

ORIGINAL ARTICLE

Handedness and breast cancer characteristics

Kadri Altundag¹, Metin Isik², Ali R Sever³

¹Department of Medical Oncology, Hacettepe University Cancer Institute, Ankara; ²Department of Internal Medicine, Hacettepe University School of Medicine, Ankara; ³Department of Radiology, Hacettepe University School of Medicine, Ankara, Turkey

Summary

Purpose: Around 10% of the population is left-handed (LH) and the new data suggests that there is genetic as well as environmental influence on the hand preference. The purpose of this study was to evaluate the relationship between breast cancer and hand preference.

Methods: Breast cancer patients diagnosed and treated at the Department of Medical Oncology, Hacettepe University, Institute of Oncology between March 2006 and May 2010 were included in the study. The preferred handedness was asked in all patients and recorded in the patients' medical database.

Results: A total of 898 patients with breast cancer were analyzed for handedness, basic characteristics and survival. The median age was 48 years (range 20-83) and all but one patient were female. Of all, 434 (48.3%) patients were pre, 61 (6.8%) were peri, and 399 patients (44.4%) were postmenopausal. Nearly all of the patients (n=869, 96.7%) were operated and modified radical mastectomy was the most frequent type of surgery (N=654, 72.8%). Invasive ductal carcinoma was observed in 659 (73.3%) and in 659 patients (73.1%) estrogen receptors (ER) were positive. Similarly 569 (63.4 %) patients were progesterone receptor (PR) positive and 181 (20.2%)

had HER2 overexpression. Most of the patients had T2 (434; 48.3%), N0 (376; 41.9%) and M0 (830; 92.4%) tumors.

Of all, 55 (6.1%) patients were LH and the remaining 843 (93.9%) were right-handed (RH). There was no statistically significant difference between the groups related to ER or PR status, TNM classification, tumor localization, menopausal status, HER2 or histological subtype. However the median age of diagnosis in right-handers was higher (48-46 years, p=0.02).

There were 10 (1.1%) patients who had already passed away at the time of analysis. The mean overall survival (OS) for RH patients was 33 months (range 1-281) and for LH patients it was 35 months (range 1-182) (p=0.751). The disease free survival (DFS) was 29 months for both groups (p=1.00).

Conclusion: In our trial the onset of breast cancer was 2 years earlier in LH patients with similar disease characteristics compared to RH patients. As a consequence, it may be advocated that the screening of LH patients should start earlier.

Key words: breast cancer, earlier onset, handedness

Introduction

Breast cancer is a complex disease with several factors affecting the survival, some of which are still under the scrutiny. Around 10% of the human population is left-handed (LH) and the new data support that there is genetic as well as environmental influence on the hand preference [1].

In a pilot study on American women with 138 patients, LH-ness and left sided breast cancers appeared to be related. To test these findings, a further 889 patients were added to the study group

and a statistically significant association between handedness and earlier development of breast cancer was found almost twice as high a percentage of left-handers as right-handers developed breast cancer before the age of 45. The authors explained these results with lateral asymmetries of neurotransmitters [2].

Intrauterine estrogens or testosterone exposure was hypothesized to be a risk factor for breast cancer [3-6]. Likewise LH-ness is known

to be linked to high fetal estrogens exposure, of LH-ness being associated with diethylstilbestrol exposure [6,7]. Combining these two data, one may argue that LH-ness may be a result of high intrauterine exposure to estrogens and may also be related with higher risk of breast cancer. Ramadhani et al., found a modest association between LH-ness and increased breast cancer risk in a case-cohort study and reported that the association was limited to premenopausal breast cancer patients [8]. On the contrary, Titus-Ernstoff et al. found a similar effect which however was only in postmenopausal women [4].

In recent trials, interest on the origins of adult chronic diseases in early life is growing and it is thought that growth in childhood may modify the effect of birth weight on diseases' risks in the later life and also mortality [9-11]. Recent hypotheses include mechanisms leading to both LH-ness and increased morbidity and mortality in later life [12]. It has been claimed that LH-ness may be associated with reduced survival, owing to the fact that left-handers are lower in number in the older age groups [13,14]. Several studies tried to explain the reduced longevity of left-handers in the elderly population and two studies reported an increased mortality, while two conflicting studies found LH-ness to be connected with a survival benefit, while several remaining studies found no significant relation at all [15-22].

The purpose of our study was to elucidate the association between handedness and breast cancer characteristics and survival in a cohort of Turkish breast cancer patients.

Methods

Breast cancer patients diagnosed and treated at the Department of Medical Oncology at Hacettepe University, Institute of Oncology between March 2006 and May 2010 were included in the study. A total of 898 patients were identified. The preferred handedness was asked in all patients and recorded in the patients' medical database. Also registered were a set of clinicopathological data.

Statistics

Distribution of the continuous variables was determined by the Student's t-test for the independent variables, and one-way ANOVA test for the dependent variables. All numeric variables were expressed as median, and categorical variables were expressed as percentages. The significance of correlations was assessed by the Pearson's correlation analysis. Survival analysis was done with Kaplan-Meier method and differences

were assessed with log rank test. For all statistics, a two-sided p value <0.05 was considered statistically significant. SPSS for Windows version 15.0 statistical package was used.

Results

Patient characteristics

Patient and tumor characteristics are summarized in Table 1. The median age was 48 years (range 20-83) and all but one patient were female. The menopausal status were recorded as

Table 1. Patient and disease characteristics

Characteristics	LH N (%)	RH N (%)	p value
N	55 (6.1)	843 (93.9)	
Age at diagnosis, median (range)	46 (20-73)	48 (20-84)	0.020
Menopausal status			0.128
pre	31 (56.3)	403 (47.8)	
peri	4 (7.2)	61 (7.2)	
post	20 (36.3)	379 (44.9)	
Tumor localization			0.947
right	25 (45.4)	401 (47.6)	
left	30 (54.5)	427 (50.7)	
bilateral	0	15 (1.7)	
Histology			0.068
invasive ductal	42 (76.4)	621 (73.7)	
others	13 (23.5)	222 (26.2)	
Estrogen receptor			0.321
positive	42 (76.4)	617 (73.1)	
negative	13 (23.5)	225 (26.8)	
Progesterone receptor			0.244
positive	40 (72.7)	562 (66.6)	
negative	15 (27.2)	281 (33.3)	
HER2			0.165
positive	14 (29.2)	167 (22)	
negative	34 (70.7)	591 (78)	
T stage			0.730
1	11 (20.4)	196 (26.1)	
2	33 (61.1)	401 (53.5)	
3	8 (14.8)	120 (16)	
4	2 (3.7)	33 (4.4)	
N stage			0.614
0	25 (46.3)	351 (44.3)	
1	15 (27.8)	198 (25)	
2	10 (18.5)	134 (16.9)	
3	4 (7.4)	109 (13.8)	
M stage			0.255
metastatic	2 (3.5)	59 (7.1)	
non-metastatic	53 (96.4)	777 (92.8)	
Mean overall survival (months)	35	33	0.751
Mean disease free survival (months)	29	29	1.00

well and 434 (48.3%) patients were pre, 61 (6.8%) were peri, and 399 patients (44.4%) were post-menopausal. The menopausal status of three patients could not be determined. Nearly all of the patients (N=869, 96.7%) were operated and modified radical mastectomy was the most frequent type of surgery (N=654, 72.8%). Breast conserving surgery was performed on 198 (22.4%) patients. Invasive ductal carcinoma was observed in 659 (73.3%), invasive lobular carcinoma in 35 (3.9%) and other types of pathology were seen in 204 (22.7%) patients. In 659 patients (73.1%), ER were positive and in 225 (26.8 %) cases they were negative. Similarly, 569 (63.4 %) patients were PR positive and 281 (31.3 %) were negative. HER2 status was also documented and 181 (20.2%) patients had HER2 overexpression while 625 (69.6%) were negative. Most of the patients had T2 (434;48.3%), N0 (376;41.9%) and M0 (830;92.4%) tumors.

Handedness

Of all, 55 (6.1%) patients were LH and the remaining 843 (93.9%) were RH. Patients were asked to declare with was their preferred hand and therefore the data are patient-originated. There was no statistically significant difference between the groups related to ER or PR status, TNM classification, tumor localization, menopausal status, HER2 or histological subtype. However, the median age at diagnosis in right-handers was higher (48-46 years, $p=0.02$).

Overall and disease-free survival

There were 10 (1.1%) patients who had already passed away at the time of analysis. OS and DFS were also recorded and analyzed from our medical database. The mean OS for RH patients was 33 months (range 1-281) and for LH patients it was 35 months (range 1-182) ($p=0.751$). The DFS was 29 months for both groups ($p=1.00$).

Discussion

In this study, we presented the basic characteristics and the survival analysis of 898 breast cancer patients in terms of handedness. Other than the median age at diagnosis all the basic characteristics and the OS and DFS rates were similar.

Up until now several studies have been performed to clarify the effect of handedness on the disease outcomes but the results were all confusing. Some of these series revealed significant differences favoring the LH patients, while some

others favored RH patients [13-21]. In our study there were no significant differences in terms of handedness other than age at diagnosis. The ratio of LH patients (6.1%) in our study was lower than that of the literature (10%), however this is, in our opinion, not related to patient selection bias because all of the patients between the defined dates were included in the database with no exception.

When the survival analyses are checked, inconsistency is to be found as well. Some results state that LH patients have worse and some state that LH patients have better results [15-22]. Regarding our data, there was no statistically significant difference in terms of survival. However, during the follow up period, only 10 patients have died and the median follow up period is less than 3 years, therefore longer follow up is required.

Perhaps the most interesting point in our trial was that we reported an earlier onset of breast cancer in the LH group. To the best of our knowledge this has never been documented in the literature previously. The TNM classification of the groups was statistically similar, meaning that the RH patients did not apply to our breast clinic in a delayed manner to set a difference in the age at diagnosis. We therefore claim this difference to be meaningful. As it was already discussed, intrauterine estrogens or testosterone exposure is blamed to be a risk factor for breast cancer and LH-ness is known to be linked with high fetal estrogens exposure. The earlier breast cancer diagnosis in LH patients may support this hypothesis [3-7].

Ramadhani et al. followed 12,178 female patients with any kind of malignancy for nearly 13 years and reported that LH-ness was related to higher mortality. Nearly 40% of those patients had breast cancer and the remaining 60% had colorectal cancer and other types of malignancies. Talking about malignancy associated mortality, LH women had 1.7-fold higher risk of dying from any type of cancer, a 4.6-fold higher risk of dying from colorectal cancer and a 2.0-fold higher risk of dying from breast cancer [23]. However, the trial set up was not optimal and the authors questioned themselves for the robustness of their results.

The results of more recent trials found no increased mortality for LH patients [18].

In conclusion, in our trial the onset of breast cancer was two years earlier in LH patients with similar disease characteristics compared to RH patients. As a consequence, it may be advocated

that the screening of LH patients should start earlier. One other important point needs to be highlighted and this is that the world is dominantly shaped for the RH people and the adaptation of LH people may not always be easy, therefore the reduced longevity of left-handers may occur due

to our own sin building a right-handed world.

Conflict of interests

The authors declare no conflict of interests.

References

- McManus C (Ed). *Right Hand, Left Hand. The Origins of Asymmetry in Brains, Bodies, Atoms, and Cultures* (1st Edn). London: Weidenfeld & Nicolson, Ltd.; 2002.
- Kramer MA, Albrecht S, Miller RA. Handedness and the laterality of breast cancer in women. *Nurs Res* 1985;34:333-337.
- Geschwind N, Galaburda AM (Eds). *Cerebral Lateralization: Biological Mechanisms, Associations and Pathology*. Cambridge, MA: MIT Press; 1987.
- Titus-Ernstoff L, Newcomb PA, Egan KM et al. Left-handedness in relation to breast cancer risk in postmenopausal women. *Epidemiology* 2000;11:181-184.
- Trichopoulos D. Hypothesis: does breast cancer originate in utero. *Lancet* 1990;335:939-940.
- Schachter SC. Handedness in women with intrauterine exposure to diethylstilbestrol. *Neuropsychologia* 1994;32:619-623.
- Scheirs JG, Vingerhoets AJ. Handedness and other laterality indices in women prenatally exposed to DES. *J Clin Exp Neuropsychol* 1995;17:725-730.
- Ramadhani MK, Elias SG, van Noord PAH, Gobbee DE, Peeters PHM, Uiterwaal CSPM. Innate left handedness and risk of breast cancer: case-cohort study. *BMJ* 2005;331:882-883.
- Eriksson JG, Forsen TJ. Childhood growth and coronary heart disease in later life. *Ann Med* 2002;34:157-161.
- Stavola BL, Hardy R, Kuh D et al. Birthweight, childhood growth and risk of breast cancer in a British cohort. *Br J Cancer*. 2000;83:964-968.
- Eriksson JG, Forsen T, Tuomilehto J et al. Catch-up growth in childhood and death from coronary heart disease: longitudinal study. *BMJ* 1999;318:427-431.
- James WH. Handedness, birth weight, mortality and Barker's hypothesis. *J Theor Biol* 2001;210:345-346.
- Coren S, Halpern DF. Left-handedness-a marker for decreased survival fitness. *Psychol Bull* 1991;109:90-106.
- Harris LJ. Left-handedness and life-span-reply. *Psychol Bull* 1993;114:242-247.
- Aggleton JP, Bland JM, Kentridge RW et al. Handedness and longevity-archival study of cricketers. *BMJ* 1994;309:1681-1684.
- Basso O, Olsen J, Holm NV et al. Handedness and mortality: a follow-up study of Danish twins born between 1900 and 1910. *Epidemiology* 2000;11:576-580.
- Cerhan JR, Folsom AR, Potter JD et al. Handedness and mortality risk in older women. *Am J Epidemiol* 1994;140:368-374.
- Ellis PJ, Marshall E, Windridge C et al. Left-handedness and premature death. *Lancet* 1998;351:1634.
- Halpern DF, Coren S. Handedness and life-span. *N Engl J Med* 1991;324:998.
- Marks JS, Williamson DF. Left-handedness and life expectancy. *N Engl J Med* 1991;325:1042-1043.
- Persson PG, Allebeck P. Do left-handers have increased mortality? *Epidemiology* 1994;5:337-340.
- Salive ME, Guralnik JM, Glynn RJ. Left-handedness and mortality. *Am J Public Health* 1993;83:265-267.
- Ramadhani MK, Elias SG, van Noord PAH, Grobbee DE, Peeters PHM Uiterwaal CSPM. Innate Handedness and Disease-Specific Mortality in Women. *Epidemiology* 2007;18:208-212.