

Radical to routine

The history of cervical cancer screening

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ABSTRACT

Cervical cancer detection and prevention has paved the way for a myriad of cancer screening programs today. At first, observing cervical lesions was for the purposes of identifying sexually transmitted diseases. Later, however, it was thought that lesions and malignancies were along the same continuum; this led to the adoption of aggressive treatments of early, benign lesions. Stagnation of the cure rates in the late 1920s was resolved by the development of the Pap smear, a procedure still in use today. Although widespread adoption of the Pap smear led to identification of cervical lesions, subjectivity and lack of standardization presented further obstacles to achieving the optimal screening program. Meanwhile, organizations invested in women's health advocated strongly for women to get regular gynecological check-ups. While the medical community was moving forward with identifying lesions, the cause of cervical cancer was still up for debate. From recognizing that cervical cancer was rare in nuns to assuming trauma played a part, the scientific community finally concluded that HPV was the causative agent. Today, the goal is to prevent cervical cancer with vaccines rather than treat lesions when they're found. The journey of cervical cancer has certainly been an arduous one, and there is still much to be improved as treatments and target populations for vaccines are still up for debate.

INTRODUCTION

Today, cytological screening for cervical cancer with the Pap smear is often presented as a success story for population-based screening for malignancy. It has become a model for similar screening programs for breast, colon, and prostate cancers. However, the development of efficient screening tools for cervical cancer was neither simple nor linear, and many aspects of such screening programs remain problematic. The history of cervical cancer management, the Pap smear, and surgical treatment for precancerous lesions reveals the complexities behind today's message that early and frequent screening will save lives. In particular, a historical perspective highlights numerous questions of how we define precancerous and cancerous lesions, and the tradeoffs we are willing to accommodate as we attempt to eliminate it with preventive efforts.

EARLY OBSERVATIONS & UNDERSTANDINGS OF CERVICAL CANCER

With the rise of gynecology as a distinct specialty in the early 19th century and the development of the modern-day speculum, physicians gained the ability to directly visualize and apply treat-

ments to smaller cervical lesions. Initially, cervical examinations were intended to screen for venereal diseases. These examinations formed the basis of the study of cervical lesions by French hygienist Alexandre Duchatelet, whose 1836 publication advanced the medical understanding of cancer etiology. Dr Duchatelet's local-to-general hypothesis assumed a continuity between a local "sore" and full-fledged malignancy, and thus treatment of a local ulceration or polyp could prevent the development of an advanced tumour and metastasis.

The development of better microscopes during the late 19th century allowed the systematic study of normal and diseased tissues, and the recognition of histological changes in malignant cells. The use of biopsy and diagnostic curettage to detect suspected cancerous changes was adopted by many leading hospitals. Occasionally, pathologists who studied cervical biopsies uncovered superficial cervical lesions. In 1888, British Professor of Midwifery John Williams was the first to describe a lesion of the cervix which was "the earliest condition which is recognizable as cancer [which] presented no distinctive symptoms, and was discovered accidentally".¹ By the 1920s, with the invention of the colposcope by German gynecologist Hans Hinselmann, and the use of acetic acid solution, superficial zones of abnormal cervical cell proliferation could be more clearly examined and followed over time. Viennese gynecologist Walter Schiller performed such longitudinal studies, and observing the transition of normal epithelium into malignant, advocated for the aggressive treatment of such "young carcinoma" lesions with radical hysterectomy.¹

TOWARDS PREVENTION: DEVELOPMENT & DISSEMINATION OF THE PAPER SMEAR

Despite important technological advances in the treatment of cervical cancer, including radiation therapy, Schiller's proposal came in the late 1920s when cure rates stagnated at 30%.¹ Specialists needed a way to detect presymptomatic cancers before the disease could spread; however, colposcopy was still an impractical and expensive proposal. The solution was the development of an exfoliative cytology test grounded in the examination of vaginal smears, now eponymously referred to as the Pap smear. George Papanicolaou, a pathologist at Cornell University, began his work in 1914 with studying the vaginal smears of animals to chart their fertility cycle. Papanicolaou's first publication failed to garner much attention, but through collaboration with gynecologist Herbert Traut, in 1941 he published a more extensive and persuasive description of the new method for the early detection of cervical malignancies.¹ With the addition of a wooden spatula to facilitate collection of cervical cells, the Pap smear was rapidly adopted by gynecologists. At

first, the sole aim was the detection of invasive carcinoma; however, with generalization of this method, many women were diagnosed with either well-defined pre-invasive lesions (carcinoma in situ) or less pronounced proliferative changes (dysplasia). In fact, the lack of homogenous diagnostic criteria meant that cytological interpretation was highly subjective; one study found that of 25 pathologists sent 20 identical borderline slides, three pathologists found no cancer while one found thirteen cases of cancer.¹ Despite no reliable way of separating the indolent from the aggressive lesions, most gynecologists in the 1940s-1950s promoted radical treatment with hysterectomy or radiation. This was the beginning of a continuing debate over the appropriate treatment of precancerous lesions, and the costs of screening.

While clinicians considered these uncertainties, charities and women's organizations campaigned consistently and effectively for the dissemination of the Pap smear. The American Society for the Control of Cancer (ASCC) and the Amanda Sims Memorial Fund had been conducting educational campaigns about the early signs and symptoms of breast and gynecological cancers since the 1920s. Using the extensive networks of women's clubs, female volunteers encouraged their fellow women to overcome their false modesty regarding gynecological examination by male physicians to seek life-saving medical care.² As it became clear that the Pap smear could detect precancerous lesions, the goal of screening campaigns shifted to cancer prevention and elimination, which would require routine Pap smears at regular intervals. Education drives in the 1940s to 1950s focused on the necessity and respectability of annual pelvic exams.

THE NORMALIZATION OF OVERTREATMENT

Two findings in the 1950s to 1960s led to important changes in the treatment of precancerous lesions. Firstly, Danish gynecologist Olaf Petersen observed that for women diagnosed with carcinoma in situ and treated only with watchful waiting by regular gynecological examinations for 10 to 15 years, the majority remained cancer-free; those who did develop cancer had lesions which evolved very slowly and were successfully treated upon identification. Second, in attempting to study the development of cervical dysplasia with serial biopsies, American gynecologist Leopold Koss discovered to his surprise that they were often unable to find the lesions at the subsequent visit. This semi-accidental observation that the biopsy procedure itself was often sufficient to destroy the fragile dysplastic cervical lesions led to the generalization of a variety of minor surgical interventions such as thermocoagulation and cryotherapy. The management of cervical cancer entered a true era of prevention, with a greater acceptability of overtreatment using minor surgical treatments, despite non-negligible complications such as hemorrhage, infection, and at times impact on future fertility.³ Original screening efforts were expected to uncover an early aggressive cancer, and to rid of it with an equally aggressive treatment. Now, the aim was elimination of a weak precancerous lesion with conservative methods. At the same time, the ease of eradication of suspicious lesions did away with the need to correlate morpholog-

ical data with clinical outcomes. Even today, the three parallel systems of classification for cervical lesions have high degrees of prognostic ambiguity. A non-negligible percentage of screened women, on average 2 to 4%, will receive a diagnosis of atypical squamous cells of unknown significance (ACSUS).⁴ Women with this diagnosis can hover in this uncertain state between health and disease for 12 months before getting a more definitive answer, at a significant psychological cost.⁵

THE BREAKTHROUGH: A VIRAL ETIOLOGY

One current strategy for the stratification of ACSUS lesions is the use of human papillomavirus (HPV) DNA testing. The cause of cervical cancer had been debated since 1842, when Italian surgeon Domenico Rigoni-Stern observed that nuns rarely suffered from cancers of the womb, and that its etiology may be related to sexual activity. In the late 19th century, scientists theorized that the abnormal proliferation of cells in cancer were induced by chronic inflammation or irritation, such as the trauma of multiple pregnancies and childbirths. This was succeeded in the early 20th century by the mutation theory of cancer, popularized after scientists observed a sharp rise in the frequency of malignancies in survivors of the Hiroshima and Nagasaki atomic bombs. Epidemiological studies of cervical cancer in childless sexually-active women in the 1970s revealed characteristics similar to a sexually transmitted infection, and scientists began pursuing a viral hypothesis. After the initial suggestion of herpes simplex virus was disproven, the recognition of histological similarities to genital warts led to the identification of HPV as the causative agent. Specifically, the oncogenic strains HPV16 and 18 were identified by German virologist Harald zur Hausen in 1983 to 1984, for which he won a Nobel Prize in 2008. This directly enabled the development of a preventive vaccine; Gardasil® was introduced in 2006.⁶ While current vaccines do not completely eliminate the chance of developing cervical cancer, this innovation has dramatically changed the approach to cervical cancer prevention. However, there remain many questions about its long-term efficacy and effects at the population level, particularly with vaccination efforts concentrated mainly on women.

CONCLUSION

Public health experts state that cervical cancer is now a fully preventable disease. To standardize the prevention of cervical cancer, many screening programs have been established; the Ontario Cervical Screening Program began in 2000 and has around 65% participation. The wide implementation of these programs has prompted many debates about screening criteria, frequency, and follow-up, continuing the historical controversies surrounding the threshold for intervention. Examining the history of cervical cancer screening also helps us understand why screening efforts for other malignancies have been less successful: cervical lesions are easily accessible, fragile, and relatively easy to eliminate – a rare combination. In addition, critical grassroots activism propelled a felicitous finding to the centre of a public health movement. Cervical cancer screening practices will continue to evolve and should continue to

be questioned and reflected upon.

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