Gynecologic Oncology xxx (2017) xxx–xxx

Contents lists available at ScienceDirect

Gynecologic Oncology

journal homepage: www.elsevier.com/locate/ygyno

Why does cervical cancer occur in a state-of-the-art screening program?

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HIGHLIGHTS

- Triennial cotesting detects and treats approximately 95% of all CIN3/AIS.
- The efficacy and efficiency of screening decrease with age.
- Many cervical cancers appeared to be prevalent at the time of the first cotest.
- There were a variety of causes for the non-prevalent cervical cancers.

ARTICLE INFO

Article history:
Received 22 April 2017
Received in revised form 22 May 2017
Accepted 1 June 2017
Available online xxxx

Keywords:
Human papillomavirus (HPV)
Cytology
Cervical cancer
CIN3
Precancer
Cotesting

ABSTRACT

Background. The goal of cervical screening is to detect and treat precancers before some become cancer. We wanted to understand why, despite state-of-the-art methods, cervical cancers occured in relationship to programmatic performance at Kaiser Permanente Northern California (KPNC), where >1,000,000 women aged ≥30 years have undergone cervical cancer screening by triennial HPV and cytology cotesting since 2003.

Methods. We reviewed clinical histories preceding cervical cancer diagnoses to assign "causes" of cancer. We calculated surrogate measures of programmatic effectiveness (precancers/(precancers and cancers)) and diagnostic yield (precancers and cancers per 1000 cotests), overall and by age at cotest (30–39, 40–49, and ≥50 years).

Results. Cancer was rare and found mainly in a localized (treatable) stage. Of 623 cervical cancers with at least one preceding or concurrent cotest, 360 (57.8%) were judged to be prevalent (diagnosed at a localized stage within one year or regional/distant stage within two years of the first cotest). Non-compliance with recommended screening and management preceded 9.0% of all cancers. False-negative cotests/sampling errors (HPV and cytology negative), false-negative histologic diagnoses, and treatment failures preceded 11.2%, 9.0%, and 4.3%, respectively, of all cancers. There was significant heterogeneity in the causes of cancer by histologic category ($p < 0.001$ for all; $p = 0.002$ excluding prevalent cases). Programmatic effectiveness (95.3%) and diagnostic yield were greater for squamous cell versus adenocarcinoma histology ($p < 0.0001$) and both decreased with older ages ($p_{trend} < 0.0001$).

Conclusions. A state-of-the-art intensive screening program results in very few cervical cancers, most of which are detected early by screening. Screening may become less efficient at older ages.

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1. Introduction

U.S. cervical cancer screening guidelines have changed over the last dozen years with the introduction of clinical testing for high-risk human papillomavirus (HPV) types, those that cause virtually all cervical cancers and their immediate precursor lesions [1], into routine practice. HPV testing has superior sensitivity compared with cytology (cytology tests) for screening and secondary prevention of cervical cancer via detection and treatment of precursor lesions [2,3]. In January 2003, just prior to U.S. FDA approval of cotesting in mid-2003 [4] and interim guidelines [5] in 2004, Kaiser Permanente Northern California (KPNC), a large integrated health care organization, introduced 3-year cotesting in women aged 30 years and older. KPNC has now screened over 1 million women by cotesting; to our knowledge, this is the most extensive experience of clinical HPV testing in the world.

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http://dx.doi.org/10.1016/j.ygyno.2017.06.003
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Please cite this article as: P.E. Castle, et al., Why does cervical cancer occur in a state-of-the-art screening program?, Gynecol Oncol (2017), http://dx.doi.org/10.1016/j.ygyno.2017.06.003

Internationally, the optimal cervical screening interval and choice of testing method remain controversial [6–10]. Most concerns have centered on the specificity of HPV testing, and the proper management of HPV-positive women. Accumulated evidence regarding cervical screening tests and program strategies is currently under re-review by the U.S. Preventive Services Task Force [11]. To optimize guidelines development and dissemination, we have undertaken a set of analyses using data from the KPNC program to examine the programmatic performance of 3-year cotesting. Here, we examine the reasons why some cervical cancers may still occur despite a concerted, high-quality program and describe the overall performance of the program to detect precancer prior to becoming invasive cancer.

2. Methods

2.1. Population

The cohort study within KPNC has been described previously [12]. From January 1, 2003 to December 31, 2015, a cohort of 1,208,710 women aged ≥30 years underwent cotesting (concurrent HPV and cytology screening). For each woman, we considered the first available cotest in this study period as "enrollment". Cervical histopathology outcomes were collected for women through December 31, 2015. The KPNC institutional review board (IRB) approved use of the data, and National Institutes of Health Office of Human Subjects Research and Albert Einstein College of Medicine IRBs deemed this study exempt from review.

2.2. Screening and clinical management

Women were screened by HPV and cytology/cervical cytology testing as previously described [13]. Women were followed according to internal Kaiser guidelines, which were broadly concordant with national standards at the time [5,14–16]. Women who cotested HPV negative and cytology negative (Negative for Intraepithelial Lesion or Malignancy) (HPV −/cytology −), were offered screening again in 3 years. Women with cytologic abnormalities were referred to colposcopy per national recommendations [14,16,17]. The KPNC management of women with HPV-positive/cytology-negative (HPV +/cytology −) or HPV-negative/cytology-equivocal (HPV −/ASC-US) results evolved over time as previously described [12]. Observation with repeated colposcopy was elected for some younger women with cervical intraepithelial neoplasia grade 2 (CIN2), as nationally recommended [17,18].

2.3. Statistical analyses

We reviewed the case histories (computerized KPNC clinic and laboratory records) of the cancers included in this analysis to understand why cancer may have occurred. We assumed that any cancer diagnosed within a year of the first cotest, any regional or distant cancers diagnosed within two years of a first cotest, or any cancer diagnosed following a cytology result of cancer was already prevalent cancer at the time of or shortly after the first cotest. The natural history of HPV infection and cervical cancer is relatively slow, typically taking decades [19], which is why screening and treatment of precursor lesions has been successful in preventing cervical cancer. One model of the natural history of HPV infection and cervical cancer estimated that the median transition time from CIN2/3 to cervical cancer is 23.6 years and only 1.6% of CIN2/3 transition to cervical cancer in <10 years [20]. Invasive cervical cancer is extremely rare within 10 years of the population median age of sexual initiation [21], when exposure to HPV first occurs. Thus, it seems highly likely that most of the cancers classified by the above criteria would be either prevalent cancers or CIN3 on the verge of invasive and virtually none resulting from an incident HPV infection or even incident CIN3.

We used contingency tables with Fisher's exact test for category variables to compare the last cotesting results prior to diagnosis, taking into account histology category, cancer stage, and prevalent versus incident cases. Kruskal-Wallis test was used to compare median values for age at diagnosis and time from last cotest to diagnosis between prevalent and incident cases. Logistic regression was used to calculate odds ratio (OR) with 95% confidence interval (95% CI) as a measure of association.

For incident cancers, we classified the programmatic correlates of cervical cancer diagnosis based on review of the clinical history. These categories were: A) *false-negative cotests/sampling errors* (HPV −/cytology −) were defined as those that preceded a cancer diagnosis by one to four years; a negative cotest within one year of diagnosis was ignored (under the assumption that the cancer was already present) and the previous cotesting history was considered; B) *algorithm delays* were defined as women with localized cancers diagnosed 1–2 years following a first cotest result of HPV +/cytology − or HPV −/ASC-US without an intervening cotest (because 1-year follow-up and retesting was routinely recommended rather than immediate referral to colposcopy); C) *false-negative diagnoses* were those colposcopic evaluations one to five years prior to the cancer diagnosis that did not yield ≥CIN2 histopathology either due to the failure of colposcopy to biopsy the ≥CIN2 lesion or failure of pathology to diagnose it; D) *treatment failures* were those women treated for ≥CIN2 one to five years prior to the cancer diagnosis. Although treatments that occurred >5 years prior to cancer diagnosis could also be categorized as treatment failures, we judged that >5 years was sufficient time to find, detect, and treat any residual precancerous lesion after the initial treatment; E) *non-compliance* indicated that women did not undergo follow-up (colposcopy or one-year retesting) or rescreening (3-year interval) within the time window of recommended time to the next visit plus a one-year grace period.

To put the occurrence of cancer into context of the cervical cancer screening program, we defined and calculated a surrogate measure of programmatic effectiveness, precancers/(precancers and cancers), assuming that detection cervical intraepithelial neoplasia grade 3 (CIN3) and adenocarcinoma in situ (AIS) (CIN3/AIS) was a screening success and cancers while were essentially failures to detect and treat CIN3/AIS prior to the development of invasive cervical cancer. For this analysis, we reasonably assumed (approximated) that all CIN3/AIS was successfully treated, given the efficacy of excisional treatments to treat CIN3/AIS [22]. We also calculated diagnostic yield, precancers per 1000 cotests or precancers and cancers per 1000 cotests, as surrogate measure of programmatic efficiency. These measures were calculated overall and stratified by age (30–39, 40–49, and 50 years and older). A trend with age was tested for statistical significance using a non-parametric test of trend [23]. We considered a higher percentage to represent greater effectiveness, while recognizing that many but not all precancers would invade if untreated [24]. At present, despite the inherent over-diagnosis, CIN3 or AIS represent our best current surrogate endpoint of cancer risk and screening target. Nor can we predict which CIN3 or AIS, if left untreated, will eventually become invasive. Although the typical treatment threshold is cervical intraepithelial neoplasia (CIN) grade 2 (CIN2), this threshold further emphasizes safety at the expense of over-treatment. Results were presented for all disease and separately for squamous disease (CIN3/SCC) and glandular disease (AIS/adenocarcinoma [ADC]). Cancers deemed prevalent were included or excluded in the cancer total in different "sensitivity" analyses.

3. Results

Using the medical records, 907 cervical cancers were identified. We excluded 55 cases (6.1%) diagnosed in women younger than 30 years because cotesting was not routinely performed in this age group, and 229 cases (25.2%) because they did not have a cotesting result prior to diagnosis, and thereby could not inform the questions that we were addressing. As result of these exclusions, there were 623 cervical cancers

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