Cancer risk and prognosis in Norway: comparing women in their first marriage with women who have never married

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Abstract

Study objective **– The difference in risk of cancer between never married women and married women in their first marriage and whether survival from cancer was any different between the two groups were studied.**

Design **– This was a population based, nested case-control study of cancer in Norwegian women diagnosed between 1966 and 1990, and followed up with regard to overall survival until the end of 1991.**

Setting **– Norway.**

Participants **– These were Norwegian women born between 1935 and 1954. The case-control study included 12 237 married and 1466 unmarried cases, and 26 075 married and 2768 unmarried controls. In the survival analysis, 11 943 married and 1473 unmarried cases were included.**

Main results **– Unmarried women had an overall increased cancer risk (OR = 1·13, 95% CI 1·05, 1·21), which could be attributed to cancer of the ovaries, uterus, brain and haematological malignancies. For cervical and thyroid cancer, the risk was lower than for married women. In the survival analysis, unmarried cases had an overall 26% increased risk of dying (HR = 1·26, 95% CI 1·15, 1·39), after adjustment for age and stage at diagnosis. The increased death rate was seen for cancer of the cervix, lung, and thyroid.**

Conclusions **– Since most unmarried women were nulliparous, this might explain their increased risk of ovarian and uterine cancer. The increased risk of brain tumours and haematological malignancies may result from selection bias, since disease among unmarried women may cause a large proportion to remain unmarried. The lower survival in unmarried cases may support the hypothesis that psychosocial factors play a role in the prognosis of cancer patients.**

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Studies of the relationship between marital status and health indicate that there is generally a protective effect of marriage on morbidity and mortality.[1–4] The results are, however, inconsistent and vary between diseases, race, and gender.[5–8] For cancer, comparisons of incidence between marital groups have shown lower rates in married people for many sites.[8,9] With regard to case fatality, Goodwin *et al* found that unmarried people with cancer had a 23% reduced overall survival compared with married cancer patients.[10] It has been suggested that psychosocial factors play a role in modifying the risk of cancer and also the prognosis of cancer once the disease has been diagnosed.[10–12] It has been suggested, however, that ill health itself may cause some unmarried people to remain unmarried and that an increased risk of cancer or a reduced survival from cancer in unmarried women may reflect this particular selection bias.[13]

In this study, we restricted analysis to women in their first marriage (married) and to never married (unmarried) middle aged Norwegian women. The main aims of the study were twofold. Firstly, we wanted to determine if there is any difference in risk of cancer between unmarried and married women. Secondly, we wanted to find out if unmarried women with cancer have a different overall and site specific survival than married patients.

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 at the Central Bureau of Statistics. The bureau has used the personal identification number as the key to establishing individual marital and maternity histories of Norwegian women for the period 1964–84. Thus, the biography of marriages and births is nearly complete for all women born after 1935.[14]

CASES

We restricted this study to women born between 1935 and 1954 (approximately 600 000). They were individually linked to information on cancer incidence from the Norwegian cancer registry for the period 1966 to 1990. Thus, all incident cases that occurred during this period were potentially eligible for the study. The cancer registry covers the whole population of Norway and registration is practically complete.[15] The information includes data on cancer site, date of diagnosis, and stage at the time of diagnosis. Stage was classified according to clinical hospital reports and histological data. In the site specific analysis, stage was included as a covariate where this was appropriate, and in the overall analysis including all sites, we divided stage into localised and metastatic dis-

Table 1 Odds ratio (OR) (95% confidence interval (CI)) of cancer at specific sites in unmarried women compared with married women

Cancer site	Cases/controls	Crude OR (95% CI)	Age adjusted OR (95% CI)
All cancer:			
Married	12237/26079	1·00	1·00
Unmarried	1466/2768	1·13 (1·06, 1·21)	1·13 (1·05, 1·21)
Breast:			
Married	3500/26079	1·00	1·00
Unmarried	383/2768	1·03 (0·92, 1·15)	1·11 (0·99, 1·25)
Cervix:			
Married	1568/26079	1·00	1·00
Unmarried	135/2768	0·81 (0·68, 0·97)	0·76 (0·63, 0·91)
Ovary:			
Married	971/26079	1·00	1·00
Unmarried	171/2768	1·66 (1·41, 1·96)	1·68 (1·42, 1·99)
Uterus:			
Married	436/26079	1·00	1·00
Unmarried	71/2768	1·53 (1·19, 1·97)	1·86 (1·44, 2·39)
Colorectum:			
Married	738/26079	1·00	1·00
Unmarried	66/2768	0·84 (0·65, 1·09)	0·95 (0·73, 1·26)
Malignant melanoma:			
Married	1438/26079	1·00	1·00
Unmarried	149/2768	0·98 (0·82, 1·16)	0·89 (0·75, 1·06)
Lung:			
Married	255/26079	1·00	1·00
Unmarried	25/2768	0·92 (0·61, 1·40)	1·04 (0·69, 1·57)
Haematological malignancies:			
Married	740/26079	1·00	1·00
Unmarried	127/2768	1·62 (1·34, 1·96)	1·42 (1·17, 1·73)
Thyroid cancer:			
Married	641/26079	1·00	1·00
Unmarried	58/2768	0·85 (0·65, 1·12)	0·73 (0·56, 0·96)
Brain tumours:			
Married	621/26079	1·00	1·00
Unmarried	110/2768	1·67 (1·36, 2·05)	1·55 (1·25, 1·92)

ease. Age at diagnosis was divided into four categories, younger than 30, 30–39, 40–49, and 50 years and older.

This study consists of two parts. Firstly, we used a nested, case-control design to study the risk of cancer in unmarried women compared with married women. Unmarried women were defined as never married, and married women as women who had not previously been divorced or widowed. Secondly, we applied survival analysis and examined the risk of dying among unmarried and married cancer cases from the time of diagnosis until the end of follow up.

RISK OF CANCER

A total of 16 951 incident cases of cancer diagnosed between 1966 and 1990 were identified among the population of women born between 1935 and 1954. Nearly 40% of these cases were diagnosed between 1985 and 1990, and information on marital changes was not available for this period. This could mean that some women were misclassified as unmarried who had actually married between 1985 and 1990. In the analysis, we assumed that this misclassification would affect cases and controls equally, and had not therefore caused a systematic bias in the estimates of relative risk.

In all, 839 (4·9%) women were excluded because of coding errors, missing information, and emigration, leaving a total of 16 112 eligible cases. For each incident case of cancer, we selected as controls two women from the total population with no diagnosis of cancer, whose marital and maternity histories were known. The controls were age matched to the cases, by identical year of birth, and there was a total of 34 460. After excluding widows and women who were separated or divorced, we used 12 237 married and 1466 unmarried cases in the analysis. Similarly, 26 079 married and 2768 unmarried controls were included.

The odds ratio (OR) was applied as a measure of relative risk of cancer for unmarried women, using married women as a reference. To adjust for a one year difference in age, we used the Mantel–Haenszel procedure in a stratified analysis.[16] The Mantel–Haenszel χ^2 statistic was used to calculate 95% confidence intervals (CI). In the analyses we used the computer program *SAS*.[17]

SURVIVAL FROM CANCER

In the survival analysis, we used death registry data made available from the central person register of the Central Bureau of Statistics. Each case of cancer was followed from the month of diagnosis (1966–90) until death or until the end of follow up, whichever event occurred first. Thus, the information included deaths from 1966 until the end of 1991. The latest update of the registry showed that 294 married cases had been reclassified as divorced, and these were excluded from the analysis, leaving 11 943 married cases to be followed up. Among unmarried cases, there were 1473 eligible cases.

We analysed the data using the χ^2 statistic to test differences in the stage at diagnosis between marital groups, and Kaplan–Meier analysis to test differences in survival.[18] To control for potentially confounding factors such as age and stage at diagnosis in the multivariate analysis,

Table 2 Hazard ratio (HR) (95% confidence interval (CI)) of dying in unmarried women compared with married women. All women were born between 1935 and 1954 and diagnosed with cancer between 1966 and 1990

Cancer site	No	Deaths	Crude HR (95% CI)	Adjusted HR (95% CI)*
All cancer:				
Married	11943	3576	1·00	1·00
Unmarried	1473	592	1·44 (1·32, 1·58)	1·26 (1·15, 1·39)
Breast:				
Married	3446	896	1·00	1·00
Unmarried	385	127	1·32 (1·10, 1·59)	1·11 (0·91, 1·34)
Cervix:				
Married	1484	315	1·00	1·00
Unmarried	134	45	1·79 (1·30, 2·46)	1·48 (1·05, 2·09)
Ovary:				
Married	945	327	1·00	1·00
Unmarried	175	57	0·93 (0·70, 1·25)	0·92 (0·68, 1·26)
Uterus:				
Married	432	57	1·00	1·00
Unmarried	69	13	1·55 (0·85, 2·83)	1·42 (0·74, 2·71)
Colorectum:				
Married	728	318	1·00	1·00
Unmarried	67	32	1·20 (0·83, 1·74)	1·04 (0·71, 1·53)
Malignant melanoma:				
Married	1403	185	1·00	1·00
Unmarried	149	25	1·37 (0·90, 2·08)	1·50 (0·95, 2·36)
Lung:				
Married	253	200	1·00	1·00
Unmarried	26	24	1·44 (0·94, 2·20)	2·06 (1·29, 3·30)
Haematological malignancies:				
Married	724	363	1·00	1·00
Unmarried	129	87	1·64 (1·28, 2·11)	1·30 (0·97, 1·74)†
Thyroid cancer:				
Married	609	26	1·00	1·00
Unmarried	57	6	3·34 (1·22, 9·14)	5·18 (1·77, 15·11)
Brain tumours:				
Married	606	250	1·00	1·00
Unmarried	111	72	1·87 (1·41, 2·48)	1·38 (0·98, 1·92)

* Hazard ratio adjusted for age at diagnosis and stage at diagnosis. In the analysis of all cancer, stage was dichotomised to localised disease and disease with metastasis.
† Hazard ratio adjusted for age at diagnosis.

the Cox regression model was used.[18] We applied the computer program *SPSS* for the survival analysis.[19]

Results

Initially, we examined the risk of cancer between unmarried and married women for all cancers and for different sites (table 1). Overall, unmarried women had an increased risk (OR=1·13, 95% CI 1·05, 1·21) which could be attributed to cancer of the ovaries, uterus, brain, and haematological malignancies. For cervical cancer, unmarried women had a lower risk than married women (HR=0·76, 95% CI 0·63, 0·91). This was also observed for thyroid cancer (OR=0·73, 95% CI 0·56, 0·96).

In the survival analysis (table 2), unmarried cases had an overall 26% increased risk of dying compared with married cases (HR=1·26, 95% CI 1·15, 1·39), after adjustment for age and stage at diagnosis. The increased death rate among unmarried cases was seen for cervical cancer (HR=1·48, 95% CI 1·05, 2·09), lung cancer (HR=2·06, 95% CI 1·29, 3·30), and cancer of the thyroid (HR=5·18, 95% CI 1·77, 15·11).

Table 3 shows the distribution of women with localised and metastatic disease in relation to marital status and age at diagnosis. In all, 65% of married cases had localised disease at diagnosis compared with 60·8% of unmarried cases ($\chi^2=13·83$, $p=0·002$). Among unmarried women, a greater percentage was diagnosed in the younger age groups. These differences showed similar patterns both for localised ($\chi^2=46·13$, $p<0·001$) and metastatic disease ($\chi^2=66·43$, $p<0·001$).

Table 4 shows that the higher death rate among unmarried cases was more evident for localised disease (HR=1·42, 95% CI 1·22, 1·66) than for metastatic disease (HR=1·18, 95% CI 1·05, 1·33) (figure). For localised disease (table 5), there were increased hazard ratios for cervical (HR=1·96, 95% CI 1·38, 2·78) and lung cancer (HR=2·09, 95% CI 1·03, 4·25). The risk of dying from breast and colorectal cancer was also higher in unmarried patients, but these associations were not statistically significant.

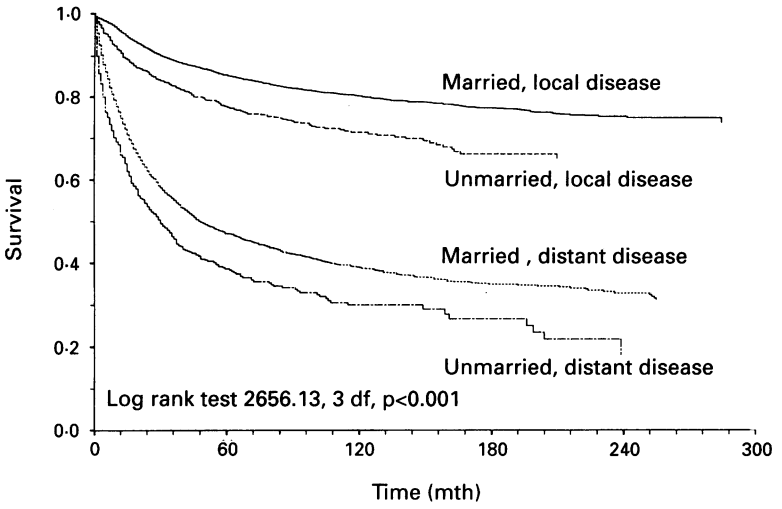
Table 3 Number of cancer patients with localised and metastatic disease at diagnosis in relation to marital status and age at diagnosis

Stage at diagnosis	Age at diagnosis (y)	Married cases No	(%)	Unmarried cases No	(%)
Localised disease	≤29	678	(8·8)	125	(14·7)
	30–39	2902	(37·6)	349	(41·1)
	40–49	3344	(43·4)	318	(37·4)
	≥50	787	(10·2)	58	(6·8)
Total		7711	(100)	850	(100)
Metastatic disease					
	≤29	257	(6·6)	81	(14·8)
	30–39	1289	(30·9)	198	(36·1)
	40–49	2018	(48·3)	226	(41·2)
	≥50	596	(14·3)	44	(8·0)
Total		4160	(100)	549	(100)

Table 4 Relative risk of death for unmarried compared with married women diagnosed with cancer, in relation to the stage of disease

Stage of disease	All cases Crude HR (95% CI)	All cases Adjusted HR (95% CI)*
Localised disease	1·58 (1·37, 1·83)	1·42 (1·22, 1·66)
Metastatic disease	1·27 (1·13, 1·42)	1·18 (1·05, 1·33)

* Adjusted for age at diagnosis



Total survival of localised and metastatic (distant) disease in married and unmarried women with cancer.

Table 5 Relative risk of death for unmarried compared with married women with localised disease at diagnosis in relation to cancer sites

Cancer sites	*Crude HR (95% CI)*	*Adjusted HR (95% CI)**
Breast	1·38 (0·97, 1·96)	1·35 (0·95, 1·92)
Cervix	1·84 (1·30, 2·61)	1·96 (1·38, 2·78)
Ovaries	1·19 (0·64, 2·23)	1·10 (0·57, 2·10)
Uterus	1·05 (0·44, 2·48)	0·87 (0·34, 2·23)
Colorectum	1·60 (0·77, 3·32)	1·61 (0·77, 3·36)
Malignant melanoma	1·18 (0·68, 2·05)	1·16 (0·66, 2·01)
Lung	2·13 (1·06, 4·27)	2·09 (1·03, 4·25)

* Adjusted for age at diagnosis.

Discussion

In this population based study of unmarried and married middle aged Norwegian women, the unmarried had a 13% overall increased risk of cancer, and a 26% increased case fatality compared with married women.

RISK OF CANCER

The increased risk was found for cancer of the ovaries, uterus, haematologic malignancies, and brain tumours. For cervical and thyroid cancer, unmarried women had a lower risk than married women.

Ernster *et al* found that single women had higher rates of cancer of the breast, uterus, ovaries, and brain, and lower rates of cervical cancer than married women.[9] Similarly, Swanson *et al* reported higher incidence rates for cancer of the breast, uterus, and ovaries in the unmarried women, but lower rates for lung cancer and leukemia.[8] Reynolds *et al* found no protective effect of marriage on the overall cancer incidence in a 17 year follow up of 6848 men and women, and, in a population based study, Ewertz did not find an increased risk of breast cancer in unmarried women.[20 21] Other authors have, however, shown that after the age of 40, never married women are at higher risk of breast cancer than ever married women.[22 23] Single women may have a higher risk of ovarian cancer, but this association may disappear after adjustment for parity.[24 25] Brinton *et al* reported that cervical cancer occurred more frequently in married than unmarried women, and this is supported by our results.[26]

For uterine and ovarian cancer, nulliparity is an established risk factor and may account for the increased risk in unmarried women in our study.[21 27–29] Nulliparity may also partly explain the decreased risk of thyroid cancer in unmarried women, since Kravdal *et al* found that thyroid cancer risk increased with the number of pregnancies.[30] This was not, however, confirmed in another Norwegian study.[31] Parity has also been associated with colorectal cancer in some, but not in other studies.[32–35]

For brain tumours and haematological malignancies, other explanations may be more relevant than confounding with reproductive factors. Approximately 60% of unmarried women with brain tumours were diagnosed before 30 years of age, compared with 20% among married patients. For haematologic malignancies, 50% of unmarried patients were diagnosed before age 30, and 27% among the married. This indicates that women who were diagnosed with these cancers at a relatively young age tend to remain unmarried, and this may be an example of the "marriage selection hypothesis".[13] We therefore suggest that the estimated increased risk of brain and haematological malignancies among unmarried women can be attributed to selection bias.

SURVIVAL FROM CANCER

We found an increased case fatality among unmarried women with cancer of the cervix, lung, and thyroid, compared with married patients.

In a population based study of 27 779 cancer cases, Goodwin *et al* found that the unmarried had a reduced total survival (HR = 1·23, 95% CI 1·19, 1·28), which was explained by stage (unmarried persons were more likely to be diagnosed at a metastatic stage) and treatment (unmarried people were more likely to be untreated for cancer).[10] After adjustment for stage and treatment, however, a poorer survival still persisted among unmarried people (HR = 1·18, 95% CI 1·12, 1·23). In another population based study of 4764 women with breast cancer, it was found that single women had a worse prognosis than married women (HR = 1·34, 95% CI 1·10, 1·62).[36] In a study of cervical cancer, Murphy *et al* found no association between being single and survival.[37]

For cervical cancer, we found that the proportion diagnosed with localised disease was higher ($p = 0·04$) in married patients, and this may indicate that unmarried women would tend to have a delayed diagnosis. For localised disease too, however, the relative risk of dying was higher among unmarried women (HR = 1·96, 95% CI 1·38, 2·78). Thus, we found that unmarried women had a lower risk of cervical cancer, but their prognosis was poorer once the disease was present. It is possible that the latter finding is a result of delayed diagnosis. As for the lower risk among unmarried women, this has been found by others, and may suggest that risk factors related to sexual activity may be more prevalent in married than unmarried women.

The stronger overall hazard ratio for localised than for distant disease may indicate a role for social factors. For distant disease, it can be assumed that biology will predominate in determining prognosis.[5] For localised disease, socioeconomic status and psychosocial support may also be important, since these factors may be associated with differences in tumour characteristics, stage, and treatment.[10–12]

Conclusion

In conclusion, this study has shown that among middle aged Norwegian women, being unmarried carries a higher risk of uterine and ovarian cancer than being married. Nulliparity is a strong risk factor for these cancers, and may well explain the results. The increased risk of brain tumours and haematological malignancies among unmarried women may be caused by selection bias, where the disease may cause a substantial proportion of unmarried patients to remain unmarried. The lower survival among unmarried cancer patients, particularly from localised disease, may support the hypothesis that for metastatic disease, biology will predominate in determining the prognosis, but for localised disease, other factors such as socioeconomic status and social support may also be important.

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