Incidence of invasive cancers following carcinoma in situ of the cervix

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Summary Women with carcinoma in situ (CIS) of the cervix uteri, notified to the population-based Cancer Registry of the Swiss Canton of Vaud between 1974 and 1993, were actively followed up to 31 December 1993 for the occurrence of subsequent invasive neoplasms. Among 2190 incident cases of CIS, followed for a total of 22 225 person-years, 95 metachronous cancers were observed vs 77.9 expected, corresponding to a standardised incidence ratio (SIR) of 1.2. Ten cases of invasive cervical cancer were observed vs 3.0 expected (SIR = 3.4, P < 0.01), the excess being larger in the first 10 years since CIS diagnosis. A total of 11 cases of four major tobacco-related sites (lung, mouth or pharynx, oesophagus and urinary bladder) were observed vs 5.1 expected, corresponding to a significant SIR of 2.2. The excess was observed 10 years after CIS diagnosis. There was also an excess of non-melanomatous skin cancers (29 observed, 16.9 expected, SIR = 1.7; P < 0.01), but not of skin melanoma and of any of the other neoplasms considered, including breast and corpus uteri. This population-based study, therefore, finds an excess of invasive cervical cancer in the short term after CIS diagnosis, and a medium- to long-term excess risk of tobacco-related and non-melanomatous skin neoplasms. These findings are discussed in terms of increased surveillance and case ascertainment after CIS, and of potential shared risk factors (tobacco and/or viral infections).

Keywords: cervix neoplasm; incidence; registries; smoking; viruses

Women diagnosed with carcinoma in situ (CIS) of the cervix uteri constitute a selected population with reference to (1) their subsequent risk of invasive cervical cancer and (2) their incidence of other neoplasms, which may share risk factors with cervical carcinogenesis, or whose diagnosis may be influenced by the changed medical surveillance after CIS.

Only scattered data, however, are available on the issue. A study of cervical carcinoma in situ registered in Norway between 1970 and 1992 (Bjorge et al., 1995) found no overall excess of cancer, but elevated rates for lung, oesophagus, nose, bladder and the urinary organs (i.e. major tobacco-related neoplasms), vulva and vagina, and skin (squamous cell). Uterine cancer rates (cervix and corpus) were lower than expected. No excess risk of cutaneous melanoma was registered in a study of cervical intraepithelial neoplasia from Washington State (Schmulewitz et al., 1993).

To provide further quantitative information on these open issues, we have linked data from 2190 women with in situ carcinoma of the cervix, registered by the Swiss Cancer Registry of Vaud between 1974 and 1993, with cancer incidence data from the same registry, with specific focus on cervical cancer, major tobacco-related neoplasms (since tobacco may influence cervical carcinogenesis; Winkelstein, 1990; Brinton, 1992), skin cancer (which may be linked to viral infections (IARC, 1995) or influenced by detection accuracy), and, for comparative purposes, other cancer sites. Thus improving completeness and accuracy of registration. The basic information available from the register comprises sociodemographic characteristics of the patient (i.e. age and sex), primary site and histological type of the tumour according to the standard International Classification of Diseases for Oncology (ICD-O; World Health Organization, 1976), and time of diagnostic confirmation (histological or clinical diagnosis). Passive and active follow-up is recorded, and each subsequent item of information concerning an already registered case is used to complete the record of that patient.

Since 1974, a registration scheme, applying the same standardised rules as for incident malignancies, has been implemented for carcinoma in situ and severe dysplasia of the uterine cervix (CIN III). All histological reports were scrutinised and reviewed when reporting a diagnosis of CIS.

After exclusion of all synchronous CIS and other cancers...
(n = 8, i.e. two cancers of the breast, four of the uterine corpus, one of the ovary and one of unspecified genital organs), the present series comprises a total of 2190 histologically (at least through a biopsy) confirmed CIS. The age range was 18–92 years (median age, 34 years). These cases of incident CIS were followed up to the end of 1993, for the occurrence of cancer, migration or death. Histological confirmation was performed in 100% of both the CIS and of the second primaries.

Calculation of expected numbers was based on site-, age- and calendar year-specific incidence rates, multiplied by the observed number of person–years at risk. The significance of the observed/expected ratios (standardised incidence ratio, SIR), and the corresponding 95% confidence interval (CI), was based on the exact Poisson distribution (Breslow and Day, 1987).

Discussion

In this population, there was an excess of invasive cervical cancer following histologically confirmed CIS, which was however restricted to the 10 years after CIS diagnosis. This may partly be due to increased ascertainment but underlines the importance of adequate treatment and surveillance of women after CIS (La Vecchia et al., 1995).

There was also a significant excess of tobacco-related neoplasms, which became evident 10 years after CIS diagnosis. This may be interpretable in terms of shared risk factors, since a role of tobacco in cervical carcinogenesis has long been suspected (Winkelstein, 1977; Brinton, 1992). In a review of 33 epidemiological studies of the relationship between cigarette smoking and cancer of the uterine cervix published over the last three decades (Winkelstein, 1990), 26 found a direct association. This association has also been reported for cervical intraepithelial neoplasia (including CIN III; Parazzini et al., 1992, 1996; Szarewski et al., 1996). Furthermore, nicotine and cotinine have been identified in cervical mucus, and their concentration was directly related to cigarette smoking (Hellberg et al., 1988; Schifman et al., 1987; McCann et al., 1992).

A significant excess of lung cancer was also observed following invasive cervical cancer in the same population (Levi et al., 1993a), and rates from several tobacco-related neoplasms were also elevated in a large study of in situ cervical cancer from Norway (Bjorge et al., 1995). Likewise, an increase for lung and bladder cancer incidence was observed in Denmark (Storm and Ewertz, 1985; Storm, 1988), and for lung, oral cavity, larynx and bladder in Connecticut following cervical cancer (Rakbin et al., 1992).

It is also possible that human papilloma virus (HPV), the major identified risk factor for cervical neoplasms, is related to oral and pharyngeal, and, possibly, squamous cell carcinomas from other epithelia (IARC, 1995; Franceschi et al., 1996; Madsen et al., 1992; Benamouzig et al., 1992; Gissmann et al., 1983).

Table II Observed (O) and expected (E) second primary cancers or groups of cancers following 2190 cases of in situ carcinoma of the uterine cervix according to time since diagnosis, and corresponding overall standardised incidence ratios (SIR) (Vaud, Switzerland, 1974–93)

| Site                        | 1–4 | 5–9 | 10–14 | 15+ | Whole period SIR (95% CI) |
|-----------------------------|-----|-----|-------|-----|-------------------------|
| Mouth of pharynx oesophagus, lung, bladder | O 1 | E 1.5 | 1.6 | 1.4 | 0.6 | 5.1 | 5.1 (2.2–1.3) |
| Skin, non-melanoma          | O 5  | E 5.1 | 5.3 | 4.5 | 1.9 | 16.9 | 16.9 (1.7–2.5) |
| Skin, melanoma              | O 1  | E 1.1 | 1.0 | 0.8 | 0.3 | 3.2 | 3.2 (0.2–2.7) |
| Breast (females)            | O 3  | E 7.3 | 7.8 | 6.5 | 2.6 | 24.4 | 24.4 (0.4–2.7) |
| Cervix uteri                | O 6  | E 1.0 | 0.9 | 0.7 | 0.3 | 3.0 | 3.0 (1.6–6.3) |
| Corpus uteri                | O 3  | E 7.0 | 7.2 | 6.2 | 2.7 | 23.1 | 23.1 (0.5–1.3) |
| Total, all sites            | O 25 | E 23.8 | 24.8 | 20.7 | 8.7 | 77.9 | 77.9 (1.2–1.5) |
The (non-melanomatous) skin cancer excess in the medium to long term following a CIS is more difficult to understand (although it has also been reported in other studies; Hartveit, 1988; Bjorge et al., 1995). In this study, ascertainment bias is unlikely, since the excess risk became evident five or more years after CIS diagnosis. Again HPV (IARC, 1995), or subtle immunological impairment, may be aspects shared by cervical and skin carcinogenesis. A confounding effect of some lifestyle habits, chiefly recreational sun exposure, cannot be excluded.

Among the strengths of the study, there are its population basis, which should render any estimate relatively free from selection bias (Levi et al., 1993a) and the complete histological confirmation of CIS cases. The absence of association with any of the other cancer sites is also reassuring with respect to surveillance bias, and provides relevant indications for the potential focus on a preventive and early diagnosis level for women diagnosed with CIS.

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