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Pap tests in the diagnosis of cervical cancer: Help or hinder?

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HIGHLIGHTS

- Pap smears are performed frequently in the 0–2 years prior to cancer diagnosis when cervical cancer is likely present.
- An increased rate of false negative cytology is associated with advanced cancer stage at diagnosis.
- False negative pap cytology can result in a significant delay in time to diagnosis of invasive cervical cancer.

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ABSTRACT

Objective. To evaluate the impact of pap tests on the time to diagnosis of cervical cancer.

Methods. In this population-based retrospective cohort study, Ontario women ≥21 years diagnosed with cervical cancer between 2011 and 2014 were identified and database data collected. The presence or absence of a pap test 0–2 years preceding cancer diagnosis was identified. Descriptive and modelling analyses were performed to determine the effect of pap results on cancer diagnosis.

Results. 2002 patients were identified, 75% received a pap test. 1250 patients had known cytology - 13% normal, 8% low-grade and 7.5% suspicious for cancer. Across all FIGO stages at diagnosis, 5–10% of cytology was low grade, 3–11.5% was positive for carcinoma and 4–41% was normal, which increased with advancing stage. For all cytology and FIGO stages (except stage 1A), OBGYNs had a significantly shorter time to diagnosis compared to family physicians. Factors increasing the odds of low-grade cytology were advanced stage (OR 4.5 (2.4–8.0), $p < 0.01$) and adenocarcinoma (OR 1.5 (1.1–2.1), $p < 0.01$). Low grade cytology resulted in the longest delay to diagnosis ($p < 0.001$).

Conclusion. Pap tests are performed frequently in the 0–2 years prior to the diagnosis of cervical cancer which can result in false negative cytology and diagnostic delay in patients with advanced cancers.

1. Introduction

Cervical cancer incidence and mortality have decreased in Canada [1] however worldwide, the incidence is still high [2]. The reduction of disease burden in Canada can be largely attributed to a combination of effective screening with cervical cytology [3] and vaccination against the human papilloma virus (HPV) [4]. The Papanicolau (pap) test of cervical cytology is a highly effective screening test which, in a study of the Canadian population, helped reduce the incidence and mortality of cervical cancer by 58% and 83% respectively between 1972 and 2006 [5]. The efficacy of this screening method is due to the pre-clinical phase of cervical cancer estimated to be as long as to 7–10 years, in which pre-malignant changes are detectable prior to the development of invasive disease [6].

Once a cancer has become invasive, patients may present with abnormal vaginal bleeding, post-coital spotting and vaginal discharge although in a recent study of 128 women with cervical cancer only 19% reported symptoms at or prior to diagnosis [7]. However, whether patients are symptomatic or not, a tumor will be visible on speculum exam for all International Federation of Gynecology and Obstetrics (FIGO) stages ≥1B. For patients with visible lesions, a directed biopsy should be performed.

Despite its success as a screening test, the pap test is not effective for cancer diagnosis as important information regarding lesion size and depth of invasion cannot be determined from cytology. Furthermore, cytologic changes due to carcinoma can be difficult to interpret, leading to false negative results [8] and potentially harmful diagnostic delays [9]. In a study by Castle et al. [10], prevalent cervical cancer was defined as locally invasive cancer diagnosed within 1 year, or advanced cancer

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diagnosed with in 2 years of last cervical cancer screen which was assumed to be present on the cervix at the time of the last screen. Thus, the purpose of this study is to evaluate the impact of performing a pap test within 0–2 years prior to the confirmation of invasive cervical cancer on the subsequent time to diagnosis in patients with prevalent cervical cancer.

2. Methods

In this population-based retrospective cohort study, Ontario women ≥21 years diagnosed with cervical cancer between 2011 and 2014 were identified using international classification of diseases (ICD) diagnosis codes on the Ontario Cancer Registry (OCR) database. Exclusion criteria included age <21 at diagnosis, Ontario health insurance plan (OHIP) registration for <1 year at diagnosis, missing identifying data or a diagnosis other than invasive cervical cancer. Histologic subtype (adenocarcinoma vs. squamous cell carcinoma) and FIGO stage were recorded. Additional cohort data was retrieved from multiple administrative databases containing health utilization data linked through a unique OHIP number. The Registered Persons Database was used to capture demographics including age, patient enrollment model (PEM - whether the patient is under the care of a family physician), and postal code which was used to identify neighborhood income quintile. Cytobase was used to record cytology results according to the Bethesda classification: normal, atypical glandular cells/adenocarcinoma-in-situ (ACG/AIS), low-grade squamous intra-epithelial lesion/atypical squamous cells of undetermined significance (LSIL/ASCUS), high-grade squamous intra-epithelial lesion/atypical squamous cells - cannot exclude HSIL (HSIL/ASC-H), squamous cell carcinoma, adenocarcinoma, unknown or other. The OHIP database was used to identify procedures including colposcopy and biopsy using physician billing information. Finally, the Corporate Provider Database was used to identify healthcare provider characteristics including gender, specialty (Family Practice, Obstetrician / Gynecologist (OB/GYN), nurse practitioner, other, unknown) and location (rural, urban or unknown). Given the retrospective database design, information regarding patient symptoms and examination findings at the time of presentation were not available. Patients who received a directed biopsy the time of presentation were assumed to be either symptomatic or to have a visible lesion at the time of examination. Patients who received a pap test were assumed to be asymptomatic however they may have had either symptoms or a visible tumor at the time of presentation.

The main study variable was the presence of an index pap test 0–2 years prior to the diagnosis of invasive cervical cancer. If ≥2 pap tests were performed within this time, the most recent result was used. If a patient had a colposcopic procedure ≤7 days prior to her pap test, a previous pap result was sought, as the more recent pap was assumed to be in conjunction with her diagnostic colposcopy. If the previous pap test was within 0–2 years of her diagnosis, this result was used.

Descriptive and modelling analyses were performed to determine the effect of pap tests on the subsequent diagnosis of cervical cancer. Patients were stratified by the presence of an index pap – pap with known results, pap with unknown results or directed cervical biopsy. Descriptive statistics were used to compare baseline patient and healthcare provider characteristics. Cytology results were compared across FIGO stage at diagnosis. The median time between index pap and diagnosis was compared across cytology results and stratified by provider specialty. The median time between index pap and diagnosis was compared across FIGO stage and stratified by provider specialty and cytology. The Wilcoxon rank-sum test was used to determine statistical significance.

Multivariate logistic regression analysis was performed to determine the likelihood of having normal or low-grade cytology on pap prior to cancer diagnosis based on variables including age, FIGO stage, and histologic subtype. A hazard ratio model was used to compare the average time to diagnosis of invasive cancer from index pap test date based on age, pap cytology, FIGO stage, and histologic subtype. SAS software version 9.4 was used to perform the all statistical analysis and statistical significance was set at $p < 0.05$. Cancer Care Ontario is a prescribed entity and is thus authorized to collect personal health information without patient consent and to use such personal health information for analysis with respect to the management, evaluation, or monitoring of the allocation of resources for all or part of the health system. As this study complies with privacy regulations ethics review was not required.

3. Results

2002 patients with invasive cervical cancer were included, 30% who were subsequently diagnosed with adenocarcinoma and 70% with squamous cell carcinoma. 1250 received a pap with known cytology, 260 received a pap with unknown cytology, and 492 received a directed cervical biopsy without an intervening pap. Demographic data is summarized in Table 1. Women that received a directed biopsy tended to be older - 28% of biopsy patients were >70 years old vs. only 5.8% of pap patients with known cytology. The majority of patients who received a pap with known cytology were under the age of 50 (61.5%). Of the 1250 patients with known results, 13% had normal cytology, 8% had low-grade cytology (LSIL/ASCUS) and only 7.5% of patients had results suspicious for cancer within 0–2 years of their cancer diagnosis. Most patients (53%) had high-grade results (HSIL/ASC-H). Given that approximately 75.5% of the pap-test cohort was considered to be at an elevated risk of malignancy based on their pap cytology, 75% of the pap cohort was subsequently sent for colposcopy vs. only 25% of the directed biopsy cohort with an overall rate of 60%. On multi-variate analysis, patients were significantly more likely to be sent to colposcopy if they were seen by a family physician (OR 2.7, $p < 0.01$). No patients had HPV co-testing performed as this was not part of the screening algorithm in the province of Ontario at this time. Patients may have individually paid for HPV co-testing however this was not captured by the provincial database. 30.1% of patients >70 also had an endometrial biopsy.

When looking at the FIGO stage at diagnosis in patients who had a pap with known cytology, 41.1% of patients had stage 1A disease whereas 58.9% had ≥stage 1B disease. Patients who received a directed biopsy were more likely to have advanced disease at presentation (FIGO stage ≥2) with only 27% having stage 1 disease (13.9% stage 1A, 13% stage 1B). Overall, 27.6% of patients FIGO stage 1A disease and 72.4% had >stage IB disease.

When looking at pap test providers, 56% were family physicians, 30% were OB/GYNs, 2% were nurses and the remainder unspecified. When looking at patients who had known cytology after their pap, 64.6% were cared for by a family physician vs. only 28.6% by an OBGYN. Most providers practiced in an urban setting (90%) while only 6% identified as practicing rurally. 75% of the cohort was PEM enrolled.

Pap cytology was compared across FIGO stage at diagnosis with results shown in Table 2. Across all stages, 5–10% of pap results were low grade (LSIL/ASCUS) and 4–41% were normal, with an increasing rate of normal results seen with more advanced stages of cancer (41.5% of pap tests were normal in stage IV disease). Furthermore, the rate of HSIL/ASC-H decreased with increasing cancer stage from 64.2% in stage 1A vs. only 28.3% in stage IV. Cervical cancer cells were only noted in 3–11.5% of results.

The time to cancer diagnosis was determined based on provider specialty and stratified by pap cytology and FIGO stage at diagnosis. Results are summarized in Table 3a, b and c. The median time to diagnosis decreased for both family physicians and OB/GYNs with increasing cytological abnormalities. Normal cytology delayed diagnosis for both provider specialties, however the maximum median time to diagnosis was significantly shorter for OB/GYNs (6 months) vs. family physicians (9 months) ($p = 0.018$). For all cytology results, OB/GYNs had a significantly shorter time to cancer diagnosis. OB/GYNs also had a