Cancer Epidemiology 45 (2016) 162–168

Contents lists available at ScienceDirect

Cancer Epidemiology

The International Journal of Cancer Epidemiology, Detection, and Prevention

journal homepage: www.cancerepidemiology.net

HR+/Her2- breast cancer in pre-menopausal women: The impact of younger age on clinical characteristics at diagnosis, disease management and survival

Marianna De Camargo Cancela[a,b,*], Harry Comber[a], Linda Sharp[a,c]

[a] National Cancer Registry, Airport Business Park, Kinsale Rd, Cork, Ireland
[b] Division of Population Research, Brazilian National Cancer Institute, Rio de Janeiro, Brazil
[c] Institute of Health & Society, Newcastle University, Newcastle upon Tyne, England, United Kingdom

ARTICLE INFO

Article history:
Received 22 June 2016
Received in revised form 4 October 2016
Accepted 31 October 2016
Available online 12 November 2016

Keywords:
Breast cancer
Young women
Survival
Breast cancer management
HR+/Her2-

ABSTRACT

Young women (20–39 years-old) with breast cancer are diagnosed with more aggressive tumours and consequently have poorer survival. However, there is an evidence gap as to whether age has an independent effect on survival of pre-menopausal women diagnosed with HR+/Her2- tumours. The aim of this population-based study was to compare characteristics at diagnosis, determinants of treatment and survival in women aged 20–39 and 40–49 years diagnosed with HR+/Her2- tumours. From the National Cancer Registry Ireland, we identified women aged 20–49 diagnosed with a first invasive HR+/Her2- breast cancer during 2002–2008. Women aged 20–39 were compared to those aged 40–49 years. Poisson regression with robust error variance was used to explore the impact of age on treatment receipt. Associations between age and survival from all causes was investigated using Cox models. In multivariate models, women aged 20–39 significantly more often having no cancer-directed surgery (IRR = 1.49, 95%CI 1.07, 2.08). In those having surgery, younger age was associated with significantly higher likelihood of receiving chemotherapy; age was not associated with receipt of adjuvant radiotherapy or endocrine therapy. Women aged 20–39 undergoing surgery were significantly more likely to die than women aged 40–49 (HR = 1.84, 95%CI: 1.31, 2.59). Age is an independent prognostic factor in younger women diagnosed with HR+/Her2- breast cancer, supporting the hypothesis that breast cancer in women under 40 has more aggressive behaviour, even within HR+/Her2- tumours. Future research should explore the reasons for poorer survival in order to inform strategies to improve outcomes in this age group.

1. Introduction

Breast cancer is the most frequent cancer among women worldwide, and, although it is relatively rare in absolute terms before the age of 40, it is the commonest cancer within this age-group [1]. Moreover, incidence in this age-group is increasing in some European countries, including Ireland [2]. International data report that women under 40 are usually diagnosed with more aggressive disease (based on stage and grade at diagnosis) and are at a greater risk of recurrence [3–8] than older women. For these reasons, they may have more aggressive treatment compared to their older counterparts [8].

However, there are limitations in the evidence-base concerning breast cancer outcomes in women under 40. For example, some studies of breast cancer characteristics in young women compare them with post-menopausal women [9,10], which may not be the most valid comparison [11]. In addition, there have been few population-based studies and findings from studies of clinical series may not be generalisable [12]. Moreover, much of the evidence rates to the more aggressive subtypes, such as HER2+ and triple negative disease; little is known about whether, among pre-menopausal women with HR+/Her2- tumours (which are more common), those diagnosed under 40 have different clinical characteristics and outcomes than older women.

In a population-based study of HR+/Her2- breast cancer in pre-menopausal women, we sought to investigate whether those

* Corresponding author at: Division of Population Research, Brazilian National Cancer Institute, Rua Marquês de Pombal, 125, Rio de Janeiro, Brazil.
E-mail addresses: marianna.cancela@inca.gov.br, cancelam@gmail.com (M. De Camargo Cancela).

http://dx.doi.org/10.1016/j.canep.2016.10.019
1877-7821/

diagnosed under 40 differ in terms of clinical characteristics, cancer-directed management and survival, than older pre-menopausal women.

2. Materials and methods

2.1. Data sources

Data for this study were obtained from the National Cancer Registry Ireland. The Registry aims to record patient-related, clinical and treatment data for all cancers diagnosed in the population usually resident in Ireland. Methods of case ascertainment, registration, and quality control are described in the Registry's website [13]. Completeness of breast cancer registration is estimated to be in excess of 98% [14]. Follow-up is achieved by linkage with death certificates from which information on date of death is abstracted.

2.2. Study dataset

Socio-demographic, clinical, healthcare-related and treatment details for women aged 20–49 diagnosed with primary invasive HR+/Her2- breast cancer (ICD-10 C50) during 2002–2008 were abstracted from the Registry. HR+/Her2- tumours were defined as those positive for oestrogen, and/or progesterone receptors and negative for HER2; and were identified based on receptor status information collected by the Registry [15]. All the patients in the dataset had been tested for HER2 status and were negative. For women with bilateral breast cancer diagnosed at different times, the first tumour diagnosed was retained for analysis; in the case of simultaneous bilateral tumours the one with more advanced stage was included in analysis.

The analyses compared two age-groups: 20–39 and 40–49 years at diagnosis. The socio-demographic variables available for analysis were: deprivation level of area of residence (based on the address at diagnosis; and ranging from 1-least deprived to 5-most deprived) [16]; urban/rural status of area of residence (based on population density of area of residence at diagnosis (rural <1 person per hectare, intermediate 1–15 people per hectare, urban >15 people per hectare)) [17]; marital status (married/cohabiting or other); and smoking status at diagnosis (whether or not a smoker at the time of diagnosis (henceforth "current smoker"), derived from information recorded in hospital records).

The available clinical variables from the time of diagnosis were: tumour size (T1, T2, T3/T4 and unknown); nodal status (N0, N+, unknown); metastases (M0, M1, unknown), grade (low/intermediate, high, unknown) and receptor status (ER + PR+, ER + PR-, ER-PR+ and PR or ER unknown). Variables relating to treatment receipt in the year following diagnosis were: breast cancer-directed surgery (mastectomy, breast-conserving surgery and no surgery; categorised following de Camargo Cancela, 2013); radiotherapy (yes/no); chemotherapy (adjuvant or neo-adjuvant; – yes/no); and endocrine therapy (yes/no). For those who had surgery, residual disease status was classified as whether or not the specimen excised had positive margins, which was defined as presence of tumour cells within 1 mm of the edge of the surgical specimen.

The available healthcare-related variables were: hospital and surgeon caseload which was based on the average number of breast cancer directed surgeries per year during the study period (all incident breast cancer cases and classified into tertiles. Of 65 hospitals, four were classified as higher-volume (≥150 breast-cancer surgeries/year), eight as intermediate-volume (70–149 breast-cancer surgeries/year) and 53 as lower-volume (<70 breast-cancer surgeries/year). Of 205 surgeons who conducted breast cancer-directed procedures, seven were classified as higher-volume (≥70 breast-cancer surgeries/year), 14 as intermediate-volume (35–69 breast-cancer surgeries/year) and 184 as lower-volume (<35 breast-cancer surgeries/year).

2.3. Statistical analysis

Analyses of age and (i) socio-demographic, clinical, healthcare and treatment characteristics and (ii) surgery non-receipt included all HR+/Her2- breast cancers. The analysis of age and (iii) type of breast-directed surgery received, (iv) receipt of (neo-)adjuvant treatment (radiotherapy, chemotherapy and endocrine therapy) and (v) survival included only patients who underwent surgery. Non surgical patients were excluded from these analyses as they constitute a small and highly selected group. The derivation of the datasets for analysis, and numbers of cases included, is shown in Fig. 1.

The distribution of socio-demographic, clinical, healthcare and treatment characteristics was compared between age-groups using chi-square tests. Hospital and surgeon volume groups were combined into high/intermediate volume vs low/unknown volume in these and subsequent analyses.

Differences in treatment receipt between the two age-groups were explored using modified Poisson regression models with robust error variance to obtain incidence rate ratios (IRR) [18]; the outcomes were: non-receipt of breast cancer-directed surgery (versus receipt); mastectomy (vs. breast-conserving surgery), radiotherapy (vs. no radiotherapy), chemotherapy vs. no chemotherapy) and endocrine therapy (vs. no endocrine therapy). Multivariate models were built using a forward stepwise approach, retaining in the model variables which had a p-value of <0.05 in Wald tests; age at diagnosis was forced into these models and women aged 40–49 were the reference category.

For survival analyses, follow-up was complete until 31/12/2011. Survival was calculated as the time from diagnosis to 5-years, the date of death, or end of follow-up, whichever came first. As non-cancer mortality is low in women aged 20–49 with breast cancer, deaths from all-causes were included. A forward stepwise

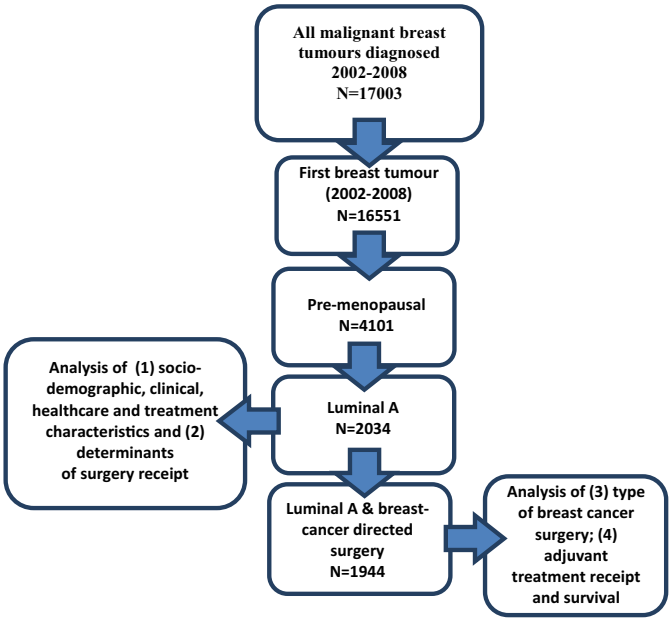

Fig. 1. Number of tumours in each data subset and correspondent analyses*. *Pre-menopausal women were defined as those aged 20–49 at diagnosis. *17,003 tumours were initially identified; after selecting the first incident breast tumour or the one with more advanced stage (in case of bilateral tumours) 16,551 women remained.