

Mortality in a long-term follow-up after treatment of CIN.

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After treatment of the cervical intraepithelial neoplasia (CIN) cervical cancer incidence remains elevated at least for 20 years. Whether the overall or cervical cancer mortality after treatment of CIN is elevated is unknown. The aim of this study was to determine the long-term survival and cause-specific mortality among women treated for CIN. The study population consisted of 7,104 women treated for CIN between 1974 and 2001 and 35,437 individually matched controls. The follow-up of mortality was based on nationwide registries and closed at death, emigration or December 31, 2005. The possible differences in mortality were assessed using Cox proportional hazard model. With follow-up time of approximately 630,000 woman-years, overall 2,781 deaths were observed, 530 among women treated for CIN and 2,251 among reference population (HR 1.1, 95% CI 1.0–1.3). Mortality from any cancer (HR 1.4, 95% CI 1.2–1.7), lung cancer (HR 2.7, 95% CI 1.8–4.1) and HPV-related anogenital cancer (HR 3.1, 95% CI 1.1–8.6) was higher among CIN patients, but mortality from cervical cancer was not (HR 1.0, 95% CI 0.3–4.0). Elevated cervical cancer incidence after treatment of CIN, documented earlier, did not predict elevation in cervical cancer mortality. This suggests high effectiveness of CIN management. Most of the excess mortality observed among CIN patients was due to increased risk of other cancers. These long-term mortality patterns should be considered when planning and evaluating the management of CIN lesions and related cervical or other cancer prevention activity.

Worldwide, cervical cancer is one of the most frequent causes of cancer deaths among women, with about 288,000 deaths annually.¹ Treatment of preinvasive lesions, cervical intraepithelial neoplasia (CIN), has decreased age-adjusted cervical cancer incidence and mortality rates by 60–90% in countries with a long history of screening programs for cervical cancer.² Rates of short-term complications for all therapies used to treat CIN are low and differences between methods in this scale are minimal.³ It has been suggested that treatment of CIN can prevent up to 99% of future cervical cancers.⁴ However, the risk of cervical cancer itself among women treated for CIN, even though based on small numbers, seems to be elevated at least for 2 decades indicating the need of systematic follow-up after the treatment.^{4–6}

Key words: cervical intraepithelial neoplasia, CIN, treatment, mortality

Abbreviations: CIN, cervical intraepithelial neoplasia; CIN 1, cervical intraepithelial neoplasia grade 1; CIN 2, cervical intraepithelial neoplasia grade 2; CIN 3, cervical intraepithelial neoplasia grade 3; CKC, cold knife conization; LEEP, loop electrosurgical excision procedure; LLETZ, large loop excision of the transformation zone.

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Persistent HPV-infection is the most important risk factor for CIN and cervical cancer.⁷ High parity, increasing age, HIV, oral contraceptive use, as well as tobacco smoking and low socioeconomic status are among the known risk factors for CIN and cervical cancer.^{7–9} Cofactors that possibly increase the cancer risk include previous exposure to *Chlamydia trachomatis* and herpes virus type 2.⁸ Also, well documented is that smoking-associated cancer incidence is elevated among women with cervical cancer or CIN.^{4,10} Low socioeconomic status can be considered to reflect exposures, habits, health behaviors (such as use of health-care services) and experiences in adult life and is also a well-documented predictor of mortality in most causes of death.¹¹ Also the risks of other cancers sharing the same etiological factor, human papilloma virus (HPV), such as cancers of vagina, vulva and anus, are elevated among women treated for CIN.^{4,6,12}

Even though the elevated risks of different cancers among women after treatment of CIN are well documented, studies and knowledge about mortality or survival patterns after treatment of CIN are rare. Hakama *et al.* reported excess mortality among women with carcinoma in situ. The risk of death (>10%) was substantially increased only at high ages and independent of age at diagnosis.¹³ They did not report cause-specific mortality and did not have information about lower grades of CIN (CIN 1 or 2). Another earlier study has presented some evidence of overall survival not significantly differing between women treated with different techniques.¹⁴

Ongoing HPV screening and HPV vaccination follow-up trials evaluate the possible cancer preventive effect by using CIN incidence as a surrogate indicator of the potential