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## APPENDIX

## Cancers studied

Oral cavity  
Oesophagus  
Stomach  
Colon  
Rectum  
Liver  
Pancreas  
Lung  
Bone  
Melanoma  
Prostate  
Testis  
Bladder  
Kidney  
Nervous system  
Hodgkin's disease  
Non-Hodgkin's lymphoma  
Myeloma  
Leukaemia  
Miscellaneous cancers



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# Death of a Husband or Marital Divorce Related to Risk of Breast Cancer in Middle-aged Women. A Nested Case-Control Study Among Norwegian Women Born 1935-1954

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A topic of general interest is whether important life changes may play a role in the onset of cancer. The hypothesis of this study was that death of a husband or marital divorce, is associated with an increased risk of breast cancer. The study included 4491 incident breast cancer cases and 44 910 controls, matched on age, in a population-based nested case-control study, among Norwegian women born between 1935 and 1954. The risk of breast cancer among widowed compared to married women showed an odds ratio (OR) of 1.13 [95% confidence interval (CI) 0.94-1.36], after adjusting for age at first birth and parity. For divorced women the analogous OR was 0.83 (95% CI 0.75-0.92), after adjusting for age at first birth, parity and place of residence. Thus, the results did not show any clear evidence that death of a husband or marital divorce was associated with an increased risk of breast cancer.

**Key words:** breast cancer, life change events, widowhood, divorce, epidemiology  
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## INTRODUCTION

WHETHER EMOTIONAL stress affects the risk of developing cancer is a question of general interest. Throughout history scientists have studied this topic, ranging back to Galen in the second century [1, 2]. Observations and personal impressions of numerous 18th

and 19th century clinicians were given a firmer basis by the first statistical study carried out by Herbert Snow at the London Cancer Hospital, reported in 1893. Of 250 cancer patients studied, 156 had experienced "immediately antecedent trouble, often in very poignant form, as the loss of a near relative" [1].

Breast cancer has been a common endpoint in many studies on the relation between stressful life events and risk of cancer. Nonetheless, reports from the last two decades have not produced consistent evidence that important life changes increase the risk [3, 4]. Some studies have shown a positive association [5–8], but others have failed to do so [9–15]. The inconsistency in results may be due to weaknesses in methodology, such as bias in study design, small sample size or use of invalid and unreliable measures of life events.

In this nested case–control study of middle-aged Norwegian women, we have examined the relation between the death of a husband or marital divorce on the subsequent risk of breast cancer. The aim of the study was to find out whether experiencing any one of these life changes may be associated with an increased risk of developing breast cancer.

## MATERIALS AND METHODS

All inhabitants in Norway have been assigned an 11-digit personal identification number and, since 1964, have been included in the Central Population Register organised by the Central Bureau of Statistics. Each individual is represented by a record containing demographic information, and there are updated codes showing whether a person is resident, has emigrated or has died [16]. The personal identification number has been the key to establishing individual marital and maternity histories of Norwegian women for the period 1964–1984. For women with children born before 1964, the information of births came from the Population Census of 1970. Thus, the biography of births up to 1985 is nearly complete for all women born after 1935 [17].

### Subjects

We have restricted the analysis to women born between 1935 and 1954 with a complete marital and maternity history, and linked these women (approximately 600 000) to information from the Norwegian Cancer Registry, which includes data on site of the cancer, time of diagnosis and stage at time of diagnosis [16]. This linkage identified 4832 women with breast cancer which had occurred in this population between 1966 and 1990. Among women with two diagnoses of breast cancer, we used the first and excluded the second.

Approximately 56% of the cases were diagnosed between 1985 and 1990 inclusive, a period during which marital changes were not registered. Thus, women who were divorced or widowed during this interval will be wrongly classified as being married, and this misclassification could dilute any differences in risk associated with divorce or widowhood.

In all, 341 (7.1%) cases were excluded from analysis. They included 71 women with coding errors, 32 who had emigrated and 106 women in whom information on marital status was incomplete. Thus, 4491 confirmed breast cancer cases were included, among whom 382 had never been married. In this study, these women were not included in the analysis.

The stage of disease was categorised by the Cancer Registry into five categories: stage 1 included tumours of all sizes confined to the breast (except cases belonging to stage 3); stage 2 included tumours with metastases to the axillary lymph nodes; stage 3 included tumours with direct extension to the skin or chest wall with or without axillary metastases; and stage 4 included breast tumours with distant metastases [18]. A fifth category was cases in whom stage was unknown.

For each incident case of breast cancer, we selected 10 controls from the general population without a cancer diagnosis, whose marital and maternity histories were known. The controls were frequency matched by age to the cases, by identical year of birth, which gave a total of 44 910 controls.

### Study factors

In this study, stressful life events were perceived as one of two separate events in a woman's life: marital divorce or the loss of a husband by death. The "exposed" cases were women with breast cancer whose cancer had been diagnosed subsequent to divorce or widowhood, and married cases without prior history of divorce or widowhood were regarded as "unexposed". Married women were used as reference in the analysis.

Among divorced women, we used the date of separation as the time of event. For women with more than one divorce or more than one loss of a husband by death, we used the first, and ignored the other registered events.

Birth cohorts were divided into four 5-year categories, and age at first birth was divided into five categories:  $\leq 19$ , 20–24, 25–29, 30–34 and 35 years and above. Parity was studied as the number of births, divided into four categories: nulliparous women, women with one to two children, three to four children, and five or more children. Since the geographical distribution of divorce and breast cancer is heterogeneous in Norway, place of residence was divided into three main categories.

In this study, we also analysed the risk of breast cancer according to age at divorce or age at widowhood, and divided the women into three categories: younger than 36, between 36 and 44, and 45 years and older.

### Statistical analysis

We made comparisons between groups at a 5% level of statistical significance, using  $\chi^2$  statistics. The odds ratio (OR) was applied as a measure of relative risk of breast cancer for divorced and widowed women, respectively, using married women as reference. To adjust for potentially confounding factors other than age, we used the Mantel–Haenszel procedure in a stratified analysis [19], and also multiple logistic regression analysis to obtain adjusted estimates of the relative risk. Thus, we adjusted for age at first birth and parity in the analysis of widowed women. Since place of residence was differently distributed between divorced and married women, we also adjusted for place of residence in the analysis of divorced women. The Mantel–Haenszel  $\chi^2$  statistics were used to calculate 95% confidence intervals [20]. We tested for trend over categories of age at event (divorce or widowhood, respectively) by using Mantel's test for trend [19]. In the analysis, we applied the computer program SAS [21].

## RESULTS

In Table 1, we have compared clinical characteristics between married, divorced and widowed cases to indicate whether any particular heterogeneity between cases of separate marital status may be present. The table shows that the clinical stage at

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Table 1. Characteristics of married, divorced and widowed cases born 1935–1954

	Married women* (n = 3495)	Divorced women (n = 484)	Widows (n = 130)
Stage at diagnosis <sup>†</sup>			
Stage 1	1962 (56.1%)	270 (55.8%)	79 (60.8%)
Stage 2	1223 (35.0%)	171 (35.3%)	40 (30.8%)
Stage 3	100 (2.9%)	13 (2.7%)	5 (3.8%)
Stage 4	143 (4.1%)	16 (3.3%)	4 (3.1%)
Unknown	67 (1.9%)	14 (2.9%)	2 (1.5%)
Age at first birth (year) <sup>‡</sup>			
≤ 19	287 (8.7%)	73 (16.8%)	22 (18.0%)
20–24	1522 (46.3%)	202 (46.5%)	58 (47.5%)
25–29	1088 (33.1%)	94 (21.7%)	27 (22.1%)
30–34	313 (9.5%)	45 (10.4%)	12 (9.8%)
≥ 35	81 (2.5%)	20 (4.6%)	3 (2.5%)
Parity <sup>‡</sup>			
0	204 (5.8%)	50 (10.3%)	8 (6.2%)
1–2	1979 (56.6%)	272 (56.2%)	73 (56.1%)
3–4	1220 (34.9%)	146 (30.1%)	43 (33.1%)
≥ 5	92 (2.6%)	16 (3.3%)	6 (4.6%)

\*Reference group. <sup>†</sup>P = 0.84. <sup>‡</sup>P < 0.01.

diagnosis was not different, but among divorced and widowed cases a greater proportion had an early first birth (≤ 19 years). Among divorced cases, there was a greater proportion of nulliparous women compared to married cases.

In this study the distribution of childbearing between cases and controls showed that cases had a consistently later age at first birth and a lower number of births than controls (data not shown). Both factors agree with previous studies.

In Table 2, the estimated overall relative risk of breast cancer

among divorced compared to married women was 0.83 (95% confidence interval 0.75–0.92), after adjustment for age at first birth, parity and place of residence. For widows, the analogous relative risk was 1.13 (95% confidence interval 0.94–1.36), after adjustment for age at first birth and parity. Additional adjustment for age did not change the point estimates, and was not included in the final analysis. The logistic regression analysis gave very similar adjusted estimates of relative risk both for divorced (0.84) and for widowed (1.12) women.

Table 2. Odds ratio of breast cancer, comparing divorced and married women, and widowed and married women, stratified by birth cohorts

Birth cohorts	Cases	Controls	OR	95% CI
1935–1939				
Married	1367	13746	1.0*	
Divorced	153	1858	0.83	0.70–0.99
Widowed	78	705	1.11	0.88–1.42
1940–1944				
Married	1111	10966	1.0*	
Divorced	159	1939	0.81	0.68–0.96
Widowed	36	337	1.05	0.74–1.50
1945–1949				
Married	754	7421	1.0*	
Divorced	125	1401	0.88	0.72–1.07
Widowed	13	139	0.92	0.52–1.63
1950–1954				
Married	263	2586	1.0*	
Divorced	47	462	1.00	0.72–1.39
Widowed	3	16	1.84	0.54–6.25
Total (1935–1954)				
Married	3495	34719	1.0*	
Divorced	484	5660	0.83 <sup>†</sup>	0.75–0.92
Widowed	130	1197	1.13 <sup>‡</sup>	0.94–1.36

OR, odds ratio; CI, confidence interval. \*Reference category. <sup>†</sup> Adjusted for age at first birth (five categories), parity (four categories), and place of residence (three categories).

<sup>‡</sup> Adjusted for age at first birth (five categories), and parity (four categories).

In Table 3, age at divorce and age at widowhood were used as surrogate measures of vulnerability for breast cancer. The table shows that for both groups belonging to a specific age category was not associated with an increase in the risk of breast cancer. In contrast, the results (Table 3) show that divorce may be negatively associated with breast cancer risk, and further, that the negative association is strengthened with increasing age at divorce. These estimates did not change after adjustment for age, age at first birth and parity, in a separate analysis using multiple logistic regression.

### DISCUSSION

In this nested case-control study of 4491 breast cancer cases and 44910 controls, the loss of the husband by death or by marital divorce was not associated with an increased risk of developing breast cancer.

Some studies have found an association between stressful life events and breast cancer risk [5–8]. In a small case-control study, Forsén [6] found that cases had significantly more life events, important losses and difficult life situations prior to diagnosis than controls. Other studies, however, have failed to show any association [9–15]. Thus, in a case-control study from the Danish Cancer Registry, Ewertz [14] could not show any association with the death of a spouse or marital divorce.

A general problem in most of these studies has been a small sample size, resulting in insufficient statistical power to detect an effect of any life events [5, 9, 11, 22]. In contrast, our study includes a large number of incident cases, allowing high precision in the relative risk estimates.

Bias in the selection of cases and controls may often represent a threat to validity. We selected controls from the general population, and used an age-matching procedure to provide comparability between cases and controls. Furthermore, our nested case-control design [19], where information on both cases and controls was identically collected prior to the diagnosis of breast cancer, precludes biased information.

Few prospective studies on stressful life events and breast cancer have been published. Thus, Hagnell [23] investigated 2550 healthy persons with Sjöbrink's Personality Model in a 10-year follow-up, and found a higher frequency of cancer among

women with an "unstable" emotional life. However, only 9 of the 22 cancer cases were women with breast cancer.

Another problem relates to the use of valid and reliable measures of life events. In particular, this may apply to the validity of questionnaires. On the other hand, such studies deserve credit for their attempts to rank the subjective meaning of events to the individual [5, 6, 13].

Although our study has used robust indicators of stress, these life changes may cover a wide range of experiences with quite different impacts for the individual woman. For most women, a divorce will be a process continuing over several years. On the other hand, the death of a spouse may be more "dramatic", especially in young women, for whom it seems fair to assume that most husbands have had a sudden death. Hahn and colleagues [24] have measured depression by using MMPI (Minnesota Multiphasic Personality Inventory) scores for 8932 women. They found no association between depression and risk of breast cancer during 14 years of follow-up.

In our study, we lacked information about changes in marital status between 1985 and 1990. Women who were divorced or became widows during this period will be misclassified as married women. However, when cases diagnosed after 1985 were excluded, the overall OR for divorced women was 0.61 (95% confidence interval 0.52–0.73), and for widowed women it was 1.07 (95% confidence interval 0.81–1.40), after adjusting for age at first birth and parity.

It would be desirable to have information on other potential confounding factors than age at first birth and parity [25, 26]. However, it is not clear that factors such as family history of breast cancer, age at menarche, age at menopause, use of oral contraceptives and information on alcohol consumption, would have any confounding effect. The major increase in the use of oral contraceptives in Norway took place in the 1970s (the Norwegian Medicinal Depot, personal communication, 1992). This indicates that a majority of women in this study could not have used oral contraceptives to an extent which could have substantially influenced their breast cancer risk. If alcohol consumption, which may be positively associated with breast cancer risk [27], was more prevalent among divorced or widowed women, an increased risk of breast cancer might be expected among them. This is clearly in contrast to what we found.

Breast cancer is a rare disease in younger women, and its detection may be difficult at an early stage [28]. Goodwin and colleagues [29] reported that widowed and divorced women were more likely to be diagnosed with non-local disease, indicating that they came to medical attention at a relatively advanced stage compared to married women. In our study, there was an equal distribution in registered stage between married, divorced and widowed cases, suggesting a clinical homogeneity between them at the time of diagnosis.

Some authors assert that stressful life events may have a stronger effect on premenopausal than on postmenopausal women, because of reduced influence of endocrine and immunological mechanisms with age [30]. However, Ravazi and colleagues [31] found that self-reported life events were not more frequent among women with hormone receptor-positive tumours than among those who were hormone receptor negative. In our study, no reliable information on hormone receptor status was available.

An unexpected finding of this study was a reduced risk of breast cancer associated with marital divorce, which is difficult to explain. It appears to be in conflict with a hypothesis suggesting that between the ages of 35 and 55 a relatively

Table 3. Odds ratio of breast cancer, comparing married and divorced women, by age at divorce and age at widowhood

	Cases	Controls	OR <sup>†</sup>	95% CI
Age at divorce (year)				
Married	3495	34719	1.00*	
Divorced ≤ 35	315	3303	0.94	0.84–1.07
Divorced 36–44	151	2041	0.74	0.62–0.87
Divorced ≥ 45	18	316	0.57	0.36–0.92
			$\chi^2 = -4.11$	
			$P < 0.001$	
Age at widowhood (year)				
Married	3495	34719	1.00*	
Widowhood ≤ 35	47	450	1.05	0.78–1.42
Widowhood 36–44	62	562	1.10	0.84–1.44
Widowhood ≥ 45	21	185	1.15	0.73–1.80
			$\chi^2 = 0.88$	
			$P = 0.28$	

OR, odds ratio; CI, confidence interval. \*Reference category. <sup>†</sup>Age-adjusted (5-year categories), Mantel-Haenszel procedure. Mantel's test for trend.

larger proportion of cancers may be attributed to increased susceptibility associated with individual stress [32]. We examined this by studying breast cancer risk according to the timing of divorce and widowhood (Table 3), and found a tendency for divorced women to have a reduced risk of breast cancer with increasing age at time of divorce. Verification of these results in future studies are clearly warranted.

In summary, the results of this study of Norwegian women born between 1935 and 1954, indicate that loss of a husband, either due to death or to marital divorce, does not increase the subsequent risk of breast cancer. Since many patients attribute their illness to emotional stress, our results may be of some consolation to these women.

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