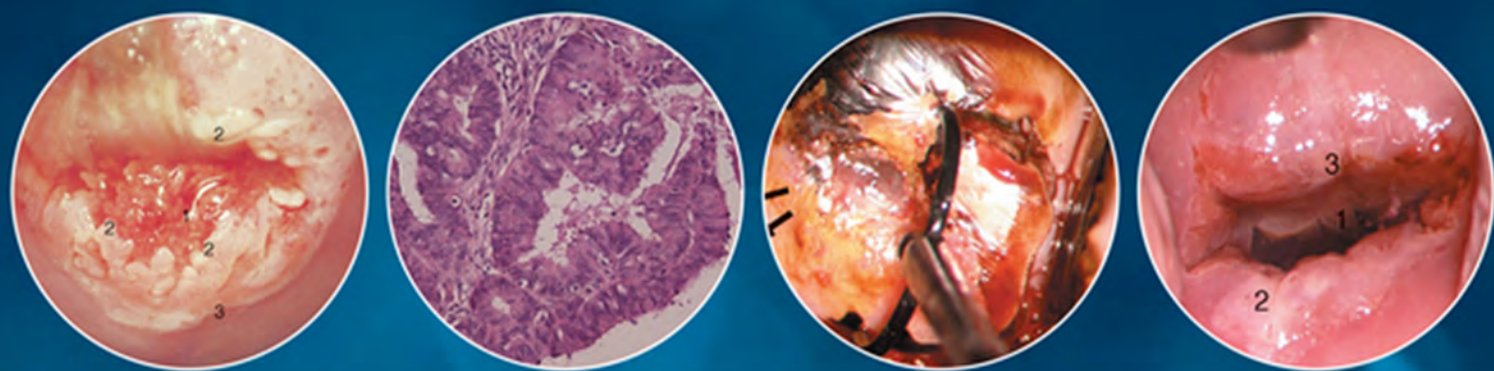




SINGER & MONAGHAN'S CERVICAL AND LOWER GENITAL TRACT PRECANCER

DIAGNOSIS AND TREATMENT

THIRD EDITION

ALBERT SINGER

and

ASHFAQ KHAN

WILEY Blackwell

Cervical and Lower Genital Tract Precancer

TO OUR WIVES AND CHILDREN,
who have supported us unreservedly
throughout this endeavour.
They are our past, present and future.

Singer & Monaghan's Cervical and Lower Genital Tract Precancer Diagnosis and Treatment

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Third Edition

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Preface to the third edition

It is now 20 years since the first edition of this text was produced and 14 years since the second edition came out. Much has happened in that time, and certainly this edition is timely. My colleague John Monaghan, who co-authored the first two editions, retired from clinical medicine during this time and is now pursuing a new career well away from medicine. However, we have his name in the title in recognition of his major contribution to the field of gynecologic oncology and colposcopy. In his place comes Ashfaq Khan, who is highly experienced in the management of cervical and lower genital tract precancer with a major interest in molecular pathology and biomarkers.

We have been assisted by two experts in their respective fields, Professor Jacob Bornstein from Nahariya, Israel, has revised the chapter on vulval intraepithelial neoplasia (Chapter 9). He is aptly suited to undertake this task, being the President of the International Society for the Study of Vulvovaginal Disease and with vast experience in this field. Dr. Rupali Aurora from University College Hospital, London, is an experienced gynecological pathologist; she has rewritten the chapter on histopathology (Chapter 1) and the chapter on screening (Chapter 5). Dr. Quek Swee Chong was an assistant author for the second edition and now works in Singapore; he has contributed valuable comments to the management chapters in this edition.

Since the last edition, many new developments have come on stream. Human papillomavirus—already confirmed as the major etiological agent for cervical and most lower genital tract precancers 14 years ago—is now more easily detected. Many studies examining its role in screening have matured and this has led to its incorporation in many national screening programs for detecting cervical precancer. This has led to a decrease in the use of cytology, although this technique is still widely employed throughout the world. In respect of this text, we have replaced the very detailed chapter on cytology that appeared in the second edition by a general chapter on screening, which, although discussing cytology, considers in some detail the increasing role of human papillomavirus in clinical practice. The role of biomarkers is also emphasized in this new edition.

Treatment of cervical precancer has undergone changes in the last few years, particularly a trend towards more conservative management. This was prompted by the publication some 6 years ago showing the increase in premature births and premature rupture of membranes in respect of excisional procedures used in treating cervical precancers. The introduction of these

new conservative concepts is critically examined. New operative techniques such as the electrocautery needle for excision are also discussed.

We have seen since the last edition a challenge to the efficacy of colposcopy, and it would seem as though the challenge is more related to the underperformance of many clinicians undertaking colposcopy who unfortunately have a lack of training and limited clinical experience. A number of studies—particularly the UK's Tombola study—and results from Professor Petry's unit in Warsburg, Germany, have shown the efficiency of colposcopy when undertaken by trained individuals. Colposcopy is still the most important aspect in the management of the abnormal cervical smear or a positive human papillomavirus result. Notwithstanding this criticism of colposcopy, there is an increased need for high-quality teaching of colposcopy and attendant subjects concerned with the management of cervical precancer. New techniques—especially those involving online teaching—will become more common in the future, and hopefully these electronic techniques will improve the quality of colposcopy. Indeed one of us (A.S.) has just produced an online course in colposcopy, covering much discussed in this text (www.colposcopycourses.com).

Precancers of the lower genital tract now present the gynecologist with specific problems. The presence of human papillomavirus and the role of smoking are major causation factors, and the recognition of these lesions in the vagina, vulva, and perianal area is described in detail with the latest management protocols clearly explained.

When we wrote the preface to the first edition John Monaghan and I clearly stated that “for the clinician seeking wider horizons this text is not simply a colposcopy atlas but a comprehensive statement of the wide range of skills needed to diagnose and manage any or all of the precancerous conditions of the lower genital tract.” The philosophy that underlined the first two editions is clearly expounded in this statement, and we hope very much that we have continued with this tradition. We commend this new edition to the modern clinician, not only those undertaking training but also those in established practice where regular updating is essential.

Albert Singer
Ashfaq Khan
London, 2014

Preface to the first edition

The term “precancer” has been used throughout this book. That word was chosen intentionally as it has a broad, generic connotation that changes are present in the tissue which indicate that a lesion, if not removed, will, with a high degree of likelihood, progress to invasive carcinoma. There is little doubt that the intraepithelial neoplasms of the male and female lower anogenital tract should, when they are high grade, be considered to be precancerous. The prospective follow-up studies of such lesions have established without a doubt that this categorization is appropriate. The use of the term “precancer” for the low-grade lesions is problematic, however, because it is now apparent—particularly for the uterine cervix—that some of the epithelial changes which include the morphological features of neoplasia may, in fact, be acute human papilloma virus (HPV) infections of the epithelium and that the majority of such lesions will not progress to high-grade intraepithelial neoplasia nor to invasive cancer. It is clear that lesions which are infected by the HPV types with no malignant potential will never progress to a true neoplasm and that even low-grade lesions which are caused by intermediate- or high-oncogenic risk HPV types may regress spontaneously or persist for long periods of time without progressing to a true neoplasm. In the low-grade lesions it is difficult, without HPV testing and typing, to predict the biological behaviour of the epithelial change, but the term “precancer” has still to be used because of the potential for such lesions to progress to high-grade intraepithelial disease and, subsequently, to invasive cancer.

The close relationship between precancerous lesions of the cervix, vagina, vulva and anus has long been recognized. Although the common embryonic origins of the epithelium of the vulva, lower vagina, and anus contrast with the origins of the cervix and upper vagina, these differences are all the more remarkable when the clinician studies the fascinating similarities among precancerous conditions of the entire lower genital tract. The authors have clearly illustrated the importance of a knowledge of the development of the epithelium of the lower genital tract with chapters on the development of the transformation

zone with its process of metaplasia and examples of the consequences of interruption to this natural process such as when the female fetus is exposed to the effects of diethylstilboestrol (DES).

For the clinician skilled in the assessment of the cervix following the identification of an abnormal smear, this text will be invaluable in perfecting that technique. For the clinician seeking wider horizons, this text is not simply a colposcopic atlas, it is a comprehensive statement of the wide range of skills needed to diagnose and manage any or all of the precancerous conditions of the lower genital tract.

This is a text book for the modern clinician who no longer wishes to be solely a colposcopist with a limited view confined to the cervix. This text emphasizes the closely integrated relationship between molecular biology, virology, cytology, histology, and colposcopic techniques required for the development of logical and safe management methods. Our clearer understanding of the natural history of conditions covered by the term lower genital tract precancer, including a better knowledge of the capacity for spontaneous resolution exhibited by low-grade lesions, has resulted in the introduction of a wide range of conservative therapies. This logical and generally more conservative approach has removed, to a large degree, the severe overtreatment which was a characteristic of management methods of yesteryear. We have no doubt, however, that this text will not be the final word. This subject has undergone radical rethinking during the last two decades. We anticipate many more changes to come.

This illustrated textbook is a comprehensive guide to our current understanding of the diagnosis, assessment and management of all genital tract precancers and conditions which may mimic them. We commend it to the modern clinician, not only for those in training but also to those in established practice where regular updating is essential.

Albert Singer
John Monaghan

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The late Professor Ray Kaufman, of the Baylor College of Medicine, Houston, Texas, contributed material as listed below, but also gave advice and comment on various aspects of the text. He was a leading exponent not only of colposcopy but also of the pathology and management of lower genital tract disorders, be they of a benign or a neoplastic origin. His texts in their own right are still regarded as classics.

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CHAPTER 1

The histopathology of lower genital tract neoplasia

1.1 Introduction

Approximately 1 in 10 female cancers diagnosed worldwide are cancers of the cervix. Except in countries with effective screening programs the incidence has changed little. The discovery of cytologically detectable and anatomically confirmed premalignant phases has successfully shifted the presentation of cervical squamous tumors from the clinical to the preclinical stage; this being associated with dramatic falls in the prevalence of the disease when effective screening is undertaken.

1.2 Terminology

It is critical that the terminologies used for cytologic and histologic diagnosis are comparable so that they can be correlated with the colposcopic findings. In the last 15 years, our understanding of the molecular events associated with lower anogenital tract neoplasia has developed rapidly. In response to this knowledge, the terminology has changed with each new classification system providing a higher degree of sophistication. Gradually the terminology has become more uniform and a histologist's implications and a clinician's inferences have become more reliable. It is imperative that the nomenclature is uniform throughout the world for ease with statistics, although currently there still remain differences in terminologies between the USA and the rest of the world.

The concept of cervical cancer precursors

The concept of cervical cancer precursors dates back to 1886 when Williams noticed, next to invasive cancers, areas of epithelium that he recognized as non-invasive. The term “carcinoma *in situ*” (CIS) was introduced by Broders in 1932, and this term has been used from its introduction to the present day. Smith and Pemberton in 1934 reported a relationship between CIS and invasive cancer when they found that the changes described as CIS by Broders were present in a retrospective review of biopsies from patients who subsequently developed invasive cancer. This combination of histologic observations and retrospective clinical analysis led to the concept that invasive squamous cell carcinoma develops from precursor lesions that can be identified by the pathologist (Figure 1.1).

Carcinoma *in situ*

With the advent of exfoliative cytology it was recognized that not all cervical abnormalities had full-thickness atypical changes as described for CIS. The lesions, which were morphologically less complex than CIS but still contained many cytologic and histologic features of that entity, were recognized to form a broad histologic spectrum, ranging from minimal deviation changes, which closely resembled the normal epithelium, through epithelia with increasingly severe atypia and disorganization to the classical CIS. Reagan and coworkers in 1956 introduced the term “dysplasia” to designate those abnormalities with histologic and cytologic features that were intermediate between normal epithelium and CIS. Following this, Walters and Reagan in 1956 subclassified the dysplasia into three groups—mild, moderate, and severe—depending upon the degree to which full thickness of the epithelium was replaced by the atypical cells. The higher the histologic grade, the more likely the lesion was to progress to invasive cancer and the higher the risk of developing cancer.

Cervical cancer precursors

- Cervical cancer has precursor lesions which can be detected by cytology.
- These precursors can be classified as mild (cervical intraepithelial neoplasia 1/low-grade squamous intraepithelial lesion), moderate (cervical intraepithelial neoplasia 2/high-grade squamous intraepithelial lesion), or severe (cervical intraepithelial neoplasia 3/high-grade squamous intraepithelial lesion).

Terminology and management (Figure 1.2a)

When the terminology was originally proposed and generally accepted, the prevailing clinical management of patients with dysplasia and CIS was that patients with CIS required a hysterectomy to prevent the development of cancer. Women with a histologic diagnosis of dysplasia, whose clinical course was not well understood but could vary from remission to persistence and progression to CIS, were ignored, followed up, or treated by a variety of means, depending upon the clinician's understanding and acceptance of the natural history data. However, the distinction between dysplasia and CIS was frequently based upon