

CERVICAL SCREENING IN CHINA: PROJECT MANAGEMENT CONSIDERATIONS

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Abstract

Screening for early cancer and pre-cancerous lesions of uterine cervix has been proven to save lives of women in their prime years. To achieve the best results, the screening must be implemented for the whole population, which requires building a very large infrastructure as well as training sufficient number of highly skilled specialists.

Although in China today there are several excellent programs in large cities for screening of cervical cancer and pre-cancerous lesions of cervix, these programs cover only a very minute population of China. To achieve a significant reduction of the incidence of invasive cervical cancer with concomitant reduction in the death rate due to this malignancy, a population-based screening program would have to be instituted reaching all women at risk in the country of 1.5 billion inhabitants. It has been estimated that for conventional approach it would take at least two decades to build the infrastructure and to train sufficient number of the required technologists. It was thus decided to employ newly developed technology that could be implemented in a couple of years and allow cervical screening for at least a third of China in the shortest possible time.

The strategy as well as short and long term planning was then developed. Since the start of the implementation of the program, many unforeseen problems have emerged that have required continuous changing and evolution of the project planning. These include a broad spectrum of problem solving measures that in most instances have led to innovative approaches dictated by the specifics of the project, culture, tradition, introduction of new technologies, and other factors.

Key words: cervical cancer, screening, new technologies, program change management, China innovative approach

Introduction

Screening for early cancer and pre-cancerous lesions of uterine cervix has been proven to save lives of women in their prime years. To achieve this, a sample of cells is taken from the border between ecto- and endo-cervical canal and the exfoliated cells are then deposited onto a microscope slide to be examined by highly trained and skilled specialists for the presence of cancerous cells. This process, also known as the Pap test, has been discovered about 80 years ago and in the countries where a well organized population-based screening program was established, the incidence of invasive cervical cancer and mortality due to cervical cancer dropped dramatically (1, 2, 3). For example in the

province of British Columbia (BC) in Canada (with a population of ~4 million inhabitants) where population -based cervical screening was introduced over 50 years ago, the incidence of invasive cervical cancer and death due to this malignancy decreased several fold (Figure 1). To achieve these results there are over ½ million cervical smears examined annually in a single, centralized laboratory.

Age Standardized Incidence and Mortality Rates in British Columbia, 1955-1995

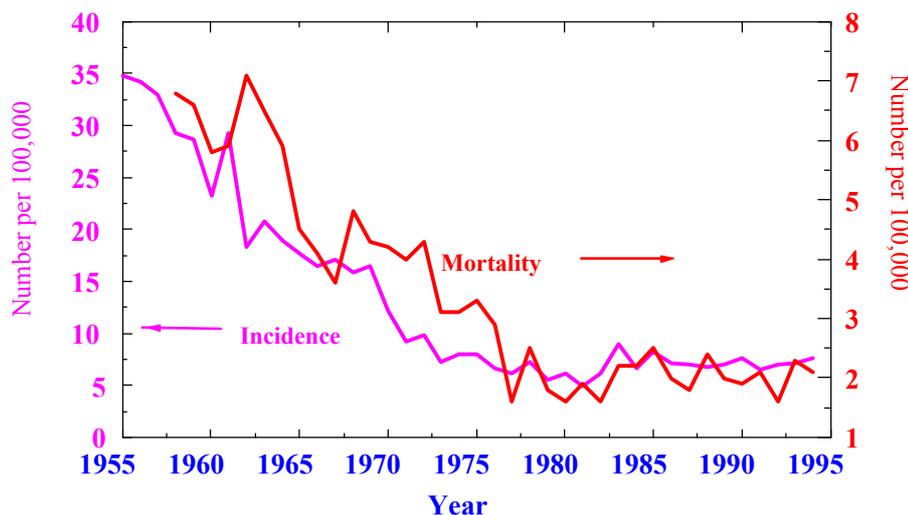


Figure 1. Age standardized incidence and mortality due to cervical cancer in British Columbia, Canada has fallen to the lowest level in the world due to population -based screening for cervical cancer starting in early 1950's.

Unfortunately, there are many countries in the world where population -based screening has not yet been implemented due to the relatively high cost and shortage of highly skilled technologists. The detection and correct diagnosis of high grade cervical intraepithelial neoplasia, carcinoma in situ (CIS) lesions and invasive cancer is a difficult task in the cytological evaluation of cervical smears (4, 5, 6). The performance of several laboratories was summarized by Van der Graaf et al. (7) who reported that only about half of biopsy-documented invasive cancers were appropriately recognized by cytology of cervical smears. To increase the diagnostic accuracy and to avoid mistakes by cytopathology, several image cytometry based systems have been developed over the past three decades for the detection of abnormal DNA content of the cervical epithelial cells (8, 9, 10, 11). We postulated that using a high resolution, fully automated system, originally developed at the British Columbia Cancer Agency (8, 12, 13), could be used to greatly reduce the need of the number of highly trained technologists and could be employed in a cost-effective manner for population -based cervical screening in China.

At present in China there are 5 – 7 million cervical samples examined annually at large medical centres in major cities, representing only a very small fraction of the estimated 300 million required to approach the BC results. In order to achieve such enormous (nearly 50 fold) increase of the capacity to examine all sexually active women on average

once every 3 years, an ambitious plan was prepared outlining a possible solution to the problem. In this paper we report a number of novel approaches that had to be implemented since the start of the program that have required continuous changes in program planning to overcome problems that could not be readily foreseen at the planning stages.

Acceptance of the Technology

From the onset of the program start it was recognized that the approach and the technology must get support and recognition of three major groups: 1) acceptance of the academic community in China that the technology is based on proven scientific facts; 2) acceptance of the political structures at the local, provincial and state levels of the country, and 3) attracting appropriate business community for realization of the plan.

To achieve the academic acceptance, first a Research Centre (Canada – China Early Cancer Research Centre) was organized and built at a major medical university (Tong Ji Medical University in Wuhan, Hubei) where basic feasibility studies and initial clinical trials were performed. The results were published in peer reviewed medical and scientific journals and in addition, numerous national and international conferences, workshops and seminars were organized with participation of the best Chinese and international medical scientists. These programs are still ongoing and will continue in the foreseeable future at even increased scope and frequency.

There were numerous presentations to local, provincial and state institutions focusing on health related and new business related authorities, presenting the merits of a well organized, population-based cervical screening program. Family Planning Committees have emerged as the key potential partners in these efforts as they could provide easy access to all women in child-bearing age in China. The unique, China based approach has provided a new and very large business opportunity based on high technology that has been a major focus in China future commercial developments. It is without doubt that the program has enjoyed significant support at all levels of political establishments.

Finally, a direct participation of the business community has been judged to be the most critical part of the program realization and success. No program, in medicine or otherwise, has a long term survival probability unless it is based on a sound, cost-effective (i.e. profitable) foundation. Already a decade ago it was noted that China has initiated moves to encourage privately run businesses to participate in all facets of commercial activities, including providing medical services. Presenting a rather Spartan and unorthodox business plan to selected established businesses in the relevant field at the end attracted a major corporation (Motic China Group Co., Ltd., Xiamen, Fujian) that has taken the lead role in this business venture, without which realization of the plan would not be possible.

Creating Corporate Structure

Figure 2 shows the corporate structure of the company (Landing – Motic Medical Services Co., Ltd.) with its administrative headquarters in Xiamen, (Fujian) including

Information technology (IT) Division, Intellectual Property Division (IP), and Systems and Supplies Division while some other key Divisions: R&D, Clinical Trials, Clinical Approvals, Technology School and Pathology Reference Centre are located in Wuhan, about an hour flight from Xiamen.

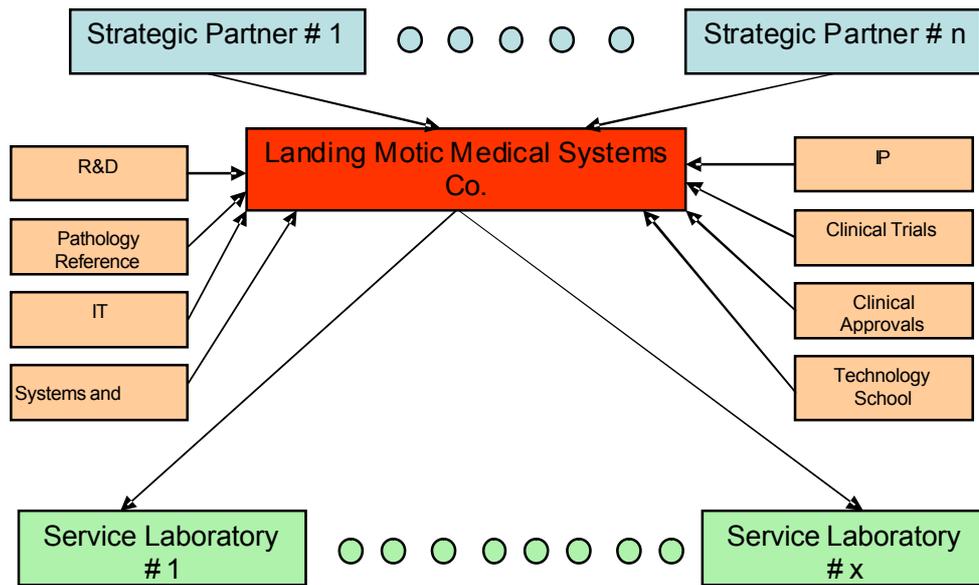


Figure 2. Corporate Structure of the Landing- Motic Medical Services Co., Ltd. (LMC)

Starting in March 2005 eleven new service providing laboratories have been established in selected major cities as well as in a couple of rural areas that have been since fully operational. By the end of this year (2006) it is planned to open 15 – 20 new service providing laboratories, and then adding 30 – 50 laboratories per year thereafter. Each new laboratory comprises of approximately 200 m² of completely renovated space, fully equipped and staffed to take samples from at least 3,000 women per month, readily expandable to at least tenfold increase in the capacity by just adding more equipment and appropriate staff without any (or just minimal) increase in the required space.

Changing Strategies and Evolution of Project Planning

Below is a description of some selected examples of seeking new (and pragmatic) solutions during the process of the plan realization.

Approval of the DNA -ploidy method for cervical screening in China. The most important task, the corner stone of the project, was obtaining SDA approval in China (an equivalent of the FDA approval in the USA or Health Protection Branch approval in Canada). To achieve this, a well designed clinical trial involving nearly 10,000 women was carried out under a tight protocol. Approximately 900 women with some indication of potential cervical lesion were then followed by colposcopy and biopsies of the potential lesions were then reviewed by a panel of experienced gyne pathologists to derive to the final diagnosis of the biopsied material (“the truth”). Cytology calls by

conventional cytology and that of the DNA -ploidy method were then evaluated and compared by accepted statistical methods. It was shown that DNA-ploidy approach was not only equivalent to the conventional method, but was statistically significantly better in detecting cancer as well as severe precancerous lesions of the uterine cervix (14). The whole clinical trial with the analyses of the results and the submission to the Chinese authorities for the approval of the method was carried out in a period of approximately one year, a task that usually takes at least 2 – 3 times as long in most countries. After a thorough review of the top specialists and academics in China, the method was granted approval in that country in 2004.

Accreditation of privately run diagnostic laboratories. Without doubt this represented one of the most difficult challenges in the plan realization. Although it was initially envisioned that the laboratories would be a part of (or at least closely associated with) major medical universities or major hospitals, after struggling for three years with numerous administrative and political problems, it was decided that free standing, independent laboratories would be the only realistic alternative. That required accredited licences for diagnostic, privately run laboratories that would create a precedent in China at the time. With persistence, impeccable academic credentials of the key participants, association with world renown Cancer Control Canadian Institution (BC Cancer Agency and University of British Columbia), strong support of the local and provincial authorities, and possibly some other factors (including a great deal of luck) this was granted in a relatively short period of time of 12 months.

Building systems, support equipment and supplies made in China. At the onset of the project it was thought that most of the sophisticated, fully automated microscopy scanning systems and other support equipment (cyto-centrifuges, fume hoods, cell shakers, etc.), as well as all required supplies and disposables would be imported to China from Canada. However, it was soon realized that this would be impossible to maintain in the long run for a great variety of reasons. The relative high cost of imported goods of any type (up to at least a factor of 2 -3 times costs in comparison with similar products in China, if available) would not make this method cost effective. In addition, importing medical products to China is expensive (high import duties) and requires extremely long term planning and cash outlays (up to a year). Most importantly, what may work well in North America or Europe may not be adequate for Asian markets. These and other factors dictated re-designing virtually all equipment and supplies to be specific for the China market, finding local manufacturers under license and achieving price structures for these items acceptable to Chinese market. The added benefit of this approach has been that the new designs resulted in significantly improved performance and utilities of virtually all equipment and supplies as well as creating some new proprietary Intellectual Property (IP). At present the capacity of China based industry can easily cover the existing and expanding needs of that country and is also capable to cover other emerging markets outside of China at highly competitive prices.

Setting up new laboratories and sample acquisition stations. Once a decision has been made that a new laboratory will be established in a territory, it is necessary to develop required space, providing the start up equipment and supplies and employ a trained staff

to operate the facilities. There are several criteria that must be fulfilled for such a decision, the most important one being the desire of local authorities and inhabitants to enter the program, providing undeveloped space, providing means for continuous information to women of the benefits of cervical screening, and by-in of a gyne pathologist to be in charge of the medical matters of the diagnostic laboratory. On average it has taken less than 8 weeks (although the record has been less than 3 weeks) from the decision to go, to the date that the laboratory was fully operational including obtaining the development and building permits, renovating ~200 m² space that would be considered excellent in any even most developed country. Every laboratory has virtually the same, well thought out outlay, identical equipment and supplies, etc, such that in case some medical or technical staff need be added or exchanged from some other existing laboratory, they can start functioning in the new environment without any delay.

In some cases it is very expensive and impractical to bring women to come to the nearby laboratory for sample acquisition. To overcome this problem a special gynaecology vans were designed and built that has since been used to regularly visit remote sites (e.g. villages) to examine women at local settings.

Training technologists. Cervical screening by conventional methods requires large number of highly skilled cytotechnologists and cytopathologists. A well trained and licensed cytotechnologist in Canada requires a minimum of 2 years of schooling past graduation in a field of general science at a university or a college, and then several more years on the job training before he or she becomes truly independent to weed out normal and benign cases while sending any samples with atypical cells to be reviewed by the cytopathologist who will sign off the sample out with the final diagnosis. The automated scanning of slides by the DNA ploidy method requires approximately 15 fold fewer technologists and in addition, with significantly lesser skills. Nevertheless it was judged that it would take at least a year of schooling using conventional approach to teach and train technologists for the new method, a time too long to achieve the stated objectives of rapid expansion of the laboratory capacities. Several new teaching methods, including employing computerized microscopes equipped with high resolution cameras and interconnected to a teacher that could simultaneously train up to 64 students at a time (Motic, DigiLab II System) has shortened the basic training to 3 months at the central school in Wuhan, with implementation of continuous further training on the job. The latter has been achieved by equipping each laboratory with a computerized Pathology Review Work Station that also has a high resolution camera attached to the microscope and is connected via a high speed internet connection to the central facilities in Wuhan where there is pathology and cytology reference centre and where very experienced pathologists could look at the slides on a high resolution monitor in real time while at the same time discussing the case with local technologists. Every day each laboratory has a scheduled session with the central reference unit to review all cancer cases and to call all hard-to-judge cases by one of the best pathologists in China. This not only assures the best possible diagnosis, but also continuously trains the technologists with the net result that in a very short time of a year or so they become as well trained and skilled as if they were working for a decade or more in this specialized field of medicine.

Research and development. Every method can be improved and every method may be (and probably will be) replaced by a new, better or more cost-effective approach. In the central laboratories in Wuhan we have been continuously testing new approaches and improvement of detecting early lesions with malignant potential of cervix as well as early cancers and pre-cancerous lesions of other tissue sites such as colon, oesophagus, breast and others. Having access to slides of hundred of thousands of high risks individuals represents a unique opportunity to improve the detection techniques as well as to provide means to a better, more objective diagnosis and prognosis of the early lesions with malignant potential. Significant progress have already been made to the original technology and this process will continue with an accelerated pace in the future.

Conclusions

The project of introducing population-based cervical screening in China is now entering the initial phase of its realization. The first dozen laboratories at present perform about 12,000 cases per month (~150,000 case per year) although their capacity is at least tenfold greater without any significant increase in the laboratory space, equipment or staff. If the initial goals will be realized, adding a few hundred additional laboratories, spaced throughout China will have the capacity to process over 200 million samples annually that would be required to keep this malignant disease under control.

Without doubt, most of our current plans will have to be modified again and again as we will be faced with the realities that are hard (if not impossible) to predict in this endeavour. At times, some of us wish that this project would have characteristics of a more conventional project that could follow well established principles of project planning. But then again, at least I must admit, that being faced with new, sometimes seemingly insurmountable problems, keeps us working even harder and more determined to succeed in this task that will save lives of thousands of women every year in their most productive and enjoyable years.

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References

1. Liu S., Semenciw R., Probert A., Mao Y. (2001): Cervical cancer in Canada: changing patterns in incidence and mortality. *Int J Gynecol Cancer* 11: 24-31.
2. Anderson G.H., Boyes D.A., Benedet J.L., LeRiche J.C., Maticic J.P., Suen K.C., Worth, A.J., Millner A., Bennett O.M. (1988): Organization and results of the cervical cytology screening programme in British Columbia, 1955-1985. *Br Med J* 296: 975-978.
3. Guidozi F. (1966): Screening for cervical cancer. *Obstet Gynecol Surv* 51:696-701.
4. Gay, J.D., Donaldson L.D., Goellner J.R. (1985): False-negative results in cervical cytologic studies. *Acta Cytol* 29: 1043-1046.

5. Kok M.R. , Boon M.E. , Schreiner-Kok P.G., Koss L.G. (2000): Cytological recognition of invasive squamous cancer of the uterine cervix: comparison of conventional light -microscopical screening and neural network -based screening. *Hum Pathol* 31: 23-28.
6. Barton S.E. , Jenkins D. , Hollingworth A. , Cuzick J., Singer A. (1989): An explanation for the problem of false -negative cervical smears . *Br J Obstet Gynaecol* 96: 482 -485.
7. Van der Graaf Y. , Vooijs G.P. , Gaillard H.L.J., Go D.M. (1087) : Screening errors in cervical cytologic screening. *Acta Cytol* 31: 434 -438.
8. Garner D.M., Harrison, A., MacAulay C.F. (1994): Cyto-Savant™ and its use in automated screening of cervical smears. *Compendium on the computerized cytology and histology laboratory*, Edited by George L Wied, Tutorial of Cytology, Chicago, Illinois, pp.346-352.
9. Bibbo M. , Bartels P.H. , Dytch H.E. , Wied G.L. (1991): Cell image analysis. *Comprehensive cytopathology*. Edited by Marluce I Bibbo, W.B.Saunders Company, Philadelphia, PA, pp. 965 -983.
10. Böcking A., Nguyen V.Q. (2004): Diagnostic and prognostic use of DNA image cytometry in cervical squamous intraepithelial lesions and invasive carcinoma . *Cancer* 102: 41 -54.
11. Mayer A. , Hockel M., Thews O. , Schlenger K., Vaupel P. (2003): Impact of oxygenation status and patient age on DNA content in cancers of the uterine cervix. *Int J Radiat Oncol Biol Phys* 56: 929-936.
12. Anderson G. , MacAulay C.F. , Maticic J., Garner D., Palcic B. (1997): The use of an automated image cytometer for screening and quantitative assessment of cervical lesions for screening. *Columbia Cervical Smear Screening Programme*. *Cytopathology* 8: 298-312.
13. Hanselaar A.G. , Poulin N. , Pahlplatz M.M. , Garner D. , MacAulay C. , Maticic J., LeRiche J., Palcic B. (1998): DNA -cytometry of progressive and regressive cervical intraepithelial neoplasia. *Anal Cell Pathol* 16:11-27.
14. Sun X.R., Wang J., Garner D. , Palcic B. (2005): Detection of cervical cancer and high grade neoplastic lesions by a combination of liquid -based sampling preparation and DNA measurements using automated image cytometry. *Cell Oncol* 27: 33-41.