Archives of Gerontology and Geriatrics 76 (2018) 60–64

Contents lists available at ScienceDirect

Archives of Gerontology and Geriatrics

journal homepage: www.elsevier.com/locate/archger

Breast cancer among older women: The influence of age and cancer stage on survival☆

Yakir Rottenberg[a,b,*,1], Arash Naeim[c,1], Beatrice Uziely[a], Tamar Peretz[a], Jeremy M. Jacobs[b,d,*,1]

[a] The Department of Oncology, Hadassah-Hebrew University Medical Center, Hebrew University-Hadassah Medical School, Jerusalem 91120, Israel
[b] The Jerusalem Institute of Aging Research, Hadassah-Hebrew University Medical Center Mount Scopus, Hebrew University-Hadassah Medical School, Mount Scopus, Jerusalem, Israel
[c] Divisions of Hematology-Oncology and Geriatric Medicine, Department of Medicine and Jonsson Comprehensive Cancer Center, David Geffen UCLA School of Medicine, 10911 Weyburn Avenue, Los Angeles, CA 90095, United States
[d] The Department of Geriatrics and Rehabilitation, Hadassah-Hebrew University Medical Center Mount Scopus, Hebrew University-Hadassah Medical School, Mount Scopus, Jerusalem, Israel

ARTICLE INFO

Keywords:
Breast cancer
Survival
Geriatric assessment
Palliative care

ABSTRACT

Purpose of study: To describe the association between increasing age and survival among women aged over 65 years, diagnosed with breast cancer.

Materials and methods: A historical prospective cohort study, comparing 3270 breast cancer patients to 13,163 non cancer age matched controls. Baseline characteristics and cancer data gathered from the Israeli Central Bureau of Statistics (1995), the Israel Cancer Registry (2000–2010). Baseline measurements included age, socioeconomic status. Cancer stage at diagnosis was clustered as stage I, stage II–III and metastatic. Cox Proportional Hazards regression models were used to determine Hazards Ratios (HR) for mortality.

Results: Between ages 65–69 and ≥85, metastatic disease rose from 3.9% to 23.4% and stage I disease declined from 58.6% to 30.1%. At age 80–84, 50% life expectancy among controls, stage I, and stage II–III disease was 95,92 and 90 months respectively, compared to 2 months for metastatic disease. Compared to controls, between the age 65–69 to ≥85, adjusted HR's progressively decreased among subjects with stage I from HR 0.96 (95% CI 0.69–1.33) to 0.60 (95%CI 0.36–1.01), stage II–III from HR 3.26 (95%CI2.58–4.12) to HR 1.60 (95%CI 1.22–2.09), and metastatic disease from HR 57.40 (95%CI 39.56–83.29) to HR 20.76 (95%CI 14.73–29.24).

Conclusions: This study describes the increasingly poor prognosis and short life expectancy observed among women aged ≥80 diagnosed with metastatic breast. In contrast, our findings confirm the positive prognosis associated with rising age, among older women presenting with stage I breast cancer, among whom survival was similar, if not slightly better, than non-cancer age matched controls.

1. Introduction

Aging is a dominant risk factor for the development of cancer, and the number of older individuals with cancer is increasing, reflecting both the demographics of global aging, as well as continued advances in early detection and treatment of cancer (Rowland & Bellizzi, 2014; Schonberg, 2016; Schonberg, Silliman, McCarthy, & Marcantonio, 2012). Breast cancer is among the leading cancers in developed countries, with the incidence reaching its maximum among women 75–79 years of age (Silliman, 2009).

In order to rationally approach decision-making in breast cancer treatment among the elderly, it is important to anchor decisions with both quantitative estimates of life expectancy and risks of death. Data from the overall population indicates that the mean 5-year survival is greater than 80% for women diagnosed with breast cancer in Europe and over 90% in the United States (Rosso et al., 2010). Unfortunately, the more advanced the patients' age group, the less evidenced-based data there is available to make decisions concerning treatment efficacy (Schonberg et al., 2012). This is due to the consistent under representation and minimal participation of older patients in well-

*Abbreviation:*OECD, Organisation for Economic Co-operation

☆ This work was supported by the Israel National Insurance Grant (2012). This work was accepted as poster in the ASCO (American Society of Clinical Oncology) meeting 2016, #161997.

* Corresponding authors at: The Jerusalem Institute of Aging Research, Hadassah-Hebrew University Medical Center Mount Scopus, Jerusalem, Israel.
E-mail addresses: ryakir@hadassah.org.il (Y. Rottenberg), JacobsJ@hadassah.org.il (J.M. Jacobs).

[1] Equal contributors.

https://doi.org/10.1016/j.archger.2018.02.004
Received 3 October 2017; Received in revised form 3 February 2018; Accepted 5 February 2018
Available online 13 February 2018
0167-4943/ © 2018 Published by Elsevier B.V.

designed studies (Lichtman et al., 2007; Scher & Hurria, 2012). For example, the Early Breast Cancer Trialists' Collaborative Group (EBCTCG) incorporates all data from individuals 70 years and older as one homogenous group, thus making modeling and generalizability challenging for individuals that are much older (Early Breast Cancer Trialists' Collaborative Group, 2011). The lack of certainty concerning survival among older women with breast cancer, particularly those over 80 years old, is compounded by conflicting data from heterogeneous age groups, various stages of illness, and lack of matched controls (Schonberg et al., 2010).

Like many other developed countries, breast cancer is the leading cancer among women in Israel, with an age adjusted incidence rate of 96.8/100,000 cases per year which is higher than the average rate among OECD countries (71.6/100,000) (State of Israel Ministry of Health Breast Cancer Data, 2010). Comprehensive health care coverage in Israel is a universal right of all citizens, is highly accessible, and is accepted as meeting the standards of Western medicine (Chernichovsky, 2009). The aim of the current study is to examine differences in survival among older women diagnosed with breast cancer, according to age and disease stage at time of diagnosis. To reach this end, we used nationwide data from the Israeli National Census, the Israel National Cancer Registry, and the Israeli Population Registry, to describe the survival of women aged 65 and older when diagnosed with breast cancer, according to cancer staging at diagnosis, and stratified into 5-year age groups, in comparison to a matched non-cancer control group.

2. Materials and methods

2.1. Study population

Israel is a small country; it is approximately 470 km long, and 135 km at its widest point, with a population of approximately 8 million people. This study is a nested case control study with cohort inception and baseline measurement from the Israeli Central Bureau of Statistics 1995 census (Rottenberg, Zick, Barchana, & Peretz, 2013). The study frame population includes two population groups: 1) a representative sample of the whole population who completed a comprehensive interview (20% of all the population in Israel) and 2) the entire population of northern Israel. These two groups were merged into a single database in order to avoid duplication. The final database consisted of 2,337,375 persons and encompassed an estimated more than one third of the entire population in Israel. Only women were included in the current study.

2.2. Subjects with Breast cancer

Data on cancer incidence was ascertained using the Israel National Cancer Registry updated to 2010. Completeness of the registry was found to be about 95% for solid tumors (Barchana, Liphshitz, & Rozen, 2004). All patients who were diagnosed with breast cancer, aged 65 years old and more at time of diagnosis between January 2000 and December 2010, were included in the current study. Breast cancers were clustered as stage I,stage II–III (tumor larger than 5 centimeters or breast cancer cells found in the lymph nodes) or metastatic disease. A total of 4966 women were identified with breast cancer between the 1st January 2000–31st December 2010, of whom 1696 had missing data concerning staging or incomplete data. The resulting 3270 women with breast cancer were included in the study.

2.3. Controls

Non-cancer controls were randomly sampled in ratio 1:4 from the general population group according to 5 year age groups (65–69, 70–74, 75–79, 80–84, > 85 years). Controls with a diagnosis of any cancer, or who had died before diagnosis of the matched breast cancer patient, were excluded. Matching using five-year age groups resulted in 13,163 non-cancer controls.

2.4. Study variables

Variables assessed in relation to mortality risk after diagnosis of breast cancer included: age; staging at diagnosis (stage I, stage II–III, metastatic); socio-economic status based upon residential location according to a verified national classification, (continuous variable graded 1–10 from lowest to highest status) (Levine et al., 2013); and ethnicity (self-defined Jewish vs. Non-Jewish). For persons in the non-cancer control group, follow-up was defined based on the time of diagnosis of the match to the cancer patient.

2.5. Survival outcome

Start of follow-up was from the date of diagnosis (between January1st 2000–December 31st 2010) until date of death or December 31st 2011, whichever was first. Mortality data were collected from January 1st 2000–31st December 2011, thus resulting in a maximum possible follow-up of 144 months (12 years), and a minimum potential follow-up of 12 months.

2.6. Statistical analyses

We compared survival by age groups using Kaplan-Meier curves, and determined survival time (months) at 25%, 50%, and 75% percentiles. To examine the impact of cancer stage upon mortality, we constructed Cox Proportional Hazards regression models, stratified per age groups (ages group: 65–69, 70–74, 75–79, 80–84 and 85 years and more), adjusting for cancer stage, socio-economic status and ethnicity. We verified the proportional hazards assumption by inspecting log-minus-log plots. Mortality Hazards (HR) ratios were calculated in reference to the control group (HR = 1.0). For all analyses $p < 0.05$ was considered statistically significant. The SPSS program (15th version; Chicago, Illinois) was used for the statistical analysis. This study was approved by the Committee on Human Research at the Hadassah Hebrew University Medical Center.

3. Results

A total of 3270 breast cancer patients and 13,163 matched controls, aged > 65 years old, were included in the current study. During the follow-up period, the overall mortality among the breast cancer patients was 27.95% (n = 914/3270) compared to 20.3% (n = 2677/13163) among the controls. The overall frequency at diagnosis of stage I, stage II–III or metastatic breast cancer was 56.7%, 37.0%, and 6.3% respectively. Between ages 65–69 and ≥85, metastatic disease rose from 3.9% to 23.4% ($p < 0.001$), stage I disease declined from 58.6% to 30.1% ($p < 0.001$), and stage II–III disease at diagnosis increased from 37.4% to 46.4%($p = 0.04$, Table 1). Certain differences between control, stage I, stage II–III, and metastatic disease at each age group were observed for socioeconomic status, ethnicity, and duration of follow-up: poor socioeconomic status was generally least frequent among subjects with stage I, Jewish ethnicity was generally more common among women with cancer, and duration of follow-up consistently declined with advancing cancer stage.

As seen in Fig. 1, survival curves among women with stage I breast cancer at diagnosis were identical to controls at ages 65–69. With advancing age survival was actually observed to be greatest among women with stage I breast cancer, such that by age > 85 years the 25%, 50%, and 75% percentile life expectancy for controls was 29, 54, and 86 months versus 40, 68, and 101 months for stage I breast cancer (Table 2). While survival was consistently worse among individuals with stage II–III breast cancer at diagnosis, the magnitude of the difference was observed to gradually decline with rising age. In contrast,

Table 1
Baseline Characteristics according to age and breast cancer stage.

	Age 65–69	Age 70–74	Age 75–79	Age 80–84	Age ≥85	Total (Age ≥65)
Controls (n)	4052	4096	2564	1607	844	13163
Socioeconomic status (low)	672 (16.6%)	619 (15.1%)	319 (12.4%)	172 (10.7%)	72 (8.5%)	1854 (14.1%)
Ethnicity Jewish	3217 (79.4%)	3437 (83.7%)	2251 (78.8%)	1444 (89.9%)	779 (92.3%)	11128 (84.5%)
Follow up (months)	70.1	66.2	67.1	59.0	42.4	65.4
Mortality n(%)	331 (8.2%)	592 (14.5%)	665 (22.9%)	641 (39.9%)	448 (53.1%)	2677 (20.3%)
Total Cancer (n)	1013	1024	641	383	209	3270
Stage I (n)	594 (58.6%)	651 (63.6%)	352 (54.9%)	193 (47.7%)	63 (30.1%)	1853
Socioeconomic status (low)	71 (12.0%)	63 (9.7%)	18 (5.1%)	10 (5.2%)	5 (7.9%)	167 (9.0%)
Ethnicity Jewish	531 (89.4%)	599 (92.0%)	337 (95.7%)	184 (95.3%)	57 (90.5%)	1708 (92.2%)
Follow up (months)	69.9	66.3	69.1	58.2	36.9	66.1
Mortality n(%)	43 (7.2%)	74 (11.4%)	73 (20.7%)	72 (37.3%)	19 (30.2%)	281 (15.3%)
stage II–III (n)	379 (37.4%)	340 (33.2%)	245 (38.2%)	150 (41.3%)	97 (46.4%)	1211
Socioeconomic status (low)	59 (15.6%)	36 (10.6%)	20 (8.2%)	13 (8.7%)	5 (5.2%)	133 (11.0%)
Ethnicity Jewish	327 (86.3%)	309 (90.9%)	229 (93.5%)	141 (94.0%)	93 (95.9%)	1099 (90.8%)
Follow up (months)	67.8	60.9	60.1	54.4	35.1	60.0
Mortality n(%)	97 (25.6%)	108 (31.8%)	107 (43.7%)	67 (44.7%)	65 (67.0%)	444 (36.7%)
Metastatic Cancer (n)	40 (3.9%)	33 (3.2%)	44 (6.9%)	40 (11.0%)	49 (23.4%)	206
Socioeconomic status (low)	5 (12.5%)	6 (18.2%)	3 (6.8%)	4 (10.0%)	4 (8.2%)	22 (10.7%)
Ethnicity Jewish	36 (90.0%)	24 (72.7%)	42 (95.5%)	37 (92.5%)	47 (95.5%)	186 (90.3%)
Follow up (months)	22.3	17.3	16.8	14.8	4.4	14.6
Mortality n(%)	37 (92.5%)	28 (84.5%)	39 (88.6%)	37 (92.5%)	48 (98.0%)	189 (91.7%)
p value[a]						
Socioeconomic status (low)	0.04	< 0.001	< 0.001	0.10	0.72	
Ethnicity Jewish	< 0.001	< 0.001	< 0.001	0.04	0.42	
Follow up (months)	< 0.001	< 0.001	< 0.001	< 0.001	< 0.001	

[a] Among controls, stage I, stage II–III and metastatic disease at each age group.

metastatic disease at diagnosis remained a very poor prognostic factor, with 25%, 50%, and 75% percentile life expectancy at ages 80–84 and > 85years being 0, 2, 12 months and 0, 0, 3 months respectively.

The results of Cox proportional hazards regression modeling for all-cause mortality analyses, stratified by age groups and adjusted for ethnicity and socio-economic status, are shown in Table 2. Compared to the non-cancer controls, stage I breast cancer subjects had a non significant decreased risk of death throughout follow-up, which actually achieved a borderline significance beyond age 85 with an adjusted HR = 0.60 (95%CI: 0.36–1.01). The adjusted HR's associated with stage II–III breast cancer gradually declined in magnitude with rising age, from an adjusted HR 3.26 (95%CI: 2.58–4.12) at age 65–69, to an

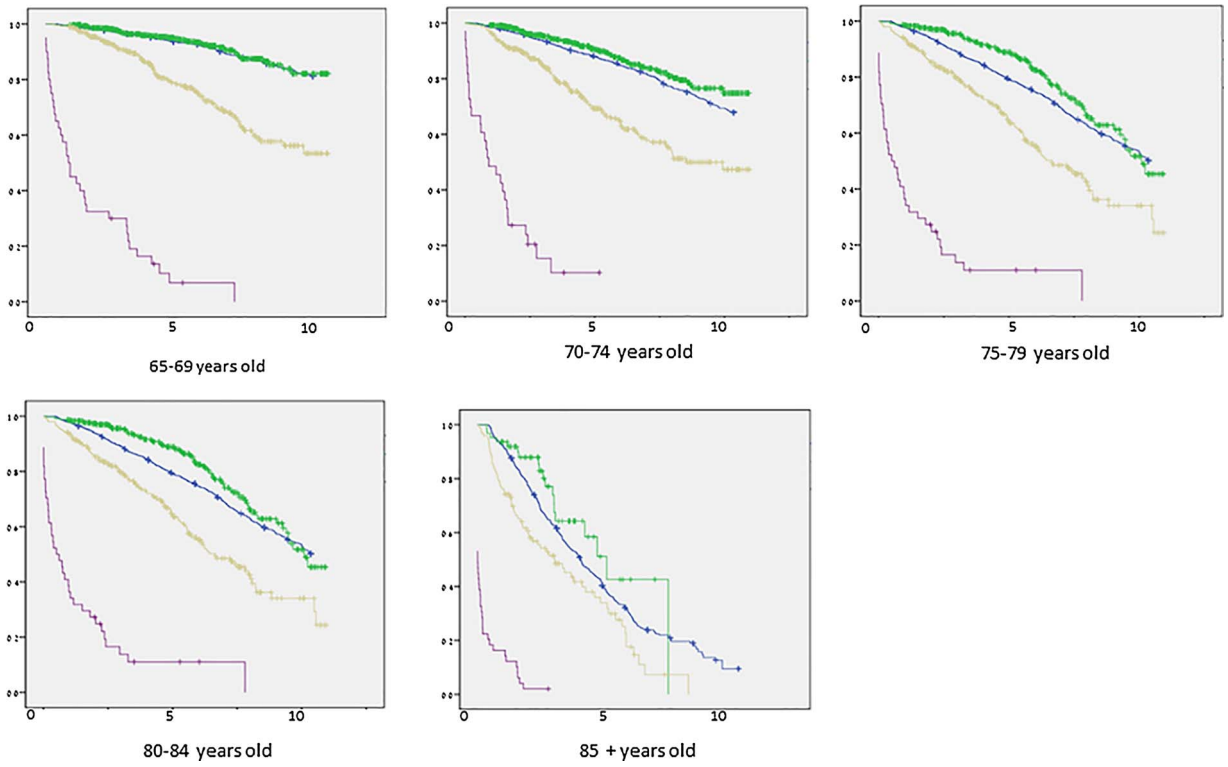

Fig. 1. Kaplan-meier curves for overall survival in years among the study groups (blue: non cancer population; green: early; orange: intermediate; purple: metastatic breast cancer).

Table 2
Upper, middle, and lower quartiles of life expectancy and adjusted[≠] all- cause mortality hazards ratios according to breast cancer stage compared to non cancer controls, stratified according to increasing age.

Age	controls		stage I		stage II-III		metastatic	
	25/50/75% survival (months)	HR (95%CI)	25/50/75% survival (months)	HR (95%CI)[a]	25/50/75% survival (months)	HR (95%CI)[a]	25/50/75% survival (months)	HR (95%CI)[a]
65–69	NR/NR/NR	1.0	NR/NR/NR	0.96 (0.69 – 1.33)	79/NR/NR	3.36 (2.58 – 4.12)**	3/12/42	57.40 (39.56–83.29)**
70–74	114/NR/NR	1.0	133/NR/NR	0.81 (0.63 – 1.04)	58/NR/NR	2.51 (2.03 – 3.10)**	2/11/24	31.39 (21.14–46.63)**
75–79	79/NR/NR	1.0	93/135/NR	0.80 (0.62 – 1.03)	48/89/140	1.94 (1. 6 – 2.4)**	1/17/27	17.55 (12.60 – 24.48)**
80–84	51/95/NR	1.0	51/92/146	0.97 (0.75 – 1.3)	39/90/139	1.20 (0.29 – 1.55)	0/2/12	11.52 (8.13–16.32)**
≥85	29/54/86	1.0	40/68/101	0.60 (0.36 – 1.01)	14/71/78	1.60 (1.22 – 2.09)*	0/0/3	20.76 (14.73 – 29.24)**

NR: not reached during the time of follow-up.
* $p < 0.01$.
** $p < 0.0001$.
[a] HR: Hazards Ratio(95% Confidence Intervals) adjusted for socioeconomic status and ethnicity.

adjusted HR of 1.20 (95%CI: 1.22–2.09) at age 80–84, slightly rising again beyond age 85. Metastatic disease was strongly associated with mortality at all ages.

4. Discussion

This is the first study of a population-based Israeli national sample of older women comparing the survival of 3270 women with breast cancer according to stage at diagnosis, to 13,163 age-matched non-cancer controls. The findings underline the poor prognosis of older women with metastatic disease, in particular the very short life expectancy observed beyond age 80 years. In contrast, our findings highlight the similar survival of older women with stage I breast cancer compared to non-cancer controls, and actually describe a trend towards reduced mortality risk with advancing age among women with stage I disease at diagnosis. Furthermore, stage II–III disease among older women became a less powerful predictor of mortality with rising age.

Within the current study, older women were more likely than younger women to present with metastatic disease. Israel's national mammography program is limited to those under the age of 75 (Eilat-Tsanan et al., 2001). Thus, the ratio between stage I and advanced stages at diagnosis is anticipated to decrease above the age of 75 years old. Other possible explanations for these findings may be changes in perception of body and health with increasing age, increased threshold for suspected mass evaluation, higher prevalence of cognitive impairment, and a modification in the biology of breast cancer among the very old. It is well documented that elderly patients more frequently present with larger and more advanced tumor (Tew, Muss, Kimmick, Von Gruenigen, & Lichtman, 2014). On the other hand literature suggests that, in comparison to younger postmenopausal women with breast cancer, more favorable biologic characteristics are common among the elderly population despite larger tumor size at presentation (Tew et al., 2014). Previous studies which have described both late diagnosis and metastatic diseases at diagnosis among elderly patients have not analyzed specific age groups (Arndt et al., 2002; Diab, Elledge, & Clark, 2000; Møller et al., 2010). Nonetheless, an overall pattern of poorer breast cancer survival in the over 70′s was observed in European populations (Møller et al., 2010). In the light of the current study we suggest that diagnosis of metastatic disease beyond the age of 80 years old has a huge negative impact, considering poorest prognosis of metastatic disease among the elderly population, particularly the oldest old.

In the current study, data concerning treatment was not ascertained, and all-cause mortality thus included both treated and untreated women with breast cancer. The inclusion of untreated subjects in the study may well have introduced a bias, most likely in the direction of shortening observed survival time. The exclusion of untreated subjects from the data would, in all likelihood, further emphasize our findings that stage I and most stage II–III breast cancer have similar survival times compared to their age matched non-cancer controls. The finding that stage I breast cancer, particularly amongst the oldest old, tended to be associated with improved survival, suggests that diagnosis might have been performed among the most robust of older subjects, and perhaps was a surrogate marker for those receiving the most comprehensive and highest quality of care.

The decision to initiate treatment for breast cancer among older women inevitably requires a comprehensive assessment of the geriatric aspects of patient care, and the growing recognition of the need for an oncogeriatric approach is reflected in recent guidelines concerning care of elderly cancer patients (Cesari et al., 2011). The value of comprehensive oncogeriatric assessment will clearly lie in its ability to risk-stratify older patient populations, and address competing comorbidities. Increased research is necessary to improve tools aimed at identifying those robust elderly patients most likely to tolerate treatment, as well as the ability to streamline certain patients for purely supportive palliative care.

The median survival among women with metastatic breast cancer in our study was about one year up to age 74 years old. In the literature, the median survival among metastatic breast cancer is higher (O'brien et al., 2004; Swain et al., 2013) even among the elderly population (Del Mastro et al., 2005). For example, a median overall survival of 15.9 months was reported among 34 patients (median age, 74 years; range, 70–84 years) who were treated with oral Vinorelbine as first line treatment (Addeo et al., 2010). Nonetheless, elderly individuals are under-represented in well-designed studies (Early Breast Cancer Trialists' Collaborative Group, 2011), which tend to exclude subjects with very advanced age, frailty, high comorbid burden, cognitive decline, and nursing home status (Cesari et al., 2011). Indeed, overall survival in unselected cohorts of metastatic breast cancer patients seems inferior to survival among clinical trials (Andre et al., 2004). The lack of exclusion criteria and thus apparent lack of selection bias in our study may well explain the worse prognosis of metastatic disease observed in the current study.

Under-treatment and poor compliance may also explain the poor outcomes among older women with metastatic breast cancer. Among older women, approximately 90% of breast cancers are estrogen receptor positive (Engels et al., 2016; Richards et al., 2016) and hormonal treatment can be prescribed for almost every patient. Nonetheless, reluctance to initiate systemic treatment among the elderly is common and requires understanding. Treatment side-effects can present in this population in an atypical way and unaddressed toxicity may decrease compliance (Biganzoli et al., 2012). Indeed, poor compliance is more common among older breast cancer patients, and has been reported in hormonal and oral bisphosphonates treatments (Biganzoli et al., 2012). Other barriers to optimal treatment may include transportation issues among older breast cancer patients (Enger et al., 2006). The poor prognosis of metastatic breast cancer, particularly among the oldest old, is a call for early integration of palliative care. Early palliative care has

been shown to improve both quality of life and mood among patients with metastatic lung cancer. Furthermore, patients receiving early palliative care not only had less aggressive care at the end of life, but actually experienced longer survival in comparison to patients receiving standard care (Temel et al., 2010).

The current study has several strengths. The current study template, using a high quality dataset and high degree of completeness of the cancer registry data throughout study period have enabled near complete ascertainment of the study's variables and endpoints. In addition, large sample size and data on ethnicity and residential socio-economic position allow us to correct the results for potential confounders. Taking into account the comprehensive health coverage within the Israeli health system (Chernichovsky, 2009) and the correction for socio demographic variables, the possibility of health inequality as being a strong confounder is unlikely.

Our study has some limitations. Data on competing comorbidities and functional status were lacking, inclusion of which into the analyses would have further helped determine prognostic markers. Since there may be a positive correlation between cancer diagnosis and impaired functional and health status, the probability of rejecting the null hypothesis increases. Thus, following adjustment for functional and health status, the survival of older women with stage I breast cancer compared to non-cancer controls may be even better than our estimate. In addition, data was unavailable concerning the biological features of the cancer, suggested treatment plans, or compliance among the study subjects. However, individualized assessment of prognosis and treatment options is indicated on the basis of biologic characteristics, patient preferences and comprehensive geriatric assessment (Arndt et al., 2002; Cesari et al., 2011). Presentation of survival data by quartile in the current study (Table 2) can serve as a tool for integrative assessment or proxy of these variables.

Lastly, we examined all-cause mortality data alone, and did not include cancer-specific mortality data. However, amongst the older population the accuracy of disease specific mortality from death certification is unreliable, particularly in the presence of rising comorbidity.

5. Conclusion

In conclusion, this study emphasizes the heterogeneity with increasing age, including increased variability in stages at diagnosis and the impact of breast cancer on life expectancy. On a more practical note, the current study highlights the need for 'personalized medicine' rather 'one size fits all' for older people, and our findings might support the possibility of considering screening mammography for selected women above the age of 75 years old. Further studies are needed in order to confirm our results in other populations and to clarify the impact of specific interventions on the life expectancy of these patients.

Acknowledgment

Funding/support: This work was supported by the Israel Cancer Association Grant – The Ethel Cohen Memorial Fund (2017).

References

Addeo, R., Sgambato, A., Cennamo, G., Montella, L., Faiola, V., Abbruzzese, A., et al. (2010). Low-dose metronomic oral administration of vinorelbine in the first-line treatment of elderly patients with metastatic breast cancer. *Clinical Breast Cancer, 10*(4), 301–306.

Andre, F., Slimane, K., Bachelot, T., Dunant, A., Namer, M., Barrelier, A., et al. (2004). Breast cancer with synchronous metastases: Trends in survival during a 14-year period. *Journal of Clinical Oncology, 22*(16), 3302–3308.

Arndt, V., Stürmer, T., Stegmaier, C., Ziegler, H., Dhom, G., & Brenner, H. (2002). Patient delay and stage of diagnosis among breast cancer patients in Germany—A population based study. *British Journal of Cancer, 86*(7), 1034.

Barchana, M., Liphshitz, I., & Rozen, P. (2004). Trends in colorectal cancer incidence and mortality in the Israeli Jewish ethnic populations. *Familial Cancer, 3*(3), 207–214.

Biganzoli, L., Wildiers, H., Oakman, C., Marotti, L., Loibl, S., Kunkler, I., et al. (2012). Management of elderly patients with breast cancer: Updated recommendations of the International Society of Geriatric Oncology (SIOG) and European Society of Breast Cancer Specialists (EUSOMA). *The Lancet Oncology, 13*(4), e148–e160.

Cesari, M., Colloca, G., Cerullo, F., Ferrini, A., Testa, A. C., Foti, E., et al. (2011). Oncogeriatric approach for the management of older patients with cancer. *Journal of the American Medical Directors Association, 12*(2), 153–159.

Chernichovsky, D. (2009). Not "socialized medicine"—An Israeli view of health care reform. *New England Journal of Medicine, 361*(21), e46.

Del Mastro, L., Perrone, F., Repetto, L., Manzione, L., Zagonel, V., Fratino, L., et al. (2005). Weekly paclitaxel as first-line chemotherapy in elderly advanced breast cancer patients: A phase II study of the Gruppo Italiano di Oncologia Geriatrica (GIOGer). *Annals of Oncology, 16*(2), 253–258.

Diab, S. G., Elledge, R. M., & Clark, G. M. (2000). Tumor characteristics and clinical outcome of elderly women with breast cancer. *JNCI: Journal of the National Cancer Institute, 92*(7), 550–556.

Early Breast Cancer Trialists' Collaborative Group (2011). Effect of radiotherapy after breast-conserving surgery on 10-year recurrence and 15-year breast cancer death: Meta-analysis of individual patient data for 10,801 women in 17 randomised trials. *The Lancet, 378*(9804), 1707–1716.

Eilat-Tsanan, S., Sorek, M., Gay, N., Chaimovitch, O., Kulton, L., & Tabenkin, H. (2001). Family physicians' initiative to increase compliance with screening mammography-an innovative community project. *Israel Medical Association Journal, 3*(12), 920–924.

Engels, C. C., Kiderlen, M., Bastiaannet, E., Mooyaart, A. L., van Vlierberghe, R., Smit, V. T., et al. (2016). The clinical prognostic value of molecular intrinsic tumor subtypes in older breast cancer patients: A FOCUS study analysis. *Molecular Oncology, 10*(4), 594–600.

Enger, S. M., Thwin, S. S., Buist, D. S., Field, T., Frost, F., Geiger, A. M., et al. (2006). Breast cancer treatment of older women in integrated health care settings. *Journal of Clinical Oncology, 24*(27), 4377–4383.

Levine, H., Afek, A., Shamiss, A., Derazne, E., Tzur, D., Zavdy, O., et al. (2013). Risk of germ cell testicular cancer according to origin: A migrant cohort study in 1,100,000 Israeli men. *International Journal of Cancer, 132*(8), 1878–1885.

Lichtman, S. M., Wildiers, H., Chatelut, E., Steer, C., Budman, D., Morrison, V. A., et al. (2007). International Society of Geriatric Oncology Chemotherapy Taskforce: Evaluation of chemotherapy in older patients—An analysis of the medical literature. *Journal of Clinical Oncology, 25*(14), 1832–1843.

Møller, H., Sandin, F., Bray, F., Klint, Linklater, K. M., Purushotham, A., et al. (2010). Breast cancer survival in England, Norway and Sweden: A population based comparison. *International Journal of Cancer, 127*(11), 2630–2638.

O'brien, M. E. R., Wigler, N., Inbar, M. C. B. C. S. G., Rosso, R., Grischke, E., Santoro, A., et al. (2004). Reduced cardiotoxicity and comparable efficacy in a phase III trial of pegylated liposomal doxorubicin HCl (CAELYX™/Doxil®) versus conventional doxorubicin for first-line treatment of metastatic breast cancer. *Annals of Oncology, 15*(3), 440–449.

Richards, P., Ward, S., Morgan, J., Lagord, C., Reed, M., Collins, K., et al. (2016). The use of surgery in the treatment of ER+ early stage breast cancer in England: Variation by time, age and patient characteristics. *European Journal of Surgical Oncology (EJSO), 42*(4), 489–496.

Rosso, S., Gondos, A., Zanetti, R., Bray, F., Zakelj, M., Zagar, T., et al. (2010). Up-to-date estimates of breast cancer survival for the years 2000–2004 in 11 European countries: The role of screening and a comparison with data from the United States. *European Journal of Cancer, 46*(18), 3351–3357.

Rottenberg, Y., Zick, A., Barchana, M., & Peretz, T. (2013). Organ specific cancer incidence in an industrial sub-district: A population-based study with 12 years follow-up. *American Journal of Cancer Epidemiology and Prevention, 1*(1), 13–22.

Rowland, J. H., & Bellizzi, K. M. (2014). Cancer survivorship issues: Life after treatment and implications for an aging population. *Journal of Clinical Oncology, 32*(24), 2662–2668.

Scher, K. S., & Hurria, A. (2012). Under-representation of older adults in cancer registration trials: Known problem, little progress. *Journal of Clinical Oncology, 30*(17), 2036–2038.

Schonberg, M. A., Marcantonio, E. R., Li, D., Silliman, R. A., Ngo, L., & McCarthy, E. P. (2010). Breast cancer among the oldest old: Tumor characteristics, treatment choices, and survival. *Journal of Clinical Oncology, 28*(12), 2038–2045.

Schonberg, M. A., Silliman, R. A., McCarthy, E. P., & Marcantonio, E. R. (2012). Factors noted to affect breast cancer treatment decisions of women aged 80 and older. *Journal of the American Geriatrics Society, 60*(3), 538–544.

Schonberg, M. A. (2016). Decision-making regarding mammography screening for older women. *Journal of the American Geriatrics Society, 64*(12), 2413–2418.

Silliman, R. A. (2009). When cancer in older adults is undermanaged: The breast cancer story. *Journal of the American Geriatrics Society, 57*(s2).

State of Israel Ministry of Health Breast Cancer Data. [cited 2014 January 18, 2014]; Available from: (http://www.health.gov.il/PublicationsFiles/breast_cancer_oct2014.pdf).

Swain, S. M., Kim, S. B., Cortés, J., Ro, J., Semiglazov, V., Campone, M., et al. (2013). Pertuzumab, trastuzumab, and docetaxel for HER2-positive metastatic breast cancer (CLEOPATRA study): Overall survival results from a randomised, double-blind, placebo-controlled, phase 3 study. *The Lancet Oncology, 14*(6), 461–471.

Temel, J. S., Greer, J. A., Muzikansky, A., Gallagher, E. R., Admane, S., Jackson, V. A., et al. (2010). Early palliative care for patients with metastatic non-small-cell lung cancer. *New England Journal of Medicine, 363*(8), 733–742.

Tew, W. P., Muss, H. B., Kimmick, G. G., Von Gruenigen, V. E., & Lichtman, S. M. (2014). Breast and ovarian cancer in the older woman. *Journal of Clinical Oncology, 32*(24), 2553–2561.