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Non-steroidal anti-inflammatory drug use and cervical cancer risk: A case-control study using the Clinical Practice Research Datalink

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ABSTRACT

Purpose: Non-steroidal anti-inflammatory drugs (NSAIDs) have many anticarcinogenic properties via the inhibition of cyclooxygenase 2 (COX-2). Only one study, a cohort study examining risk of all cancers, investigated their role in cervical cancer with inconsistent findings between non-aspirin NSAIDs and aspirin. The aim of this study was to further investigate NSAID/aspirin use and cervical cancer risk. *Methods*: Using the United Kingdom Clinical Practice Research Datalink, 724 women diagnosed with cervical cancer between 1 January, 1995 and December 2010 were compared to 3479 women (without cervical cancer) matched on year of birth and general practice. Conditional logistic regression analysis adjusted for smoking, sexually transmitted infections, HRT and contraceptive use, was used to calculate odds ratios (OR) and 95% confidence intervals (CI) for cervical cancer risk among users of any oral NSAIDs, non-aspirin NSAIDs and aspirin, as assessed from primary care prescribing data. *Results*: Excluding the year prior to diagnosis, there was no association in adjusted analyses between ever vs. never use of an NSAID (OR 0.92, 95% CI 0.77–1.09), non-aspirin NSAID (OR 0.95, 95% CI 0.80–1.13) or low-dose aspirin (OR 1.07, 0.80–1.44) and cervical cancer risk. In analysis of daily defined doses, there was no association with cervical cancer risk comparing the highest users to non-users of NSAIDs (OR 0.98, 95% CI 0.69–1.39) or non-aspirin NSAIDs (OR 1.00, 95% CI 0.70–1.43) or low-dose aspirin (OR 1.04, 95% CI 0.59–1.81). *Conclusion*: This large historical cohort study found no evidence of an association between non-aspirin NSAID or aspirin use and cervical cancer risk.

1. Introduction

Cervical cancer is the 11th most common cancer among women in the United Kingdom (UK) [1]. In 2009, there were 3378 incident cancers and 957 cervical cancer deaths; giving a European age-standardised incidence rate of 10.1 and mortality of 2.4 per 100,000 females in the UK [1]. In the UK, five-year survival from cervical cancer is relatively high, 66.6% on average over the period 2005–2009, but is significantly lower in the elderly [1].

Human papillomavirus (HPV) accounts for more than 99% of all cervical cancers [2,3], the highest attributable fraction ever identified for a specific cause of cancer [4]. More than 100 different HPV genotypes have been identified [5]. While the majority of human papillomavirus infections (HPV) are transient in nature [6], persistent infection with high-risk oncogenic types HPV 16 and 18, have been associated with most cervical cancers [2,7,8]. Other cervical cancer risk factors and/or surrogate markers for HPV infection have been identified including certain sexual practices such as having multiple sexual partners and a younger age at sexual debut [9], smoking [10,11], long-term hormonal contraceptive use [12], multiple full-term pregnancies [13] and co-infection with sexually transmitted diseases [14,15].

Accumulating evidence shows that inflammation via cellular, innate and adaptive responses in which several cytokines are secreted [16], likely plays a role in HPV-associated carcinogenesis. Therefore, identification of drug agents that can suppress these inflammatory pathways may offer therapeutic potential. Preclinical studies investigating aspirin and non-steroidal anti-inflammatory drug (NSAID) use and cervical cancer cell lines have shown some promising chemopreventive effects including, decreased cell proliferation [17,18] and increased apoptosis [19,20]. Cyclooxygenase-2 (COX-2) is an enzyme required in the conversion of prostaglandins from arachidonic acid. COX-2 has been shown to be

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up-regulated in both pre-invasive and invasive cervical carcinomas [21–24], which has been associated with an increase in pro-carcinogenic downstream effectors including prostaglandin production in cervical cancer [25] and pre-invasive disease [26].

Only one prior observational study has been conducted examining the association between NSAID use and cervical cancer risk, the findings from which were reported on separately for NSAIDs [27] and aspirin [28]. Importantly, this population-based cohort study investigated the risk of colorectal and other cancers, and so did not control for specific confounders associated with cervical cancer. A slight, but non-significant, reduction in cervical cancer risk was found among users of low-dose aspirin [27]. However a 40% significant reduction in cervical cancer risk was noted among non-aspirin NSAID users [28] but this inverse association was not confirmed in analyses by number of NSAID prescriptions.

Given the supporting experimental evidence and the lack of epidemiological studies in this area, the aim of this study was to investigate the association between the use of aspirin and non-aspirin NSAIDs and cervical cancer risk using reliable clinical and prescribing data from the Clinical Practice Research Datalink (CPRD).

2. Patients and methods

2.1. Study design

A nested case-control study was undertaken using data from the UK CPRD (formerly known as the General Practice Research Database). The CPRD is the world's largest database of anonymised longitudinal patient records and is representative of the UK population in terms of gender and age [29]. Data collected includes basic demographic information, outcomes from consultations and diagnoses made, specialist referrals as well as details on all prescribed medications. The quality of CPRD data is assessed in terms of continuity of recording, completeness and plausibility, GP practices which meet these data standards are termed 'up-to-standard' (UTS). Read/Oxford Medical Information System (OXMIS) codes are used to classify medical diagnoses. The high quality of CPRD prescription and diagnosis information has been previously documented [30]. Ethical approval for all observational research is obtained by CPRD from the Multi-centre Research Ethics Committee (MREC).

3. Study population

Cases were defined as all women, ≥18 and <85 years of age, with a read code for incident malignant neoplasm of the cervix (B41.00 Malignant neoplasm of cervix uteri or B41z.00 Malignant neoplasm of cervix uteri NOS) from the 1 January, 1995 to the 31 December, 2010. The first date of cervical cancer diagnosis was taken as the index date and this was assigned to each matched control. Each case was randomly matched by CPRD staff (via computer) to at least 5 controls by age (year of birth ±2 years) and general practice. Controls were defined as women, ≥18 and <85 years of age with no history of cervical cancer on or before the index date of their matched case. Both cases and controls were required to have at least 5 years of UTS follow-up (medical history) prior to the index date. Cases were permitted to be included as controls prior to the development of their cancer.

As recommended by a previous CPRD study [31] to ensure the accuracy of the date of diagnosis, the dates of cervical cancer codes for all potential cases were reviewed. Where appropriate, the date of diagnosis was thus taken as the earliest date documented by the GP. In order to identify individuals with a prior history of cancer (other than non-melanoma skin cancer) a list of relevant Read codes was generated and reviewed by three authors (JW, LAA, JC). Fig. 1 illustrates a flow diagram of patient inclusion and exclusion criteria. Women (17 cases and their 85 matched controls) with a history of hysterectomy >3 months prior to the index date were excluded as it was not possible to determine whether these were complete or subtotal hysterectomies (where the cervix can remain) and thus whether these women were still at risk of cervical cancer. An additional 141 controls who had a hysterectomy <3 months prior to their index date were also excluded. A small number of cases ($n = 45$) with a history of hysterectomy ≤3 months prior to their cervical cancer diagnosis were retained in the final analysis, as this likely led to the diagnosis of their cervical cancer.

3.1. Classification of drug exposure

The exposure period of interest was defined as the start date of the case (case's first registration date or UTS date if this occurred after), to a year before the index date. Only controls which had complete follow-up over the same exposure period as the case were included. The total number of prescriptions received for all

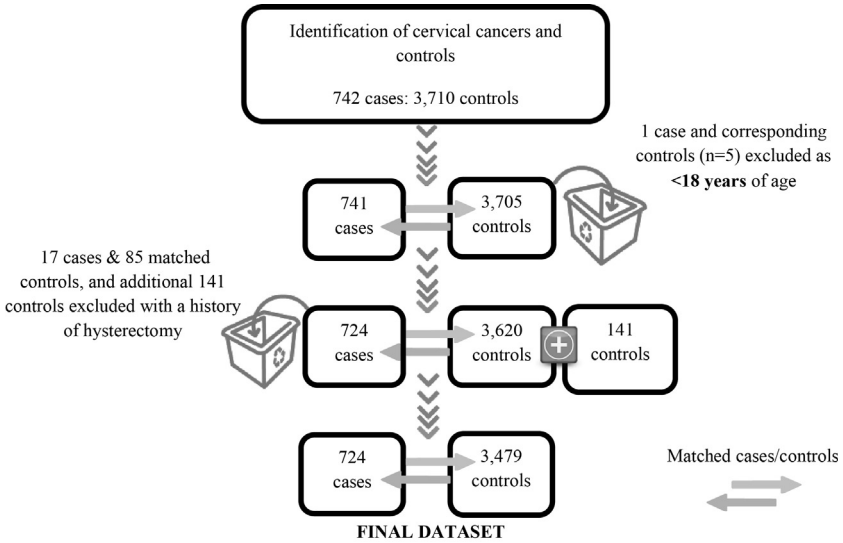

Fig. 1. Flow diagram illustrating the construction of the final dataset and study exclusions.