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Lung cancer risks in women with previous breast cancer

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Abstract

Evaluation of the adverse effects of breast cancer treatment is becoming increasingly important in light of the earlier detection and prolonged survival of the patients. The beneficial effect of post-surgical radiotherapy has lately been challenged. The Swedish Cancer Registry (SCR) was used to identify approximately 141 000 women with breast cancer, diagnosed between 1958 and 1997, followed-up for the occurrence of lung cancer. Standardised incidence ratios and expected number of lung cancers were calculated using incidence rates from the SCR. There were 613 subsequent lung cancers and a statistically significant increased risk of lung cancer was seen >5 years after breast cancer diagnosis, in contrast to a significantly decreased risk the first five years after the breast cancer diagnosis. The latter finding was confined to those >60 years of age when diagnosed with breast cancer. When restricting the analyses to those cases with information on the laterality of breast and lung cancer, an increased risk of a lung cancer on the same side as the breast cancer was seen >10 years after the breast cancer diagnosis. Birth cohorts with a higher smoking prevalence, i.e. 1930–1949, revealed a higher risk of lung cancer, than previous birth cohorts. Women with breast cancer have a significantly increased risk of developing a subsequent lung cancer possibly related to an interaction between radiotherapy and smoking. © 2002 Elsevier Science Ltd. All rights reserved.

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1. Introduction

Studies of multiple tumours arising in the same individual could be used to increase our knowledge of the relationship between aetiological factors, individual susceptibility, and gene–environment interactions with the ultimate goal of reducing exposure to carcinogens. Iatrogenic effects following treatment for the first cancer are also of additional concern and clinical importance.

Women with early stage breast cancer normally receive post-surgical adjuvant therapy, either as radio-, chemo- or hormonal treatment, or as a combination of any of these modalities. Due to the increasing use of mammography screening, and thus the earlier detection of the tumour, better survival, and favourable effects of the adjuvant treatments, any possible adverse effect of the treatments will have a great impact from a population health perspective [1,2].

During the past 30 years, the use of chemotherapy has undergone a dramatic evolution from single-agent to multiple-drug regimes and a benefit for the use of adjuvant chemotherapy in resectable breast cancers has been proven [3], although these findings have recently been questioned [4]. Adjuvant tamoxifen in oestrogen receptor-positive woman has been found to reduce breast cancer mortality by 26% [5], and has even been shown to reduce the risk of invasive breast cancer in women without a previous breast cancer [6]. Adverse effects of tamoxifen, such as an increase in endometrial and colon cancer, have also been described [7–9].

The favourable effects of adjuvant radiotherapy for breast cancer have been questioned, since only a slight reduction in breast cancer mortality and an increase in overall mortality among the radiotherapy-treated women compared with those treated by other means has been shown [10]. The major non-malignant cause of death was mortality from cardio-vascular disorders especially in the older age groups. In addition, there are reports of an increased risk of lung cancer among women receiving radiotherapy for breast cancer [11,12].

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Additionally, a number of studies have established a causal relationship between external radiotherapy to the chest wall and an increased risk of second primary cancers, such as thyroid, breast and lung cancer [8,13,14]. This has led to an increased demand to optimise the radiation technique for breast cancer [15]. The improved technique generally results in a reduced dose to the heart [16,17]. However, a slightly higher incidence of radiation pneumonitis and a small increase in the mean lung dose has been found [17]. Lung cancer is strongly related to smoking habits and it has been estimated that 90% of all men and 70% of all women who died of lung cancer were former cigarette smokers [18]. Pershagen and colleagues [19] found that residential exposure to radon is an important cause of lung cancer in the general population, but that the risk was confined to smokers. Little is known about to what extent an interaction exists between exposure to tobacco and ionising radiation and how such an interaction influences lung cancer risk.

The aim of this study was to evaluate the lung cancer risk in relation to a possible interaction of smoking habits and radiotherapy in Swedish female breast cancer patients using the unique Swedish registry sources.

2. Patients and methods

Nearly all breast cancer patients in Sweden are treated within the national healthcare system and treatment regimens are similar in different parts of the country. A personal identification number is used for all population registers in Sweden and consists of six digits for year, month, and day of birth, supplemented with four digits representing the place of birth, sex and a check digit. The Swedish Cancer Registry (SCR) was started in 1958 and receives reports on newly diagnosed cancers from both pathologists/cytologists and physicians. Reporting to the register is compulsory, and most diagnosed patients are thus reported from at least two independent sources and 96% of all cancers in Sweden are reported to the register [20].

In all, 147 756 women with a histologically-confirmed invasive breast cancer as the first cancer was reported to SCR between 1958 and 1997. The cohort was matched with the Swedish emigration and cause of death registries. Excluded were patients lost to follow-up because of insufficient information on the date of birth or death ($n=44$), individuals dying within the first 30 days of follow-up ($n=2849$), and those who were diagnosed with another cancer within the first 30 days of follow-up ($n=399$). Altogether 2466 patients were identified as immigrants and were excluded since data on previous cancers were unavailable. Additional 945 patients had emigrated before the diagnosis of breast cancer and later returned to Sweden and it was impossible to establish if the breast cancer was the first cancer. Thus, 141 053 women were included in the study.

2.1. Statistical methods

The person years at risk were calculated starting 30 days after the date of breast cancer diagnosis and ending at the date of death, emigration, lung cancer diagnosis or 31 December 1997, whichever date came first. The reason for excluding the first 30 days was to avoid uncertainties in whatever cancer was diagnosed first. The expected number of lung cancers was calculated by multiplying the age-, sex-, and calendar-year-specific rates from the SCR with the generated person years at risk. Standardised incidence ratios (SIR) were calculated as the ratio between observed and expected number of lung cancers and the 95% confidence intervals (CI) assuming the observed cases to be Poisson distributed. The effect of birth year cohort was studied by Cox's regression, with attained age as the time scale, adjusting for age at breast cancer diagnosis.

In order to study the potential impact of radiation therapy on the lung cancer risk, the predictive value of laterality of breast cancer on the laterality of subsequent lung cancer was analysed. The concordance (the likelihood of finding both cancers on the same side of the body) was possible only on a restricted set of patients since laterality for breast cancer was not reported to SCR until 1970 and gradually for lung cancer from 1986 onwards.

The risk of lung cancer was also assessed in a case-only approach where each woman contributes a pair of lungs, which can be considered as matched for unobserved genetic and environmental factors (primarily smoking). The lung on the breast cancer side was considered as exposed and the contra-lateral lung as unexposed. Since we have no individual information about radiotherapy, the laterality of breast cancer is used as a surrogate variable. Hence the risks are underestimated due to the unobserved fraction of women not treated with radiotherapy. In an ongoing case-control study, the irradiated fraction of patients is preliminary estimated to 62% based on 108 out of the 613 breast and lung cancer cases. The bias in the risk estimates were corrected by subtracting the estimated number of women not receiving radiotherapy, assuming that this fraction is equally distributed over the cells in Table 1. The relative risks and 95% CIs were estimated, as in twin-study design, by conditional logistic regression.

3. Results

The median age at diagnosis of breast cancer among the 141 053 women included in the study was 63.8 years (1st quartile 52.3 years and 3rd quartile 73.8 years). The

Table 1
Relative risk, laterality for breast cancer and lung cancer in relation to years between breast and lung cancer diagnosis

	Lung cancer			
	Time between breast and lung cancer diagnosis			
	≤10 years		>10 years	
Breast:	Right	Left	Right	Left
Breast cancer, no. right	21	25	24	15
left	20	16	16	37
Relative risk for lung cancer on the same side as the breast cancer (95% CI)	0.8 (0.5–1.3)		2.0 (1.3–3.0)	
Corrected relative risk assuming 38% did not receive radiotherapy	1.3		3.2	

Table 3
Observed number of lung cancers (Obs.), relative risk (RR),[a] and 95% confidence interval (CI) in relation to birth year cohort

Birth year cohort	Obs.	RR	95% CI
<1909	146	1.00	–
1910–1919	185	1.35	1.05–1.73
1920–1929	182	1.81	1.73–2.40
1930–1939	80	2.63	1.83–3.79
>1940	20	2.48	1.35–4.55

[a] Adjusted for age at breast cancer diagnosis and with attained age as the time scale.

mean period between the initial diagnosis of breast cancer and the development of primary lung cancer was 12.2 years (1st quartile 5.5 years and 3rd quartile 18.1 years). During the 40-year study period (1958–1997), 613 primary lung cancers occurred, SIR = 1.32 (95% CI 1.21–1.42). Throughout the first 5 years, there was a significantly decreased risk of lung cancer followed by significantly increased risks in the subsequent periods, reaching its maximum >20 years after breast diagnosis SIR = 2.53 (95% CI 2.10–3.04, Table 2). When the lung cancer risk was divided in relation to age at breast cancer diagnosis, the decreased risk during the first 5 years was confined to those >60 years of age at breast cancer diagnosis (Table 2). The highest risk of a subsequent lung cancer was observed among those <50 years of age at the time of the breast cancer diagnosis (SIR = 2.30; 95% CI 1.97–2.63). No trend over time since breast cancer diagnosis was observed for those >69 years at the time of the breast cancer diagnosis.

Since SIR was adjusted to calendar period and age, the general effect of the increased smoking prevalence cannot be assessed using SIR as a measure. Instead a Cox's regression analysis within the cohort including age at the diagnosis of breast cancer and birth year cohort as covariates was used. The risk of lung cancer increased with birth year cohort (Table 3), which mirrors the increasing smoking prevalence among women seen in Sweden (Fig. 1). Introducing birth year as a continuous variable in the model yielded an increasing lung cancer incidence of 3% per birth year.

There were 174 lung cancer cases with information on laterality of both lung and breast cancers. By utilising the fact that both organs are paired, these data could be used to assess the lung cancer risk in a similar fashion as in a disease discordant twin pair study. The risk of developing lung cancer on the same side as the breast cancer compared with the contra-lateral side was increased after more than 10 years from the breast cancer diagnosis relative risk (RR) = 2.0; 95% CI 1.3–3.0). Within 10 years from the breast cancer diagnosis no elevated risk was seen (Table 1).

However, the risk estimation in this approach is biased towards the null since we included a fraction of patients not receiving radiotherapy, anticipated to show no association with laterality. In an ongoing effort this fraction was preliminarily estimated to be 38%. By using this estimate for bias correction, the RR seen after more than 10 years from the breast cancer diagnosis was increased from 2.0 to 3.2 (Table 1).

Table 2
Observed number of lung cancers (OBS.), standardised incidence ratio (SIR), and 95% confidence interval (CI) in relation to age at breast cancer diagnosis and time after initial breast cancer diagnosis

Years after diagnosis	Age at breast cancer diagnosis														
	<50 years			50–59 years			60–69 years			>69 years			Total		
	Obs.	SIR	95% CI	Obs.	SIR	95% CI	Obs.	SIR	95% CI	Obs.	SIR	95% CI	Obs.	SIR	95% CI
<5	14	1.18	0.65–1.98	40	1.34	0.96–1.82	47	0.74	0.54–0.98	42	0.51	0.37–0.68	143	0.76	0.64–0.89
5–9	28	2.17	1.44–3.13	44	1.67	1.22–2.25	42	0.98	0.70–1.32	32	0.97	0.66–1.37	146	1.27	1.07–1.49
10–14	32	2.26	1.55–3.20	42	1.85	1.33–2.50	30	1.27	0.86–1.82	13	1.19	0.60–2.20	117	1.66	1.37–1.99
15–19	35	2.34	1.63–3.26	33	1.96	1.35–2.75	20	1.91	1.17–2.95	1	0.46	0.01–2.57	89	2.00	1.61–2.47
>20	78	2.86	2.26–3.57	31	2.10	1.42–2.97	9	2.18	1.00–4.14	0	-	0–10.95	118	2.53	2.10–3.04
Total	187	2.30	1.97–2.63	190	1.72	1.47–1.96	148	1.02	0.86–1.19	88	0.69	0.55–0.83	613	1.32	1.21–1.42

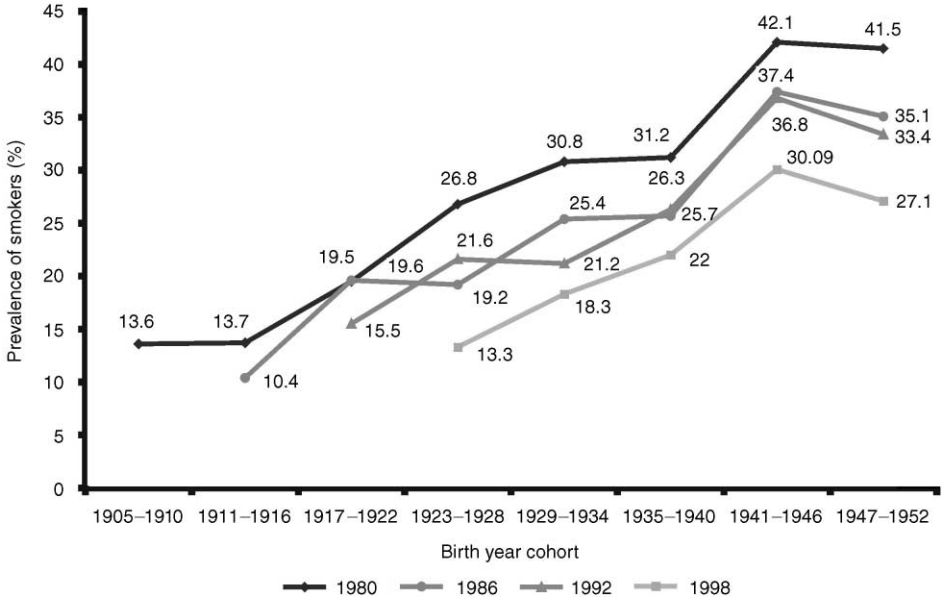

Fig. 1. Prevalence of smokers in Swedish females in relation to birth year cohort and calendar period [40].

4. Discussion

Our finding of an increased risk of primary lung cancer following a diagnosis of breast cancer is important since adjuvant radiotherapy has been one of the most important parts of the multidisciplinary treatment of breast cancer. An increasing number of women are treated with partial mastectomies and the use of adjuvant radiotherapy may increase this use even further [21,22]. Recent data suggest an improvement in local control and an increase in overall survival when radiation therapy is used selectively following mastectomy [23]. These data have lately been challenged as a 37.1% overall survival was seen among radiotherapy-treated women compared with 35.9% among the non-treated group [10].

The most important risk factor for breast cancer is age. Cigarette smoking is a risk factor for many cancers, but no clear association with breast cancer has been identified [24–26]. In a recent study, smoking women, supposedly slow acetylators of aromatic amines were found to have a dose-dependent increased risk of postmenopausal breast cancer [27]. No other known and accepted risk factors are shared with lung cancer, possibly with the exception of tuberculosis. Previous lung tuberculosis has been found to increase the risk of a subsequent lung cancer [28,29] and repeated fluoroscopies because of lung tuberculosis increases the risk of breast cancer [30,31].

Our findings are consistent with the hypothesis that radiation therapy and smoking have a profound carcinogenic effect on the risk of lung cancer among women. However, it should be underlined that this is a register study and we do not have individual data for the cases under study. As has previously been shown, it requires a latency period of at least 10 years between the breast cancer diagnosis and the lung cancer diagnosis [12,32–34]. Furthermore, the carcinogenic effect of radiotherapy seems to be limited to the ipsilateral lung, with little or no effect of radiation on the contralateral lung.

Similar data were reported in a follow-up study by Neugut and colleagues [35] with a relatively large, but non-significant trend towards the development of lung cancer among non-smokers who received radiation therapy (RR = 3.2). For irradiated smokers, the RR was 32.7 (95% CI 6.9–154), and for the non-irradiated smokers, the RR was 14.5 (95% CI 4.0–53.1), at least for patients treated before 1980 [35]. These studies were limited to a small number of cases and lacked reliable information on exposure for both external radiotherapy and smoking. In addition, the studies included only patients given radiotherapy after a total mastectomy and not after the now more common partial mastectomy.

In this study, there was also a significantly decreased risk of lung cancer within the first 5 years following a diagnosis of breast cancer. This could of course be due to underreporting since a finding of an irregularity at pulmonary X-ray examination among breast cancer patients could be interpreted as metastases and not adequately diagnosed especially during the first years after a breast cancer diagnosis. It could also be that tamoxifen has a protective effect on the development of lung cancer since hormonal treatment is more common in the elderly. Lung cancer risk increased with time since the breast cancer diagnosis, reaching a significant increase after 5 years and a maximum after more than 20 years. This is in agreement with the findings among

Japanese A-bomb survivors indicating that an induction and latent period of at least 10 years is necessary for most solid tumours, including lung cancer [36]. This time pattern argues against a profound influence of misclassified breast cancer metastases of the lung.

The age at exposure to ionising radiation may influence the risk of a subsequent cancer. In our series, the highest risk of a subsequent lung cancer was seen among those aged less than 50 years at the time of breast cancer diagnosis (Table 2). It could be that this is a reflection of acquired or inherited factors that may influence both the risk of breast and lung cancer. Rebbeck [37] has described that low penetrance susceptibility genes involved in carcinogen metabolism or DNA damage response influences not only age of onset of the cancer, but the risk of multiple cancers.

A selection based on radiotherapy treatment and lifestyle factors or an interaction of several factors might also have the most profound effect in those exposed when young. It could also be that the lower risk in older women is due to competing causes of death as recently described in a meta-analysis of cause of death-specific data on approximately 20 000 women with previous breast cancer [10]. In women aged 60–69 years at the breast cancer diagnosis, the adverse affect, i.e. increased mortality from cardio-vascular disorders, outweighs the beneficial effects of radiotherapy.

This study is unique among studies of second primary lung cancer following treatment for breast cancer because of the size, the long follow-up, the information on laterality for the breast cancer since 1970, and lung cancer since mid-1980s. However, there are weaknesses that have to be discussed. In the present cohort, individual data on exposure to smoking and ionising radiation were not available and this will be a future challenge. Furthermore, it cannot be ruled out that other risk factors such as reproductive factors and hormonal replacement therapy influence the risk of not only breast, but lung cancer.

The prevalence of Swedish female smokers increased from 10% in the 1940s to 35% in the 1970s, followed by an ongoing decline [38,39]. Since the early 1990s, Sweden is one of the few countries in the world where the fraction of smoking women is higher than that of males [40].

Recent studies have implicated that women are more sensitive than men to the carcinogenic effect of tobacco, since lung cancer risk seems to be approximately 2-fold higher in women for a similar cigarette smoking level [41–43]. An increase in lung cancer incidence of 3% per year was seen in the general population [44] mirroring the increasing smoking prevalence among Swedish women (Fig. 1).

In conclusion, our study shows that women with breast cancer have an increased risk of lung cancer possibly related to radiotherapy and smoking. Although a causal relationship still remains to be elucidated, the results of this study strongly suggest that women with breast cancer especially those selected for radiotherapy should be encouraged to give up smoking.

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