
LIFE PROJECT

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The Section of Early Detection and Prevention (EDP) conducts research on the efficacy, safety, and cost–effectiveness of cancer prevention and early detection interventions to guide rational cancer control policies, with a particular emphasis on low- and middle-income countries (LMICs). One of the principles that guide the work is the search for simplified, affordable technology adaptable to the available resources of LMICs. EDP provides technical support to current and planned population-based prevention and screening programmes in LMICs in the context of cancer control, conducts clinical and screening trials, and conducts implementation and health economics research. In addition, the Section develops educational materials and conducts training activities for cancer control.

One of the main topics has been the evaluation of alternative administration schedules of human papillomavirus (HPV) vaccines, including the reduction in the number of doses for more affordable and logistically feasible programmes. The gastric cancer research programme includes two large randomized clinical trials to evaluate the impact of *Helicobacter pylori* eradication and other interventions on the incidence of and mortality from gastric cancer. In secondary prevention, EDP projects include several large research and

implementation studies on early detection and screening of major cancer types, including cancers of the cervix, stomach, breast, colorectum, and oral cavity.

In general, the studies are multicentre and multidisciplinary, and EDP has established extensive networks involving highly capable clinicians, epidemiologists, and other staff. The networks facilitate the transfer of research technology to local researchers and often their students, who actively participate in the design and conduct of studies and the analysis of data. Finally, an important part of the work of EDP is the dissemination of the available scientific evidence base and the provision of technical assistance to governments and policy-makers in countries that are developing cancer control programmes.

Prevention and Implementation Group (PRI)

Cervical cancer vaccination and screening

The Prevention and Implementation Group (PRI) demonstrated the durable immunogenicity and protection of one-dose HPV vaccination in previous studies (Kreimer et al., 2018a; Safaeian et al., 2018). Given the public health potential, in collaboration with the United States National Cancer Institute, PRI is conducting a large randomized trial (the ESCUDDO study) of the non-inferiority of one versus two doses of the bivalent and nonavalent vaccines in 20 000 adolescent girls aged 12–16 years in Costa Rica (Sampson et al., 2018). In addition, 4000 women aged 17–20 years are being recruited as controls to estimate the efficacy of the vaccination schedules. Recruitment is currently at 16 000 women and will be completed in early 2020, with a 4-year follow-up.

Figure 1. Prevalence of cervical precancerous lesions and cancer in women aged 30–64 years in the ESTAMPA study of human papillomavirus (HPV) screening and triage. CIN, cervical intraepithelial neoplasia. © IARC.

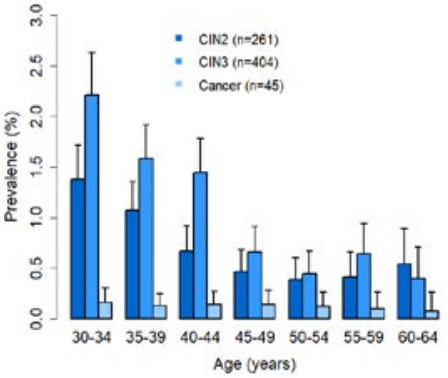

Table 1. Performance of the HPV 16/18 E6 oncoprotein for the detection of high-grade squamous intraepithelial lesion (HSIL) precancer (< HSIL) and/or cancer (≥ HSIL). Reproduced from Ferrera et al. (2019), with permission by John Wiley and Sons.

Cases	Disease status (n)		Sensitivity (%) (95% CI)[a]	Specificity (%) (95% CI)[a]
	< HSIL	≥ HSIL		
All cases included				
E6 16/18−	155	24	56.4 (43.3–68.6)	97.5 (93.7–99.0)
E6 16/18+	4	31		
Associated with HPV 16/18[b]				
E6 16/18−	155	1	96.8 (83.8–99.8)	97.5 (93.7–99.0)
E6 16/18+	4	30		
Associated only with HPV 16[b]				
E6 16−	157	0	100.0 (85.1–100.0)	98.7 (95.5–99.7)
E6 16+	2	22		
Associated only with HPV 18[b]				
E6 18−	157	1	87.5 (52.9–99.4)	98.7 (95.5–99.7)
E6 18+	2	7		

CI, confidence interval; HPV, human papillomavirus; HSIL, high-grade squamous intraepithelial lesion.

[a] Confidence intervals for binomial probabilities. As part of assessing the performance of the E6 protein, we also estimated the sensitivity for cancer detection: 61.3% (95% CI: 43.8–76.3%) for all cases included and 100% (95% CI: 51–100%) for the other groups.

[b] Cases with ≥ HSIL not associated with HPV 16/18, HPV 16, or HPV 18 excluded. Genotyping based on GP5/GP6.

The ESTAMPA study, which is under way in 12 centres, is currently investigating emerging cervical cancer screening and triage techniques in Latin America in 50 000 women aged 30–64 years (recruitment is currently at about 36 000 women). HPV-positive women receive a colposcopy, biopsy, and treatment as needed, and a second screening after 18 months. The main outcome is advanced cancer precursors. The global prevalence of high-risk HPV infection is currently 14.2% (95% confidence interval: 13.8–14.6%), decreasing from 21% in those aged 30–34 years to 11% in those older than 60 years, with a similar age pattern for the prevalence of cervical cancer precursors (Figure 1). An evaluation of the performance of the E6 oncoprotein for the detection of cervical lesions demonstrated high sensitivity and specificity (Ferrera et al., 2019) (Table 1).

The study also enables the investigation of risk factors for HPV infection and precursors at the participating sites (Kasamatsu et al., 2019).

The CESTA study is investigating cervical cancer screening algorithms and treatment modalities in Africa, with an emphasis on HIV-positive women (Figure 2).

PRI continues to provide support to cervical cancer screening programmes in Belarus, Mongolia, Myanmar, Romania, and several countries in Latin America (Arrossi et al., 2019). In addition, PRI actively participates in the Cervical Cancer Elimination Initiative recently launched by the World Health Organization (WHO), and coordinates the Working Group on research within that initiative.

Figure 2. Site visit for the CESTA study, Dakar, Senegal, August 2019. © IARC.

Epidemiology and prevention of *H. pylori* infection and gastric cancer

In collaboration with the National Cancer Center of the Republic of Korea, PRI is conducting a randomized controlled trial of *H. pylori* eradication for gastric cancer prevention (the HELPER study), recruiting 11 000 subjects aged 40–65 years to attend endoscopic screening (completion in 2019). *H. pylori*-positive subjects are randomized to quadruple eradication therapy or placebo. All participants are followed up with endoscopic screening every 2 years within the country's National Cancer Screening Program for 10 years.

Another large randomized clinical trial (GISTAR), in collaboration with the University of Latvia, aims to determine whether combined *H. pylori* and pepsinogen screening, followed by *H. pylori* eradication in positive subjects and endoscopic follow-up of those with serologic atrophic gastritis, compared with routine care, reduces gastric cancer mortality. Recruitment for GISTAR continues in Latvia, where 8000 participants are included to date; the aim is to expand the study to eastern European countries, where the burden of gastric cancer remains high (Figure 3).

Figure 3. International Gastric Cancer Prevention Research Forum, introduction to the GISTAR study, Riga, Latvia, February 2018. © IARC.

PRI continues to investigate the prevalence of *H. pylori* and gastric lesions in low- and high-risk areas for gastric cancer around the world (the ENIGMA study), in an attempt to explain regional differences and generate etiological hypotheses (Figure 4).

Gambia Hepatitis Intervention Study

The Gambia Hepatitis Intervention Study (GHIS) was started in 1986. During 1986–1990, the vaccination of babies against hepatitis B virus was implemented in The Gambia with a "stepped-wedge" trial design. At the time, palm prints and footprints were collected from every baby in the study. In 2011, the third phase of the study started, aiming to evaluate the long-term efficacy of childhood hepatitis B virus vaccination in the prevention of liver cancer in adulthood.

Dr Ramou Njie, a hepatologist, was appointed as the head of the GHIS Group, based in The Gambia, to set up a liver disease clinic to ensure the identification of cases of liver cancer and to strengthen the national cancer registry, led by Mr Lamin Bojang. Cancer registrars based at the main hospitals around the country were also appointed to support the identification of cases of liver cancer as well as the registration of all cancer cases presenting at the hospitals.

About 100 cases of liver cancer have been identified in subjects born in 1984–1992, and three of them have been correctly matched to children's files with the help of Interpol in Lyon, where the linkage of palm prints and footprints of children and adult cases is carried out. This third phase of the GHIS will end in December 2019, but efforts in matching – both by improved data linkage through different methods and by matching prints – will continue. Potential collaborations are under considerations, including with engineering schools with expertise in the use of artificial intelligence to characterize images, in order to improve the rate of print matching.

Figure 4. ENIGMA study coordination meeting in the Islamic Republic of Iran, June 2019: (left) endoscopy clinic of ENIGMA study, Ardabil; and (right) collaborators of the ENIGMA study. © IARC.

Application of economics to cancer

Descriptive studies on the economics of cancer provide important insights into the economic burden (costs) of cancer, both for individuals and their households and for society as a whole. In collaboration with the Section of Cancer Surveillance (CSU) and other partners, PRI seeks to document the financial and economic costs of cancer, including studies on global productivity losses as a result of premature mortality from cancer (Pearce et al., 2018), a systematic review of the level of (catastrophic) out-of-pocket expenditures, and an invited chapter on the role of health systems in addressing inequalities in access to cancer control that was included in an IARC Scientific Publication.

Priority setting in cancer prevention and control seeks to achieve health system goals of health maximization, equity, and efficiency by providing guidance to countries on cancer control interventions that are cost-effective, affordable, and feasible to implement. Collaborating with WHO, PRI is developing: (i) an interactive platform to model the impact and costs associated with priority cancer control interventions; and (ii) an investment case for cancer prevention and control, to assist national policy-makers in obtaining the best value for money by identifying priority interventions.

Screening Group (SCR)

Cervical cancer vaccination and screening

In a multicentre cohort study involving 17 064 females vaccinated at age 10–18 years with one, two, or three doses of quadrivalent HPV vaccine, the Screening Group (SCR) demonstrated that two doses were adequate to protect girls aged 15–18 years (the current recommendation is three doses) against persistent HPV 16/18 infection (Basu et al., 2019b). The L1-binding antibody titres at 7 months against vaccine-targeted HPV types (HPV 16/18/6/11) in 15–18-year-old two-dose recipients were non-inferior compared with those in 15–18-year-old three-dose recipients or 10–14-year-old two-dose recipients (Bhatla et al., 2018a). Persistent infection was significantly lower in vaccinated participants, irrespective of age at vaccination and number of doses. A single dose of quadrivalent vaccine was as protective as two or three doses against persistent HPV 16/18 infections (Sankaranarayanan et al., 2018). The study outcomes were shared with the WHO Strategic Advisory Group of Experts.

In a publication that had a high impact on public health, SCR described the rising cervical cancer incidence and mortality in young Japanese women over the past 25 years (Subramanian and Sauvaget, 2018; Utada et al., 2019) as a result of altered risk factors (sexual behaviour, smoking, and HPV prevalence) as well as limited screening coverage (only 34% in 2016). Another SCR study in Japan demonstrated that detection rates of high-grade precancer and cancer were significantly lower in HPV-vaccinated women (2.6 per 1000) compared with unvaccinated women (7.1 per 1000) at screening at age 25–29 years (Konno et al., 2018).

The collaborative project between SCR and the National Cancer Institute of Thailand showed that HPV messenger RNA (mRNA) and HPV DNA tests had similar performance characteristics (Sangrajrang et al., 2019). The sensitivity, specificity, and positive predictive value of the mRNA test to detect high-grade lesions were 73.1%, 97.8%, and 16.3%, respectively; for the DNA test, the values were 67.4%, 97.1%, and 12.1%, respectively. Triaging of HPV-positive women with cytology alone or HPV 16/18 genotyping and cytology in combination yielded comparable test accuracies. The study outcomes facilitated the drafting of the screening and triaging

protocol for HPV-based cervical screening in Thailand.

SCR supported the development and evaluation of a new battery-powered portable thermal ablator to treat cervical precancers (Figure 5). The success rate of treating cervical precancers with the new device in a screen-and-treat setting in Zambia was similar to that of standard cryotherapy (64.1% vs 60.0%) (Table 2). This new device avoids many of the practical disadvantages of cryotherapy, is preferred by health-care providers, and produces minimal complications or discomfort. A recent meta-analysis by SCR also demonstrated the high efficacy of thermal ablation in the treatment of high-grade cervical precancers (success, 93.8%) (Randall et al., 2019a). The SCR studies informed the recent drafting of thermal ablation guidelines by WHO.

Figure 5. The new battery-powered portable thermal ablator was developed with funding support from the National Institutes of Health, USA. SCR collaborator Professor Groesbeck Parham demonstrating the device. Courtesy of Dr Nothema Simelela.

Evaluation of national cancer screening programmes

SCR evaluated the cancer screening programme in Morocco through a project supported by the Ministry of Health and the Lalla Salma Foundation for the Prevention and Treatment of Cancers (Basu et al., 2018a; Selmouni et al., 2019). Breast and cervical cancer screening initiated in 2010 by the Ministry of Health in Morocco was high-volume opportunistic. Nurses at the primary care facilities offered clinical breast examination to women aged 40–69 years and cervical visual inspection with acetic acid to women aged 30–49 years. Screening coverage was moderate for breast cancer (63%) and low for cervical cancer (24%) in 2016. Detection rates of breast cancer (1 per 1000) and of cervical precancer and cancer (0.9 per 1000) were lower than expected.

Another SCR study demonstrated the large variability in colorectal cancer screening within the European Union (Senore et al., 2019); participation rates varied from 4.5% to 71.3%, and compliance with referral for colonoscopy assessment ranged from 64% to 92%. The detection rates of advanced adenomas and colorectal cancer were higher for the faecal immunochemical test programmes than for the guaiac faecal occult blood test programmes.

Table 2. Cervical precancer treatment success ratesa at 6 months follow-up in a randomized controlled trial, in Zambia, comparing battery-powered thermal ablator, cryotherapy, and large loop excision of the transformation zone. Reprinted from *The Lancet Oncology*, Pinder et al., Thermal ablation versus cryotherapy or loop excision to treat women positive for cervical precancer on visual inspection with acetic acid test: pilot phase of a randomised controlled trial, Copyright 2019, with permission from Elsevier.

Participants	Number (%)				*P* value
	Cryotherapy (*n* = 250)	Thermal ablation (*n* = 250)	LLETZ (*n* = 250)	Total (*n* = 750)	
Eligible for 6-month follow-up	246 (98.4)	244 (97.6)	245 (98.0)	735 (98.0)	NA
Followed up at 6 months	206 (83.7)	197 (80.7)	204 (83.3)	607 (82.6)	NA
Overall					
Participants followed up[b]	200 (100.0)	192 (100.0)	199 (100.0)	591 (100.0)	NA
Participants with no evidence of disease[a]	120 (60.0)	123 (64.1)	134 (67.3)	377 (63.8)	0.311
HIV-negative at baseline					
Participants followed up	85 (100.0)	93 (100.0)	93 (100.0)	271 (100.0)	NA
Participants with no evidence of disease[a]	68 (80.0)	77 (82.8)	76 (81.7)	221 (81.5)	0.890
HIV-positive at baseline					
Participants followed up	109 (100.0)	95 (100.0)	101 (100.0)	305 (100.0)	NA
Participants with no evidence of disease[a]	50 (45.9)	42 (44.2)	55 (54.5)	147 (48.2)	0.297

HPV, human papillomavirus; LLETZ, large loop excision of the transformation zone; NA, not applicable; VIA, visual inspection with acetic acid.

[a] Treatment success was defined as either HPV type-specific clearance at 6 months among women positive for the same HPV type at baseline, or negative VIA test at follow-up if the baseline HPV test was negative.

[b] HPV reports were missing for 6, 5, and 5 women who received cryotherapy, thermal ablation, and LLETZ treatment, respectively; these patients were excluded from the analysis of treatment success rates.

Screening for noncommunicable diseases

An SCR study conducted in rural India demonstrated that community health workers could be trained to provide comprehensive noncommunicable disease detection services at home (Basu et al., 2019a) (Figure 6). High blood pressure and blood sugar were detected in 32.6% and 7.5% of participants, respectively (1988 men and 4997 women aged 30–60 years); hypertension and diabetes were confirmed in 42.3% and 35.0%, respectively, among those undergoing follow-up. Nearly 90.0% of women agreed to provide self-collected samples for HPV testing for cervical cancer screening, and 76.5% of the HPV-positive women attended a primary health centre for further evaluation and treatment.

Training of screening programme managers and service providers

SCR conducted training of programme managers and different levels of service providers in different countries (Bangladesh, Benin, China, Côte d'Ivoire, India, Senegal, and Zambia) (Figure 7).

Figure 6. Early detection of common noncommunicable diseases, including breast, cervical, and oral cancers, at home by community health workers in rural India. Community health workers performing check-ups of women at home. © IARC.

Figure 7. Snapshots from training programmes conducted by SCR: (left) in Cotonou, Benin, and (right) in Udaipur, India. © IARC.

Cancer Screening in Five Continents

The Cancer Screening in Five Continents (CanScreen5) project of SCR aims to uniformly collect, analyse, store, and disseminate information on the characteristics and performance of cancer screening programmes in different countries, with the core objective of motivating and supporting countries to collect and use cancer screening data in a consistent manner on a regular basis using an effective information system. A web-based open access platform (http://canscreen5.iarc.fr) was launched to facilitate access to and interpretation of data from the screening programmes, and to enable the individual programmes to compare their performance over time and with that of other similar programmes. The new initiative will impress upon the programme managers the value of monitoring and quality improvement of cancer screening programmes, and will also support capacity-building in the field.

CanScreen5 has led to two new projects: (i) a collaboration with the Centre for Global Health Inequalities Research (CHAIN) in Norway (supported by the Research Council of Norway) to evaluate how health inequalities affect cancer screening programmes in Latin America and identify evidence-based interventions to tackle such inequalities; and (ii) capacity-building of programme managers (supported by the National Institutes of Health, USA), focusing on improving data collection for better quality assurance of cancer screening programmes, to be attended by participants from 20 African countries.

CanScreen5 website. © IARC.