Conisation as a marker of persistent human papilloma virus infection and risk of breast cancer

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Background: Human papillomavirus (HPV) infection may increase breast cancer (BC) risk.

Methods: To examine this, we used nationwide medical registries to identify all Danish women who underwent conisation to remove HPV-associated cervical precancerous lesions (n = 87,782) from 1978 to 2013. We computed the absolute risk of BC and standardised incidence ratios (SIRs) and 95% confidence intervals (95% CIs) for breast cancer, based on national breast cancer incidence rates.

Results: Conisation was associated with slightly increased BC incidence (SIR = 1.1, 95% CI = 1.0–1.1), and an absolute BC risk of 7.7% (95% CI = 7.3–8.1%) in 35.9 years of follow-up. BC risk was elevated throughout follow-up, especially in the first 5 years (<1 year: SIR = 1.2, 95% CI = 0.92–1.5; 1–5 years: SIR = 1.2, 95% CI = 1.1–1.3; ≥5 years: SIR = 1.1, 95% CI = 1.0–1.1). Women who underwent conisation and had autoimmune disease had elevated BC risk after 5 years of follow-up (SIR = 1.4, 95% CI = 1.0–1.8).

Conclusions: BC risk is slightly elevated in women with persistent HPV infection, possibly due to detection bias.

Conisation is a surgery that removes abnormal cervical lesions—cervical intraepithelial neoplasia. Human papilloma virus (HPV) infection is associated with almost all cervical cancers; conisation is therefore a definitive marker of HPV infection (Gosvig et al., 2015). HPV DNA (oncogenic subtypes 16 and 18) can transform normal breast cells into a growth factor-independent phenotype (Dimri et al., 2005). HPV DNA and koilocytes—hallmarks of HPV infection—have been identified in breast tumours (Lawson et al., 2009, 2016). HPV may therefore contribute to breast carcinogenesis, although the underlying biology is poorly understood (Ohba et al., 2014; Vieira et al., 2014). Most HPV cervical infections resolve untreated (Jaisamrarn et al., 2013), but persistent infection warranting treatment intervention may signify impaired immune function (Bosch and Munoz, 2002).

Three meta-analyses have investigated the association between HPV infection and breast cancer (BC), including 9, 10, and 16 case–control studies, respectively (Li et al., 2011; Simoes et al., 2012; Zhou et al., 2015). The summary effect estimates suggested three- to six-fold increased BC incidence among women with HPV infection. Each called for large studies on HPV and BC incidence.

The existing research has limited follow-up, small sample size, and no information on comorbid diseases, which may compromise immune function (de Visser et al., 2006). A large Norwegian study suggested a 10% increased risk of in situ and localised but not metastatic breast tumours among women with precancerous cervical lesions (Hansen et al., 2012).

Given the high incidence of BC in developed countries, any association between HPV and BC risk requires confirmation. We therefore conducted a large nationwide population-based study using prospectively collected data from Danish registries to investigate the association between cervical conisation as a marker of chronic HPV infection and risk of BC.

MATERIALS AND METHODS

The Danish National Health Service guarantees tax-supported health care for all residents. Health service utilisation is recorded in nationwide registries using each resident’s unique personal

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Our large population-based cohort study suggests slightly elevated BC risk associated with a history of cervical conisation. Among women diagnosed with local stage breast tumours, risk remained elevated regardless of follow-up time. Our findings may therefore be partly attributable to more intense disease surveillance, that is, women who undergo conisation are more likely to avail themselves of other cancer screening procedures, such as mammography (Hansen et al, 2012; Corkum et al, 2013). In addition, BC risk increased with longer follow-up, particularly among women with a history of autoimmune disease.

The increased BC risk among women with a history of autoimmune disease is intriguing, and counters the perception that autoimmune disease correlates with decreased BC incidence (Hemminki et al, 2012). However, our finding may reflect reports of an increased risk of cervical dysplasia/cancer among individuals with autoimmune disease (Kim et al, 2015). The mechanisms underlying this association are unclear but could involve increased healthcare contact among patients with autoimmune conditions. The observed association also may reflect use of immunosuppressive drugs or steroids—indicated for autoimmune disease—which may facilitate HPV immunoevasion. However, our previous research suggests no association between glucocorticoid use and BC risk (Sorensen et al, 2005, 2012). Our findings provide important rationale to promote uptake of the HPV vaccine among women with autoimmunities (Kim et al, 2015).

The increased BC risk among those younger at conisation may be due to heightened screening. However, it may also reflect findings by Lawson et al (2016), where BC patients with a history of cervical cancer were on average 10 years younger at BC diagnosis than those without cervical cancer.
Strengths of our study include its population-based design in a country with unfettered access to healthcare and complete follow-up. Data were prospectively collected for administrative purposes, which may modify BC risk (Dimri et al., 2005). However, the oncogenic HPV subtypes (16, 18, 33, and 35) are those most likely to lead to persistent infection, for which conisation is indicated in Denmark. We lacked information on parity. Multi-parity correlates with increased cervical cancer risk (Jensen et al., 2013), but with decreased BC risk (depending on age at first birth) (Rosner et al., 1994). Thus adjusting for parity may attenuate our findings.

BC imposes a substantial burden on health and health services. Contrary to the three- to six-fold increased risk of BC associated with HPV infection observed in meta-analyses (Li et al., 2011; Simoes et al., 2012; Zhou et al., 2015), our findings suggest a long-term slight increase in BC risk among women with a history of chronic HPV infection. Priorities for future research involve evaluating the association of HPV subtypes with BC risk and investigating the incidence of BC among individuals vaccinated for HPV.

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CONFLICT OF INTEREST

The authors declare no conflicts of interest.

Table 2. Standardised incidence ratios of breast cancer among women who underwent conisation in Denmark between 1978 through 2013 according to follow-up time

|                        | Overall | <1 year | 1–5 years | >5 years |
|------------------------|---------|---------|-----------|----------|
|                        | n       | SIR     | n         | SIR      | n         | SIR     |
| Age at conisation (years) |         |         |           |          |           |         |
| 0–29                   | 401     | 1.0 (0.94, 1.2) | 4         | 2.5 (0.68, 6.4) | 18     | 1.4 (0.84, 2.2) | 379     | 1.0 (0.92, 1.1) |
| 30–49                  | 1870    | 1.1 (1.0, 1.1) | 45        | 1.3 (0.92, 1.7) | 208    | 1.2 (1.0, 1.3) | 1617    | 1.0 (0.99, 1.1) |
| 50–69                  | 405     | 1.2 (1.0, 1.3) | 21        | 1.0 (0.63, 1.6) | 99     | 1.3 (1.0, 1.5) | 285     | 1.1 (1.0, 1.3) |
| 70+                    | 18      | 0.89 (0.53, 1.4) | 1        | 0.45 (0.01, 2.5) | 9      | 1.2 (0.57, 2.4) | 8       | 0.74 (0.32, 1.5) |
| Year of conisation      |         |         |           |          |           |         |
| 1978–1982              | 819     | 1.1 (1.0, 1.2) | 7         | 1.0 (0.42, 2.1) | 38     | 1.1 (0.78, 1.5) | 774     | 1.1 (1.0, 1.2) |
| 1983–1987              | 571     | 1.0 (0.94, 1.1) | 12        | 1.2 (0.52, 2.4) | 37     | 1.0 (0.76, 1.5) | 526     | 1.0 (0.93, 1.1) |
| 1988–1992              | 491     | 1.0 (0.92, 1.1) | 10        | 1.1 (0.54, 2.1) | 47     | 1.1 (0.81, 1.5) | 434     | 1.0 (0.90, 1.1) |
| 1993–1997              | 379     | 1.1 (0.96, 1.2) | 8         | 0.86 (0.37, 1.7) | 50     | 1.1 (0.80, 1.4) | 321     | 1.1 (0.95, 1.2) |
| 1998–2002              | 248     | 1.1 (0.94, 1.2) | 14        | 1.4 (0.79, 2.4) | 60     | 1.3 (0.95, 1.6) | 174     | 1.0 (0.86, 1.2) |
| 2003–2007              | 136     | 1.3 (1.1, 1.5) | 10        | 1.2 (0.59, 2.3) | 67     | 1.5 (1.2, 2.0) | 59      | 1.1 (0.85, 1.5) |
| 2008–2013              | 50      | 1.2 (0.92, 1.6) | 14        | 1.3 (0.68, 2.1) | 35     | 1.3 (0.87, 1.7) | 1       | 0.78 (0.04, 2.3) |
| Charlson Comorbidity Index |     |         |           |          |           |         |
| Low (CCI = 0–1)        | 2560    | 1.1 (1.0, 1.1) | 61        | 1.2 (0.88, 1.5) | 304    | 1.2 (1.1, 1.4) | 2195    | 1.1 (1.0, 1.1) |
| Medium (CCI = 1–2)     | 126     | 1.1 (0.91, 1.3) | 10        | 1.5 (0.72, 2.8) | 28     | 1.1 (0.74, 1.6) | 88      | 1.1 (0.85, 1.3) |
| High (CCI > 3)         | 8       | 0.93 (0.40, 1.8) | 0        | 2.0 (0.70, 1.5) | 2       | 1.0 (0.51, 1.8) | 6       | 1.2 (0.46, 2.7) |
| Autoimmune disease     |         |         |           |          |           |         |
| No                     | 2629    | 1.1 (1.0, 1.1) | 65        | 1.1 (0.87, 1.4) | 323    | 1.2 (1.1, 1.4) | 2241    | 1.0 (1.0, 1.1) |
| Yes                    | 65      | 1.3 (1.0, 1.7) | 6         | 2.2 (0.80, 4.7) | 11     | 1.0 (0.51, 1.8) | 48      | 1.4 (1.0, 1.8) |
| Obesity diagnosis      |         |         |           |          |           |         |
| No                     | 2674    | 1.1 (1.0, 1.1) | 70        | 1.2 (0.92, 1.5) | 329    | 1.2 (1.1, 1.3) | 2275    | 1.1 (1.0, 1.1) |
| Yes                    | 20      | 0.88 (0.54, 1.4) | 1        | 0.51 (0.01, 2.9) | 5      | 1.9 (0.93, 3.6) | 14      | 1.1 (0.65, 1.7) |
| Alcohol-related disease |         |         |           |          |           |         |
| No                     | 2667    | 1.1 (1.0, 1.1) | 70        | 1.2 (0.92, 1.5) | 324    | 1.2 (1.1, 1.3) | 2270    | 1.1 (1.0, 1.1) |
| Yes                    | 30      | 1.3 (0.84, 1.8) | 1        | 0.76 (0.02, 4.2) | 10     | 1.9 (0.93, 3.6) | 19      | 1.1 (0.65, 1.7) |
| Oestrogen receptor positive |   |         |           |          |           |         |
| No                     | 377     | 1.2 (1.1, 1.3) | 27        | 1.4 (0.90, 2.0) | 121    | 1.4 (1.2, 1.7) | 229     | 1.1 (0.99, 1.3) |
| Yes                    | 75      | 0.94 (0.74, 1.2) | 3        | 0.49 (0.10, 1.4) | 29     | 1.1 (0.76, 1.6) | 43      | 0.84 (0.64, 1.2) |
| Localised breast cancer |         |         |           |          |           |         |
| No                     | 1414    | 1.1 (1.1, 1.2) | 35        | 1.2 (0.84, 1.7) | 170    | 1.3 (1.1, 1.5) | 1209    | 1.1 (1.1, 1.2) |
| Non-localised breast cancer | 1144  | 1.0 (0.94, 1.1) | 32        | 1.1 (0.78, 1.6) | 155    | 1.2 (1.0, 1.4) | 957     | 0.97 (0.91, 1.0) |

Abbreviations: CCI = Charlson Comorbidity Index, SIR = standardised incidence ratio.
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