Cervical cancer screening for young women

First do no harm

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> In clinical practice, caregivers dealing with individual patients must make binary decisions—"do it" or "don't do it" … however, for many preventive interventions, the scientific evidence does not lend itself to such simple two-dimensional alternatives.[1]

How can the same evidence dictate that a 21-year-old Canadian woman living east of Alberta should have a Papanicolaou test while her twin sister in Alberta or British Columbia (BC) need not until the age of 25? This demonstrates the inconsistent and conflicting guidelines for cervical cancer screening within Canada. The most reliable evidence shows that screening before the age of 25 is likely to cause more harm than benefit.[2] Here we review that evidence, as well as provincial and international guidelines, and discuss how family physicians can best provide screening that is based on evidence rather than expert opinion.

History

Canadian guidelines have evolved substantially over the past decade. From the earlier approach of annual screening from onset of sexual activity or age 18 (sometimes regardless of previous sexual activity), they now align more closely with long-standing evidence. In 2009, Alberta's guidelines adjusted the age for a first cervical screen upward to age 21, with subsequent testing at intervals of 3 years.[3] Thereafter, other provinces adopted this protocol with repeat testing to be done every 2 or 3 years.

It is unfortunate that in Canada, many competing groups (at the provincial, territorial, and national levels) attempt to guide the evidence-based practice of health care professionals. Membership of guideline committees is seldom public. Guideline committees vary in composition, their skills in interpreting evidence are unclear, and recommendations are seldom based on formal systematic reviews. Despite the best of intentions, their recommendations often reflect differences in member knowledge, experience, values, and anxieties more than they reflect the evidence. They seldom prioritize patient expectations and preferences. The net result is competing guidelines.

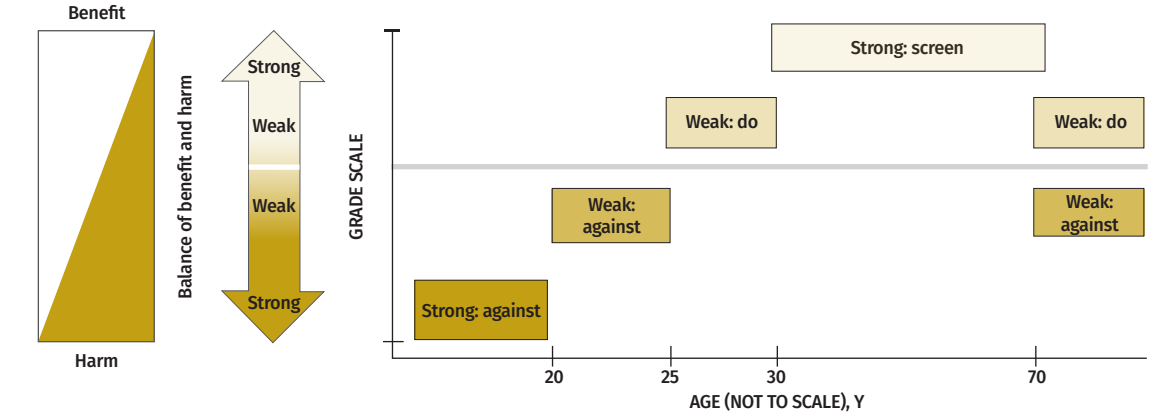
The Canadian Task Force on Preventive Health Care (CTFPHC) follows "best practice" guidelines in developing its guidelines. In 2013 the CTFPHC recommended strongly against screening among those younger than age 20 and in favour of routine screening for those older than 30.[2] For those aged between 20 and 24, it gave a weak recommendation against screening (now called a *conditional recommendation*). This changed to a weak recommendation in favour of screening for those aged between 25 and 29. **Figure 1** shows how the evidence of a continuous change in balance of risk is converted to stepwise recommendations through the GRADE (Grading of Recommendations Assessment, Development and Evaluation) process.[4] The intent of these weak or conditional recommendations is to encourage each woman to make an individual decision based on a discussion with her health care provider about the harms and benefits of screening.

Following the CTFPHC report, BC and Alberta amended their guidelines to recommend initiating screening at age 25.[3,5] Nova Scotia followed suit beginning April 1, 2019.[6] All other provinces and territories still endorse commencing at age 21, but some are considering age 25 (**Table 1**).[3,5-25] Some provinces have delayed revising guidelines on the grounds that they are waiting for the decisions to fund human papillomavirus (HPV) tests as the primary screening test, or for the cohort of women who are immunized against HPV to reach the age of 25. We do not address evidence for HPV testing or the possibility of self-testing in this commentary, as neither should affect the age for onset of screening. Some argue that because the HPV test is more sensitive, it is "safer" to use this as the first test after age 25 to detect any developing HPV infections at that time. It might be, but HPV tests are also less specific, especially among young women, and therefore more women would be referred for colposcopy—a harm that we discuss below.

Evidence

Even before cervical screening began, cervical cancer was almost unheard of among women younger than age 20, and very rare among those younger than 25. Despite the intensive screening endured by these young women since widespread use of Pap testing, their rates of cervical cancer were unaffected.[26] Some argue that there is no trial evidence showing that delaying the first screen is safe,[27] but the disease is so rare at these ages that no trial could ever be done. Only observational evidence is possible. In Australia, like Canada, regular screening of a large proportion of women younger than age 25 for many years has led to no discernible reduction in the incidence of cervical cancer or in mortality for these young women.[28] This might be partially explained by findings of a UK case-control study on the extent to which screening

Figure 1. How the evidence of a continuous change in balance of risk is converted to stepwise recommendations through the GRADE process



GRADE—Grading of Recommendations Assessment, Development and Evaluation.

reduced the risk of invasive cancer across age cohorts.[29] It showed that screening has little effect on outcomes of the few cancers that occur among young women, but has much more effect as age increases.

Such evidence reflects the factors that affect the chance of developing cervical cancer. Recall that cervical intraepithelial neoplasia is largely caused by the sexually transmitted HPV. More than 80% of women are infected, often soon after initiating sexual activity. Most infections are asymptomatic and are cleared by the immune system, but a few oncogenic HPV types might persist and eventually lead to invasive cancer. It usually takes more than 10 years from first infection to development of cancer.[30] Cervical screening is so effective because of this lag time in which precancers can be detected. However, because early testing picks up many transient infections that will be defeated by immune responses, there is little value in testing until several years after commencement of sexual activity, which could mean well beyond age 30. On the other hand, women whose first sexual activity occurred when they were very young might choose to be screened before age 25. This highlights the need for a patient-centred, individualized approach with a discussion of sexual history to help young women make the best decision.

Potential benefits

Some argue that doing Pap tests in young women ensures frequent screening for sexually transmitted infections (STIs), as testing can be done for both at the same examination.[31] This is not a good approach: is it not better to explain the need for STI testing than to tie this to an unneeded test that might do harm? Family physicians might need to learn new habits to check for STI risk on other occasions. Most sexually active young women attend regularly for contraception, providing an opportunity for discussing or performing STI testing.

The World Health Organization and the Canadian Partnership Against Cancer are part of a campaign to "eliminate" cervical cancer.[32] This requires the combination of HPV immunization and screening. The greatest achievable reduction with cytology is more than 90%.[33] Adding HPV testing adds value, especially for older women, but some cancer will still occur. For women who are screened regularly, most cancers will be early stage and still treatable. That stated, while some screening is good, a whole lot more is not necessarily better, and often will cause more harm.

Potential harms

What are the harms of unnecessary screening? Most obviously, women often find the examination intrusive. Beyond that, the high rate of abnormalities, especially in younger women, precipitates more testing, and sometimes colposcopy referral. Subsequently, there is anxiety while waiting for further testing and results. This can have an enduring negative psychological effect on women.[34] If biopsies are taken, there is short-term bleeding and discharge; if a LEEP (loop electrosurgical excision procedure) biopsy is performed, the function of the cervix might be impaired. Aggressive management of cervical intraepithelial neoplasia, including LEEP, doubles the rate of preterm birth from 5.4% to 10.7%.[35] This harm arising from testing is more common in young women, and more important to those who intend to have children in future. Finally, insurance companies sometimes refuse, delay, or charge higher premiums for policies after abnormal test results.

Adding to the debate, nonessential, invasive investigations could be viewed in an ominous light. Despite

Table 1. Cervical screening guidelines across Canada

	CERVICAL CANCER SCREENING GUIDELINES				
PROVINCE OR TERRITORY	START AGE	INTERVAL	EXCLUDES THOSE NOT SEXUALLY ACTIVE	MENTIONS RISKS AND HARMS IN PATIENT RESOURCES	MENTIONS RISKS AND HARMS IN PROFESSIONAL GUIDELINES
British Columbia[5,7]	25	3 y	Yes	Yes	Yes
Alberta[3,8]	25	3 y	Yes, 3 y after first contact	Yes	Yes
Saskatchewan[9]	21	3 y; after 3 biannual normal test results	Yes, 3 y after first contact	No	No
Manitoba[10,11]	21	3 y	Yes	Yes	Yes
Ontario[12,13]	21	3 y	Yes	No	No
Quebec[14,15]	21	2-3 y	Yes	Yes	No
New Brunswick[16,17]	21	2-3 y; after 3 annual normal test results	Yes, 3 y after first contact	No	No
Prince Edward Island[18,19]	21	2 y	Yes	No	No
Nova Scotia[6,20]	25	3 y	Yes, 3 y after first contact	No	No
Newfoundland and Labrador[21,22]	21	3 y; after 3 annual normal test results	Not mentioned	No	No
Nunavut[23]	21	3 y	Yes	No information found	No
Northwest Territories[24]	21	2 y; after 3 annual normal test results	No	No	No information found
Yukon[24]	21	2 y; after 3 annual normal test results	No	No information found	No information found

Data from Canadian Partnership Against Cancer.[25]

well-meaning physicians intending to do good, unnecessary Pap tests and internal pelvic examinations are inappropriate.[36] They violate the physician-patient relationship of trust and our responsibility to uphold the ethical principles of beneficence and nonmaleficence. Such examinations could rightly lead to formal complaints. Thus the "patient context" discussion recommended by the CTFPHC is an essential precursor to informed consent for screening, especially on the first occasion.

Additional considerations

The LGBTQ+ (lesbian, gay, bisexual, transgender, queer or questioning, and other gender identities) population adds a further twist: data on the probability of developing cancer and its time to development are particularly limited for these groups. Behaviour such as penetrating the vagina digitally or with sex toys might introduce HPV infection. Guidelines that make pronouncements for these populations necessarily do so based on general principles, case reports, or experience rather than systematic evidence. Discussions with LGBTQ+ patients should reflect that uncertainty and what their practices are, and offer choices of whether and when to screen. For those who have undergone gender-change procedures, we must also consider whether they still have a cervix.

Patient expectations often come into play; many of our patients have learned to expect their regular Pap test. Women and their physicians need to consider the balance between benefits of appropriate screening and harms of overscreening. Women who are used to annual screens deserve accurate information about sufficient and optimal timing of screening. While some are concerned that reducing the number of tests is an attempt to save health care costs, we must emphasize that that is irrelevant: the focus here is on harms and benefits for individual women rather than for funders.

Finally, some argue that women might misreport their age for starting sexual activity, and therefore screening of all women should start at a younger age. We reject this argument as judgmental and prefer to believe our patients. We also believe that it is the provider's responsibility to create a "safe space" for patients to disclose sensitive information, without judgment. Some patients might choose not to accurately reveal their activity, for their own reasons. However, that is no reason to inappropriately test everyone.

International perspective

Although the United States has historically recommended intensive screening, most other developed countries do not. Among 19 other high-income countries, only the United States, New Zealand, Japan, Switzerland, Austria, and Germany start at age 21, while 13 start later. For example, the Netherlands screens from age 30 with repeat testing every 5 years to age 60 (a total of 7 screens in a lifetime), while the United Kingdom screens from age 25.[37] Such countries have reductions in and actual rates of cervical cancer as good as or better than those that screen more regularly,[38] largely because they obtain high participation rates for sufficient but not excessive tests.

Solution for family medicine

The evidence is strong that cervical screening should start some time when a woman is in her 20s: when, on balance, benefits outweigh harms for a particular individual. We have heard upsetting stories, however, of young women being refused contraception until they have been screened for cervical cancer. A specific age for onset of screening in a guideline is just that, a guideline, to be personalized for each woman and her circumstances. Nothing suddenly changes on the 25th birthday. We should focus clinical efforts and government policies on screening women considering individual risk more than age, and identifying women who are not accessing care. Audits of screening rates should exclude younger women where screening is discretionary and focus on women older than 30, when such screening is demonstrably valuable.

Materials available from the screening programs in many provinces or territories to help us inform our patients tend to be directive rather than informative (**Table 1**).[3,5-25] While some mention both benefits and harms, numbers are described only in Alberta.[3] Other provinces describe limitations to testing but in vague terms. Knowing actual probabilities helps to reassure women who overestimate the danger of this disease, and therefore request excessive testing. Even patient information from Alberta and BC states simply that screening should start at age 25, rather than giving any sense of the change in probabilities with time since sexual debut, and thus is inadequate to assist with answering detailed questions. The CTFPHC website has more nuanced information that includes probabilities.[39]

The CanMEDS principles value advocacy.[40] As family physicians and as teachers, we must resolve to practise, teach, and convey the evidence, even if it contradicts provincial guidelines or incentives.

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Competing interests

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