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Obesity is associated with a poorer prognosis in women with hormone receptor positive breast cancer

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ABSTRACT

Objective: Whether moderate to severe obesity (body mass index (BMI) ≥ 30 to <40 kg/m^2) contributes to breast cancer recurrence and mortality remains uncertain.
Subjects and methods: 1199 women, recruited within 12 months of their diagnosis of hormone receptor positive (HR+), human epidermal growth factor receptor 2 negative (HER2−) invasive breast cancer completed an enrolment questionnaire and an annual follow-up questionnaire every 12 months for another 5 years. The impact of obesity on time to either local or distant recurrence or new breast cancer, or death due to breast cancer was determined by Cox regression. Women in the most extreme categories of BMI (<18.5 and ≥40) were excluded from the analysis.
Results: Of the 1155 included women, mean age, 58.4 ± 11.6 years, 53.8% had Stage 1 disease and 88.9% received oral adjuvant endocrine therapy (OAET) within 2 years of diagnosis. The likelihood of an event was significantly associated with moderate to severe obesity (HR = 1.71, 95%CI, 1.12–2.62, $p = 0.014$), disease beyond Stage 1 (HR = 2.87, 95% CI 1.73–4.75, $p < 0.001$), OAET (HR = 0.26, 95%CI 0.14–0.46, $p < 0.001$), mastectomy (HR = 3.28, 95%CI 1.98–5.44, $p < 0.001$) and radiotherapy (HR = 2.12, 95%CI 1.24–3.63, $p = 0.006$). For Stage 1 disease, only moderate to severe obesity (HR 3.23, 95%CI 1.48–7.03, $p = 0.003$) and OAET use (HR 0.41, 95%CI 0.17–0.98, $p = 0.046$) were significantly associated with an event.
Conclusion: Moderate to severe obesity is associated with a poorer invasive breast cancer prognosis; this is also true for women with Stage 1 disease, and is independent of age and treatment.

1. Introduction

Being overweight or obese is an established independent risk factor for breast cancer [1,2]. Several studies suggest that obesity also contributes to a greater risk of disease recurrence and breast cancer-specific mortality (BCM) [3–7]. Most studies that have explored the association between obesity and recurrence or death were conducted prior to aromatase inhibitors (AIs) being used as first line oral adjuvant endocrine therapy (OAET) [4–8]. Kwan and others found the adverse effect of body mass index (BMI) on BCM to be limited to morbid obesity (BMI ≥ 40 kg/m^2) [8], whereas Pajares and others found severe obesity (BMI ≥ 35 kg/m^2) was associated with greater risk of recurrence, BCM and overall mortality in women treated with anthracyclines and taxanes [9]. In the study of Kwan and others [8], the BMI of the Chinese participants, who made up one-third of the study population, was classified by Caucasian standards. This may have resulted in women who were overweight or obese by Asian standards, being misclassified as normal weight or overweight respectively [10]. Thus, the impact of overweight or moderate–severe obesity on breast cancer recurrence and BCM, in the context of current OAET usage, remains uncertain.

The Bupa Health Foundation Health and Wellbeing after Breast Cancer Study (Bupa Study) has provided us with a unique opportunity to explore this issue further. The 1683 participants in the Bupa Study were recruited within 12 months of their first diagnosis of invasive breast cancer and were followed annually for a further 5 years. We have shown that this community-based cohort is representative of women diagnosed with breast cancer in the Australian state of Victoria in terms of age distribution, tumour characteristics and location of residence [11]. The national health insurance program in Australian enables women with breast cancer to be treated according to current guidelines, such that two-thirds of the women with hormone receptor positive (HR+) cancer in the Bupa Study, who survived for nearly 6 years, had at least 4 years of OAET therapy [12]. Fifty-five percent of the women with HR+ cancer in our

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study took an AI at some point during the period of observation [12].

In this paper we report on the associations between overweight (BMI 25 to <30 kg/m^2) and moderate to severe obesity (BMI 30 to <40 kg/m^2) at diagnosis, and breast cancer recurrence and breast cancer-specific mortality (BCM), in women with HR+, human epidermal growth factor receptor 2 negative (HER2−) disease, taking into account age, tumour characteristics and treatment.

2. Methods

2.1. Participants

Women were recruited to the Bupa Study between June 2004 and December 2006. Recruitment was mainly (78%) through the Victorian Cancer Registry, with the remainder of recruits volunteering directly to the Monash University Women's Health Research Program in response to advertisements about the study [13].

The participants completed an enrolment questionnaire, on average 41 weeks from the time of diagnosis (90% completed between 8 and 58 weeks from diagnosis), and then completed an annual follow-up questionnaire every 12 months for another 5 years (follow-up questionnaires FQ 1–5). The Victorian Cancer Registry provided us with monthly death registry checks that minimized the chance of us sending a questionnaire to the home of a woman who had died after completing their previous questionnaire.

This analysis was restricted to women who had HR+ disease, as we were interested in the impact of OAET on outcome. The analysis was also restricted to women who had HER2− disease because, although we knew the HER2 receptor status of all the participants, our information on exposure to trastuzumab was incomplete.

The study was approved by the Ethics Committee of the Cancer Council of Victoria and the Monash University Human Research Ethics Committee. All participants provided written informed consent and could withdraw at any time.

2.2. Data collected

We collected demographics, initial and subsequent treatment (surgery, radiotherapy, chemotherapy and oophorectomy) and the use of OAET. Women were asked to identify what, if any, OAET they were currently taking in each questionnaire. OAET included tamoxifen, and the aromatase inhibitors, anastrozole, letrozole and exemestane.

In FQ 1–5, we asked women if they had been diagnosed with a recurrence or a new breast cancer. We asked the location of any recurrence: same breast, lymph nodes, elsewhere in body, chest wall, bone or liver. Women were asked to specify a date of their recurrence or new cancer. The report of recurrence or new breast cancer was checked for consistency against reported changes to treatment including further surgery, chemotherapy, radiotherapy and OAET.

If a woman, or family member on her behalf, advised us that she was withdrawing from the study, she was classified as an active withdrawal. Women who did not return a questionnaire despite follow up, but did not actively withdraw, were classified as passive withdrawals. If a woman's questionnaire was returned by the postal service and she could not be contacted via post, home, work or mobile phone, nor via her alternative contact, she was classified as lost to contact. Five women who were inadvertently not sent a questionnaire were classified as an administration error. Each month the Victorian Cancer Registry provided us with death updates that included the date of death and cause (breast cancer or non-breast cancer).

2.3. Tumour characteristics

The Victorian Cancer Registry provided data for oestrogen receptor (ER) and progesterone receptor (PR) status, tumour diameter, number of nodes taken and number of nodes positive for all the study participants. HR+ disease was defined of having an ER or PR positive tumour, or both. Pathology data was provided to us on all study participants irrespective of how they were recruited. Stage 1 disease was disease confined to the breast where the primary cancer had a diameter less than 2 cm. The cut-off for describing a tumour as ER or PR positive was 1%.

2.4. Outcome measures

BMI was calculated as the weight in kilograms (kg) divided by height in metres squared (m^2), both of which women reported in the enrolment questionnaire. We used the World Health Organization BMI classifications of normal weight 18.5 to <25 kg/m^2, underweight < 18.5, overweight ≥ 25 to <30 kg/m^2, and obese ≥ 30 kg/m^2 [14]. We further classified obesity as moderate to severe obesity (30 to <40 kg/m^2) and morbid obesity (≥40 kg/m^2) [14]. Normal-weight women (BMI 18.5 to ≤25 kg/m^2) comprised the reference group. The analysis did not include women at the extreme ends of the spectrum of BMI. Therefore it did not include 14 women who had a BMI <18.5 kg/m^2 or 30 women with a BMI of ≥40 kg/m^2. This was done deliberately to ensure that any association found between obesity and prognosis was not a function of extreme values.

An event was defined as either the first report of active disease (a recurrence in the same breast, metastatic disease or cancer involving the other breast, after completion of the enrolment questionnaire) or death recorded as due to breast cancer (in cases where there was no report of active disease in the previous questionnaires so that recurrence or new cancer and death had all occurred in the period since completion of the previous questionnaire). Where the complete date of first diagnosis of active disease was not reported, the following rules applied: if no day of the month was given, day 15 of the specified month was used and if only the year of the recurrence was provided, then the 30th June of that year was used.

For the survival analysis, the date of a recurrence or new breast cancer or death from breast cancer constituted an event. Throughout the study, as 95% of questionnaires were returned within 1.2 years of completion of the previous questionnaire, we waited until 1.2 years from return of the previous questionnaire before further classification. If a questionnaire was not received after 1.2 years but the woman died during that time period, the date of death was the date of event (if the death was due to breast cancer and she had not previously reported a recurrence) or date of censoring (if the cause of death was not breast cancer). Women who withdrew (active or passive), who were lost to follow-up or were administration errors were all censored at the date of the last questionnaire they completed.

2.5. Analysis

Stata Version 12.1 was used for all analysis (Stata Corp, College Station, TX, USA). Categorical variables were first compared by event status using crosstabs and chi-square tests, and descriptive statistics (median and quartiles) were used for continuous variables. As we were interested in "time to event", we analyzed events by survival analysis using Cox proportional hazard ratio modelling and Kaplan–Meier survival curves. In the survival analysis, follow-up was from the date of diagnosis to either the date of an event or

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