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Second cancer

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

Melina Arnold [a,b], Lifang Liu [a], Gemma G. Kenter [c], Carien L. Creutzberg [d], Jan Willem Coebergh [a,e,*], Isabelle Soerjomataram [b]

[a] Department of Public Health, Erasmus University Medical Center, Rotterdam, The Netherlands; [b] Section of Cancer Information, International Agency for Research on Cancer, Lyon, France; [c] Department of Obstetrics and Gynecology, Center for Gynecologic Oncology, Amsterdam; [d] Department of Clinical Oncology, Leiden University Medical Center; and [e] Comprehensive Cancer Center South, Eindhoven Cancer Registry, Eindhoven, The Netherlands

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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

* Corresponding author at: Erasmus Medical Center, Department of Public Health, P.O. Box 2040, 3000 CA Rotterdam, The Netherlands.
E-mail address: j.coebergh@erasmusmc.nl (J.W. Coebergh).

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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.

Table 2
Characteristics of cohort diagnosed with invasive cervical cancer in the Netherlands, 1989–2008.

			Invasive second cancers after cervical cancer*									
	First cervical cancers (n = 12,048)		All second cancers (n = 676)		HPV-related second cancers[a] (n = 32)		Irradiated sites[a] (n = 142)		Smoking-related second cancers[a] (n = 318)		Breast cancer (n = 174)	
	n	%	n	%	n	%	n	%	n	%	n	%
Age at first/second cancer diagnosis (in years)												
20–29	614	5.1	1	0.2	1	3.1	1	0.7	0	0.0	0	0
30–49	6356	52.8	167	24.7	10	31.3	32	22.5	60	18.9	61	35.1
50–69	3107	25.8	272	40.2	11	34.4	48	33.8	138	43.4	69	39.7
70+	1972	16.4	236	34.9	10	31.3	61	43.0	120	37.7	44	25.3
Year of birth												
Before 1935	2944	24.4	273	40.4	11	34.4	68	47.9	142	44.7	46	26.4
1935–1951	3012	25.0	222	32.7	13	40.6	43	30.3	111	34.9	62	35.6
1952–1960	2811	23.3	134	19.8	4	12.5	22	15.5	54	17.0	49	28.2
After 1960	3281	27.2	47	7.0	4	12.5	9	6.3	11	3.5	17	9.8
Calendar year of first/second cancer diagnosis												
1989–1993	2987	24.8	41	6.0	5	15.6	10	7.0	27	8.5	8	4.6
1994–1998	3082	25.6	97	14.4	7	21.9	25	17.6	49	15.4	27	15.5
1999–2003	2891	24.0	211	31.2	10	31.3	37	26.1	103	32.4	53	30.5
2004–2008	3088	25.6	327	48.4	10	31.3	70	49.3	139	43.7	86	49.4
Stage at first/second cancer diagnosis												
Stage I	6524	54.1	176	26.0	14	43.8	40	28.2	52	16.4	76	43.7
Stage II	2172	18.0	122	18.0	3	9.4	28	19.7	44	13.8	69	39.7
Stage III	2375	19.7	124	18.3	5	15.6	30	21.1	86	27.0	23	13.2
Stage IV	665	5.5	108	16.0	8	25.0	24	16.9	98	30.4	3	1.7
Unknown	312	2.6	146	21.6	2	6.3	20	14.1	38	12.0	3	1.7
Histological type of first cancer												
Squamous cell carcinoma	9051	75.1	541	80.0	31	96.9	114	80.3	265	83.3	132	75.9
Adenocarcinoma	2011	16.7	96	14.2	0	0.0	23	16.2	38	12.0	27	15.5
Other	986	8.2	39	5.8	1	3.1	5	3.5	15	4.7	15	8.6
Initial treatment of first cancer												
No radiotherapy	6185	51.3	307	45.4	21	65.6	62	43.7	120	37.7	101	58.0
Any radiotherapy	5863	48.7	369	54.6	11	34.4	80	56.3	198	62.3	73	42.0
Socio-economic status (SES) at diagnosis of first cancer												
High	3672	30.5	178	26.3	10	31.3	38	26.8	80	25.2	50	28.7
Intermediate	2963	24.6	162	24.0	10	31.3	29	20.4	67	21.1	47	27.0
Low	4756	39.5	268	39.6	9	28.1	53	37.3	138	43.4	60	34.5
Unknown	657	5.5	68	10.1	3	9.4	22	15.5	33	10.4	17	9.8
p-value (chi^2), excluding "unknown"		*<.0001*		*<.0001*		*0.9661*		*0.0253*		*<.0001*		*0.4126*
Follow-up between first and second cancer diagnosis (in years)												
Mean				6.4		4.4		5.9		6.2		6.8
Median				6		2		5		5		6
RT no (mean FU)				7.2		4.4		6		7.2		7.7
RT yes (mean FU)				5.6		4.5		6.3		5.6		5.6

FU = follow-up; RT = radiotherapy.
* Occurring 6 months or later after the initial cervical cancer.
[a] Groupings (smoking-, HPV- and radiation-related sites) may overlap (see Table 1 and See Appendix table 1).

(1.3%) lung cancers), 174 (1.4%) breast cancers and 142 (1.2%) cancers in irradiated sites (Table 2). The mean age at the first cervical cancer was 49.6 years in the full cohort and 54.9 years among those who developed a second cancer (results not shown). Mean age at the second cancer diagnosis was 61.8 years. Whereas more than half (54.1%) of the first cervical cancers were diagnosed in stage 1 and only 5.5% in stage 4, second cancers were on average detected in a later stage, especially smoking-related second cancers (30.4% in stage 4). Three quarters of the first cervical cancers were squamous cell carcinomas. About 40% of all patients lived in neighborhoods with a low SES at the time of their first cancer diagnosis.

The median follow-up between the first and the second cancer ranged between 2.0 (HPV-related sites) and 6.0 years (breast cancer), and was 5 years for smoking-related cancers and cancers at irradiated sites. The interval between the first and second primary cancer was significantly longer among patients who did not receive radiotherapy as their initial treatment as compared to those who did (7.2 vs. 5.6 years).

Patients with a first cervical cancer had an 80% increased risk to develop cancer than the general population (SIR = 1.8; 95% CI: 1.6–1.9) (Table 3). This risk was slightly higher among patients above age 70 (SIR = 2.1; 95% CI: 1.8–2.5). The excess number of all second cancers in the cohort was 34 per 10,000 person-years. Smoking-related cancers, in particular lung cancer, contributed the most to the overall burden of second cancers (AER = 21 and 13 per 10,000 person-years, respectively), whereas the highest SIR (12.4, 95% CI: 9.4–16.2) was found for squamous cell carcinomas (SCC) of the lung. AER was 6 per 10,000 cancer cases at irradiated sites.

The risk of developing a second cancer decreased with increasing interval since the primary diagnosis for many sites, but remained significantly elevated even ten years after the first cancer for all sites (SIR = 1.4; 95% CI: 1.2–1.7), for smoking-related sites (SIR = 1.8; 95% CI: 1.4–2.2), especially lung cancer (SIR = 2.7; 95% CI: 1.8–4.0) and for irradiated sites (SIR = 1.4; 95% CI: 1.0–2.0) (Fig. 1). In contrast, the increased risk for HPV-related cancers in the first five years after cervical cancer disappeared in later follow-up years.

Among patients with cervical cancer, neither histology nor stage at the initial cancer diagnosis had an influence on the occurrence of a subsequent cancer (Table 4). In contrast, higher age at the first cancer diagnosis (>50 years) increased the risk for a second cancer, same as having undergone radiotherapy especially for smoking-related sites (IRR = 1.6; 95% CI: 1.2–2.3).

Table 3
Standardized incidence ratios (SIR) and absolute excess risks (AER) per 10 000 person-years of second primary malignancies by site and age at initial cancer diagnosis in patients with invasive cervical cancer in the Netherlands, 1989–2008.

Second cancer	Age	Observed (*n*)	Expected (*n*)	SIR	95% CI	AER
All	All ages	676	383	**1.8**	1.6–1.9	34
	<50	287	175	**1.6**	1.5–1.8	18
	50–69	245	139	**1.8**	1.6–2.0	57
	⩾70	148	69	**2.1**	1.8–2.5	110
Breast	All ages	174	138	**1.3**	1.1–1.5	4
	<50	99	81	1.2	1.0–1.5	3
	50–69	46	41	1.1	0.8–1.5	3
	⩾70	29	16	**1.8**	1.2–2.7	18
HPV-related sites[a]	All ages	32	16	**2.0**	1.4–2.9	2
	<50	15	9	1.7	0.9–2.8	1
	50–69	9	4	2.1	0.9–4.0	2
	⩾70	8	2	**3.4**	1.5–6.9	8
Colorectum	All ages	65	46	**1.4**	1.1–1.8	2
	<50	18	12	1.4	0.9–2.3	1
	50–69	26	21	1.2	0.8–1.8	3
	⩾70	21	13	1.6	1.0–2.5	11
Smoking-related sites[a]	All ages	318	135	**2.4**	2.1–2.6	21
	<50	113	50	**2.3**	1.9–2.7	10
	50–69	132	56	**2.3**	2.0–2.8	40
	⩾70	73	29	**2.5**	2.0–3.2	61
Lung	All ages	147	31	**4.7**	4.0–5.5	13
	<50	50	14	**3.5**	2.6–4.6	6
	50–69	70	13	**5.3**	4.1–6.7	30
	⩾70	27	4	**7.7**	5.1–11.2	33
Lung – squamous cell carcinoma	All ages	56	5	**12.4**	9.4–16.2	6
	<50	17	2	**10.5**	6.1–17.0	3
	50–69	26	2	**11.3**	7.3–16.6	13
	⩾70	13	1	**22.5**	12.0–39	17
Lung – adenocarcinoma	All ages	33	10	**3.3**	2.3–4.7	3
	<50	15	5	**2.8**	1.6–4.7	2
	50–69	13	4	**3.5**	1.8–6.0	5
	⩾70	5	1	**5.9**	1.9–14.4	6
Irradiated sites[a]	All ages	142	87	**1.6**	1.4–1.9	6
	<50	53	28	**1.9**	1.4–2.4	4
	50–69	50	38	1.3	1.0–1.7	6
	⩾70	39	21	**1.8**	1.3–2.5	25

Bold numbers are statistically significant at $p \leqslant 0.05$ level.
[a] See Table 1 for groupings.

Similarly, patients with a low SES at diagnosis of the first cancer had an elevated risk for developing a smoking-related second cancer (non-significant). A marked cohort effect appeared to explain the higher risk for developing a subsequent smoking-related cancer among those born before 1930 (IRR = 1.8; 95% CI: 1.0–3.1) and between 1930 and 1946 (IRR = 1.9; 95% CI: 1.3–3.0) and the lower risk among those born after 1946, especially after 1962 (IRR = 0.2; 95% CI: 0.2–0.5) when compared to patients born between 1947 and 1955.

Discussion

Cervical cancer survivors have an 80% increased risk to develop a second malignancy when compared to the general population. This was particularly pronounced for smoking- and irradiation-related tumors, where risks remained significantly elevated even after ten years of follow-up. Higher age at diagnosis of the cervical cancer and treatment with radiotherapy were found to be important predictors that increased the risk for a second cancer in cervical cancer survivors. Higher risk of smoking-related cancer was found in patients who received radiation therapy, underlining the association between the two risk factors. In addition, a cohort effect was found for smoking-related sites, with lower risk among cohort who were born more recently. Our findings are similar, however higher, than those from other big population-based studies from the U.S. (32% increased risk) [24] and Australia (24%) [5]. Possible reasons for this difference might be a shorter follow-up in our study, as it has been reported earlier that the risk goes down with longer follow-up duration for most tumors, resulting in less person-years. Another possibility refers to different population characteristics such as stage of smoking epidemic. Whereas Americans and Australians are to-date deep in the final stage of the smoking epidemic with decreasing smoking prevalence since the 1980s, Dutch women have only recently shown a decreasing prevalence of smoking starting around the year 2000 [25].

HPV infection is the primary cause of cervical cancer [26], but also known to be involved in the causation of other sites such as oral cancers [20]. The mean duration of a prevalent infection with high oncogenic risk HPV has been estimated to range between 15 and 24 months [27,28]. Clearance of HPV- induced tissue changes might thus explain the diminishing risk for HPV-related second cancers after five years of follow-up. Yet, HPV infection may be the reason for the variation in risk of HPV-related cancers by age; risk was especially high in patients older than 70 years. This might be due to the natural history of HPV infection, normally affecting mostly the younger age group and clearing off among older ages. The high incidence of these cancers in older cervical cancer survivors in our cohort when compared to the general population increased the risk significantly. This suggests that increasing awareness and counseling on these risks is needed among cervical cancer survivors. In the future, effective screening in combination with vaccination of young women against HPV types 16 and 18 will make cervical cancer a rare disease and the risk for all other HPV (16–18)-related cancer sites is expected to decrease. Implemented nationwide in the Netherlands in 2009, the HPV vaccination program targets girls 12-years of age and

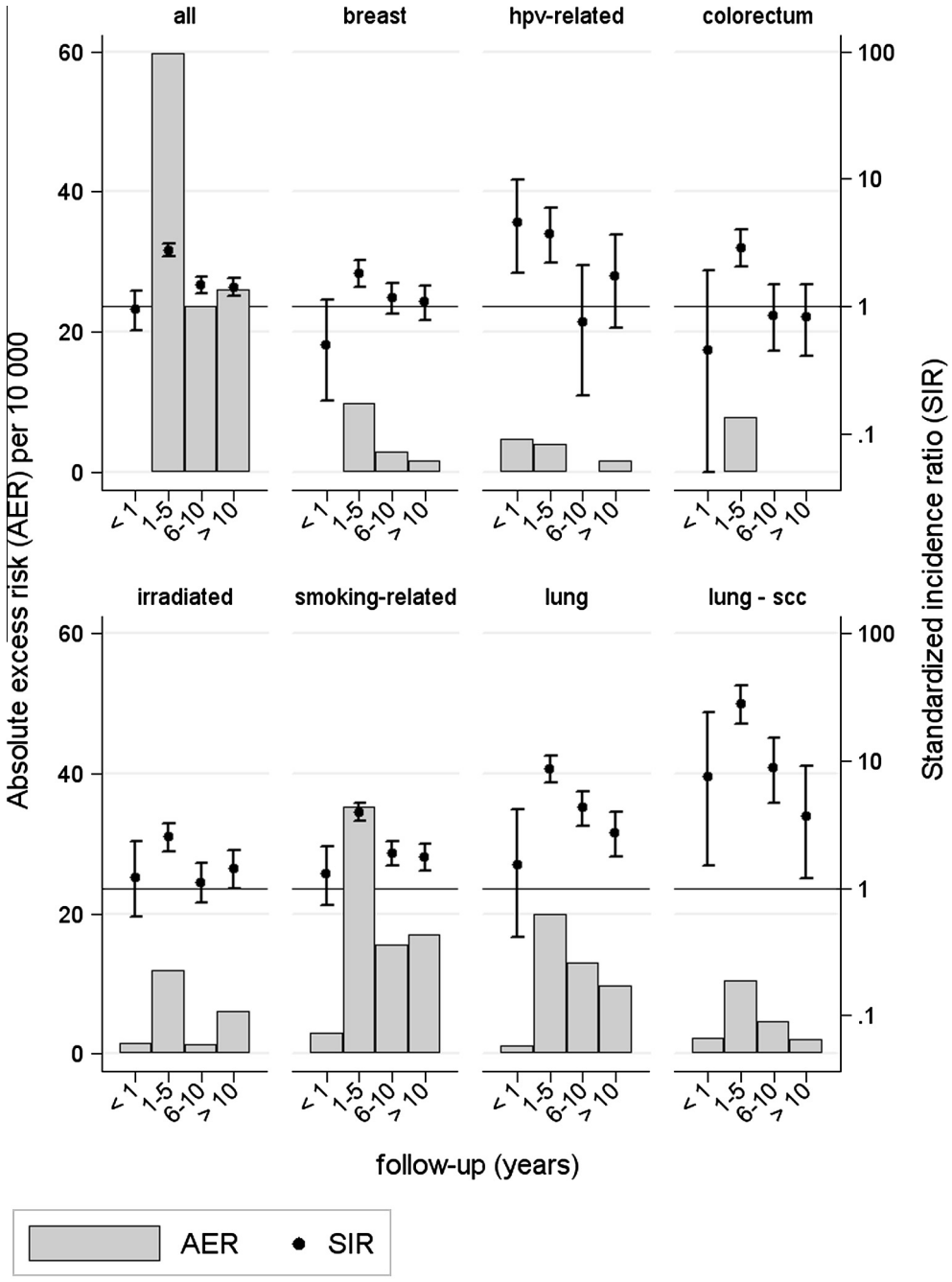

Fig. 1. Standardized incidence ratios (SIR), its 95% confidence intervals and absolute excess risks (AER) per 10,000 person-years of invasive second cancers among cervical cancer patients by follow-up time after first cancer diagnosis, in the Netherlands in 1989–2008 **note: in the group <1 year, only cases with a follow-up ⩾6 months are included.

provided free of charge through healthcare professionals. However, due to many cohorts without vaccination we expect a long lag period until the effects of the vaccine will be reflected in cancer incidence. As such prevention strategies should remain focused on other known risk factors, most importantly education on safe sexual behavior and smoking.

The increased risk for developing a smoking-related subsequent cancer confirms that smoking is a key risk factor in this patient group. Smoking-related cancers represented the majority of excess subsequent cancers after cervical cancer in our study, but also in other studies [5,24,29]. Smoking has also been found to be significantly associated with a poorer survival in cervical cancer patients [30]. In the Netherlands, the prevalence of smoking in females has been decreasing since the early 1970s [31,32]. Our study also showed the remarkable decrease of smoking-related cancer rates among the younger Dutch female cohort. This development would consequently lead to a declining burden from smoking-related cancers, including cervical cancer. However, cervical cancer patients tend to smoke more than the general population and in view of the early age at diagnosis (<50 years), smoking cessation at an early age would prospectively be an effective means in the prevention of this cancer and subsequent cancers. As this not easily achievable [33], proactive counseling and referral to smoking cessation clinics are vital for this patient group.

Patients from low socioeconomic backgrounds are at higher risk to develop cervical cancer [34] and incidence rates are decreasing

Table 4
Incidence rate ratios (IRR) for second primary malignancies among patients diagnosed with invasive cervical cancer, in the Netherlands in 1989–2008.

	All second malignancies (n = 676)*		Breast cancer (n = 174)*		HPV-related sites (n = 32)[a,*]		Irradiated sites (n = 142)[a,*]		Smoking-related sites (n = 318)[a,*]		Smoking-related sites (n = 318)[a]	
	IRR	95% CI	IRR	95% CI	IRR	95% CI	IRR	95% CI	IRR	95% CI	IRR	95% CI
Histology												
SCC	1.0		1.0		1.0		1.0		1.0		1.0	
AC	1.0	(0.8–1.2)	0.9	(0.7–1.3)	0.0		1.3	(0.8–2.0)	0.9	(0.7–1.3)	1.0	(0.7–1.3)
Other	0.9	(0.7–1.1)	1.0	(0.7–1.5)	1380.2		0.6	(0.3–1.2)	0.8	(0.6–1.2)	0.8	(0.6–1.2)
Stage												
I	1.0			1.0		1.0		1.0		1.0		
II	0.9	(0.7–1.2)	0.7	(0.4–1.2)	0.7	(0.2–3.1)	1.0	(0.6–1.8)	1.1	(0.8–1.5)	0.9	(0.7–1.3)
III	0.8	(0.6–1.0)	0.6	(0.3–1.0)	1.8	(0.5–6.7)	0.8	(0.4–1.5)	0.9	(0.6–1.3)	0.9	(0.6–1.3)
IV	0.7	(0.4–1.2)	0.8	(0.3–2.2)	3.3	(0.6–17.3)	1.1	(0.4–2.8)	0.7	(0.4–1.5)	0.9	(0.5–1.8)
Unknown	1.4	(0.8–2.2)	2.0	(1.0–4.4)	0.0	0	1.9	(0.8–5.1)	1.2	(0.5–2.6)	1.0	(0.5–2.1)
Age at diagnosis												
0–29 years	**0.3**	(0.1–0.7)	0.3	(0.1–1.2)	0.8	(0.1–6.4)	0.6	(0.2–2.5)	**0.1**	(0.0–0.9)	0.3	(0.0–2.4)
30–49 years	1.0		1.0		1.0		1.0		1.0		1.0	
50–69 years	**2.0**	(1.6–2.4)	1.2	(0.8–1.8)	1.3	(0.5–3.4)	**2.5**	(1.6–3.9)	**2.5**	(1.9–3.3)	1.4	(0.9–2.0)
70+ years	**2.5**	(2.0–3.1)	**1.7**	(1.0–2.7)	**4.7**	(1.8–12.6)	**4.3**	(2.6–7.1)	**2.6**	(1.9–3.7)	1.5	(0.9–2.6)
p-trend		*<0.0001*		*0.0011*		*0.0260*		*<0.0001*		*<0.0001*		*0.6901*
Radiotherapy												
No	1.0		1.0		1.0		1.0		1.0		1.0	
Yes	**1.3**	(1.1–1.7)	1.0	(0.7–1.6)	0.4	(0.1–1.1)	1.2	(0.7–1.9)	**1.6**	(1.2–2.3)	**1.9**	(1.4–2.7)
SES												
High	1.0			1.0		1.0		1.0		1.0		
Intermediate	1.1	(0.9–1.3)	1.1	(0.8–1.7)	1.2	(0.5–3.0)	0.9	(0.6–1.5)	1.0	(0.7–1.4)	1.0	(0.7–1.4)
Low	1.1	(1.0–1.4)	1.0	(0.7–1.4)	0.7	(0.3–1.7)	1.1	(0.7–1.6)	1.3	(1.0–1.7)	1.3	(1.0–1.7)
p-trend		*0.1528*		*0.7190*		*0.3835*		*0.7661*		*0.0480*		*0.0489*
Birth cohort												
Born before 1930											**1.8**	(1.0–3.1)
Born between 1930–1946											**1.9**	(1.3–3.0)
Born between 1947–1955											1.0	
Born between 1955–1962											0.7	(0.5–1.2)
Born after 1962											**0.2**	(0.2–0.5)
p-trend												*<0.0001*

Bold numbers are statistically significant at $p \leqslant 0.05$ level.
[a] See Appendix table 1 for groupings.
* Additionally adjusted for incidence year (continuous).

much slower than in high SES groups [35]. Smoking is certainly playing an important role here, as the smoking prevalence in the Netherlands is still high in this population group [32]. At the same time, infection with a high-risk HPV type is more common in socially deprived groups, while they are less likely to participate in cervical cancer screening and vaccination programs [36,37]. Cervical cancer has also been found to be more common in immigrant women, who are coming from countries with a higher HPV prevalence and are more often living in more deprived neighborhoods [34,38]. Altogether, this makes cervical cancer a main contributor to socio-economic disparities in cancer in the Netherlands, including the risk for second malignancies, which is expected to remain higher in this group. In our study, patients with low SES had a slightly higher risk to develop a smoking-related second malignancy than high SES patients, this was however only borderline statistically significant (Table 4). Primary prevention of cervical cancer (and potential second malignancies) should target low SES groups in order to curb socioeconomic disparities.

Smoking and radiotherapy are both risk factors for subsequent cancers and are known to reinforce each other, even if the lungs only received very little unintended radiation in the case of cervical cancer treatment. This has already been studied more comprehensively in survivors of Hodgkin's disease [39]. In our study, women who underwent radiotherapy exhibited a 30% increased risk for a second tumor when compared to women without radiotherapy; for smoking-related sites this figure was 60%. In line with this, we found an elevated AER for tumors at irradiated sites that remained high even after 10 years of follow-up, similar to the findings of earlier studies [4,12]. The observed long-term increase in risk could thus be a reflection of the interaction between smoking and radiotherapy [40]. This highlights the need for smoking cessation, especially among cervical cancer patients treated with radiotherapy.

Limitations

We restricted our analyses to patients who were followed for more than six months after their initial cervical cancer diagnosis in order to exclude synchronous cancers. High excess risks shortly after the initial cancer diagnosis may be ascribed to an exceptional diagnostic intensity in the course of treatment during the first months of follow-up. From our results, it seems as if we successfully controlled for this as shown by a non-significant SIR for all second cancers at 6–12 months after cervical cancer diagnosis. Yet, we cannot exclude the possibility that cancer survivors may have increased awareness, increasing demand for detection and thus higher incidence of cancer when compared to the general population.

Cervical cancer incidence rate in the Netherlands has dropped in the past decades due to screening for pre-invasive lesions [41]. Most early, non-invasive cervical cancers are thus no longer captured by cancer registration and thus not included in our study. The applied SES measure in this study is ecological and thus cannot rule out that the effects for SES would be different if individual SES was used. However, neighborhood data have been proven to reliably predict socioeconomic differences at the individual level [42]. No individual-level data on smoking behavior, HPV infection status and other important lifestyle factors were available.

Table A1
Overlap between second cancer groupings.*

	n	Overlap with (n)			Overlap (*n*/%)
		Smoking-related	HPV-related	Irradiated sites	
Smoking-related	318	–	10	101	110 (35)
HPV-related	32	10	–	19	29 (91)
Irradiated sites	142	101	19	–	120 (85)

* See Table 1 for definitions.

Conclusion

Cervical cancer survivors in the Netherlands have a 80% higher risk for a second cancer when compared to the general population. Smoking-related second cancers contributed most to this excess burden and high risks persisted for many years, especially in patients who received radiotherapy as initial treatment. Proactive counseling to support quitting smoking may prevent subsequent cancers and could be cost effective especially when targeted to high-risk populations, e.g. persons with a low SES or patients treated with radiotherapy. Long-term follow-up emphasized the importance of primary prevention, namely active smoking cessation and increasing awareness of adverse effects of concomitant risk factors, beyond the first cancer diagnosis.

Conflict of interest statement

All authors declare no conflict of interest.

Appendix A.

See Table A1.

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