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ORIGINAL REPORT

Incidence and Outcome of Male Breast Cancer: An International Population-Based Study

Hui Miao, Helena M. Verkooijen, Kee-Seng Chia, Christine Bouchardy, Eero Pukkala, Siri Larønningen, Lene Mellemkjær, Kamila Czene, and Mikael Hartman

Hui Miao, Helena M. Verkooijen, Kee-Seng Chia, and Mikael Hartman, Yong Loo Lin School of Medicine, National University of Singapore, Singapore; Helena M. Verkooijen, University Medical Center Utrecht, Utrecht, the Netherlands; Christine Bouchardy, Geneva Cancer Registry, Institute for Social and Preventive Medicine, Geneva University, Geneva, Switzerland; Eero Pukkala, Finnish Cancer Registry, Institute for Statistical and Epidemiological Cancer Research, Helsinki, Finland; Siri Larønningen, Cancer Registry of Norway, Oslo, Norway; Lene Mellemkjær, Institute of Cancer Epidemiology, Copenhagen, Denmark; and Kamila Czene and Mikael Hartman, Karolinska Institute, Stockholm, Sweden.

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Corresponding author: Mikael Hartman, MD, PhD, Department of Epidemiology and Public Health, Block MD3, 16 Medical Dr, Singapore 117597, Singapore; e-mail: ephbamh@nus.edu.sg.

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ABSTRACT

Purpose
Male breast cancer is a rare disease with an incidence rate less than 1% of that of female breast cancer. Given its low incidence, few studies have assessed risk and prognosis.

Methods
This population-based study, including 459,846 women and 2,665 men diagnosed with breast cancer in Denmark, Finland, Geneva, Norway, Singapore, and Sweden over the last 40 years, compares trends in incidence, relative survival, and relative excess mortality between the sexes.

Results
World standardized incidence rates of breast cancer were 66.7 per 10^5 person-years in women and 0.40 per 10^5 person-years in men. Women were diagnosed at a younger median age (61.7 years) than men (69.6 years). Male patients had a poorer 5-year relative survival ratio than women (0.72 [95% CI, 0.70 to 0.75] *v* 0.78 [95% CI, 0.78 to 0.78], respectively), corresponding to a relative excess risk (RER) of 1.27 (95% CI, 1.13 to 1.42). However, after adjustment for age and year of diagnosis, stage, and treatment, male patients had a significantly better relative survival from breast cancer than female patients (RER, 0.78; 95% CI, 0.62 to 0.97).

Conclusion
Male patients with breast cancer have later onset of disease and more advanced disease than female patients. Male patients with breast cancer have lower risk of death from breast cancer than comparable female patients.

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INTRODUCTION

Male breast cancer is a rare disease, with an incidence rate of 0.5% to 1% compared with female breast cancer.[1-4] Similar to female breast cancer, the risk of male breast cancer increases steadily with age,[3,5] although men are, on average, diagnosed at later ages and do not display the typical deceleration in risk after the age of 50 years as seen in women, described by Clemmesen 63 years ago.[1,3,5-8]

Male breast cancer is reportedly associated with worse outcome compared with female breast cancer.[4,9] Some studies have suggested that survival differences between sexes disappear after stratification for age and stage.[6,9,10] However, given the low incidence of male breast cancer, many of these studies suffered from small sample sizes, short follow-up time, and a non–population-based design, limiting their interpretability.

Over the last few decades, survival of female breast cancer has improved substantially. This is likely a combined result of earlier detection and improvements in treatment.[11,12] Given the scarcity of male breast cancer, solid recent data on risk and outcome for male disease is lacking. We have undertaken a population-based international study with the aim to improve our understanding of risk and outcome of male breast cancer in relation to female breast cancer.

METHODS

Six population-based cancer registries in Denmark, Finland, Geneva, Norway, Singapore, and Sweden contributed incident cases of breast cancer. In those six regions, all medical practitioners, health care institutions, and pathology laboratories are required to notify the cancer registry of any incident cancer.

The Danish Cancer Registry has registered all patients with cancer since 1943.[13] The completeness and validity of the registry was assessed to be 95% to 98%.[14] TNM stage information is available only after 2004, whereas there is no information on treatment. Information on death was obtained from the Central Population Register or national death certificate system.

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The Finnish Cancer Registry started in 1953, and registration of incident patients with cancer has been compulsory since 1961.[14] The completeness of registration of solid tumors was reported to be over 99%.[15] Data on stage and basic treatment have been recorded since the beginning of cancer registration. Data on vital status and date and causes of death were regularly updated by linkage to the Cause of Death Register and Central Population Register.

The Geneva Cancer Registry records all incident cancers occurring in the population of the canton since 1970. Completeness of registration was reported to be greater than 98%, including information on stage and treatment.[16] Vital status is regularly assessed by linkage to the Cantonal Population Office.

The Cancer Registry of Norway has collected cancer notifications since 1952. Estimated completeness of the registry was 98.8% and included information on stage and treatment.[17] Death records come from National Population Registry and are compared with data from the Cause of Death Register run by Statistics Norway at least once a year.[18]

The Singapore Cancer Registry has received notification of incident cancers since 1968. Completeness of the register was 96% between 1968 and 1997 and 99% between 1998 and 2002, and vital status is retrieved through linkage to the death registry.[19,20] Information on stage is available from 2003, whereas no information on treatment is available.

The Swedish Cancer Registry has collected information on incident cancers since 1958 and has a completeness of 98%.[21,22] Vital status and date of death and migration are obtained via linkages to the Cause of Death Register and the Total Population Register. The register has no information on stage and treatment.

For the current study, we included patients with breast cancer from all participating regions diagnosed between 1970 and 2007 with the exception of Denmark, where patients diagnosed up to 2006 were included. All data sets contained information on sex, date of birth, date of diagnosis, duration of follow-up, vital status, date of death, and date of migration for all individuals. Stage at diagnosis was available for patients diagnosed in Finland (localized, regional, distant, or unknown). For patients from Geneva, Norway, and Singapore, TNM stage was transformed to localized, regional, or distant, with stage I as localized, stages II and III as regional, and stage IV as distant. Basic treatment information was available for Finland, Geneva, and Norway and included surgery (yes, no, or unknown), chemotherapy (yes, no, or unknown), radiotherapy (yes, no, or unknown), and hormonal therapy (yes, no, or unknown).

Patients with an invasive cancer diagnosis before first breast cancer were excluded, as were individuals who immigrated from another region before diagnosis, because of the possibility of misclassification of cancer history. For individuals with multiple breast cancer diagnoses, only the first cancer was included in analysis. Our final study population comprised 459,846 women and 2,665 men diagnosed with invasive breast cancer. Follow-up started at time of diagnosis, and survival time was defined as the time between the date of diagnosis and date of death, emigration, or end of follow-up (December 31, 2007), whichever occurred first.

Statistical Analysis

Mann-Whitney *U* test and χ^2 test were performed to test sex differences in distribution of age, stage, and treatment. Significance level of the associations was based on valid proportions only (ie, after excluding missing information).

The age-standardized incidence rate of invasive breast cancer was calculated using the total female and male population of the six regions as denominators and was directly standardized to the world standard population with 5-year age groups.

Overall survival was evaluated using Kaplan-Meier analysis stratified by sex and stage. We applied relative survival analysis, which is an approximation of disease-specific survival, to account for differences in life expectancy between men and women. For this purpose, the cumulative relative survival ratio was calculated as the ratio of the observed cumulative survival of the patients with breast cancer under study over the cumulative survival expected in the background population with similar sex, region, age, and period characteristics. Expected survival was obtained from population life-tables and matched with the observed survival of the study population according to the Ederer II method.[23,24] Life-tables of the six regions were obtained from The Human Mortality Database[25] and Singapore Disease Registry. Overall relative survival ratios for both sexes were estimated at 5 and 15 years of follow-up. To investigate improvements in relative survival over calendar time for men and women, we evaluated trends in 5-year relative survival rates by stage and over time (10-year categories).

To adjust sex differences in relative survival for age at diagnosis, stage, and treatment, we modeled the excess risk using Poisson regression. The excess

Table 1. Characteristics of Female and Male Patients With Breast Cancer Diagnosed in Denmark, Finland, Geneva, Norway, Singapore, and Sweden Between 1970 and 2007*

Characteristics	Male Patients		Female Patients		*P*
	No.	%	No.	%	
Total patients	2,665	0.6	459,846	99.4	
Region					< .001†
Denmark	677	25.4	97,228	21.1	
Finland	347	13.0	86,083	18.7	
Geneva	61	2.3	9,980	2.2	
Norway	435	16.3	70,263	15.3	
Singapore	74	2.8	22,787	5.0	
Sweden	1,071	40.2	173,505	37.7	
Age, years					
Median age	69.6		61.7		< .001‡
0-40	62	2.3	25,154	5.5	< .001†
40-60	612	23.0	185,901	40.4	
60+	1,991	74.7	248,791	54.1	
Calendar period					< .001†
1970-1977	490	18.4	67,478	14.7	
1978-1987	607	22.8	101,755	22.1	
1988-1997	728	27.3	130,029	28.3	
1998-2007	840	31.5	160,584	35.0	
Stage					< .001§
Localized	379	41.3	83,828	44.3	
Regional	311	33.9	64,945	34.3	
Distant	100	10.9	10,561	5.6	
Unknown	127	13.9	29,779	15.8	
Total	917		189,113		
Treatment					
Surgery					< .001‖
Yes	728	86.4	150,769	90.7	
No	79	9.4	9,572	5.8	
Unknown	36	4.3	5,985	3.6	
Radiotherapy					< .001‖
Yes	251	29.8	63,751	38.3	
No	447	53.0	81,775	49.2	
Unknown	145	17.2	20,800	12.5	
Chemotherapy					.06‖
Yes	127	15.1	31,125	18.7	
No	542	64.3	110,749	66.6	
Unknown	174	20.6	24,452	14.7	
Hormonal therapy					.09‖
Yes	190	22.5	35,400	21.3	
No	508	60.3	109,199	65.7	
Unknown	145	17.2	21,727	13.1	
Total	843	100	166,326	100	

*Denmark contributed patients diagnosed between 1970 and 2006.
†χ^2 test.
‡Mann-Whitney *U* test.
§χ^2 test on valid proportion only, using subset with stage information (Finland, Geneva, Norway, and Singapore).
‖χ^2 test on valid proportion only, using subset with treatment information (Finland, Geneva, and Norway).

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risk is the difference of observed mortality risk and expected mortality risk. The relative excess risk (RER) is then the excess risk in males divided by females, which is the exponentiation of the parameter estimate from the Poisson regression. It can be interpreted as the adjusted relative risk of death from breast cancer for men compared with women. A generalized linear model was fitted to the collapsed observations (group all subject-band observations into one observation for each covariate pattern) with grouped survival time and meanwhile adjusted for potential confounders such as age and calendar period of diagnosis (grouped by every 5 years), follow-up time (grouped by every 1 year), region, stage, and treatment. The reference category for sex comparisons was the female group. Regression models were built using the following three data sets: all individuals (ie, analysis including individuals from all regions), individuals from regions with stage information (ie, Finland, Geneva, Norway, and Singapore), and individuals from regions with both stage and treatment information (ie, Finland, Geneva, and Norway). On the basis of the latter data set, we stepwise evaluated the effect of adjustment for age, stage, and treatment on the relative risk of death from breast cancer for males compared with females. Statistical analysis was done using the SAS statistical package (version 9.2; SAS Institute, Cary, NC).

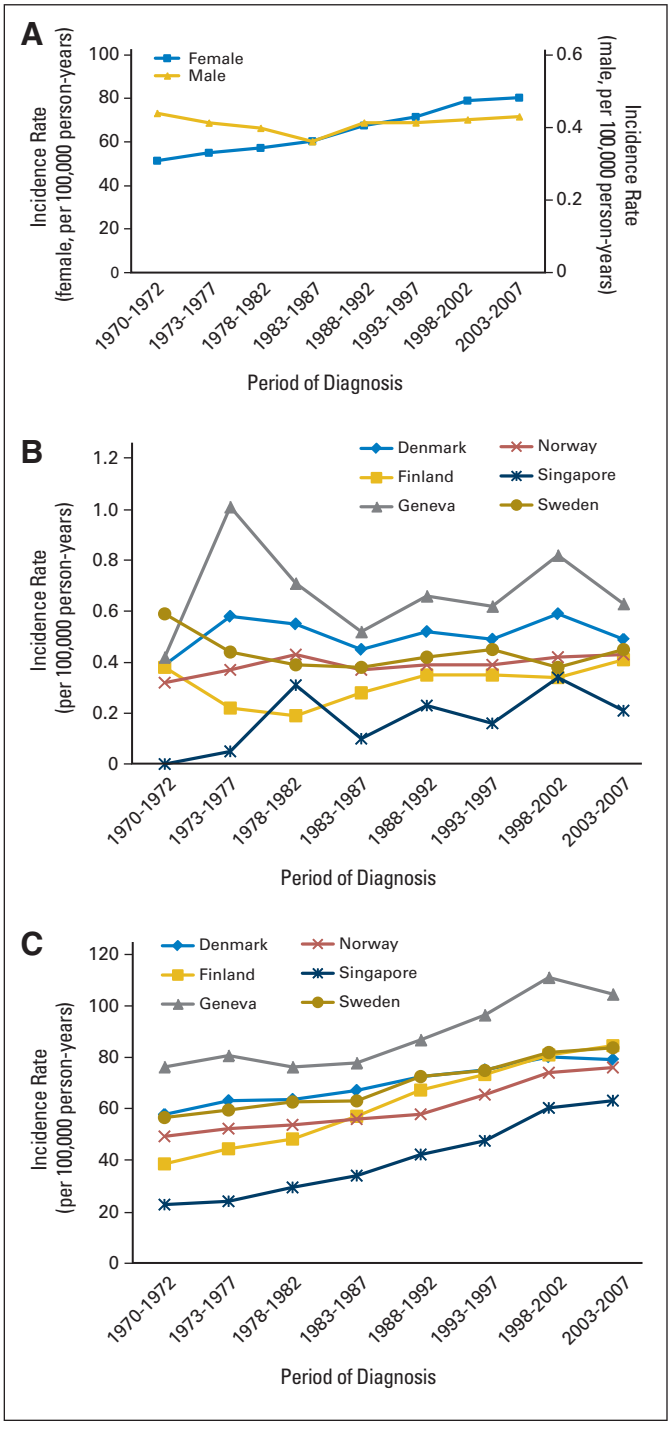
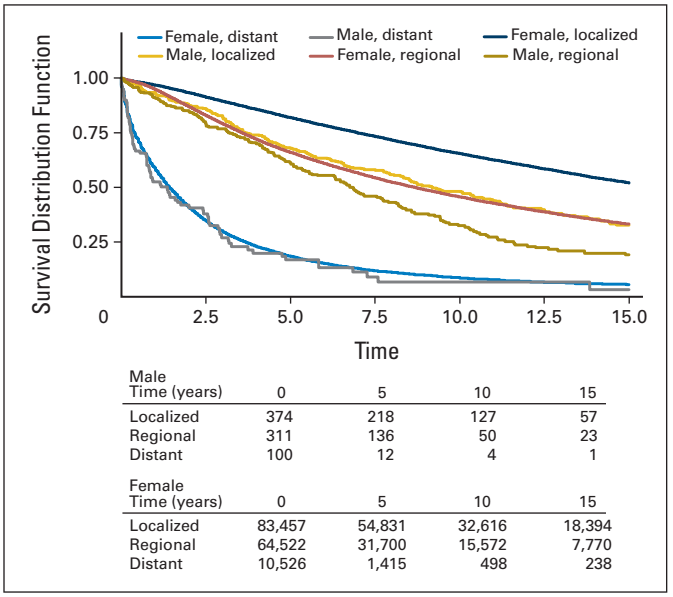


Fig 1. Incidence rates of invasive breast cancer (standardized to world population) by period of diagnosis. (A) By sex; (B) male by region; (C) female by region.

RESULTS

Male breast cancers (n = 2,665) represented 0.6% of all breast cancers (Table 1), and this proportion was similar for all six regions. Women were diagnosed with breast cancer at a younger median age than men (61.7 years *v* 69.6 years, respectively; $P < .001$). Among the 190,030 patients with breast cancer (41%) with information on stage, 41% of the men and 44% of women were classified as having localized disease. Distant disease extent accounted for 11% and 6% for men and women, respectively ($P < .001$). For 167,169 patients (36%) with information on treatment, men were significantly less likely to receive surgery and radiotherapy, but there were no differences in the administration of chemotherapy and hormonal therapy.

The overall age-standardized incidence rates were 0.4 per 100,000 person-years in men and 66.7 per 100,000 person-years in women. The incidence of breast cancer in women increased by more than 50%, from 51.4 per 100,000 person-years in the early 1970s to 80.3 per 100,000 person-years after the year 2000 (Fig 1A). The overall incidence of disease in men remained stable at approximately 0.4 per 100,000 person-years all the time (Fig 1A). Compared with the European countries, Singapore had a lower incidence rate for both sexes, but a faster increase in incidence, which tripled in women and quadrupled in men from the early 1970s to the 2000s (females: 23.97 to



Male Time (years)	0	5	10	15
Localized	374	218	127	57
Regional	311	136	50	23
Distant	100	12	4	1

Female Time (years)	0	5	10	15
Localized	83,457	54,831	32,616	18,394
Regional	64,522	31,700	15,572	7,770
Distant	10,526	1,415	498	238

Fig 2. Kaplan-Meier curve for overall survival of patients with breast cancer by sex and stage.

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Table 2. The 5- and 15-Year RSRs and RER Differences Between Male and Female Patients With Breast Cancer

Sex	RSR	95% CI for RSR	Model 1a RER	Model 1a 95% CI	Model 1b RER	Model 1b 95% CI	Model 2a RER	Model 2a 95% CI	Model 2b RER	Model 2b 95% CI	Model 3a RER	Model 3a 95% CI	Model 3b RER	Model 3b 95% CI	Model 4 RER	Model 4 95% CI
5-Year follow-up																
Male	0.72	0.70 to 0.75	1.27	1.13 to 1.42	1.20	0.97 to 1.50	1.13	1.01 to 1.26	1.08	0.88 to 1.33	0.96	0.80 to 1.15	0.91	0.75 to 1.12	0.78	0.62 to 0.97
Female	0.78	0.78 to 0.78	1.00	Ref	1.00	Ref	1.00	Ref	1.00	Ref	1.00	Ref	1.00	Ref	1.00	Ref
15-Year follow-up																
Male	0.50	0.46 to 0.54	1.36	1.24 to 1.50	1.24	1.03 to 1.49	1.16	1.06 to 1.28	1.09	0.91 to 1.30	1.00	0.85 to 1.18	0.96	0.81 to 1.15	0.80	0.65 to 0.98
Female	0.61	0.60 to 0.61	1.00	Ref	1.00	Ref	1.00	Ref	1.00	Ref	1.00	Ref	1.00	Ref	1.00	Ref

NOTE. Models are defined as follows: RSR and models 1a and 1b: crude; models 2a and 2b: adjusted for region, time since diagnosis, and age and year of diagnosis; models 3a and 3b: adjusted for region, time since diagnosis, age and year of diagnosis, and stage; and model 4: adjusted for region, time since diagnosis, age and year of diagnosis, stage, and treatment (surgery, chemotherapy, radiotherapy, and hormonal therapy). RSR and models 1a and 2a included the entire data set (N = 462,511). Model 3a included the subset with information on stage (Finland, Geneva, Norway, and Singapore; n = 190,030). Models 1b, 2b, 3b, and 4 included the subset with information on stage and treatment (Finland, Geneva, and Norway; n = 167,169).
Abbreviations: Ref, reference; RER, relative excess risk; RSR, relative survival ratio.

63.17 per 10^5 person-years; males: 0.05 to 0.21 per 10^5 person-years) (Figs 1B and 1C). The increased incidence for men in Singapore was not statistically significant. Men had a worse overall survival compared with women (Fig 2), except for patients with distant spread of disease, for whom overall survival was similar for both sexes. Disease-specific survival (as estimated by relative survival) was significantly worse for male patients at both 5 and 15 years compared with female patients (5-year relative survival ratio, 0.72 *v* 0.78, respectively; 15-year relative survival ratio, 0.50 *v* 0.61, respectively; Table 2). This corresponds to a 27% higher unadjusted 5-year excess mortality risk for men compared with women (RER, 1.27; 95% CI, 1.13 to 1.42; Table 2, model 1a) and a 36% higher 15-year excess risk (RER, 1.36; 95% CI, 1.24 to 1.50; Table 2, model 1a). After adjusting for region, age, and year of diagnosis, follow-up time, and stage, there was no significant difference in 5- and 15-year excess mortality between men and women (Table 2, models 3a and 3b). Additional adjustment for treatment further reduced the RER to 0.78 (95% CI, 0.62 to 0.97; Table 2, model 4). A similar pattern was observed when assessing 15-year follow-up. For female patients with breast cancer, 5-year relative survival increased from 0.66 (95% CI, 0.66 to 0.67) in 1970 to 1977 to 0.87 (95% CI, 0.86 to 0.87) in 1998 to 2007 (Table 3). Men experienced an improvement in relative survival as well, from 0.67 (95% CI, 0.60 to 0.72) in 1970 to 1977 to 0.78 (95% CI, 0.73 to 0.83) in 1998 to 2007.

DISCUSSION

With this international population-based study, we show that over the last 38 years, male breast cancer incidence has remained at a stable low rate, whereas female breast cancer has become increasingly common. In a crude comparison, survival is worse among men than among women. The poorer observed survival of male patients is largely explained by their more advanced stage at diagnosis, their higher age at diagnosis, and less standard locoregional treatment. After adjusting for these factors, men actually had better relative survival than women.

Over the last 40 years, the risk of breast cancer in women has continued to increase at a steady pace, largely explained by the introduction of mammography screening and hormone replacement therapy in the 1980s.[26] Additionally, changes in lifestyle and reproductive patterns (ie, age at menarche, age at first birth, parity, and frequency and duration of breast feeding) have influenced female breast cancer

Table 3. Breast Cancer 5-Year Relative Survival by Sex, Calendar Period, and Stage

Calendar Period	Overall* RSR	Overall* 95% CI	Disease Stage: Localized RSR	Localized 95% CI	Regional RSR	Regional 95% CI	Distant RSR	Distant 95% CI
Male (n = 917)								
1970-1977	0.67	0.60 to 0.72	0.81	0.65 to 0.95	0.70	0.47 to 0.90	0.16	0.03 to 0.43
1978-1987	0.68	0.63 to 0.73	0.85	0.71 to 0.97	0.68	0.51 to 0.82	0.26	0.06 to 0.57
1988-1997	0.73	0.68 to 0.78	0.97	0.86 to 1.05	0.72	0.56 to 0.85	0.08	0.01 to 0.22
1998-2007	0.78	0.73 to 0.83	0.81	0.65 to 0.93	0.92	0.80 to 1.01	0.39	0.17 to 0.63
Overall	0.72	0.70 to 0.75	0.87	0.81 to 0.93	0.78	0.71 to 0.85	0.23	0.13 to 0.34
Female (n = 189,113)								
1970-1977	0.66	0.66 to 0.67	0.84	0.83 to 0.85	0.54	0.53 to 0.56	0.13	0.12 to 0.15
1978-1987	0.73	0.73 to 0.74	0.89	0.88 to 0.90	0.65	0.64 to 0.66	0.17	0.15 to 0.19
1988-1997	0.80	0.80 to 0.80	0.93	0.92 to 0.93	0.74	0.74 to 0.75	0.22	0.20 to 0.24
1998-2007	0.87	0.86 to 0.87	0.97	0.96 to 0.97	0.86	0.85 to 0.86	0.31	0.29 to 0.33
Overall	0.78	0.78 to 0.78	0.92	0.92 to 0.92	0.73	0.73 to 0.74	0.22	0.21 to 0.23

Abbreviation: RSR, relative survival ratio.
*Estimated using entire data set (N = 462,511).

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risks. Virtually all of these factors, except changes in lifestyle, have not affected men over time.

Breast cancer is diagnosed on average 5 to 10 years later in men than in women.[1,3,6,7] Because of the lack of early detection by mammography and awareness of early signs of breast cancer, the duration of symptoms before diagnosis has been reported to be longer in men, with a median of 4 to 6 months.[1,27] This may contribute to the differences in stage distribution between men and women. In our study, the proportion of distant spread of disease stage was two-fold in men compared with women.

Female patients with breast cancer have experienced substantial improvements in survival over the last 30 years. The improvement in male breast cancer survival is not as pronounced. The survival improvement in women is partly explained by the introduction of screening (both opportunistic and within national programs targeted to women only), leading to earlier detection and detection of indolent tumors and overdiagnosis (ie, detection of breast cancers of low malignant potential). Advances in treatment (in particular, the introduction of tamoxifen in the 1980s) and standardization of treatment regimens in international guidelines have improved breast cancer survival probabilities.[12,28]

Lack of evidence-based treatment guidelines and differences in compliance with treatment may explain why men experience less survival benefit than women. Locoregional and adjuvant treatment of male breast cancer has not yet been evaluated in randomized trials, and evidence-based treatment guidelines are lacking. As a result, most clinicians base their treatment strategy on guidelines for female breast cancer. However, systemic treatment, especially antihormonal treatment, is not as straightforward in men. Antiestrogen treatments like tamoxifen are not well tolerated by men, resulting in lower treatment compliance.[29-31] In addition, National Comprehensive Cancer Network guidelines suggest that administration of aromatase inhibitors to men is not effective without simultaneous suppression of testicular steroidogenesis.[32]

Although the observed survival of male breast cancer is worse than that of female disease, male sex is not an independent risk factor of poor outcome after breast cancer. Actually, our results suggest the opposite, that male sex is a favorable prognostic factor, as shown by the reduced RER of death after breast cancer, after adjustment for age at diagnosis, stage, and treatment. This is in line with other studies[9,10] that found a similar relative survival for women and men with early-stage breast cancer, whereas men with late-stage breast cancer had better survival than women. Our stepwise adjustment shows that stage and treatment differences between female and male patients explain most of the poorer (unadjusted) relative survival of men. These results suggest that much improvement in outcome of male breast cancer can be achieved by improving earlier detection (through awareness and promotion of breast self-examination) and development of treatment guidelines.

We acknowledge that our study suffers from limitations. An unavoidable limitation of a study with a time frame of almost 40 years involves the improvements in diagnostic performance and the increased diagnostic intensity in women, which has led to an increased uptake of small, often indolent cancers. Other limitations are discrepancies in staging systems among registries and lack of information on tumor characteristics such as grade and estrogen receptor status and details on systemic treatment.

Strengths of our study include the large number of male patients, the long observation time, the high-quality (population-based) data, and the completeness of follow-up, which allow for unbiased ascertainment of cancers and deaths. Unlike previous studies that compared outcome in male and female breast cancer,[4,33] we accounted for sex differences in life expectancy by looking at relative survival and RER.

In conclusion, male breast cancer risk has remained constant over the last 40 years. Male patients have later onset and more advanced disease than female patients. Overall survival of male breast cancer is worse; however, after adjustment of life expectancy, age and year of diagnosis, stage, and treatment, male patients with breast cancer actually emerged as having a survival benefit compared with women.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

The author(s) indicated no potential conflicts of interest.

AUTHOR CONTRIBUTIONS

Conception and design: Hui Miao, Helena M. Verkooijen, Kee-Seng Chia, Christine Bouchardy, Eero Pukkala, Mikael Hartman
Provision of study materials or patients: Christine Bouchardy, Eero Pukkala, Siri Larønningen, Lene Mellemkjær, Kamila Czene, Mikael Hartman
Collection and assembly of data: Hui Miao, Christine Bouchardy, Eero Pukkala, Siri Larønningen, Lene Mellemkjær, Kamila Czene, Mikael Hartman
Data analysis and interpretation: Hui Miao, Helena M. Verkooijen, Christine Bouchardy, Eero Pukkala, Kamila Czene, Mikael Hartman
Manuscript writing: All authors
Final approval of manuscript: All authors

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