Gynecologic Oncology 142 (2016) 128–132

Contents lists available at ScienceDirect

Gynecologic Oncology

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

Risk of head-and-neck cancer following a diagnosis of severe cervical intraepithelial neoplasia: a nationwide population-based cohort study in Denmark

M.F. Svahn [a], C. Munk [a], S.M. Jensen [b], C. von Buchwald [c], K. Frederiksen [b], S.K. Kjaer [a,d,*]

[a] Unit of Virus, Lifestyle and Genes, Danish Cancer Society Research Centre, Copenhagen, Denmark
[b] Unit of Statistics, Bioinformatics and Registry, Danish Cancer Society Research Center, Copenhagen, Denmark
[c] Department of ORL, H&N surgery and audiology, Rigshospitalet, Copenhagen University Hospital, Denmark
[d] Department of Gynecology, Rigshospitalet, Copenhagen University Hospital, Denmark

HIGHLIGHTS

- Research on the risks of women with a history of CIN3/AIS for head-and-neck cancer is limited.
- There is a strong association between a history of CIN3/AIS and risk of various head-and-neck cancers.
- The increased relative risk appears to persist >20 years after CIN3/AIS diagnosis.

ARTICLE INFO

Article history:
Received 2 December 2015
Received in revised form 17 April 2016
Accepted 18 April 2016
Available online 23 April 2016

Keywords:
Human papillomavirus
Cervical intraepithelial neoplasia
Follow-up
Head-and-neck-cancer

ABSTRACT

Objective. Women with a history of cervical intraepithelial neoplasia grade 3 including adenocarcinoma in situ (CIN3/AIS) may be more prone to develop cancers of the ano-genital region and head-and-neck cancers. The current literature is, however, limited.

Methods. We established a nationwide cohort of approximately 2,500,000 Danish women born in 1918–1990. By linking the cohort to population-based health registries, we obtained information on CIN3/AIS, cancer, migration, death, education, and smoking. Cox proportional hazards models were used to estimate hazard ratios (HRs) and confidence intervals (CIs) for the association between CIN3/AIS and risk of head-and-neck squamous cell carcinoma (HNSCC). HRs were presented for any HNSCC and for four subgroups categorized by their anticipated degree of association with human papillomavirus (HPV).

Results. A history of CIN3/AIS was significantly associated with an increased overall relative risk of HNSCC after adjustment for year of birth, attained age, and length of education. The risk was especially high for sites anticipated to be strongly associated with HPV (e.g. base of tongue, tonsils) (HR, 2.49; 95% CI, 1.84–3.36). Lower risks were found for sites anticipated to be not or weakly associated with HPV (e.g. nasal cavity, middle ear, sinuses) (HR, 1.29; 95% CI, 0.61–2.76).

Conclusion. Women with a history of CIN3/AIS have a significantly higher risk of HNSCC than women without such a history. The increased relative risk persisted for at least 20 years after the CIN3/AIS diagnosis. Women with CIN3/AIS may be more susceptible to the consequences of HPV and/or may have higher risk behavior, such as smoking.

1. Introduction

Genital infection with human papillomavirus (HPV) is very common in both women [1] and men [2,3]. Most HPV infections are transient, but some become persistent. Persistent cervical infection with a high-risk HPV type can cause high-grade cervical intraepithelial neoplasia (CIN2/3) and cervical cancer [4]. The natural history of persistent infections is not fully understood, but it has been hypothesized that persistence may be related to characteristics of the immune system in the host and/or genetic predisposition [5]. Persistent cervical infection

Abbreviations: AIS, adenocarcinoma in situ; CI, confidence interval; CIN, cervical intraepithelial neoplasia; HPV, human papillomavirus; HNC, head-and-neck cancer; HNSCC, head-and-neck squamous cell carcinoma; HR, hazard ratio; PIN, personal identification number.

* Corresponding author at: Virus, Lifestyle and Genes, Danish Cancer Society Research Centre, Strandboulevarden 49, DK-2100 Copenhagen, Denmark.
E-mail address: susanne@cancer.dk (S.K. Kjaer).

http://dx.doi.org/10.1016/j.ygyno.2016.04.023
0090-8258/

with HPV might therefore be a marker of impaired functioning of the immune system, leading to decreased clearance of HPV and may thereby be associated with an increased risk of HPV-related cancers.

Some studies have shown that women with a previous history of high-grade CIN, despite treatment, are not only at increased risk of cervical cancer [6–9] but also of other HPV-associated cancers, such as of the vagina, vulva, and anus [8,10,11]. Few studies have been conducted, however, on head-and-neck cancer (HNC) [6,11]. Furthermore, the previous studies on the risk of HNCs after a history of CIN were limited by lack of adjustment for potential confounders, they included different grades of CIN, they were based on broad categorizations of HNC, and none quantified the risk of specific HNCs in relation to tumor site and thereby the anticipated degree of association with HPV. Such differentiation is important, as the degree of association with HPV varies by tumor site and the histology of the HNC. The strongest association has been found with squamous cell carcinomas of the oropharynx, particularly in the tonsils and the base of the tongue, where HPV is present in 51–82% of cases [12,13].

In the present study of approximately 2,500,000 women based on prospectively collected data, we examined whether women with a history of CIN3 including adenocarcinoma in situ (AIS), serving as a marker of persistent HPV infection, are at greater risk of HNC than women without this exposure history. Furthermore, we determined the relative risk in relation to degree of association with HPV and time since diagnosis of CIN3/AIS.

2. Material and methods

2.1. Study population

Since the late 1960s, all residents of Denmark have been assigned a unique personal identification number (PIN), which is registered in the computerized Civil Registration System [14]. The PIN includes date of birth and sex and is used in all Danish health registries, ensuring accurate linkage of information among these registries. The Civil Registration System also contains information on vital status, including date of migration and date of death, for all Danish citizens. From this system, we identified all women born between January 1, 1918 and December 31, 1990, who were alive and living in Denmark at some time during the study period (January 1, 1995 and December 31, 2012) ($n = 2{,}607{,}222$). Women with a history of cancer (except for non-melanoma skin cancer) before follow-up in 1995 were excluded ($n = 65{,}112$). Consequently, our final study population consisted of 2,542,110 women. The study protocol was approved by the Danish Data Protection Agency. As the study is register-based, Danish legislation did not require written informed consent.

2.2. Ascertainment of exposure

We identified exposure status (occurrence of CIN3 including AIS between 1943 and 2012) by linking the study population to the Danish Cancer Registry and to the Danish Pathology Databank using the PIN as the key identifier. The Danish Cancer Registry holds information (topography and morphology) on virtually all cases of cancer since 1943. Information on cases of precancerous lesions of the cervix is also available but is not complete [15]. The Danish Pathology Databank is a nationwide registry of complete information on diagnosis, date of diagnosis, topography, and morphology (both normal and abnormal) of all histologic and cytologic specimens from all Danish pathology departments since the mid-1990s. In addition, most pathology departments have transferred information to the Pathology Data Bank from the mid-1990s back to 1978, but data from this period are not entirely complete [16]. The availability of information on exposure from both registries ensured best possible completeness of data. For women with more than one diagnosis of CIN3/AIS, the date of the first diagnosis was considered the exposure date.

2.3. Follow-up for cancer

The PINs of the women in the study population were linked to the Danish Cancer Registry to obtain information on HNC. Only invasive HNSCC (i.e. morphological subtypes 8050–8084 and 8120–8131 and with 3 as the last digit) was considered to be the outcome of interest, as these are the types most strongly associated with HPV [17].

As the study was register-based, we had no information on the HPV status of women with specific HNSCCs. On the basis of the current literature [18,19], the overall group of HNSSCs ("any HNSCC") was divided into four main groups according to the anticipated degree of association with HPV: "strongly associated" (oropharynx), including ICD O-3 codes C019, C024, C051, C052, C090–103, C108–109, C140, and C142; "potentially associated" (oral cavity), coded C020–C023, C028–C031, C039–C041, C048–C050, C058–C062 and C068–C069; "uncertain association" (larynx), coded C32; and "not/weakly associated" (other HNSCC), coded C110–C139, C300–C319. The last group was included to determine any difference in risk estimates among HNSCC sites. Patients with HNSCC at sites of anticipated strong association with HPV were further divided into two groups – (i) base of tongue and tonsillar cancer and (ii) other oropharyngeal cancers – because base of tongue and tonsillar cancer are most strongly associated with HPV. In addition, the not/weakly HPV-associated HNSCCs were divided into cancers of the nasal cavity, middle ear, and sinuses and cancers of the recessus piriformis, naso- and hypopharynx, as the latter are anatomically adjacent to strongly HPV-associated HNCs and therefore more likely to be misclassified, while cancers of the nasal cavity, middle ear, and sinuses are anatomically furthest away from HNSCC anticipated to be strongly associated with HPV.

2.4. Information on socioeconomic status and smoking

We linked the study population with Statistics Denmark to obtain information on the highest attained educational level (basic, vocational, higher, or unknown), which was available for the whole population from 1981 through 2012.

Data on smoking status was obtained from the Danish Medical Birth Registry, which contains information on all women who have given birth since 1973 [20]. During their first visit to a midwife (at 16–17 weeks of gestation), women are asked whether they are non-, previous, or current smokers in the present pregnancy. Information on smoking status has been registered since 1997 and was available for 515,253 (20.3%) of the 2,542,110 women in our study population.

2.5. Statistical analysis

The association between a history of CIN3/AIS and HNSCC was estimated in a Cox proportional hazards model with age as the underlying time scale. Women were followed from the age at immigration, January 1, 1995, or 18 years of age, whichever occurred last until their age at exit, defined as the age of any HNSCC diagnosis, death, emigration, loss to follow-up, or end of follow-up (December 31, 2012), whichever came first. In all analyses, the underlying hazard was stratified according to birth year in 1-year intervals to control for differences in exposure assessment and cancer incidence. The exposure variable (a history of CIN3/AIS) was considered as a time-dependent covariate. Consequently, women who were exposed during follow–up contributed person–time as unexposed until the age at first registered diagnosis of CIN3/AIS. As CIN2 is a heterogeneous group comprising true high-grade lesions as well as low-grade lesions, the person-years occurring between a CIN2 and a CIN3/AIS lesion were excluded instead of counting as unexposed follow-up time. The analyses were adjusted for smoking and education, as these factors could potentially confound the risk estimates. Education was treated as a time-dependent covariate and was allowed to change