Survival of Women with Breast Cancer in Relation to Smoking

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ABSTRACT

Objective: To compare survival of patients with breast cancer who had never smoked, were smokers, and who were ex-smokers.

Design: Observational study.

Setting: City of Malmö, Sweden.

Patients: 792 patients with breast cancer diagnosed between 1977–1986 in the Malmö mammographic screening trial.

Interventions: Follow-up of breast cancer cases through record-linkage with the Swedish Cause of Death Registry.

Main outcome measures: Death from breast cancer. Relative risk (RR) with 95% confidence interval (CI) of death from breast cancer was calculated for different smoking groups using Cox's proportional hazards analysis.

Results: During a mean follow-up of 12.1 years, 145 patients died of breast cancer. Breast cancer mortality was $1347/10^5$ person-years in those who had never smoked, $1941/10^5$ in smokers, and $1493/10^5$ in ex-smokers. The crude RR for smokers and ex-smokers, compared with those who had never smoked were 1.44 (1.01 to 2.06) and 1.13 (0.66 to 1.94), respectively. The RR associated with smoking remained significant after adjustment for age and stage at diagnosis, 2.14 (1.47 to 3.10), and other potential confounders.

Conclusions: Survival after breast cancer was, as expected, strongly related to stage at diagnosis. However, stage by stage there was considerable variation between individual patients. We conclude that differences with regard to exposure to smoking contribute to this heterogeneity.

Key words: breast cancer, survival, smoking.

INTRODUCTION

Survival after breast cancer is strongly related to stage at diagnosis (7), yet stage by stage there are pronounced variations in the outcome between patients even when differences with regard to treatment, including surgery and adjuvant radiotherapy and chemotherapy, are taken into account.

Several epidemiological studies have indicated that smoking may increase the risk of breast cancer (1, 10, 14). Whether smoking influences survival as well has been given less scientific attention, but according to at least two studies it seems that smokers have a less favourable prognosis than non-smokers (21, 22).

The aim of this follow-up-study of 792 women with breast cancer diagnosed in the Malmö mammographic screening trial between 1977 and 1986 was to compare survival rates in those who had never smoked, smokers, and ex-smokers.

PATIENTS

In all 42 283 women born between 1908 and 1932 were the subjects in the Malmö mammographic screening trial from 1977 to 1986 (3). During this period, 1034 of these women were diagnosed with breast cancer of whom 34 had been diagnosed previously. All but five of them were treated at Malmö University Hospital. The primary objective of the trial was to find out whether invitation to screening was associated with reduced mortality from breast cancer (3).

A second objective was to study the clinical course of the disease in relation to established and potential prognostic markers, including mode of detection, clinical stage, histological type, treatment, body height and weight, menopause, parity, history of oophorectomy, and use of hormone replacement therapy (HRT). We used case sheets from the hospital records and a database created by one of the authors [JPG] to retrieve this information. Information on smoking habits was retrieved by review of hospital records. Patients were categorised as those who had never smoked, current smokers, and ex-smokers. Information on smoking habits was missing in 242 of the 1034 cases, so the study group comprised 792 women.

Clinical stage was based on the TNM-system

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(tumour, nodes, metastases) (2). The histological classification that was used was a modification of the WHO classification proposed by Linell et al. (12). It divides invasive ductal carcinoma into comedo and tubuloductal carcinomas. Tubuloductal tumours are further subdivided into two groups according to the content of tubular structures.

Cause of death

Deaths from the time of recruitment until 31 December 1996 were retrieved by record linkage with the Swedish Cause of Death Register. Underlying cause of death was coded according to the 8th and 9th versions of the ICD-code issued by WHO (20). During a mean follow-up of 12.1 years there were 145 deaths from breast cancer and 347 deaths from all causes. Mean (SD) time from diagnosis to death was 5.2 years (3.8) for those who had never smoked, 5.7 (3.8) for smokers and 4.8 (3.2) for ex-smokers.

Statistical methods

Each woman was followed from diagnosis until death or the end of follow up, 31 December 1996. All statistical tests were made with the SPSS package (19). Cox's proportional hazards analysis was used to calculate relative risks of dying of breast cancer for smokers and ex-smokers (with a 95% confidence interval (CI)), compared with those who had never smoked, after adjustment for age and stage at diagnosis.

To adjust for other potential confounders, we used a second model in which anthropometric measures, menstrual status, parity, oophorectomy, whether they had used HRT, and way of detection were introduced as covariates using backward stepwise selection in the Cox's analysis (19). The score statistic ($p < 0.05$) decided entry and removal was done by the likelihood-ratio statistic based on conditional parameters estimates, ($p < 0.10$). Tumour histology and treatment in relation to smoking habits were evaluated after stratification of stage at diagnosis.

Differences in stage at diagnosis across smoking categories were assessed by computing the odds for stage II+ compared with stage 0-I tumours in smokers and ex-smokers in relation to never smokers. The odds ratios were calculated by unconditional logistic regression analysis after adjustment for age at diagnosis, menopausal status, BMI, and mode of detection.

The 242 cases who were excluded from the analysis because of missing information on smoking habits, were compared to the 792 in the study cohort in terms of survival and prevalence of prognostic markers to assess potential selection bias.

Table I. *Breast cancer mortality in relation to smoking habits*

Smoking status	No. of subjects	No. of deaths from breast cancer (all deaths)	Person years	Breast cancer mortality/ 100 000	RR (95% CI)	RR (95% CI) Adjusted for age and stage	RR (95% CI) Adjusted for stage and menopausal status
Never smoked	491	81 (211)	6014	1347	1.00	1.00	1.00
Current smoker	216	48 (105)	2473	1941	1.44 (1.01 to 2.06)	2.14 (1.47 to 3.10)	1.95 (1.22 to 3.13)
Ex-smoker	85	16 (31)	1072	1493	1.13 (0.66 to 1.94)	1.05 (0.60 to 1.83)	1.28 (0.60 to 2.74)
Total	792	145 (347)	9559	1517			

RESULTS

Breast cancer mortality in women with stage 0-I tumours was $443/10^5$ person-years, in stage II: $2225/10^5$, in stage III: $11\,374/10^5$ and in stage IV: $32\,927/10^5$.

In all these groups, some women died of breast cancer within three years of diagnosis but others survived until the end of follow-up, more than 10 years (among women with stage IV tumours the longest survival was 7.6 years).

Breast cancer mortality was $1347/10^5$ in those who had never smoked, $1941/10^5$ in smokers, and $1493/10^5$ person-years in ex-smokers. Crude relative risk, compared with those who had never smoked, were 1.44 (1.01 to 2.06) and 1.13 (0.66 to 1.94) for smokers and ex-smokers, respectively, (Table I).

All-cause mortality was $3508/10^5$ in never smokers, $4246/10^5$ in smokers, and $2892/10^5$ person-years in ex-smokers. The age-adjusted relative risk was 1.46 (1.15 to 1.86) for smokers and 0.98 (0.67 to 1.44) for ex-smokers.

The increased breast cancer mortality associated with smoking remained significant after adjustment for age and stage at diagnosis, RR 2.14 (1.47 to 3.10), (Fig. 1), and other potential confounders, (Tables I and II). The extended Cox's analysis was limited to 555 cases because of missing information. Exclusion of 34 cases who had been diagnosed with breast cancer before the screening trial did not change the association. The analyses were repeated using only the 35 deaths from breast cancer that had been classified according to ICD-9 and had been confirmed by necropsy. In these 35 women the RR of death from breast cancer, as compared to never smokers was 3.31 (1.57 to 6.95) for current smokers and 1.62 (0.51 to 5.07) for ex-smokers.

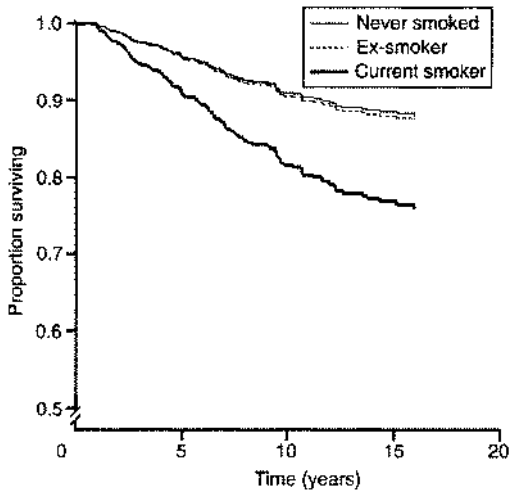

Fig. 1. Survival from breast cancer according to smoking status at the time of diagnosis.

Comedo carcinoma and treatment by complete mastectomy was most common among never smokers with stage 0-I tumours, while comedo carcinoma and treatment with adjuvant chemotherapy was most common among ex-smokers in stage II+ tumours, (Table III).

The odds ratio for a stage II+ compared with a stage 0-I tumour was 0.79 (0.52 to 1.21) in smokers compared with 1.00 in never smokers and adjusted for age at diagnosis, menopausal status, BMI, and mode of detection. Corresponding comparison for ex-smokers showed an odds ratio of 0.90 (0.56 to 1.44).

Smokers who died of breast cancer were compared with those who did not, to assess potential modifiers, (Tables IV and V). The influence of these factors on survival was evaluated in a Cox's proportional hazards model with adjustment for age and stage. In the analysis of the effect of adjuvant hormonal and chemotherapy, menopausal status was added as a third covariate. The only factor that significantly affected survival in smokers was use of HRT, RR for ever use compared with never use: 0.34 (0.12 to 0.97).

Breast cancer mortality was higher among the 242 cases for whom there was no information on smoking habits, $2521/10^5$ person-years compared with $1517/10^5$ for the study group. The prevalence of stage III and IV tumours was similarly higher in this group, (Table VI). If all 242 women with missing information on smoking had been never smokers, the RR of breast cancer death, adjusted for stage and menopausal status, in current compared with never smokers would have been 1.61 (1.15 to 2.26).

DISCUSSION

We conclude that differences in exposure to smoking contribute to the heterogeneity in long term survival of women with breast cancer. The appropriateness of that conclusion should be assessed in relation to certain methodological issues.

Differences between groups with regard to completeness of follow up and confirmation of end-points could have confounded the results. As vital status was updated on each patient and it has been confirmed that cause of death in women with breast cancer is accurate (3, 16), we consider it unlikely that the results were confounded by biased retrieval or low validity of end-points. In addition, when we restricted the analysis to deaths that had been coded according to ICD-9 and which had been confirmed by necropsy, the main findings remained.

Misclassification with regard to exposure to smoking is another relevant issue. Some of the women who did not smoke were described as non-smokers in the hospital records. These women were counted as never

Table II. *Age, mode of detection, and risk factors for breast cancer in relation to smoking habits. Figures, except those in italics, are percentages*

Factor	Never smoked (n = 491)	Current smoker (n = 216)	Ex-smoker (n = 85)
Mean (SD) age at diagnosis, (years)	*63.1 (7.2)*	*60.0 (7.0)*	*60.2 (7.1)*
Mean (SD) body height, (meter)	*1.63 (0.06)*	*1.64 (0.06)*	*1.64 (0.06)*
Mean (SD) BMI, (kg/m^2)	*25.8 (4.3)*	*24.6 (4.1)*	*25.5 (4.9)*
Postmenopausal	89.6	86.1	82.4
Nullipara	19.4	22.3	17.9
Oophorectomy	9.3	9.5	9.3
Ever taken HRT	14.7	22.0	19.0
Detected by mammography	50.0	47.7	50.6
Stage			
0	11.7	12.5	9.4
I	44.6	49.5	49.4
II	34.4	31.5	30.6
III	5.9	3.2	2.4
IV	3.5	3.2	8.2

Table III. *Histopathology and treatment in relation to smoking habits and stage at diagnosis. Figures are percentages*

	Stage 0-I			Stage II+		
Factor	Never smoked (n = 275)	Current smoker (n = 134)	Ex-smoker (n = 50)	Never smoked (n = 214)	Current smoker (n = 82)	Ex-smoker (n = 35)
Histological type						
Tubular (++++, +++)	18.8	25.4	20.4	11.0	7.3	12.1
Tubuloductal (++, +, 0)	26.8	23.9	30.6	34.9	36.6	24.2
Comedo	24.3	16.4	12.2	31.1	36.6	45.5
Lobular	4.4	9.7	14.3	12.9	11.0	15.2
Invasive, varia	4.8	4.5	6.1	10.0	8.5	3.0
Carcinoma in situ	21.0	20.1	16.3	–	–	–
Treatment						
Mastectomy	72.1	61.9	62.0	87.7	85.0	82.9
Local excision	27.9	38.1	38.0	7.5	7.5	5.7
Inoperable	0	0	0	4.7	7.5	11.4
Extent of operation						
Restricted to breast	14.0	16.4	20.0	0.9	1.3	0
Removal of axillary lymph nodes	86.0	83.6	80.0	94.3	91.3	88.6
Inoperable	0	0	0	4.7	7.5	11.4
Adjuvant hormonal therapy	0.7	0	2.0	40.3	40.7	42.9
Adjuvant chemotherapy	0	0	0	11.8	14.8	34.3
Postoperative radiotherapy	35.4	35.8	34.0	71.6	65.4	65.7

having smoked in our study, although a certain proportion of them probably should have been labelled ex-smokers. The prevalence of never smokers in our cohort was however similar to that observed in health surveys of women in corresponding age groups in the city (11).

Changes in exposure is a problem in long-term cohort studies. Studies on tobacco consumption in Sweden (17) indicate that about 10% of those who smoked in 1977 may have stopped by the end of follow-up. Whether this figure is applicable to women with breast cancer as well and whether breast cancer may cause ex-smokers to take up smoking is unknown.

Use of HRT is associated with an increased incidence of breast cancer (4). It remains controversial, however, whether HRT influences survival (8, 18). If HRT is associated with survival, misclassification as a reason of changed behaviour during follow-up may

Table IV. *Age, mode of detection, and risk factors for breast cancer in relation to death from breast cancer among smokers. Figures, except those in italics, are percentages*

	Stage 0-I		Stage II+	
Factor	Current smokers dead from breast cancer (n = 12)	Rest of current smokers (n = 122)	Current smokers dead from breast cancer (n = 36)	Rest of current smokers (n = 46)
Mean (SD) age at diagnosis, (years)	*58.7 (5.4)*	*59.9 (6.7)*	*59.9 (6.5)*	*60.8 (8.5)*
Mean (SD) body height, (meter)	*1.67 (0.04)*	*1.63 (0.06)*	*1.61 (0.06)*	*1.66 (0.06)*
Mean (SD) BMI, (kg/m^2)	*26.9 (5.1)*	*24.0 (3.9)*	*26.0 (4.8)*	*24.8 (4.0)*
Postmenopausal	91.7	87.7	88.9	78.3
Nulliparous	20.0	21.7	25.0	22.2
Oophorectomy	9.1	6.3	15.2	13.6
Ever taken HRT	0.0	25.2	12.1	26.2
Detected by mammography	40.0	66.4	13.9	26.1

Table V. *Histopathology and treatment in relation to death from breast cancer among smokers. Figures are percentages*

	Stage 0-I		Stage II+	
Factor	Current smokers dead from breast cancer (n = 12)	Rest of current smokers (n = 122)	Current smokers dead from breast cancer (n = 36)	Rest of current smokers (n = 46)
Histological type				
Tubular (++++, +++)	0.0	27.9	13.0	0.0
Tubuloductal (++, +, 0)	41.7	22.1	37.0	36.1
Comedo	16.7	16.4	28.3	47.2
Lobular	16.7	9.0	8.7	13.9
Invasive, varia	8.3	4.1	13.0	2.8
Carcinoma in situ	16.7	20.5	–	–
Treatment				
Mastectomy	66.7	61.5	80.0	88.9
Local excision	33.3	38.5	2.9	11.1
Inoperable	0.0	0.0	17.1	0.0
Extent of operation				
Restricted to breast	16.7	16.4	2.9	0.0
Removal of axillary lymph nodes	83.3	83.6	80.0	100.0
Inoperable	0.0	0.0	17.1	0.0
Adjuvant hormonal therapy	0.0	0.0	54.3	30.4
Adjuvant chemotherapy	0.0	0.0	20.0	10.9
Postoperative radiotherapy	41.7	35.2	68.6	63.0

have confounded the results. As HRT is contraindicated in women with breast cancer, we consider that few non-users began HRT during follow-up and this ought not to have confounded the results.

The 792 women in the study cohort cannot in terms of mode of detection, stage at diagnosis, exposure to known risk factors, and survival rate be considered representative of all 1034 women diagnosed within the Malmö mammographic screening trial. This raises the question of a potential selection bias associated with smoking. However, if all cases with missing values were assumed to have never smoked, there was still a significantly higher mortality in current compared with never smokers. It is our view that it is unlikely that the results were confounded by biased selection of cases.

Differences in age, stage at diagnosis, and risk factors were accounted for in the analysis. To what extent the more common use of complete mastectomy among never smokers with stage 0-I tumours may have influenced the results is unknown.

Our results are in line with the findings in two other studies (21, 22). It has been suggested that the lower

Table VI. *Age, mode of detection, and risk factors for breast cancer in cases were information on smoking was available and missing respectively. Figures, except those in italics, are percentages*

Factor	Information on smoking available (n = 792)	Information on smoking missing (n = 242)
Mean (SD) age at diagnosis, (years)	*61.9 (7.3)*	*62.4 (8.3)*
Mean (SD) body height, (meter)	*1.63 (0.06)*	*1.63 (0.06)*
Mean (SD) BMI, (kg/m^2)	*25.4 (4.4)*	*24.2 (4.2)*
Postmenopausal	87.9	87.6
Nulliparous	20.1	26.9
Oophorectomy	9.4	8.7
Ever taken HRT	17.1	17.6
Detected by mammography	49.4	43.5
Stage		
0	11.6	21.5
I	46.5	38.8
II	33.2	23.2
III	4.8	6.3
IV	3.9	10.1

survival rate of smokers may be the result of an impairment of the immune defence system (6) or that smoking may promote the development of more aggressive, oestrogen-receptor negative, tumours (15).

Smokers and never smokers may differ in many other respects that may influence survival. Breast cancer survival correlates with several socioeconomic circumstances (9). The increased mortality among women of low socioeconomic status seems to be related to stage at diagnosis (5). Whether socioeconomic deprivation may influence individual susceptibility as well is not known.

According to some studies it seems that high intake of fat may be associated with reduced survival (23). In nutrition surveys it has been found that smokers consume more fat than never smokers (13).

Exposure to HRT before diagnosis was associated with an improved prognosis among smokers. This effect remained significant after adjustment for age and stage at diagnosis. As use of HRT was more common among smokers than among never smokers this may have contributed to a more favourable prognosis in that group. The association with smoking remained significant, however, after adjustment for this potential confounder.

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