EARLY DETECTION OF CANCER IN PRIMARY CARE IN LESS-DEVELOPED COUNTRIES

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Early detection linked with appropriate treatment improves long-term survival and cure from breast and cervix cancer with good quality of life. Strengthening the capacity of primary care services in providing affordable early detection tests for breast and cervical cancer such as clinical breast examination (CBE), visual screening with acetic acid (VIA) and visual screening with Lugol's iodine (VILI) and to refer women with suspected lesions for further investigations and treatment will improve early diagnosis and cure rates, given the fact that more than 90% of patient contact occurs at this level. Pre- and in-service training to improve the skills of primary care practitioners in cancer early detection are critically important for improved early diagnosis and prognosis from these cancers globally.

Early detection is an important approach for controlling cancers for which an effective treatment is available. For cancers such as breast, uterine cervix, ovary, head and neck and colorectum, early detection and appropriate treatment contribute to significant improvement in survival and good quality of life. There is wide variation in the proportion of cancer patients presenting in early clinical stages that permit successful treatment and avoid death from cancer[1-4]. Unfortunately, a significant proportion of patients with these cancers present in advanced stages in less-developed countries and thus have poor prospects of long-term survival as compared to the scenario in developed countries[1,2] (Table 1). Cancer early detection approaches include screening programs, early clinical diagnosis and a high level of awareness among the general public and health professionals in addition to well-developed and accessible health services supported with adequate infrastructure and trained human resources. Developing and implementing national cancer control programmes as advocated by the World Health Organization provides an effective and pragmatic framework to develop early detection, treatment and follow-up care services as a continuum in less developed countries[5].

Organized screening programmes aim to detect predominantly preclinical invasive cancers (e.g. breast cancer screening) or precancerous lesions (e.g. cervix cancer screening) in systematically invited asymptomatic subjects in the general population. Given the level of resources required, cancer screening programmes are not feasible in the vast majority of less-developed countries. A more widely applicable early detection approach relies on early clinical diagnosis among people with symptoms and signs. This requires improved awareness among the public of the disease, its symptoms and signs and on the health services available to support diagnosis and treatment in the region; it requires well-trained and empowered health care personnel in primary care who can promptly recognize and refer people with suspected signs and symptoms for early diagnosis or to rule out disease in higher levels of health services. We briefly discuss what is pragmatically feasible and what skills are required at the primary health care level to enhance early detection, referral and prevention of cervix and breast cancer in this publication

Table 1: 5-year age-standardized relative survival (ASRS %) by country and cancer site		
	Breast	**Cervix**
USA	89.0%	67.8%
China	82.5%	67.0%
Costa Rica	69.6%	53.5%
Cuba	70.4%	56.3%
India	51.6%	46.4%
Philippines	47.4%	37.4%
Republic of Korea	78.6%	79.2%
Saudi Arabia	64.5%	
Singapore	76.4%	65.7%
Thailand	62.8%	60.7%
The Gambia	12.5%	21.8%
Turkey	77.2%	63.5%
Uganda	45.9%	13.1%
Zimbabwe	57.8%	39.1%

Source: Sankaranarayanan R et al. Cancer survival in Africa, Asia, the Caribbean and Central America (SurvCan). IARC Scientific Publications volume 162, Lyon, IARC, 2011. US National Cancer Institute. Surveillance Epidemiology and End Results (US SEER) http://surveillance.cancer.gov/statistics/types/survival.html

to promote early clinical diagnosis and treatment. We plan to cover early diagnosis of other cancer sites at the primary health care level in future editions.

The role of primary health care services in early detection

Effective cancer early detection efforts at the primary care level is critically important for the success of clinical early diagnosis efforts, since more than 90% of patient contacts within any health care system in the world occur at the primary care level in health centres, dispensaries and in the offices of general and family practitioners. Millions of people interact with primary care services on a daily basis, which provides a highly useful platform within health services to improve population awareness of common cancers, to provide simple screening tests and refer clinically suspect patients for diagnosis and treatment in the secondary or tertiary care levels as deemed appropriate, provided the doctors, nurses and health workers at the primary care level are knowledgeable and competent to provide these interventions amidst their routine responsibilities. Prompt recognition of symptoms and signs that may give an early warning of cancer, however, should also trigger an informed and empowered lay individual to seek medical care. Most cancers could be detected earlier if the index of suspicion of cancer on the part of primary health care workers was higher, particularly when providing routine care for persons known to be at high risk for cancer.

Early detection of cervical cancer in primary care

Early detection tests such as visual screening with acetic acid

(VIA) and visual screening with Lugol's iodine (VILI) can be administered to women between the ages of 30–50 at the primary care level if the health centres are equipped with facilities for pelvic examination and necessary consumables. The primary care practitioners can be readily trained in performing these tests and in interpreting the real time test results competently in short in-service training courses or by self-learning using manuals, atlases and digital training courses[6,7].

Visual screening tests are the most feasible cervical screening tests that can be administered at the primary care level, since they do not require a laboratory infrastructure, and consumables such as 3–5% dilute acetic acid and Lugol's iodine can be readily made available in health centres and the test results are interpreted in real time. If a definite acetowhite area is detected on the cervix 1-minute after the application of acetic acid, VIA testing is positive and if a well-defined mustard-yellow area appears on the cervix after application of Lugol's iodine, VILI testing is positive; VIA- or VILI-positive women have a high probability of harbouring high-grade cervical intraepithelial neoplasia (CIN II or III), which are cervical cancer precursor lesions. Detecting and effectively treating CIN II and III lesions will result in the prevention of subsequent invasive cancer among these women. In a setting where there are no resources for directing biopsies, colposcopy and histopathology services in secondary care such as is the case in many sub-Saharan African countries, VIA- and/or VILI-positive women without clinical features suggestive of invasive cancer may be treated using cryotherapy or cold coagulation without further investigations, in a "screen and treat" mode[8,9]. The safety, acceptability and efficacy of the screen and treat approach in preventing CIN has been well documented in less-developed countries[8-10]. In settings where there is capacity for further investigations, patients may be referred to secondary care facilities where colposcopy, biopsy and further management can be carried out[11-13]. Women with negative VIA or VILI tests may be advised a repeat screening after 3–5 years.

In settings where there are facilities for performing Pap smear or HPV testing, women above the age of 30 years, who can afford them, may be advised of these tests; those with atypia or worse results on Pap smear or testing positive for HPV infection should be referred for investigations and treatment. A single baseline HPV-negative test in women above the age of 30 has a high negative predictive value for subsequent cervical neoplasia and thus has an extremely low risk of invasive cancer or CIN in the next 7–10 years or so[14,15].

Women presenting in primary care services may be routinely asked if they suffer from symptoms such as abnormal

vaginal bleeding such as passing blood clots or inter-menstrual bleeding, bleeding after sexual intercourse or pain during vaginal intercourse, persistent, foul-smelling discharge, persistent low backache. Such women should be offered a speculum examination under bright light and the presence of ulcero-proliferative or indurated growth on the cervix should receive prompt referral to secondary or tertiary care (depending on where diagnosis and treatment services are available in that region) for diagnostic confirmation and management. The 5-year survival from stage I cervical cancer exceeds 90% whereas from stage IV, cancer survival seldom exceeds 10%. In women with a normal appearing cervix, the appearance of aceto-white lesions following the application of 3–5% acetic acid or mustard-yellow lesion following application of Lugol's iodine should arouse suspicion of cervical precancerous lesions or subclinical invasive cancer and such women should be referred for further management.

Primary care workers have a major responsibility in improving awareness among the general public who report to their services about the preventability and curability of cervical cancer when detected early, symptoms and signs of cervical cancer, the safety and efficacy of treatment for cervical neoplasia. They should also advise on the possibility of preventing cervical cancer by HPV vaccination of young adolescents aged 9–18 by person to person communication and by displaying educational materials and posters in the health centres and by delivering general awareness talks in their communities. Such educational messages from primary care practitioners are very valuable in improving general awareness of cervical cancer and its control in the general population and in empowering women to seek services. Improved public awareness and early diagnosis and treatment significantly contributed to reduced mortality from cervical cancer even before the introduction of screening programmes in developed countries[16,17].

Early detection of breast cancer in primary care

Systematic screening with breast imaging is not feasible in many less-developed countries leaving improved awareness and early clinical diagnosis as the major options for breast cancer early detection. Presence of a lump in the breast is the single most important symptom and sign in the early detection of breast cancer. It is generally considered that breast lumps of ≥1cm diameter are readily palpable by health care workers, although even breast lumps of 5mm may be palpable[18,19].

Women presenting with symptoms such as breast lumps, skin changes in breasts, nipple discharge, nipple retraction or ulceration of the breast skin should undergo clinical breast examination (CBE) by the primary care physician or a nurse

well versed in providing CBE. CBE consists of physical examination of both breasts, both axillae, and the neck. CBE can be readily taught to primary health workers using manuals and digital learning resources[7]. Equipping primary health centres with silicon breast models is a valuable investment in improving CBE skills of health workers and in creating breast awareness among women attending the health centres. The silicon models can be used for training health care workers in performing CBE and women may be made familiar with the concept of breast awareness and detecting breast lumps using these models.

Women with a palpable breast lump or any change in the shape, consistency, or density of the breast, unilateral nipple discharge, skin changes such as eczematous changes in or around the nipple or areola, skin tethering, and skin or nipple retraction, whether associated with other symptoms or risk factors, should be referred to a secondary or tertiary care facility (depending upon where such services are available) where diagnosis, staging, and treatment of breast cancer can be efficiently carried out.

Women found with no abnormalities on CBE should be educated on breast cancer signs and symptoms, encouraging them to be aware of what is "normal" for them and of the occurrence of any changes by periodic self-palpation when getting dressed or bathing. They should be advised to seek medical care promptly in case of any future abnormalities. Breast awareness and empowering women to seek prompt care have far reaching implications for breast cancer control, given the fact that breast cancer survival significantly improved and breast cancer mortality started declining well before the introduction of mammography screening programmes in many developed countries around 1975. The frequency of advanced breast cancers fell significantly and survival rates increased considerably in the United Kingdom and in Connecticut, USA mainly due to increased awareness among women and health care providers, before the introduction of mammography screening programmes[20,21].

Conclusion

In low-income countries, the vast majority of cancer patients are diagnosed in advanced clinical stages and health care services are extremely limited. Hence, early clinical diagnosis of cancer is the most feasible and effective strategy for early detection in less-developed countries. Screening is a resource intensive early detection strategy that may be considered as a cancer control option when the resources are committed and the health systems have sufficiently evolved. Strengthening the capacity of primary care services in providing affordable early detection tests for breast and cervical cancer and to

Table 2: Consumables and equipment needed for providing breast and cervical cancer early detection tests in primary health centres		
Intervention	**Equipment/tools**	**Consumables**
Visual screening with acetic acid (VIA) or Lugol's iodine (VILI)	• Examination couch • Halogen focus lamp • Vaginal speculum • Sponge holding forceps • Sharp cutting punch biopsy forceps • Water boiler • Autoclave • Plastic bucket to hold 0.5% chlorine solution for decontamination • Waste bin	• 3–5% acetic acid • 3–5% Lugol's iodine • Monsel's paste • 0.5% chlorine solution or Gluteraldehyde • Gloves • Cleanly laundered linen • Cotton and gauze
Clinical breast examination (CBE)	Examination couch	• Cleanly laundered linen • Cotton and gauze
Creating breast awareness	Silicon breast model Posters on breast awareness	• Cleanly laundered linen • Cotton and gauze

refer women suspected with lesions for further investigations and treatment will improve the prospects of early detection, improve survival and reduced mortality. Developing and implementing in-service training programmes to guide primary care practitioners in the early identification of patients with signs and symptoms suspicious of breast and cervical cancer and to improve their skills in administering the relevant early detection tests will go a long way in facilitating early diagnosis and prognosis from these major cancers among women globally.

Effective early cancer detection efforts in primary care settings require that people be able to undergo recommended early detection procedures in health centres and that primary health workers be well trained and competent enough to provide these interventions. The basic equipment and consumable needs for providing breast and cervical cancer early detection tests in health centres is given in Table 2. Unfortunately, health centres in the public health sector in many less-developed countries are poorly equipped in terms of basic infrastructure and required staff. Unless investments are made to optimize infrastructure, consumables and clinical practice at the primary care level, the potential for early detection and referral of these early cancers through primary care will not be fully realised. For instance, health centres in many sub-Saharan African countries lack examination couches, specula, sterilization equipment, light sources, linen and basic consumables and it is obvious that early detection cannot be facilitated by such appalling primary care infrastructures. On the other hand, the well-developed health centres in Thailand successfully provide VIA or cytology screening which has enormous potential to improve cervical cancer control in Thailand[22-25]. Improved investments in primary health care in Bangladesh, Thailand and Tamil Nadu

state in India through the Tamil Nadu Health Systems project have significantly enhanced capacity for VIA screening in health centres there[11,25].

Introducing an early detection register in the health centre to document information on subjects availing such services, their referral details and final outcome will be useful for clinical audits and to improve compliance of screen-positive women with further diagnostic investigations and treatment.

Inadequate awareness and skills among primary health care practitioners is a major obstacle for a strategy based on early clinical diagnosis. Development of evidence-based guidelines, provision of adequate facilities in health centres and provision of in-service, training and monitoring will improve the skills of primary health care providers in clinical suspicion and prompt referral women to facilitate the diagnosis of breast and cervical cancers in early stages. Developing adequate facilities for diagnosis and treatment of cancer in secondary or tertiary care facilities in less-developed countries is another important prerequisite for successful earlier clinical diagnosis and, better outcomes of treatment at considerably lower costs. ●

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References

1. Sankaranarayanan R, Swaminathan R, Brenner H, Chen K, Chia KS, Chen JG et al. Cancer survival in Africa, Asia, and Central America: a population-based study. *Lancet Oncol* 2010; 11(2):165-173.

2. Sankaranarayanan R, Swaminathan R. Cancer survival in Africa, Asia, the Caribbean and Central America. IARC Scientific Publications No. 162. Lyon: International Agency for Research on Cancer, 2011.

3. US National Cancer Institute. Surveillance Epidemiology and End Results (US SEER). Available from: http://seer.cancer.gov.

4. Sant M, Allemani C, Santaquilani M, Knijn A, Marchesi F, Capocaccia R. EUROCARE-4. Survival of cancer patients diagnosed in 1995-1999. Results and commentary. *Eur J Cancer* 2009; 45(6):931-991.

5. National cancer control programmes: policies and managerial guidelines. 2nd ed. Geneva: World Health Organization, 2002.

6. Sankaranarayanan R, Wesley RS. A practical manual on visual screening for cervical neoplasia. IARC Technical Publication No. 41. Lyon: International Agency for Research on Cancer, 2003.

7. Screening Group. International Agency for Research on Cancer. Available from: http://screening.iarc.fr/.

8. Denny L, Kuhn L, Hu CC, Tsai WY, Wright TC, Jr. Human papillomavirus-based cervical cancer prevention: long-term results of a randomized screening trial. *J Natl Cancer Inst* 2010; 102(20):1557-1567.

9. Blumenthal PD, Gaffikin L, Deganus S, Lewis R, Emerson M, Adadevoh S. Cervical cancer prevention: safety, acceptability, and feasibility of a single-visit approach in Accra, Ghana. *Am J Obstet Gynecol* 2007; 196(4):407-408.

10. Gaffikin L, Blumenthal PD, Emerson M, Limpaphayom K. Safety, acceptability, and feasibility of a single-visit approach to cervical-cancer prevention in rural Thailand: a demonstration project. *Lancet* 2003; 361(9360):814-820.

11. Nessa A, Hussain MA, Rahman JN, Rashid MH, Muwonge R, Sankaranarayanan R. Screening for cervical neoplasia in Bangladesh using visual inspection with acetic acid. *Int J Gynaecol Obstet* 2010; 111(2):115-118.

12. Sankaranarayanan R, Esmy PO, Rajkumar R, Muwonge R, Swaminathan R, Shanthakumari S et al. Effect of visual screening on cervical cancer incidence and mortality in Tamil Nadu, India: a cluster-randomised trial. *Lancet* 2007; 370(9585):398-406.

13. Sankaranarayanan R, Chatterji R, Shastri SS, Wesley RS, Basu P, Mahe C et al. Accuracy of human papillomavirus testing in primary screening of cervical neoplasia: results from a multicenter study in India. *Int J Cancer* 2004; 112(2):341-347.

14. Sankaranarayanan R, Nene BM, Shastri SS, Jayant K, Muwonge R, Budukh AM et al. HPV screening for cervical cancer in rural India. *N Engl J Med* 2009; 360(14):1385-1394.

15. Katki HA, Kinney WK, Fetterman B, Lorey T, Poitras NE, Cheung L et al. Cervical cancer risk for women undergoing concurrent testing for human papillomavirus and cervical cytology: a population-based study in routine clinical practice. *Lancet Oncol* 2011; 12(7):663-672.

16. Ponten J, Adami HO, Bergstrom R, Dillner J, Friberg LG, Gustafsson L et al. Strategies for global control of cervical cancer. *Int J Cancer* 1995; 60(1):1-26.

17. Gustafsson L, Ponten J, Bergstrom R, Adami HO. International incidence rates of invasive cervical cancer before cytological screening. *Int J Cancer* 1997; 71(2):159-165.

18. Reintgen D, Berman C, Cox C, Baekey P, Nicosia S, Greenberg H et al. The anatomy of missed breast cancers. *Surg Oncol* 1993; 2(1):65-75.

19. Mahoney L, Csima A. Efficiency of palpation in clinical detection of breast cancer. *Can Med Assoc J* 1982; 127(8):729-730.

20. Stockton D, Davies T, Day N, McCann J. Retrospective study of reasons for improved survival in patients with breast cancer in east Anglia: earlier diagnosis or better treatment. *BMJ* 1997; 314(7079):472-475.

21. Jatoi I, Anderson WF, Rao SR, Devesa SS. Breast cancer trends among black and white women in the United States. *J Clin Oncol* 2005; 23(31):7836-7841.

22. Khuhaprema T, Attasara P, Srivatanakul P, Sangrajrang S, Muwonge R, Sauvaget C et al. Organization and evolution of organized cervical cytology screening in Thailand. *Int J Gynaecol Obstet* 2012; 118(2):107-111.

23. Sanghvi H, Limpaphayom KK, Plotkin M, Charurat E, Kleine A, Lu E et al. Cervical cancer screening using visual inspection with acetic acid: operational experiences from Ghana and Thailand. *Reprod Health Matters* 2008; 16(32):67-77.

24. Chumworathayi B, Thinkhamrop J, Blumenthal PD, Thinkhamrop B, Pientong C, Ekalaksanan T. Cryotherapy for HPV clearance in women with biopsy-confirmed cervical low-grade squamous intraepithelial lesions. *Int J Gynaecol Obstet* 2010; 108(2):119-122.

25. Editorial. Women's health in rural China. *Lancet* 2009; 374(9687):358.

26. Selvam J. Personal Communication. 2012.