

Causes of death among women with breast cancer: A follow-up study of 50 481 women with breast cancer in Finland

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Abstract

Our study aims to assess mortality from causes other than breast cancer among women with breast cancer with focus on indications of joint aetiology. Data on female breast cancer patients were obtained from the Finnish Cancer Registry and their underlying causes of death in 54 categories from the Statistics Finland. Standardised mortality ratios (SMR) and their 95% confidence intervals (CIs) were calculated for 50 481 patients diagnosed between 1971 and 2000 and followed until December 2012, stratified by histology, age at diagnosis and time since diagnosis. The expected numbers of deaths were based on respective mortality rates among the Finnish general population. Hazard ratio (HR) was estimated from Poisson regression model to compare risks of cause of death by histology. 41% of 30 841 deaths were due to causes other than breast cancer. Significant excess mortality was observed for stomach cancer (SMR 1.43, 95% CI 1.26-1.62), circulatory system diseases (SMR 1.17, 95% CI 1.14-1.20) and suicide (SMR 1.51, 95% CI 1.28-1.78). In an age-adjusted analysis, significantly higher relative risk of stomach cancer mortality was observed for lobular vs ductal subtype (HR 2.00, 95% CI 1.32-3.02). Significantly increased SMRs were observed for cancers of respiratory organs among premenopausal women, and for other respiratory system diseases, dementia and Alzheimer disease among postmenopausal women. We conclude that female breast cancer patients are at increased risk of death from causes other than the breast cancer diagnosis including circulatory and respiratory system diseases and cancer of stomach, ovary and respiratory systems. The excess mortality because of different causes varies based on menopausal status and histology. There might be shared aetiological factors between the diagnosis of breast cancer and the causes of death among these patients.

KEYWORDS

aetiology, breast cancer, cause of death, risk factors, SMR

Abbreviations: BRCA, breast cancer gene; CI, confidence interval; FCR, Finnish Cancer Registry; ICD, International Classification of Diseases; SMR, standardised mortality ratio.

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1 | INTRODUCTION

Breast cancer is the most frequent cancer diagnosis and the leading cause of cancer death among women globally.¹ In 2018, there were 2.1 million estimated new breast cancer cases and 630 000 estimated deaths worldwide in women, which corresponds to about 24% of total cancer incidence and 15% of total cancer mortality.¹ In Finland, according to the latest estimates, breast cancer constituted 30% of all cancer cases and 15% of cancer deaths among women, and the 5-year relative survival was 90%.² The survival has increased mainly due to earlier diagnoses in mammographic screening and adjuvant treatments.^{3,4} The risk of death among breast cancer patients also depends on many other factors such as hormone receptor status, histology of breast cancer and pre-existing health conditions.^{5,6}

Along with improving survival, the age and follow-up time increases after the breast cancer diagnosis, and there might be increased risk of dying from causes other than breast cancer, which might vary by the tumour characteristics, stage and calendar year at diagnosis.⁷⁻⁹ Pulmonary circulation diseases, heart failures, other cardiovascular diseases, diabetes and

What's new?

Gains in early detection, treatment, and survival in breast cancer presumably increase the chances that patients will die from causes other than breast cancer. Here, mortality patterns and indications of joint etiology with other diseases was investigated among Finnish breast cancer patients. Observations indicate that female breast cancer patients experience excess mortality from circulatory system disease and from other cancers, particularly those of the lung, stomach, and ovary. Mortality from different causes varied by menopausal status and histology. The findings suggest that certain risk factors are involved in the etiology of breast cancer and eventual cause of mortality.

gastrointestinal disease have been reported as causes of death among breast cancer patients more frequently than among other women.^{10,11}

TABLE 1 Observed (Obs) number of deaths and standardised mortality ratios (SMR) with 95% confidence interval (CI) for causes of death among women with breast cancer by menopausal status

Cause of death	Menopausal status								
	Total			Premenopausal			Postmenopausal		
	Obs	SMR	95% CI	Obs	SMR	95% CI	Obs	SMR	95% CI
Breast cancer	18 215	41.8	41.2-42.4	6053	57.3	55.9-58.7	12 162	36.8	36.2-37.5
All causes, excl. breast cancer	12 626	2.71	2.68-2.74	1480	1.36	1.29-1.43	11 146	1.13	1.11-1.15
All diseases, excl. breast cancer	11 910	2.76	2.73-2.79	1275	1.30	1.23-1.37	10 635	1.12	1.11-1.14
Infections and parasitic diseases	119	1.21	1.01-1.45	7	0.67	0.27-1.37	112	1.28	1.05-1.52
Malignant neoplasms excluding breast cancer	2558	1.10	1.06-1.14	517	1.44	1.32-1.56	2041	1.04	0.99-1.08
Malignant neoplasm of stomach	242	1.43	1.26-1.62	50	2.25	1.67-2.96	192	1.31	1.13-1.49
Malignant neoplasm of larynx, trachea, lung	307	1.10	0.99-1.24	96	1.84	1.49-2.24	211	0.93	0.81-1.06
Malignant neoplasm of ovary	199	1.10	0.96-1.26	55	1.49	1.12-1.94	144	1.00	0.84-1.17
Malignant neoplasm of lymphoid/haematopoietic tissue	313	1.11	0.99-1.24	53	1.32	0.99-1.73	260	1.07	0.95-1.20
Diseases of circulatory system	6108	1.17	1.14-1.20	473	1.41	1.28-1.53	5635	1.15	1.12-1.18
Ischaemic heart diseases	3447	1.21	1.17-1.25	253	1.54	1.35-1.73	3194	1.19	1.15-1.23
Other heart diseases	639	1.31	1.22-1.42	76	2.15	1.70-2.69	563	1.25	1.15-1.35
Cerebrovascular diseases	1489	1.07	1.01-1.12	109	1.09	0.90-1.30	1380	1.06	1.01-1.12
Diseases of respiratory system	721	1.16	1.08-1.24	60	1.30	0.99-1.67	661	1.14	1.06-1.23
Dementia, Alzheimer's disease	1046	1.17	1.10-1.25	49	1.32	0.98-1.75	997	1.17	1.09-1.23
Diabetes mellitus	163	1.05	0.90-1.23	10	0.68	0.33-1.24	153	1.09	0.93-1.27
Suicide	139	1.51	1.28-1.78	68	1.76	1.36-2.22	71	1.32	1.03-1.67
Other accidents and violence excl. accidental alcohol poisoning	401	1.19	1.10-1.30	60	0.94	0.72-1.21	341	1.15	1.03-1.27

The bold values were indicated to represent the odds ratio and 95% CI that are statistically significant.

There are limited studies documenting mortality from other causes than the breast cancer diagnosis among breast cancer patients. Most of these studies have discussed the cause of death in relation to the outcome of treatments from breast cancer, while lesser or no emphasis is put on understanding causes of death among women with breast cancer as indications of joint aetiology of the diseases. If it is not plausible that the breast cancer itself or its treatment would explain all of the excess mortality due to given disease among breast cancer patients, we can assume that common factors might have played a role in the aetiology of both diseases. In our study, we aim to collect indirect evidence of the complex and incompletely understood aetiology of breast cancer from the mortality patterns of women with breast cancer.

2 | MATERIALS AND METHODS

The study cohort consists of 50 481 female breast cancer patients diagnosed between 1971 and 2000 and registered in the national population-based Finnish Cancer Registry (FCR). Of the patients, 15 742 were diagnosed at age 25 to 49 years, and 34 739 at the age of 50 to 74 years. The population-based registration of cancer in Finland began in 1953.¹² FCR collects data from three sources: from hospitals, pathological laboratories and from the National Causes of Death Registry. FCR has continuous quality control by systematically checking all incoming data, and if needed additional data are requested.

The cohort was followed up until the end of 2012 by data linkage with the National Causes of Death Registry of Statistics Finland. The unique personal identity code introduced in Finland in 1967 and given to all people living in Finland serves as the key in record linkages between registries. The National Cause of Death Registry covers all deaths occurred in Finland and most of the deaths of the Finnish citizens occurred abroad. The variables used in our study were the date and underlying cause of death defined as “the disease which has initiated the series of illnesses leading directly to death, or the circumstances connected with an accident or an act of violence which caused the injury or poisoning leading to death.” The underlying cause of death as given in death certificate was categorised into 54 categories based on the different versions of the International Classification of Diseases (ICD). ICD-8 was used in Finland from 1969 to 1986, national adaption of ICD-9 from 1987 to 1995 and ICD-10 from 1996 onwards (https://www.stat.fi/til/ksyyt/ksyyt_2018-11-12_luo_001_en.pdf).¹³

Standardised mortality ratios (SMRs) for the different cause of deaths among breast cancer patients were calculated by age at diagnosis of breast cancer (<50 years, later called “premenopausal,” and 50+ years, “postmenopausal”) and histology (ductal, lobular). The follow-up time started from the breast cancer diagnosis and ended at emigration, at death or at the end of 2012. Follow-up beyond 12 years was excluded from our analysis because one of the aims of the study was to assess time trends of comparable SMRs for breast cancer patients from different decades and we had only limited duration of follow-up of 12+ years for patients diagnosed from 1991 to 2000. The numbers of observed deaths for each cause of death category and person-years at risk at follow-up were counted, which

started from the breast cancer diagnosis and ended at emigration, at death or at the end of 2012, by 5-year age strata, and for 76-year calendar periods between 1971 and 2012. The expected numbers of deaths (for specific causes and overall) were calculated by multiplying the number of person-years in each stratum by the corresponding mortality rate among the Finnish general population. The reference mortality rates of the Finnish general population for each 5-year age category were retrieved from the Statistics Finland. To calculate the SMR for broader age ranges, the stratum-specific observed number of deaths were added up and divided by the sum of expected numbers of respective 5-year age categories. The 95% confidence intervals (CIs) for the SMR were based on the assumption that the number of observed deaths followed a Poisson distribution.

A Poisson regression model was used to estimate hazard ratio (HR) and its 95% CI to compare differences in risk of each cause of death between breast cancer histology. To run a Poisson regression model, age was grouped into seven categories (20-29, 30-39, 40-49, 50-59, 60-69, 79-79 and 80+ years). The observed and expected numbers of subjects were tabulated in each of these 10/y age groups for each cause of death category. Subsequently, a generalised regression model with Poisson distribution was run, where response variable was the observed number of cases and explanatory variables were histology and age strata.

3 | RESULTS

Overall, 50 481 patients with breast cancer diagnosed between 1971 and 2000 were followed up for 682 044 person-years. Among 30 841 women who died during the follow-up, 41% were due to causes other than breast cancer; the proportion of non-breast cancer deaths was 20% among premenopausal and 48% among postmenopausal breast cancer patients (Table 1). Mortality due to diseases other than breast cancer was increased (SMR 2.76, 95% CI 2.73-2.79), with significant excess mortality for infections (SMR 1.21); stomach cancer (SMR 1.43); diseases of circulatory system including ischaemic heart diseases (SMR 1.21), other heart diseases (SMR 1.31) and cerebrovascular diseases (SMR 1.07); diseases of respiratory system (SMR 1.16); dementia (SMR 1.17).

Among women with premenopausal breast cancer, significant excess mortality was observed for malignant neoplasms of the stomach, larynx, trachea, lung and ovary (Table 1). Among women with postmenopausal breast cancer, the SMR was significantly elevated only for stomach cancer. Increased SMR was observed for the diseases of the circulatory system including ischaemic heart diseases and other diseases of heart for both premenopausal and postmenopausal women. Suicide mortality was significantly increased among both premenopausal (SMR 1.76, 95% CI 1.36-2.22) and postmenopausal (SMR 1.32, 95% CI 1.03-1.67) breast cancer patients.

Significantly elevated SMRs for all diseases excluding breast cancer were seen for women diagnosed with both ductal and lobular breast cancer subtypes (Table 2). Age-adjusted analyses showed that women diagnosed with lobular cancer had significantly higher relative risk of death due to stomach cancer than women with ductal breast

TABLE 2 Observed (Obs) numbers of deaths, standardised mortality ratio (SMR) and 95% confidence interval (CI) for causes of death among women with breast cancer, by histology

Cause of death	Histology							
	Ductal			Lobular			Lobular vs ductal ^a	
	Obs	SMR	95% CI	Obs	SMR	95% CI	HR	95% CI
Breast cancer	11 763	38.5	37.9-39.2	1439	40.43	38.4-42.5	1.05	0.99-1.10
All causes, excluding breast cancer	8211	1.13	1.10-1.15	802	1.12	1.04-1.20	0.99	0.92-1.06
All diseases, excluding breast cancer	7719	1.11	1.09-1.13	744	1.09	1.01-1.17	0.98	0.91-1.06
Infectious and parasitic diseases	73	1.11	0.87-1.39	8	1.21	0.52-2.38	1.09	0.53-2.26
Malignant neoplasm excluding breast cancer	1687	1.05	1.00-1.11	201	1.13	0.98-1.30	1.08	0.93-1.25
Malignant neoplasm of stomach	140	1.26	1.06-1.47	27	2.52	1.66-3.66	2.00	1.32-3.02
Malignant neoplasm of larynx, trachea, lung	214	1.09	0.95-1.23	23	0.97	0.61-1.44	0.85	0.55-1.32
Malignant neoplasm of ovary	133	1.06	0.88-1.24	17	1.17	0.68-1.86	1.11	0.67-1.84
Malignant neoplasm of lymphoid/haematopoietic tissue	209	1.08	0.94-1.22	20	0.93	0.57-1.43	0.86	0.55-1.37
Disease of circulatory system	3906	1.15	1.11-1.18	339	1.09	0.98-1.21	0.95	0.85-1.06
Ischaemic heart diseases	2181	1.17	1.13-1.22	186	1.10	0.95-1.26	0.94	0.81-1.09
Other heart diseases	396	1.27	1.15-1.39	39	1.42	1.01-1.93	0.80	0.63-1.01
Cerebrovascular diseases	966	1.06	0.99-1.12	85	1.02	0.81-1.26	1.34	0.97-1.84
Diseases of respiratory system	428	1.05	0.95-1.15	41	1.09	0.78-1.48	1.02	0.74-1.41
Dementia, Alzheimer's disease	710	1.19	1.10-1.27	58	1.01	0.77-1.30	0.85	0.65-1.12
Diabetes mellitus	102	1.00	0.82-1.20	10	1.03	0.49-1.88	1.04	0.55-2.00
Suicide	96	1.47	1.19-1.78	17	2.21	1.29-3.54	1.47	0.89-2.50
Other accidents and violence excl. accidental alcohol poisoning	268	0.96	0.82-1.11	28	1.08	0.74-1.55	0.96	0.68-1.49

^aHR and 95% CI for ductal vs lobular breast cancer was calculated using Poisson regression model adjusted for each 10-year age group starting from 20 years of age.

The bold values were indicated to represent the odds ratio and 95% CI that are statistically significant.

cancer (HR 2.00, 95% CI 1.32-3.02). Increased risk of death due to ischaemic heart diseases was observed in ductal breast cancer groups only (SMR 1.17, 95% CI 1.13-1.22), while other heart diseases were a significant cause of mortality in both ductal and lobular subtypes.

4 | DISCUSSION

We utilised data from nationwide registries to identify the causes of death and changes in the causes of death over the time among women diagnosed with breast cancer in Finland. The SMR for breast cancer as well as all other causes combined was higher among women with breast cancer diagnosed before 50 years than among older women.

5 | CANCER MORTALITY

We observed that risk of dying from other malignancies in women with breast cancer was higher than that in the general population. Excess mortality was most marked for cancer of stomach in both premenopausal (SMR 2.25) and postmenopausal (SMR 1.31) women. Excess mortality was also observed for ovarian cancer (SMR 1.49)

among women with premenopausal but not among women with postmenopausal breast cancer. These excesses might have some association with the germline mutations in the breast cancer type 1/2 (*BRCA1/2*) genes. Germline mutations in the tumour suppressor genes *BRCA1* and *BRCA2* expose individuals to early onset breast and ovarian cancer.¹⁴⁻¹⁶ Mutations in *BRCA1* and *BRCA2* have also been reported to be associated with increased risk of developing stomach cancer.¹⁷⁻¹⁹

Increased SMRs observed in our study for cancers of the lung, stomach and ovary observed in our study might be related to tobacco smoking. Nicotine is likely to promote proliferation and progression of cells as well as increased cell migration in cell lines of gastric, breast and ovarian cancer cells.²⁰⁻²³ Several studies consistently show an association between cigarette smoking and breast cancer.^{20,24-28} A recent study based on a large Norwegian cohort estimated that among smokers, one in nine breast cancer cases could have been avoided in the absence of active smoking.²⁹ The carcinogens found in tobacco are described more effective in inducing cancer in less differentiated breast tissue, which might be the reason for the stronger increase in breast cancer risk among younger women.^{30,31} Smoking is an established strong risk factor for lung cancer and has repeatedly been shown to also be associated with stomach cancer with a dose-

response relationship.³² A large meta-analysis indicated that smoking significantly increases the risk of ovarian cancer among premenopausal women but not among postmenopausal women.³³ Excess mortality of ovarian cancer observed only among premenopausal women in our study is consistent with this finding.

A large prospective study of European countries showed a significant association of alcohol intake with breast cancer and more than 4% increase in risk for each 10 g/d increase in alcohol intake.^{34,35} Alcohol consumption is also suggested to increase the risk of stomach cancer.³⁶ Hence, our finding on an increased SMR of stomach cancer might also point to the common risk associated with alcohol consumption. Additionally, studies have shown that alcohol consumption is strongly associated with the increased risk up to two-fold of lobular breast cancer than ductal breast cancer as alcohol increases the production of oestrogen.³⁷⁻³⁹ The significantly higher HR of stomach cancer mortality among women with lobular breast cancer as compared to ductal subtype might be another indication of an association with alcohol consumption.

In the line of our study, earlier studies have reported an increased risk of developing ovarian cancer after breast cancer⁴⁰ and increased ovarian cancer mortality among breast cancer patients.⁴¹ In addition to the earlier discussed risk factors such as genetic mutations and smoking, shared risk factors associated with childbirth and female hormones might explain the association between breast and ovarian cancer.⁴²⁻⁴⁴ Obesity increases the risk of both breast cancer and ovarian cancer⁴⁵ and may hence offer another partial explanation to the coexistence of these diseases.

6 | NONCANCER MORTALITY

6.1 | Diseases of circulatory system

Our study demonstrated a significantly increased SMR for circulatory diseases (including ischaemic and other heart diseases, and cerebrovascular disease) in women with breast cancer, more clearly among premenopausal (SMR 1.54) than postmenopausal (SMR 1.19) women. Some early studies noted that the increased risk of cardiovascular disease among breast cancer survivors would be mostly due to the treatment for breast cancer. Recent studies, however, claim that the greater cardiovascular disease-specific mortality among breast cancer patients is related to common modifiable and non-modifiable risk factors of these two diseases.⁴⁶⁻⁴⁸ Obesity is associated with both cardiovascular disease and breast cancer by several factors such as physical activity, diet and hormones. Moreover, genetic risk factors of breast cancer and cardiovascular disease are linked. The non-modifiable risk factor of breast cancer, *BRCA* genes, could also cause cardiac dysfunction.⁴⁸ It was notable that diseases of the circulatory system were a more important cause of death among ductal breast cancer than among lobular breast cancer patients. Some previous studies have indicated a protective role of endogenous hormones as well as hormonal replacement therapy against cardiovascular disease.^{49,50} Conversely, lobular breast cancer is more strongly associated with increased exposure to endogenous oestrogens such as early

menarche, late menopause and exogenous hormones.⁵¹ Therefore, the higher level of endogenous hormones and use of hormonal therapy leading to lobular breast cancer might have worked as the protective factor against circulatory system diseases among these women.

Type 2 diabetes mellitus (T2DM) has been reported as an important cause of death among breast cancer patients in previous studies.^{41,52} A meta-analysis reported that women with T2DM are at increased risk of developing breast cancer.⁵³ The association between breast cancer and T2DM could possibly be due to common risk factors for these two diseases such as physical inactivity, dietary patterns and obesity. However, in our study among Finnish female breast cancer patients, no excess mortality was observed for T2DM in any age and histology category. A recent large Finnish study also indicated that there is no excess incidence of breast among women with T2DM.⁵⁴ Hence, these two diseases seem not to have joint aetiology in Finland.

Diseases of the respiratory system were observed as a cause of significant excess mortality among women diagnosed with breast cancer after age 50. It could be possible that breast cancer patients have a weakened immune system as compared to other women of the same age and are more prone to infections, including the respiratory system.

We observed significantly elevated mortality from accidents and violence among postmenopausal breast cancer patients, which is hardly due to shared risk factors with breast cancer. Women treated with chemotherapy after breast cancer treatment are at increased risk of osteoporosis and fractures.⁵⁵ An increased risk of suicides was observed among both premenopausal and postmenopausal women diagnosed with breast cancer who might find it difficult to cope better with cancer diagnosis and its threat to the functionality of life.⁵⁶

7 | STRENGTHS AND LIMITATIONS OF THE STUDY

The strengths of our study include the long-term follow-up of a large number of Finnish women diagnosed with breast cancer and completeness of the information. The study is based on high-coverage and accurate nationwide registers that allow us to overcome the selection bias. We studied a wide range of causes of death among breast cancer patients, some of which may not be directly important for the main objective of our study—to get indirect hints of aetiology of breast cancer—but may provide a reference for further studies. A limitation of our study is that we are unable to separate the proportion of the mortality attributed to shared risk factors from the effects of treatment of the breast cancer. The treatment procedures may be different for cancer patients with different histology and of different age and have advanced over decades, which could partly explain differences in mortality risks between subgroups of breast cancer patients. Similarly, it was not within the scope of our study to trace back the lifestyle and hormonal factors of breast cancer patients in order to associate them with breast cancer and also the mortality cause.

8 | CONCLUSION

Our study concludes that there might be shared genetic, reproductive, lifestyle and environmental risk factors between breast cancer and mortality outcomes among breast cancer patients. The mortality patterns provide indirect information on which risk factors might have played a role in the development of breast cancer. It is noticeable that modification of lifestyle and risk behaviours would reduce both the incidence of breast cancer and other related diseases.

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CONFLICT OF INTEREST

All authors declare that they have no conflict of interest.

ETHICS STATEMENT

This is a register-based study conducted according to Finnish regulations. It does not require permission/consent of the participants. This study has passed the ethical and privacy protection control and got the study permission from the National Institute for Health and Welfare (THL).

Data Availability Statement.

The data that are used in this study are available from the corresponding author upon reasonable request. The Finnish Cancer Registry data are available upon request and approval of the Finnish Institute of Health and Welfare.

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