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Self-sampling for cervical cancer screening: Empowering women to lead a paradigm change in cancer control

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In this new era of precision medicine and patient-centred care, the advent of self-sampling in cervical cancer screening is among the most disruptive innovations in cancer control and prevention. However, it has taken a long time to mature as an idea. The concept of self-sampling with swabs or brushes as a reliable substitute for provider-collected cervical specimens has been the focus of at least 25 years of research. Although obtaining an adequate cytology specimen for cervical cancer screening served as the initial rationale[1], it was the pragmatic goal of obtaining repeated samples for studying the natural history of genital human papillomavirus infection that drove much of this research[2,3]. The original aim of making the experience of participating in cervical cancer screening less daunting to women failed to be realized initially because the trade-off between convenience to the woman and quality of the cervical sample was far from ideal.

Given that it is an intuitively simple and attractive idea, why did it take so long for self-sampling to mature as a technological innovation? During most of the last 70 years, cervical cancer screening has been based on the Papanicolaou (Pap) cytology technique, which relies on the microscopic identification by a cytotechnician or cytopathologist of cellular abnormalities in optimally stained cervical samples smeared on glass slides. These samples must be representative of the ecto- and endocervix to be deemed adequate. For this to happen, a properly trained health care provider, i.e., a physician or nurse, must use a speculum to visualize the cervical os and transformation zone and collect cellular samples from the inner and outer perimeter of the latter using devices such as a wooden spatula, cytobrush, or broom-like device. The transformation zone perimeter is the origin of most neoplastic cervical lesions. Samples that do not properly reflect the cellular composition of the ecto- and endocervix are thus likely to yield false-negative cytology results in women with precancerous or cancerous lesions. Exceptionally, a cytotechnician reading such a Pap smear with meticulous attention to detail may fortuitously find an isolated cluster of dysplastic or malignant cells. However, an exhaustive smear scanning takes time. In the high-volume routine of most cytopathology laboratories, not more than a few minutes are spent per slide, which makes sample quality paramount in cervical cancer screening via cytology. The advent of liquid-based cytology improved the efficiency and ease of smear processing and reading but did not eliminate the need for a speculum-assisted and properly collected cervical sample by a health care provider. It is thus of no surprise that under the stringent quality control of specimen adequacy for cytology screening self-sampling never became much of a promise.

The advent of molecular testing for nucleic acid of oncogenic genotypes of human papillomavirus (HPV) made self-sampling an attractive idea for cervical cancer screening again. Clinically validated HPV tests are considerably more sensitive than cytology—whether conventional or liquid-based—to detect cervical precancer and cancer[4]. This comes at the expense of a small loss in specificity relative to cytology. Many positive HPV test results in women undergoing routine screening do not represent underlying cervical lesions and thus they must be triaged before these women can be referred to diagnostic workup via colposcopy. Except for this minor complication of a triage step, which is the subject of much research[5], HPV testing represents an unequivocal progress and cost-effective improvement in cervical cancer screening. It detects existing precancerous lesions more effectively than cytology, thereby decreasing the number of missed lesions on repeated rounds of screening. Relative to cytology, HPV testing permits lengthening of screening intervals because of the much greater reassurance of safety to women. Should a woman's HPV test turn out negative, her short- and long-term risks of cervical lesions are very low relative to the implied safety conferred by a negative Pap test collected at the same time[6]. Testing for HPV DNA or RNA uses chemically-defined, standardized, reproducible, and automatable assays that are much more tolerant to variations of specimen adequacy than cytology, a technique that requires subjective reading of smears prepared under rigorous quality control. With these superior attributes relative to the 70-year-old status quo of cytology, it is little wonder that there is now public health evidence from randomized controlled trials that HPV screening leads to a reduction in the incidence[7] of and mortality[8] from cervical cancer.

Why does self-sampling work well with molecular HPV testing? The aforementioned issues of specimen adequacy in cytology are not fatal flaws with HPV testing. Cellular sourcing and integrity are not critical when the target

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of the assay is a specific DNA or RNA sequence. There is no need to preserve morphological features that need to be interpreted by a well-trained microscopist. Cytology requires overwhelming representation of cervical cells in a smear for it to perform optimally. A vaginal sample lacks this critical attribute. Exfoliated cells from cervical lesions become eventually deposited along the vaginal surface. In a self-collected vaginal sample, exfoliated cervical cells will be only a fraction of the cellularity that is represented in a Pap smear. However, the exquisite sensitivity of HPV assays permits detecting cervical lesions despite this dilution effect. To be sure, there is a minor loss of sensitivity and specificity relative to a provider-collected sample, but the trade-off is well worth it. As another advantage, there is a broader range of collection devices that work well for HPV testing than there is for cytology. For instance, cotton-tipped swabs are not recommended for cytology because cells tend to stick to the fibres and do not transfer well to glass slides[9]. On the other hand, they are well suited to HPV testing, which targets subcellular, molecular components of a sample.

Now that Canada and much of the Western world ponder the considerable paradigm change represented by the switch to HPV testing in cervical cancer screening, we can finally devote resources and energy to making sure all women are reached by screening, not only those who are captive to opportunistic or organized programs that require attendance at a clinic or hospital. This worthwhile public health goal makes self-sampling a powerful idea whose time has most definitely arrived after a quarter-century wait. It is no longer a simple promise hindered by the lack of a technological improvement in screening methodology. Self-sampling has the potential to permit screening coverage to reach the most vulnerable segments of the population, i.e., women who live in remote areas, lack access to health promotion, distrust the health care system, or feel alienated because they perceive sociocultural or religious insensitivity by those delivering health care. Self-sampling eliminates the social discomfort or frank emotional distress that comes from a pelvic examination by a male provider. It represents a new advance in cancer control that is unequivocally empowering to women.

It is a tenet of the science of cervical cancer screening that nearly half of all cases of invasive cervical cancer occur among women who were never screened and a little more than half if we consider also those with insufficient screening attendance[10]. Self-sampling can change this state of affairs by enabling screening programs to reach marginalized women and ultimately increase attendance. There is increasing evidence to that effect[11-15]. It stands to reason to assume that women who do not benefit from screening are also less likely to be reached by HPV vaccination programs[16], which augments the disparity in health promotion that self-sampling can help reduce or eliminate. Moreover, self-sampling allows scarce resources to be focused on the deployment of the screening program infrastructure and follow-up of screen-positive women, rather than on the complexity of the network of providers and clinics that serve as the point of entry for specimen collection[17]. Sample collection kits can be distributed at a variety of places and events in the community that tend to attract women of screening age. Self-collected samples can be brought or mailed to a clinic or to a screening program testing site. Self-sampling enables ongoing large-scale monitoring of the prevalence of HPV infection[18], an essential component of epidemiologic surveillance of the impact of HPV vaccination in the population.

The guest editors of this special issue of *Current Oncology*, Drs. Mandana Vahabi and Aisha Lofters, assembled important contributions on the value of self-sampling in screening that cover a variety of perspectives, from individual to societal, and extend the range of possible uses of self-sampling to anal cancer screening. Although there is excitement about the prospect of realizing many dividends in cancer control consequent to large-scale adoption of self-sampling, there is a critical obstacle to its implementation as official public health policy. As explained above, self-sampling requires a paradigm change in the anchor technology for cervical cancer screening. It must be paired with molecular HPV testing for it to serve its intended purpose; cytology does not work with a self-collected specimen. The groundswell of support for self-sampling, demonstrated in this issue of *Current Oncology* and in previous authoritative reviews[13,17,19], may actually be the proverbial straw that broke the camel's back of resistance to this paradigm change. Such resistance has been strong. Those who fear the entry of HPV testing as primary screening technology replacing Pap cytology have provoked vigorous debate, particularly in Canada[20-23].

"There is nothing more powerful than an idea whose time has come" is a quote often misattributed to Victor Hugo but likely a simple paraphrased variant of "there is something more powerful than the brute force of bayonets: it is the idea whose time has come and hour struck"[24]. The analogy to self-sampling could not be more appropriate; an idea that is now mature and more powerful than the strong opposition to HPV testing. Such is the force of self-sampling as one of the most auspicious changes to cancer control in decades. Who would have guessed that empowering women to be the key actors in preventing cervical cancer spoke louder than the tiresome scientific debate about which technology had to be used for screening?

CONFLICT OF INTEREST DISCLOSURES

I have no conflicts of interest on the topic and contents of this editorial but throughout my career I have served as occasional consultant or advisory board member to companies involved with HPV diagnostics (Qiagen, Roche, Gen-Probe, BD, Abbott), HPV vaccination (GSK, Merck), and cervical cancer screening or control (3M, Ikonisys, Cytyc). My institution has received unconditional grants from Merck and Roche to supplement publicly funded investigator-initiated studies in my unit. My entire research program has been funded by the Canadian Institutes of Health Research (CIHR), US National Institutes of Health, National Cancer Institute of Canada, Cancer Research Society, Canadian Cancer Society Research Institute, Fonds de Recherche Quebec-Santé (FRQS); salary awards: CIHR Distinguished Scientist, FRQS Chercheur National, James McGill Chair, Minda de Gunzburg Endowed Chair.

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