

ORIGINAL ARTICLE

Influence of metabolic indicators, smoking, alcohol and socioeconomic position on mortality after breast cancer

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ABSTRACT

Background. Factors differently distributed among social groups like obesity, metabolic syndrome, diabetes, smoking, and alcohol intake predict survival after breast cancer diagnosis and therefore might mediate part of the observed social inequality in survival.

Material and methods. We conducted a cohort study among 1250 postmenopausal breast cancer patients identified among 29 875 women in the Danish Diet, Cancer and Health Study. Participants completed questionnaires and anthropometric measurements were made at enrollment. Information on survival, socioeconomic position, and comorbidity was obtained by linkage to national Danish registries. Clinical information was obtained from the nationwide Danish Breast Cancer Database. Selected information was obtained from hospital records at time of diagnosis. All analyses were based on Cox proportional hazard models, using death from all causes as outcome.

Results. Median follow-up was 9.6 years [interquartile range (IQR), 2.2–17.0 years]. The hazard ratio (HR) for death from all causes increased with lower education (p for trend, 0.01). Adjustment for disease-related prognostic factors, comorbidity and metabolic indicators measured as BMI, waist circumference and diabetes, and smoking and alcohol affected but did not explain the social gradient.

Conclusion. The findings indicate that these factors explain some but not all the social inequality in survival after breast cancer and that improvement of lifestyle to some extent would improve survival among women with low socioeconomic position.

In Denmark women with higher education or higher income are found to have higher incidence of breast cancer whereas women with low socioeconomic position have poorer survival rate [1]. The higher incidence among well-educated and highly paid women is largely explained by differences in lifestyle and disparity between social groups [2]. Regarding survival after breast cancer diagnosis, factors like stage at diagnosis, participation in mammography screening, access to treatment, and comorbidity have been found to explain some but not all differences by socioeconomic position in survival rates [3–6]. Furthermore, obesity, metabolic syndrome, and type 2 diabetes have been shown to predict poorer survival

after breast cancer diagnosis and are also differently distributed by social group [7–9].

Obesity may affect breast cancer prognosis in several ways. First, obese women are often diagnosed with more advanced disease [8]. Second, obesity affects the level of various hormones including estrogen, insulin, and the insulin-like growth factor (IGF) system and thereby tumor growth [10]. Third, treatment may be affected by obesity and therefore be less effective than among non-obese women [11].

Likewise, smoking and alcohol intake are both associated with poorer survival after diagnosis of breast cancer [12] and thus such lifestyle factors may further contribute to the social inequality in survival

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after diagnosis by affecting general health and the risk of having any comorbidity at the time of breast cancer diagnosis.

The initiation of the carcinogenesis process in the breast takes place up to 10–20 years before diagnosis, and lifestyle factors like smoking and alcohol intake as well as metabolic indicators like overweight, obesity and type 2 diabetes at that time may therefore not only increase the risk of breast cancer, but also affect the tumor environment determining tumor characteristics which will affect prognosis later on. Closer to diagnosis the same lifestyle factors and metabolic indicators may, however, also affect progression and even metastasizing [13].

Drawing on the Danish Diet, Cancer and Health cohort we assessed whether metabolic indicators related to overweight and obesity [body mass index (BMI), waist circumference, diabetes], smoking and alcohol intake measured years before or at diagnosis were associated with death from all causes. Furthermore, we investigated if socioeconomic differences in overall survival after diagnosis of breast cancer could be explained by differences in disease stage, comorbidity, metabolic indicators, smoking, and alcohol intake.

Material and methods

Between December 1993 and May 1997, 79 729 women aged 50–64 born in Denmark and living in the Copenhagen or Aarhus area were invited to participate in the cohort study Diet, Cancer and Health. Of these, 29 875 accepted the invitation, corresponding to 37% of those invited. The study was approved by the regional ethical committees on human studies in Copenhagen and Aarhus [jr.nr.(KF)11-037/01] and by the Danish Data Protection Agency.

All participants completed a validated 192-item food-frequency questionnaire and attended a clinic where anthropometric measurements were made and where they filled in a questionnaire on lifestyle- and health-related issues. For a detailed description of the cohort, see [14].

In Denmark, all citizens are registered in the Danish Central Population Register with a unique 10-digit Personal Identification Number that makes it possible to obtain information on vital status and migration, along with linkage to information from other Danish registries. In the Danish Cancer Registry, which has accurate, almost complete registration of cancer patients [15], we identified 1250 postmenopausal cohort members with a primary diagnosis of breast cancer through December 31, 2008. Information on educational level and income was obtained through linkage with the population-based Integrated Database for Labour Market

Research in Statistics Denmark for 1995, which was in the middle of the enrollment period for the cohort.

Information on somatic comorbid disease was obtained from the Danish National Patients Registry, which registers discharge diagnoses from hospital admissions, outpatient and emergency ward contacts. From the National Diabetes Register, which links information from multiple health registries from 1995 and onwards we obtained information on diabetes diagnoses [16]. Based on the information used to construct the register it is not possible to distinguish between type 1 and type 2 diabetes. From the Danish Breast Cancer Cooperative Group's nationwide database we obtained information on tumor size, number of positive lymph nodes, hormone receptor status, malignancy grade and distant metastases [17]. Patients were followed from date of diagnosis until either date of death from any causes, emigration, or end of study period on 31 December 2013, whichever came first.

We collected selected information from hospital records on weight, height, current smoking status and alcohol intake at time of diagnosis for all patients. Information on smoking and alcohol was self-reported in questionnaires filled in at admission. All information was to be given in the period around the time of diagnosis. Information on weight and height was collected from the questionnaires or the anesthesia sheet.

Definition of variables

BMI was calculated as weight in kilograms divided by height in cm². Height at baseline was used to calculate BMI at diagnosis. BMI was used linearly or categorized as < 25 (normal weight), 25–30 (overweight) and > 30 (obese). Diabetes was a dichotomized variable (yes/no).

Smoking status at baseline was divided into never, former, or current. Smoking status at time of diagnosis was divided into never, former at baseline (if former at baseline), former at diagnosis (if current at baseline), and current (including never and former at baseline). Alcohol intake at baseline and diagnosis was divided into three groups: abstainers, 1–14 drinks/wk, and > 14 drinks/wk.

Highest attained education was categorized as basic school/high school, vocational training or higher education and income as individual gross income deflated according to the 1995 value of the Danish crone in quartiles based on all individuals invited to enroll in the cohort.

We used Charlson Comorbidity Index (CCI) to classify comorbidity [18]. The index provides an overall score for comorbidity based on composite

values weighted by level of severity assigned to 19 selected conditions scoring from 1 to 6. To eliminate the risk of conditions related to the subsequent breast cancer diagnosis, we used information up to one year before diagnosis. Disease-related prognostic variables included tumor size in mm, tumor positive lymph nodes (yes/no and linear if yes), malignancy grade (1–3 or non-classified) and receptor status (estrogen receptor positive, negative, or unknown).

Statistical analyses

Substitution of data was applied by multiple imputation due to incomplete information on socioeconomic parameters (2%), tumor characteristics (7–10%) and lifestyle at diagnosis (12–18%). Multiple imputation relies on the assumption that information is missing at random and that it is related to other variables [19]. Through the multiple imputation we generated five new data set and afterwards each of them were analyzed by Cox proportional hazard models, using death from all causes as outcome and time since diagnosis at the underlying time axis. Subsequently, the results from these analyses were pooled to calculate the gathered estimate of the model. Two-sided 95% confidence intervals for the hazard ratios (HRs) were calculated on the basis of a Wald test of the Cox regression parameter, that is, on a log scale. The statistical software SAS (release 9.3) was used for the analyses.

HRs for death from all causes for the metabolic indicators, smoking status and alcohol intake were due to possible differences in the underlying hazard, stratified by age at diagnosis and hereafter stepwise adjusted for disease-related prognostic factors entered as individual covariates and comorbidity. In analyses of diabetes we used the CCI with diabetes excluded. Analyses regarding socioeconomic position were stratified for age at diagnosis and stepwise in Model 1 for disease-related prognostic factors (tumor size, lymph node status, number of positive lymph nodes, malignancy grade and receptor status), comorbidity in Model 2 [CCI (linear)], and metabolic indicators and lifestyle in model 3 [BMI (linear), waist circumference (linear), diabetes, smoking and alcohol at baseline, as well as same variables at time of diagnosis]. Since educational level may affect income, analyses of income were adjusted for educational level.

Results

From a total of 1250 identified postmenopausal breast cancer patients, we excluded 20 patients with distant metastasis at diagnosis and one with negative follow-up time leaving 1229 (98%) patients for analyses. Median follow-up from date of diagnosis to date

of death, emigration or end of study was 9.6 years [interquartile range (IQR), 2.2–17.0 years]. Median time from baseline to diagnosis was 6.5 years (IQR 0.70–12.0 years). Median age at diagnosis was 64.3 (IQR 54.9–73.3 years). Among the 1229 patients, 656 (53%) were normal weight, 406 (33%) overweight, and 167 (14%) obese. Table I shows the characteristics of the breast cancer patients by educational level. In total 41% of the patients had vocational training and 24% had higher education, while 41% had an income in the highest quartile.

At baseline, women with a BMI above 30 and current smokers had a statistically significant higher HR for death from all causes than their references, also after adjustment for stage and comorbidity (Table II). Having diabetes, consuming more than 14 drinks per week and no intake of alcohol were non-significantly associated with risk of death from all causes.

Obesity at diagnosis was associated with a higher mortality from all causes (Table III). However, after adjustment for disease-related prognostic factors, the HR estimate leveled out. Current smoking and diabetes were significantly associated with higher HR for death from all causes, also after adjustment for disease-related prognostic factors and comorbidity. Regarding alcohol, there was a statistically significant increased HR for death only among women reporting no alcohol intake at time of diagnosis. This association was not affected by adjustment for stage and comorbidity.

Table IV shows HRs for death from all causes by educational level and income. The age-stratified HR for women with basic or high school education was 1.40 (95% CI 1.05–1.86) compared to women with higher education. Adjustment for disease-related prognostic factors and comorbidity had only minor influence on the HRs for education whereas adjustment for lifestyle indicated by metabolic indicators, smoking and alcohol to some extent lowers the social gradient. Regarding income, there was no significant trend in death from all causes between the income quartiles and adjustments only had minor effects on the estimates, although a significantly increased HR of 1.32 (95% CI 1.02–1.72) was observed among women with 2nd–3rd quartile income.

Discussion

Obesity, diabetes, smoking status and alcohol intake measured years before and at time of diagnosis affected death from all causes after a breast cancer diagnosis. After adjustment for disease-related prognostic factors and comorbidity, the most positively associated prognostic factors were obesity at baseline, being a smoker both at baseline and at diagnosis, and

Table I. Characteristics of 1229 breast cancer patients from the Danish prospective Diet, Cancer and Health cohort diagnosed 1993–2008 by educational level.

	Total N (%)	Educational level			
		Basic or high school N (%)	Vocational training N (%)	Higher education N (%)	Missing education N (%)
Sociodemographic characteristics					
Number of patients	1229	388	499	300	42
Personal income in 1995					
1st quartile	191 (16)	85 (22)	75 (15)	24 (8)	7 (17)
2nd–3rd quartile	538 (43)	201 (52)	243 (49)	81 (27)	13 (31)
4th quartile	498 (41)	201 (26)	181 (36)	195 (65)	20 (48)
Missing	2 (0)	0 (0)	0 (0)	0 (0)	2 (5)
Characteristics at baseline					
BMI					
Normal (≤ 25)	656 (53)	194 (50)	246 (49)	195 (65)	21 (50)
Overweight (25–30)	406 (33)	136 (35)	177 (36)	78 (26)	15 (36)
Obese (> 30)	167 (14)	58 (15)	76 (15)	27 (9)	6 (14)
Waist circumference					
≤ 74	349 (28)	102 (26)	135 (27)	100 (33)	12 (29)
> 74 –80	294 (24)	88 (23)	102 (20)	93 (31)	11 (26)
> 80 –88	295 (24)	99 (26)	131 (26)	57 (19)	8 (19)
> 88	291 (24)	99 (26)	131 (26)	50 (17)	11 (26)
Diabetes					
No	1203 (98)	378 (97)	490 (98)	295 (98)	40 (95)
Yes	26 (2)	10 (3)	9 (2)	5 (2)	2 (5)
Smoking status					
Current	412 (34)	166 (43)	164 (33)	68 (23)	14 (33)
Former	296 (24)	88 (23)	109 (22)	88 (29)	11 (26)
Never	521 (42)	134 (35)	226 (45)	144 (48)	17 (41)
Alcohol intake					
1–14 drinks/wk	924 (75)	275 (71)	395 (79)	223 (74)	31 (74)
> 14 drinks/wk	166 (14)	45 (12)	53 (11)	58 (19)	10 (23)
Abstainers	134 (11)	66 (17)	48 (10)	19 (6)	1 (2)
Missing	5 (0)	2 (1)	3 (1)	0 (0)	0 (0)
Characteristics at diagnosis					
CCI one year before diagnosis					
0	945 (77)	280 (72)	391 (78)	244 (81)	30 (71)
1	200 (16)	75 (19)	72 (14)	44 (15)	9 (21)
2+	84 (7)	33 (9)	36 (7)	12 (4)	3 (7)
BMI					
Normal (≤ 25)	578 (47)	167 (43)	219 (44)	168 (56)	24 (57)
Overweight (25–30)	323 (26)	113 (29)	146 (29)	57 (19)	7 (17)
Obese (> 30)	147 (12)	54 (14)	64 (13)	25 (8)	4 (10)
Missing	181 (15)	54 (14)	70 (14)	50 (17)	7(17)
Diabetes at diagnosis					
No	1157 (94)	356 (92)	475 (95)	288 (96)	38 (90)
Yes	72 (6)	32 (8)	24 (5)	12 (4)	4 (10)
BC stage					
Stage 1	496 (40)	158 (41)	208 (42)	116 (39)	14 (33)
Stage 2	612 (50)	200 (52)	238 (48)	152 (51)	22 (52)
Stage 3	19 (2)	6 (2)	9 (2)	4 (1)	0 (0)
Missing	102 (8)	24 (6)	44 (9)	28 (9)	6 (14)
Tumor size					
≤ 20 mm	740 (60)	247 (64)	306 (61)	168 (56)	19 (45)
21–50 mm	361 (29)	107 (28)	138 (28)	97 (32)	19 (45)
≥ 51 mm	24 (2)	7 (2)	13 (3)	4 (1)	0 (0)
Missing	104 (8)	27 (7)	42 (8)	31 (10)	4 (10)
No. of positive lymph nodes					
0	638 (52)	195 (50)	268 (54)	156 (52)	19 (45)
1	184 (15)	55 (14)	77 (15)	47 (16)	5 (12)
2	89 (7)	34 (9)	36 (7)	16 (5)	3 (7)
≥ 3	216 (18)	80 (21)	74 (15)	53 (18)	9 (22)
Missing	102 (8)	24 (6)	44 (9)	28 (9)	6 (15)

(Continued)

Table I. (Continued)

	Total N (%)	Educational level			
		Basic or high school N (%)	Vocational training N (%)	Higher education N (%)	Missing education N (%)
Estrogen receptor status					
Positive	928 (76)	290 (75)	382 (77)	226 (75)	30 (71)
Negative	196 (16)	67 (17)	76 (15)	46 (15)	7 (17)
Missing	105 (9)	31 (8)	41 (8)	28 (9)	5 (12)
Malignancy grade					
1	333 (27)	107 (28)	130 (26)	85 (28)	11 (26)
2	358 (29)	113 (29)	147 (39)	89 (30)	9 (22)
3	178 (14)	61 (16)	73 (15)	38 (13)	6 (14)
Non-classified (non-ductal)	236 (19)	72 (19)	92 (19)	56 (19)	12 (29)
Missing	124 (10)	6 (2)	9 (2)	5 (2)	4 (10)
Smoking status					
Never	454 (37)	115 (30)	200 (40)	125 (42)	14 (33)
Former at baseline	248 (20)	74 (19)	92 (19)	78 (26)	4 (10)
Former at diagnosis	98 (8)	50 (13)	30 (6)	15 (5)	3 (7)
Current	278 (23)	102 (26)	116 (23)	46 (15)	14 (33)
Missing	151 (12)	47 (12)	61 (12)	36 (12)	7 (17)
Alcohol intake					
≤ 14 drinks/wk	659 (54)	210 (54)	255 (51)	172 (57)	22 (53)
> 14 drinks/wk	123 (10)	29 (7)	107 (22)	36 (12)	6 (14)
Abstainers	226 (18)	73 (19)	52 (10)	41 (14)	5 (12)
Missing	221 (18)	76 (20)	85 (17)	51 (17)	9 (22)
Overall mortality					
Yes	324 (26)	124 (32)	123 (25)	63 (21)	14 (33)
No	905 (74)	264 (68)	376 (75)	237 (79)	28 (67)

CCI, Charlson Comorbidity Index (modified). Breast cancers were divided into 3 stages: stage I, tumor size ≤ 20 mm and no positive lymph nodes; stage II, tumor size 21–50 mm and positive lymph nodes or tumor size > 50 mm and no positive lymph node; and stage III, tumor size > 50 and positive lymph nodes.

reporting no alcohol intake at time of diagnosis. Furthermore, the socioeconomic difference in death after breast cancer by education was affected by metabolic indicators, smoking status and alcohol intake.

We found that BMI at baseline up to 17 years before diagnosis was more strongly associated with death from all causes than BMI measured at time of diagnosis. Weight at time of diagnosis might be affected by the cancer, but due to exclusion of patients with distant metastasis, this would only have a minor effect on our results. Previous studies have likewise found significant associations between BMI at time of diagnosis and survival after breast cancer diagnosis [7]. A possible explanation may be the varying influence of overweight and obesity in different age groups. Another possible explanation is that overweight and obesity affect initiation of the cancer, and that measurements at baseline reflect this influence.

Although the evidence is not entirely consistent, obesity seems to be associated with higher stage at diagnosis, larger tumors and a greater number of positive lymph nodes [20]. This may be due to detection bias caused by larger breasts among obese women [21] or indicate that the metabolic changes of the microenvironment affect tumor promotion and progression causing more aggressive cancers [13]. Higher

levels of estrogen might affect estrogen receptor positive breast cancer, although among our breast cancer patients no differences were shown in the distribution of receptor positive cancers among BMI groups (results not shown). Furthermore, adipose tissue secretes some important cytokines including plasminogen activator inhibitor 1, interleukin-6, and tumor necrosis factor- α , which all affect inflammation and contribute to insulin resistance in obese humans. All these cytokines are highly involved in angiogenesis and development of metastasis [13]. This indicates that tumors in overweight and obese women may evolve more progressively than in normal weight women, which may explain the higher stage at time of diagnosis. Other factors like hormone replacement therapy (HRT) may also affect the microenvironment of the tumor. In a recent study based on the same cohort as the present, a significantly decreased mortality was found for breast cancer patients that were current users of HRT at time of enrollment to the cohort compared to those that were never or previous users [22]. Further, HRT users at baseline had a lower BMI. The analyses did not include socioeconomic position which is associated with the use of HRT and BMI [2] and, as shown here, with overall mortality after breast cancer.

Table II. Metabolic indicators and lifestyle factors measured at baseline and death from all causes among breast cancer patients among 1229 breast cancer patients from the Danish prospective Diet, Cancer and Health cohort.

	Death from all causes		
	HR (95% CI) Age	HR (95% CI) + Disease-related prognostic factors	HR (95% CI) + Comorbidity
BMI			
< 25	Reference	Reference	Reference
25–30	1.09 (0.86–1.41)	0.95 (0.73–1.23)	0.97 (0.75–1.25)
> 30	1.68 (1.25–2.26)	1.46 (1.08–1.98)	1.43 (1.06–1.93)
Waist circumference			
≤ 74	Reference	Reference	Reference
> 74–80	0.98 (0.72–1.35)	0.85 (0.62–1.18)	0.81 (0.59–1.13)
> 80–88	0.89 (0.64–1.23)	0.73 (0.52–1.02)	0.69 (0.50–0.97)
> 88	1.56 (1.17–2.08)	1.34 (1.00–1.80)	1.26 (0.94–1.70)
Diabetes ^a			
No	Reference	Reference	Reference
Yes	1.77 (0.99–3.15)	1.62 (0.90–2.91)	1.31 (0.72–2.40)
Smoking			
Never	Reference	Reference	Reference
Former	1.12 (0.84–1.51)	1.05 (0.78–1.42)	1.01 (0.75–1.36)
Current	1.61 (1.25–2.07)	1.70 (1.32–2.19)	1.56 (1.21–2.03)
Alcohol			
1–14 drinks/wk	Reference	Reference	Reference
> 14 drinks/wk	1.30 (0.95–1.77)	1.16 (0.84–1.59)	1.16 (0.82–1.63)
Abstainers	1.28 (0.92–1.79)	1.23 (0.87–1.72)	1.14 (0.83–1.57)

Disease-related prognostic factors: tumor size in mm, lymph node status (yes/no), no. of positive lymph nodes (linear), malignancy grade, estrogen receptor status (positive, negative, unknown). Comorbidity, Charlson Comorbidity Index entered as linear covariate. ^aDiabetes excluded from the comorbidity score.

We did not find any significant association with diabetes either at baseline or at diagnosis although a previous meta-analysis found a significantly higher mortality after breast cancer diagnosis [8]. Comorbidity may cause later diagnosis and affect both progression of the disease and ability to tolerate the treatment [23]. In general, adjustment for comorbidities only had minor effects on the HRs for death from all causes in relation to the metabolic indicators, smoking and alcohol in our study.

Like adipose tissue, alcohol affects the aromatase activity and causes increased levels of estrogen [24]. It is therefore possible that alcohol consumption interacts with the metabolic changes related to overweight and obesity and thereby affects the microenvironment of the developing tumor. The only significant association between alcohol intake and overall survival, was, however, found among women who reported no intake of alcohol at diagnosis. This indicates that among women in this cohort abstinence from alcohol may be associated with a generally poor health, disease or previous abuse [25]. Earlier findings from the cohort of a significant association between baseline alcohol intake and breast cancer recurrence but not breast cancer mortality [25] indicate a too short follow-up period for breast cancer death as well as for death from all causes in the cohort. Smoking at baseline and at time of diagnosis

was associated with death from all causes after breast cancer diagnosis in our study, which has also been observed in other studies [26].

In the present study we found a significant association between socioeconomic position and death from all causes after a breast cancer diagnosis by educational level but not income quartiles. Participation in the population-based cohort was associated with socioeconomic position, and overall mortality among non-participants was more than twice as high as the overall mortality among participants up to 15 years after baseline [27]. Furthermore, there were significant differences in overall mortality between participants and non-participants within all socioeconomic groups indicating that participants were healthier than non-participants within the same socioeconomic group. In the present study we found that 41% of the breast cancer patients had an income in the highest quartile indicating that the breast cancer patients had a generally high socioeconomic position and better general health, which might explain the much less clear social gradient in survival after breast cancer after a median of almost nine years than what was previously found among nationwide samples of Danish women diagnosed with breast cancer [1]. However, we have no reason to believe that the extent, to which cancer-related factors, comorbidity or lifestyle factors explain the

Table III. Metabolic indicators and lifestyle factors measured at time of diagnosis and death from all cause among patients among 1229 breast cancer patients from the Danish prospective Diet, Cancer and Health cohort.

	Death from all causes		
	HR (95% CI) Age	HR (95% CI) + Disease-related prognostic factors	HR (95% CI) + Comorbidity
BMI			
< 25	Reference	Reference	Reference
25–30	1.05 (0.81–1.36)	0.93 (0.72–1.21)	0.95 (0.72–1.22)
> 30	1.36 (0.99–1.88)	1.10 (0.79–1.54)	1.09 (0.78–1.51)
Diabetes ^a			
No	Reference	Reference	Reference
Yes	1.76 (1.19–2.60)	1.90 (1.27–2.84)	1.65 (1.09–2.49)
Smoking			
Never	Reference	Reference	Reference
Former at baseline	1.07 (0.79–1.46)	1.03 (0.76–1.40)	1.01 (0.74–1.37)
Former at diagnosis	1.50 (1.00–2.25)	1.42 (0.94–2.16)	1.27 (0.83–1.93)
Current	1.62 (1.25–2.11)	1.82 (1.39–2.37)	1.71 (1.30–2.23)
Alcohol			
1–14 drinks/wk	Reference	Reference	Reference
> 14 drinks/wk	1.38 (0.98–1.95)	1.32 (0.92–1.89)	1.03 (0.71–1.50)
Abstainers	1.57 (1.21–2.03)	1.56 (1.20–2.04)	1.57 (1.20–2.05)

Disease-related prognostic factors: tumor size in mm, lymph node status (yes/no), no. of positive lymph nodes (linear), malignancy grade, estrogen receptor status (positive, negative, unknown). Comorbidity, Charlson Comorbidity Index entered as linear covariate. ^aDiabetes excluded from the comorbidity score.

socioeconomic disparities in survival, would be different among non-participants than what was found among participants.

We had the unique opportunity to investigate the influence of lifestyle measures at different points in time. The prospectively collected information at baseline eliminates systematic recall bias among cancer patients. Furthermore, the unique Danish personal registration numbers secure almost complete follow-up for cancer diagnoses and death. We used educational level and personal income as the socioeconomic indicators and due to linkage with registries the level of missing information was very low. Household income may have been a better measure of socioeconomic position in these older women, but this was not available in our data. We used all-cause mortality as outcome to avoid the misclassification that can occur between breast cancer-specific death and death from other causes [28]. Also, all-cause survival to some extent captures the combined effects because it is likely that in some cases comorbidity and breast cancer are not mutually exclusive but in combination contribute to shortened survival [3]. Thus survival to all-cause death serves as a useful outcome for summarizing the overall impact of socioeconomic position on the present sample of breast cancer patients.

Information on weight at time of diagnosis was either self-reported in the hospital record or collected from the anesthesia sheet, which is not as reliable as measurements at baseline. Information on smoking and alcohol intake were self-reported both at baseline

and diagnosis and the level of precision was lower at time of diagnosis. Therefore it was only possible to categorize these lifestyle variables rather crudely into above or below recommended alcohol intake or smoking status. Despite of the general loss of information, we chose to use the same categories at baseline and diagnosis to facilitate the comparison of the estimates for BMI, alcohol intake and smoking. At diagnosis, several women indicated a very recent smoking cessation in the questionnaires, possibly due to the request for smoking cessation prior to surgery and thus a proportion of these might not be permanent smoking cessations, which probably explains the observed high hazard for overall survival among former smokers. Another limitation of the present study is that it is not possible to distinguish between type 1 and type 2 diabetes in the National Diabetes Register. Type 1 diabetes does not cause hyperinsulinemia and is not associated with overweight and obesity or breast cancer risk [29]. Usages of multiple imputation was based on the assumption that data was missing at random. This might not have been the case for all included variables thus the methods may have introduces bias. However, sub-analyses using complete cases showed similar estimates but wider confidence intervals.

The findings from the present study underline the importance of a targeted prevention and rehabilitation of cancer patients with low socioeconomic position [30,31]. A previous study among breast cancer patients in the same cohort showed that despite the obvious

Table IV. Socioeconomic position and death of all causes among 1229 breast cancer patients from the Danish prospective Diet, Cancer and Health cohort.

	Death of all causes			
	HR (95% CI) Age	HR (95% CI) Model 1	HR (95% CI) Model 2	HR (95% CI) Model 3
Education				
Basic/high school	1.40 (1.05–1.86)	1.35 (1.01–1.81)	1.33 (0.99–1.78)	1.24 (0.91–1.68)
Vocational	1.07 (0.81–1.43)	1.13 (0.84–1.50)	1.12 (0.84–1.49)	1.03 (0.77–1.40)
Higher education	Reference	Reference	Reference	Reference
p for trend	0.01	0.02	0.04	0.11
Income				
1st quartile	0.96 (0.67–1.36)	1.09 (0.76–1.56)	1.01 (0.70–1.45)	0.93 (0.64–1.34)
2nd–3rd quartile	1.19 (0.92–1.53)	1.32 (1.02–1.70)	1.32 (1.02–1.70)	1.32 (1.02–1.72)
4th quartile	Reference	Reference	Reference	Reference
p for trend	0.78	0.28	0.46	0.75

Model 1: Further adjusted for disease-related prognostic factors: tumor size, lymph node status, no. of positive lymph nodes, malignancy grade and receptor status; Model 2: Further adjusted for Charlson Comorbidity Index: (linear), up to one year before diagnosis without diabetes; Model 3: Further adjusted for BMI (linear), waist circumference (linear), diabetes, smoking and alcohol at baseline, and BMI (linear), diabetes, smoking and alcohol at time of diagnosis.

benefits of a healthy lifestyle, women did not reduce their BMI or modify smoking or alcohol consumption after a breast cancer diagnosis [32].

In conclusion, metabolic indicators and lifestyle factors both as measured years before and at time of breast cancer diagnosis to some extent affect overall survival after a breast cancer diagnosis. We found a significant difference in overall survival after breast cancer diagnosis by education, which seemed to be partly mediated by metabolic indicators, smoking status, and alcohol intake and less so by disease-related prognostic factors and comorbidity. The findings indicate that metabolic indicators, smoking status and alcohol intake explain some but not all the social inequality in survival after breast cancer and that improvement of lifestyle to some extent would improve survival among women with low socioeconomic position.

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