Comparison of risk factors for squamous cell and adenocarcinomas of the cervix: a meta-analysis

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While most cancers of the uterine cervix are squamous cell carcinomas, the relative and absolute incidence of adenocarcinoma of the uterine cervix has risen in recent years. It is not clear to what extent risk factors identified for squamous cell carcinoma of the cervix are shared by cervical adenocarcinomas. We used data from six case–control studies to compare directly risk factors for cervical adenocarcinoma (910 cases) and squamous cell carcinoma (5649 cases) in a published data meta-analysis. The summary odds ratios and tests for differences between these summaries for the two histological types were estimated using empirically weighted least squares. A higher lifetime number of sexual partners, earlier age at first intercourse, higher parity and long duration of oral contraceptive use were risk factors for both histological types. Current smoking was associated with a significantly increased risk of squamous cell carcinoma, with a summary odds ratio of 1.47 (95% confidence interval: 1.15–1.88), but not of adenocarcinoma (summary odds ratio = 0.82 (0.60–1.11); test for heterogeneity between squamous cell and adenocarcinoma for current smoking: \( P = 0.001 \)). The results of this meta-analysis of published data suggest that squamous cell and adenocarcinomas of the uterine cervix, while sharing many risk factors, may differ in relation to smoking. Further evidence is needed to confirm this in view of the limited data available.

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Most cancers of the uterine cervix are squamous cell carcinomas, but the relative and absolute incidence of adenocarcinoma has risen in recent years and adenocarcinomas now account for about 20% of incident invasive cervical cancers in screened populations worldwide (Sasieni and Adams, 2001). It remains unclear to what extent risk factors identified for squamous cell carcinoma of the cervix are shared by cervical adenocarcinomas (Parazzini and La Vecchia, 1990; Kjaer and Brinton, 1993; Altekruse et al, 2003; Green et al, 2003). While infection with the human papillomavirus (HPV) appears to be the most important cause of both types of cervical cancer (Walboomers et al, 1999; Clifford et al, 2003), some controlled studies have found differences between adenocarcinoma and squamous cell carcinoma in the importance of other factors such as smoking (Lacey et al, 2001; Green et al, 2003) and reproductive factors (Altekruse et al, 2003). Individual studies have generally been limited by small numbers of adenocarcinoma cases and in some instances by lack of adjustment for confounding factors. In the 10 years since this subject was last reviewed (Parazzini and La Vecchia, 1990; Kjaer and Brinton, 1993), a number of new studies have been published. In this meta-analysis of published data, we have combined results from those controlled studies that provided a direct comparison between risk factors for squamous cell and adenocarcinoma, to assess the current evidence.

MATERIALS AND METHODS

Studies were identified through searches of MEDLINE (1966–June 2003, using combinations of the search terms ‘cervix neoplasms’, ‘risk factors’, ‘adenocarcinoma’ and ‘squamous cell carcinoma’) and of bibliographies of identified papers. We included any controlled study that provided the age-adjusted odds ratios and 95% confidence intervals (CIs) for both adenocarcinoma (including adenosquamous carcinoma) and squamous cell carcinoma of the cervix (invasive or in situ) for at least one of the following risk factors (but not necessarily in the same publication): duration of oral contraceptive use, smoking, reproductive factors and sexual behaviour. Studies providing information on only one of the two histological types were not included, to ensure that any potential differences between the types were not due to study design or setting. No limit was placed on the number of cases. The most adjusted odds ratio available was used for analysis. In most studies, oral contraceptive use was not further defined and may include combined and progestagen-only oral contraceptives; however, the large majority of oral contraceptive users in these studies are likely to have used combined preparations (IARC, 1999).

Statistical methods

The odds ratios from each study were grouped into the closest of the prespecified categories for each risk factor (e.g. for duration of oral contraceptive use \(<5, 5–9\) and \(10 + \) years). To enable the results for the studies that had been divided into more categories to be included, it was necessary to combine some of the categories
using a method for combining nonindependent strata (Berrington and Cox, 2003).

The summary (odds ratios, OR) for the pooled data were calculated under a fixed effects model using the method of empirically weighted least squares, where the weights are defined as the inverse of the variance of the log odds ratios (Cox and Snell, 1989). Heterogeneity between individual study results and between summary risk estimates for the two histological types was also calculated using this method.

In Figure 1, summary OR for groups of studies are shown as black circles whose size does not represent the amount of data available. In Figure 2, OR for individual studies are plotted as black squares whose size is inversely proportional to the variance of the logarithm of the odds ratios diamonds represent the summary odds ratios with 95% CIs indicated by their horizontal extent.

RESULTS

Data were available from six case–control studies: by Brinton and co-workers in the USA (Brinton et al, 1986) and Latin America (Brinton et al, 1990, 1993); the World Health Organisation (WHO) multicentre study (WHO, 1985; Thomas and Ray, 1996); a multicentre study by Lacey and co-workers in the USA (Lacey et al, 1999, 2001; Altekruse et al, 2003); a pooled analysis from the International Agency for Research on Cancer (IARC) (Munoz et al, 2002; Plummer et al, 2003) of data from 10 individual studies, of which two (Chichareon et al, 1998; Ngelangel et al, 1998) were included individually in analyses for which the pooled IARC data were not available; and the UK National Case–Control Study of Cervical Cancer (Green et al, 2003). In total, data were available for 5649 cases of squamous cell carcinoma, 910 cases of adenocarcinoma and 17384 controls. Details of the studies are given in Table 1.

Figure 1 shows summary OR in relation to sexual behaviour, reproductive factors, oral contraceptive use and smoking status, based on data from between three and six studies. Both histological types of cervical cancer showed a strong association with the number of sexual partners, with cancer risk increasing with the increasing number of partners. Summary OR (and 95% CIs) for three or more lifetime partners compared with one partner were 1.94 (1.35 – 2.79) for adenocarcinoma and 2.44 (1.94 – 3.07) for squamous cell carcinoma. There were no significant differences between the results for adenocarcinoma and for squamous cell carcinoma. Early age at first intercourse was associated with increased risk of both types of cervical cancer, although the association was stronger for squamous cell carcinoma (OR for age at first intercourse of less than 17 years compared with more than 20 years 1.41 (0.99 – 2.00) for adenocarcinoma and 2.32 (1.89 – 2.85) for squamous cell carcinoma; the difference between these ORs was statistically significant (P = 0.009)).

Parity was strongly related to the risk of squamous cell carcinoma (summary OR for three or more live births or full-term pregnancies compared with none 2.71 (2.08 – 3.53)). It was less strongly related to the risk of adenocarcinoma, although there was still a statistically significant association (OR for parity of three or more 1.51 (1.02 – 2.22)), and there appears to be a trend of increasing risk with increasing parity for adenocarcinoma as for squamous cell carcinoma. The difference between the OR for adenocarcinoma and for squamous cell carcinoma in relation to parity of three or more compared to none was statistically
The results of this meta-analysis show consistent qualitative differences between the risks for squamous cell and adenocarcinomas of the cervix in relation to cigarette smoking. Smoking appears to be a risk factor for squamous cell carcinoma, with an increased risk of around 1.5 for current smokers, but not for adenocarcinoma. The other risk factors investigated did not differ qualitatively between squamous cell and adenocarcinomas; both types of cervical cancer were strongly related to the number of sexual partners and to duration of oral contraceptive use, and both were related to early age at first intercourse and to parity. Neither type of cervical cancer was related to age at first birth in this analysis.

**DISCUSSION**

Data on smoking intensity were available from two studies only: the summary risk of squamous cell carcinoma increased with increasing intensity of smoking (summary OR 1.22 (0.91–1.65) and 1.39 (1.01–1.91) for less than 20 and 20 or more cigarettes per day, respectively, compared to never smokers). The risk of adenocarcinoma was not significantly increased for either group of intensity of smoking compared to never smokers (summary OR 0.80 (0.56–1.13) and 0.77 (0.53–1.13) for less than 20 and 20 or more cigarettes per day, respectively.) There was a statistically significant difference between the results for squamous cell and for adenocarcinoma for both levels of intensity (less than 20 cigarettes per day, P = 0.04; 20 or more cigarettes per day, P = 0.01). No heterogeneity between studies was present in any group. Only three studies published results according to duration of smoking, and of these only one (Green et al, 2003) published results for duration of smoking restricted to current smokers. Because of the difference in risk seen for squamous cell cervical cancer between current and past smokers, it was not considered appropriate to combine the results for duration of smoking.

**Figure 2** Odds ratios and 95% CIs for cervical cancer for ever, past and current smokers vs never smokers.
Table 1. Studies included in published data meta-analysis of risk factors for squamous cell and adenocarcinoma of the cervix

| Study | Date of diagnosis | Histology | Cases squamous | Adeno | Results adjusted for* |
|-------|-------------------|-----------|----------------|-------|-----------------------|
| Brinton et al (1986), USA | 1982–1984 | Invasive | 417 | 67 | Yes |
| Brinton et al (1989/1993), Latin America | 1986–1987 | Invasive | 1413 | 17 | Yes |
| WHO pooled studies (1993), 1979–1988 | Invasive | 2361 | 377 | No |
| Lacey et al (1993–2003), USA | 1992–1996 | Invasive | 91 inv, 33 in situ | Yes |
| Greenberg et al (2003), multicentre | 1995–1997 | Invasive | 338 | 39 | Yes |
| IARC pooled (2002/2003+), 1985–1997 | 124 inv, 134 inv | Yes |
| Ngelangel et al (1998), Philippines | 1991–1993 | Invasive | 323 | 33 | Yes |
| UK National Case–Control Study of Cervical Cancer | 1984–1988 | Invasive | 391 | 180 | Yes |

Included in meta-analysis of smoking: OC = oral contraceptive use; AFB = age at first intercourse; ATR = age at first birth; HPV = human papilloma virus (status); SE = social-economic status; Eth = ethnicity; Ctr = center; OC use = smoking OC use.

*Results adjusted for smoking, OC use, age, social-economic status, parity, AFB, sexual partners, HPV infection (Altekruse et al, 2003) or adjusted for HPV-positive women, two of these studies were included only in the meta-analysis of oral contraceptive use, and the results of this analysis were not materially altered when these two studies were omitted. Differences in the risk factor categories used, for example for duration of oral contraceptive use, may also contribute to the statistical heterogeneity seen between studies in some groups. Overall, the number of studies that have published results in a similar way for both squamous cell and adenocarcinoma of the cervix is small, and for some of the analyses the number of studies was very limited.

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