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Original article

Second primary cancers in survivors of cervical cancer in the Netherlands: Implications for prevention and surveillance

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ABSTRACT

Background and purpose: We investigated the effects of socio-demographic, treatment- and tumor-specific determinants on the risk of developing a second malignancy among patients treated for cervical cancer.

Material and methods: We included patients with a first cervical cancer (N = 12,048) from the Netherlands Cancer Registry (NCR), 1989–2008. Standardized incidence ratios (SIR) and absolute excess risks (AER) per 10,000 person-years were calculated to estimate the burden of second cancers in cervical cancer survivors. Incidence rate ratios (IRR) were computed to identify predictors for second cancers among cervical cancer survivors.

Results: During the study period, 676 (5.6%) patients were diagnosed with a second cancer. Smoking-related cancers contributed the most to the overall burden of second cancers (AER = 21) and risks remained elevated after 10 years of follow-up (SIR = 1.8, 95% CI: 1.4–2.2), yet it decreased markedly in the younger birth cohorts. Cervical cancer survivors who underwent radiotherapy were at higher risk for a second tumor when compared to those without radiotherapy, especially at smoking-related sites (IRR = 1.6 (1.2–2.3)).

Conclusion: Patients with cervical cancer had a significantly increased risk for a second cancer compared to the general population, especially for smoking- and irradiation-related tumors. Long-term follow-up suggested the importance of smoking cessation and the benefits of counseling cervical cancer patients accordingly, particularly those who received radiotherapy.

Cervical cancer ranks 11th in the most common cancers in women in the Netherlands, representing 1.6% of all newly diagnosed and 1% of all cancer deaths in 2011 [1]. Although incidence and mortality from cervical cancer have been declining in the Netherlands over the past decades, the absolute number of newly diagnosed cases per year has remained more or less stable since 2007; with slight increases since 2001 [1]. The declining mortality rate can partly be attributed to the successful implementation of nationwide screening efforts, initiated in 1996, that target women aged 30–60 years at a screening interval of 5 years [2,3]. This also implies that the number of women with a history of cervical cancer has been growing, being about 5000 in 2012 (10-year prevalence) [1]. Cancer survivors however often live with long-term consequences of the disease and its treatment, besides being at a higher risk of developing new primary cancers. This risk has been quantified to be 14% higher in cancer survivors in the U.S. when compared to the general population; for cervical cancer survivors this was 32% [4]. A report from Australia found a 24% increased risk after 23 years of follow-up, which was most pronounced in smoking-related cancers [5].

Persistent infection with the human papillomavirus (HPV) and smoking are considered the most important risk factors for cervical cancer. They have been found to not only to act independently [6–8], but also jointly as smoking was repeatedly found to increase the risk of invasive cervical cancer among HPV-positive women by 2–3-fold when compared to non-smoking HPV-positive women [9,10]. Assessing the epidemiology of second cancers can help understand the underlying causal factors and their interaction shared by multiple, consecutive cancers as well as the impact of treatment. Smoking is not only the single most important risk factor for several cancers, but has been proven to act past the first cancer diagnosis and to affect outcomes of cancer treatment [11]. A

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study with pooled data from 13 population-based cancer registries from Northern Europe and the U.S. highlighted the high risk for second malignancies in cervical cancer patients receiving high doses of radiation during treatment, which increased with follow-up and stayed significantly elevated even after 40 years [12].

Given the growing number of cervical cancer survivors, counseling cervical cancer survivors regarding the risk of second malignancies and active measures against smoking may need to become an important indicator for patient and clinicians during follow-up. In addition, long-term follow-up can teach us about the impact of smoking and various treatment- and patient-related determinants on the development of second cancers. Therefore, this study aimed to study the risk and determinants of secondary cancers in cervical cancer survivors in the Netherlands and their implication for cancer prevention.

Material and methods

Data and patient selection

We used population-based data from the nationwide Netherlands Cancer Registry (NCR), which combines data from eight regional Comprehensive Cancer Centers since 1989. Information on patient characteristics – such as gender, date of birth and area-based socioeconomic status – as well as tumor characteristics - such as date of diagnosis, subsite (International Classification of Diseases for Oncology (ICD-O-3) [13]), morphology, stage (Tumor Lymph Node Metastasis (TNM) classification [14–17]) and treatment – are obtained routinely from the medical records at about 6–9 months after diagnosis. Completeness is estimated to be at least 95% [18]. In addition to passive follow-up via hospitals, date of death is also retrieved from the Municipal Personal Records Database that contains all deaths or emigrations in the Netherlands since October 1994. For patients diagnosed before October 1994, follow-up was completed through NCR by merging the database with municipality death records or with the Central Bureau for Genealogy, which registers all deaths in the Netherlands.

Definition of first and second cancers

We included all first invasive cervical cancers (ICD-O C53; $n = 13{,}557$) in patients age 20+ diagnosed between 1989 and 2008. Second primary cancers were defined using IARC multiple primary coding rules, i.e. as invasive tumors that occurred in a different site or tissue than the first primary cancer at least 6 months after the first cancer diagnosis and is neither an extension, nor a recurrence, nor a metastasis [13]. Thus, patients with a follow-up of less than six months after the initial cancer diagnosis were excluded ($n = 132$), leaving 12,048 patients for the analysis.

Statistical analysis

Standardized incidence ratios (SIR) were calculated in order to determine the risk of developing a second cancer among cervical cancer survivors in comparison with the general population. The number of expected second cancer cases was computed by applying five-year age group-, calendar year- and site-specific cancer incidence rates of the general female population to the corresponding person-time of cervical cancer patients in the cohort. SIRs were calculated as the ratio of observed to expected numbers of patients with second primary cancer and were computed by age group (<50, 50–69, ⩾70) and follow-up time (6–12 months, 1–5 years, 6–10 years, >10 years). Poisson regression was used to compute 95% confidence intervals (95% CI).

To measure the overall excess burden of subsequent cancers, the absolute excess risk (AER) was calculated, representing additional incidence beyond the background incidence in the general population. It was defined as the difference between the observed and the expected number of patients with a second primary cancer, divided by the number of person years at risk, multiplied by 10,000. Person years at risk were calculated by summing up individual follow-up times at the date of first cancer diagnosis until the occurrence of the second cancer, end of study (December 31st, 2008), or death, whichever occurred first. All analyses were carried out for all second cancers combined as well as for the most common second cancer sites, including lung, breast and colorectal cancer. Moreover, second malignancies were grouped into smoking- and HPV-related cancers as well as irradiated sites according to current scientific evidence [19–22] (Table 1).

In a second step, the predicted values of socio-demographic-, tumor- and treatment-related determinants on the risk of developing a second malignancy were assessed among all cervical cancer patients in the cohort. We analyzed incidence rate ratios (IRR) using Poisson regression with the log of the follow-up time as offset for all second cancers, breast cancer, smoking-, radiation- and HPV-related second cancers. Covariates in the model were calendar year of incidence (continuous), tumor histology (squamous cell carcinoma, adenocarcinomas or other), stage at first cancer diagnosis (FIGO stage I, II, III, IV or unknown, derived from clinical TNM), any radiotherapy (yes/no), age at first cancer diagnosis (20–29, 30–49, 50–69 or 70+ years), birth cohort (in quintiles: born before 1930, 1930–46, 1947–55, 1956–62 or after 1962) and socioeconomic status (SES) at first cancer diagnosis (high, intermediate or low). Socioeconomic status scores were obtained from the Netherlands Institute for Social Research, which were based on mean income per household, the percentage of households with a low income and the percentage of households with a low education by 4-digit postal code area, each consisting of on average 1765 households. This approach has been used earlier in a study from the Netherlands, where low SES was found to be associated with higher cervical cancer incidence and more advanced disease at diagnosis [23]. The role of birth cohort was only introduced in the analysis of smoking-related second cancers. Tests for linear trend were performed by treating the variables age, SES and birth cohort as continuous.

All statistical analyses were performed in SAS 9.2, SAS Institute, Cary, NC.

Results

Of the 12,048 patients with cervical cancer in the cohort, 676 (5.6%) developed a second primary cancer during the study period, including 318 (2.6%) smoking-related cancers (among which 147

Table 1
Categorization* of smoking-, HPV- and radiation-related cancer sites.

Smoking-related cancers [19]	Oral cavity, oropharynx, nasopharynx, hypopharynx, stomach, colon, rectum, liver, pancreas, nasal cavity, paranasal sinuses, larynx, esophagus, lung/trachea, uterine cervix, ovary, kidney, urinary bladder, ureter, bone marrow
HPV-related cancers [20,21]	Anus, vulva, vagina, oropharynx, tonsil, oral cavity
Irradiated sites** [22]	Small intestine, colon, rectum, urinary bladder, uterine corpus, ovary, vagina, vulva, female genital sites NOS, bone, soft tissue

* Groups are not mutually exclusive (one cancer site can be assigned to several groups; See Appendix table 1).
** Irradiated sites were approximated by cancers of the pelvic region and patients with those cancers did not necessarily receive actual radiotherapy.

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