Obesity and Outcomes in Premenopausal and Postmenopausal Breast Cancer

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Abstract

Purpose: **Obesity is associated with adverse outcomes in postmenopausal women with breast cancer. In premenopausal women, the association is less clear.**

Methods: **A population-based sample of 1,360 Australian women with breast cancer before the age of 60 years, 47% diagnosed before age 40, and 74% premenopausal, was studied prospectively for a median of 5 years (range, 0.2-10.8 years). Obesity was defined as a body mass index of $\geq$30 kg/m^2. The hazard ratio (HR) for adverse clinical outcome associated with obesity was estimated using Cox proportional hazard survival models.**

Results: **Obesity increased with age ($P < 0.001$) and was associated with increased breast cancer recurrence ($P = 0.02$) and death ($P = 0.06$), larger tumors ($P = 0.002$), and more involved axillary nodes ($P = 0.003$) but not with hormone receptor status ($P \geq 0.6$) or with first cycle adjuvant chemotherapy dose reductions ($P = 0.1$). Adjusting for number of axillary nodes, age at diagnosis, tumor size, grade, and hormone receptor status, obese women of all ages were more likely than nonobese women to have disease recurrence [HR, 1.57; 95% confidence interval (95% CI), 1.11-2.22; $P = 0.02$] and to die from any cause during follow-up (HR, 1.56; 95% CI, 1.01-2.40; $P = 0.05$). In premenopausal women, the adjusted HRs were 1.50 (95% CI, 1.00-2.26; $P = 0.06$) and 1.71 (95% CI, 1.05-2.77; $P = 0.04$), respectively.**

Conclusions: **Obesity is independently associated with poorer outcomes in premenopausal women, as it is in postmenopausal women, and this is not entirely explained by differences in tumor size or nodal status. Given the high and increasing prevalence of obesity in western countries, more research on improving the treatment of obese breast cancer patients is warranted.** (Cancer Epidemiol Biomarkers Prev 2005;14(7):1686–91)

Introduction

Obesity is associated with increased risk of breast cancer and adverse outcomes in postmenopausal women with the disease (1-3). In premenopausal women however, these associations are less clear. In this age group, obesity is associated with decreased breast cancer risk (4, 5), but the literature provides only limited support for an adverse prognostic effect of increasing body size in premenopausal women with breast cancer (refs. 6-16; Table 1).

Traditionally, the adverse effect of obesity on breast cancer prognosis has been thought to be mediated by higher estrogen levels due to greater aromatase activity in the excess adipose tissue (17). If this were so, it could be hypothesized that an adverse prognostic effect of obesity might not be seen in premenopausal women due to the already relatively high levels of ovarian estrogen production. It has also been postulated that treatment-related factors may contribute to worse outcomes in obese breast cancer patients as these women may receive less adjuvant chemotherapy due to comorbidities. In recent times, decreased dose intensity of adjuvant chemotherapy has been associated with poorer outcomes from breast cancer (18). Previous studies have shown significantly more empirical first-cycle adjuvant chemotherapy dose reductions (FCDR) in both premenopausal and postmenopausal obese compared with nonobese women (19, 20). This is an important issue as treatment factors are modifiable.

We studied the effect of obesity on breast cancer recurrence and mortality in patients recruited to the population-based Australian Breast Cancer Family Study (ABCFS). The study concentrated on premenopausal women as there are conflicting reports in the literature about the association of obesity with prognosis in this group. We also studied potential differences in adjuvant treatment between obese and nonobese women as there is a paucity of information concerning this in previous studies of younger women.

Materials and Methods

The ABCFS is a population-based case-control-family study of the genetic, environmental, and lifestyle factors associated with breast cancer. The study commenced in 1992 and recruited women with incident primary breast cancer and who were living in Sydney or Melbourne, Australia. Recruitment was via the respective state Cancer registries (reporting of cancer to these registries is a legislative requirement). Approval for the study was obtained from the ethics committees of The University of Melbourne and The Cancer Councils of Victoria and New South Wales. All subjects provided written informed consent for participation in the study. The overall participation for breast cancer patients in the ABCFS was 69%. Nonparticipation was due to attrition by

Received 1/17/05; revised 4/5/05; accepted 4/5/05.

Grant support: National Health and Medical Research Council of Australia grant 145604; National Health and Medical Research Council of Australia (Australian Breast Cancer Family Study); the New South Wales Cancer Council (Australian Breast Cancer Family Study), the Victorian Health Promotion Foundation (Australian Breast Cancer Family Study); and the U.S. National Cancer Institute, NIH grant RFA CA-95-003 as part of the Breast Cancer Family Registries (Australian Breast Cancer Family Study); Fox Chase Cancer Center, Huntsman Cancer Institute, Columbia University, Northern California Cancer Center, Cancer Care Ontario, and The University of Melbourne cooperative agreements (Australian Breast Cancer Family Study); and Inkster Ross Memorial Fund of the University of Otago, New Zealand (M. McCredie).

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Table 1. Published studies of the effect of obesity on breast cancer prognosis in premenopausal women

Author/year published	Patient source	Reference BMI	No. women	Median follow-up (y)	Association found?*	Result: HR	
						DFS, HR (95% CI)	OS, HR (95% CI)
Berclaz, 2004 (6)	Trials†	≥30 versus <25	3,494	14	Yes	1.16 (1.02-1.33)	1.22 (1.05-1.42)
Dignam, 2003 (7)	Trial‡	≥30 versus <25	1,035	13.8	No	NR	NR
Daling, 2001 (8)	Population based	>25.8 versus ≤20	1,177	NR	Yes	NR	1.7 (1.0-2.9)
Hebert, 1998 (9)	Hospital	N/A	222	8-10	Yes	1.09 (1.02-1.17§)	1.12 (1.03-1.22§)
Lethaby, 1996 (10)	Population based‖	≥28 versus <28	275	10.2	No	NR	NR
Holmberg, 1994 (11)	Mixed¶	≥29 versus <19	422	NR	Yes	5.9 (2.0-17.8)	NR
Jain, 1994 (12)	Population based	>27 versus <22	363	5.2	No	NR	0.96 (0.90-1.03)
Kamby, 1989 (13)	Population based	≥24 versus <24	543	4.9	No	NR	NR
Greenberg, 1985 (14)	Hospital	≥27 versus ≤20	582	NR	No	NR	1.8 (0.87-3.7**)
Mohle-Boetani, 1988 (15)	Population based	<30.5 versus ≥30.5	226	6	No	NR	1.6 (0.94-2.7**)

Abbreviations: OS, overall survival; DFS, disease-free survival; NS, not significant; NR, not reported; N/A, not applicable because BMI analyzed as a continuous variable.

*Yes means statistically significant.

†Patients from International Breast Cancer Study Group trials 1-IV, V, and VI-VII.

‡All node-negative, hormone receptor–positive tumors treated with tamoxifen or placebo (NSABP-B14).

§HR for each kg/m^2 gained.

‖All node negative early breast cancers.

¶Swedish group: population based, Norwegian group: hospital based.

**95% CI not given but was calculated using estimate and *P* and assuming a log-normal distribution.

death (2%), refusal by the attending doctor (8%), refusal by the case patient (16%), nonresponse by the attending doctor (1%), nonresponse by patient (1%), or unable to locate cases (2%). Details of recruitment strategy, participation, and baseline data collection methods have previously been described (21).

To be eligible for the current study, women had to be diagnosed with nonmetastatic breast cancer before the age of 60 years and have no previous history of invasive cancer (apart from nonmelanocytic skin cancer). Cases that were enrolled via the New South Wales Cancer Registry before 1996 were excluded from this study because the consent they gave at the time of entry specifically prohibited any further approaches from the researchers.

Of the 1,360 potential subjects, 28 were ineligible and body size measures were missing for an additional nine. Information on vital status after interview was unavailable for a further 65, leaving 1,258 patients available for inclusion in analyses of death as the outcome of interest. For analyses of time to distal recurrence, consent to access information on cancer progression from medical records was not obtained from 222 women thus leaving 1,101 cases.

Data Collection. Participants completed a face-to-face, interviewer-given epidemiologic questionnaire as previously described (21). The median time between diagnosis and interview was 8 months. Respondents were asked about their body size history, including current height and weight, weight 1 year before diagnosis, maximum lifetime weight, and weight at age 18 years old. Height, weight, and body surface area were also abstracted from chemotherapy charts where applicable.

Tumor characteristics, including size, grade, number of involved axillary nodes, and estrogen and progesterone receptor status, were abstracted from the relevant diagnostic pathology reports by trained research assistants at recruitment. Other information abstracted from medical records included adjuvant therapy details (chemotherapy, hormonal therapy, duration, and doses) and details on first distant recurrence and death.

Body Composition. Obesity was defined according to Quetelet's index or body mass index (BMI), defined by weight (kg)/height^2 (m). In line with the National Centre for Disease Control and Prevention guidelines (22), categories of BMI were defined as underweight, ≤18.5 kg/m^2; normal weight, >18.5 to 24.9 kg/m^2; overweight, 25.0 to 29.9 kg/m^2; obese, ≥30 kg/m^2. Self-reported height and weight 1 year before diagnosis, as reported at interview, were used.

Statistical Methods. Hazard ratios (HR) for death and distal recurrence associated with BMI were estimated separately using Cox proportional hazards survival models, with and without adjustment for one or more of the following factors: number of involved axillary nodes, tumor size, tumor grade, hormone receptor status, age at diagnosis, adjuvant treatment, and menopausal status. BMI was included both as a categorical variable (using standard cutoffs) with ''normal'' as the reference category, as a binary variable classified as obese and nonobese, and as a continuous variable, the latter including consideration of linear and quadratic associations with log HR.

The primary end point was distant recurrence. Time to failure was considered from the date of diagnosis. Date of distant recurrence (abstracted from medical records) was used as the time of failure. Women who were not known to have had a distant recurrence but died were assumed to have failed at the date of death. All other women were censored at the date last known to be alive (i.e., date of last contact with ABCFS study staff, or date of last medical follow-up as abstracted from the medical record).

For death from any cause during follow-up period, time to failure was considered from the date of diagnosis, with subjects left-truncated at the date of interview. For subjects who died, date of death was used as the time of failure. Women who were not known to have died were censored at the date last known to be alive. For all Cox model analyses, the proportional hazards assumption was assessed using Schoenfeld residuals.

Comparisons of HR estimates from different studies were based on the assumption that they were independent and log-normally distributed. Equality of proportions was tested using the χ^2 test. Trend associations between obesity and prognostic factors were assessed using unconditional logistic regression with obesity as the outcome variable and including nonbinary prognostic measures as continuous variables. All statistical analyses were done using STATA 8.0 and all tests and *P* values were two tailed.

Menopausal status was determined from the interviewer-given questionnaire for 1,185 (87%) of those approached for consent; the remaining 170 were categorized as premenopausal if they were under age 50 at diagnosis.

Differential treatment with chemotherapy was investigated by comparing obese versus nonobese women both on whether or not chemotherapy was given and whether FCDRs were prescribed. Ideal dose of chemotherapy was calculated for each subject using recommended doses per unit of body surface area (square root of height (cm)^2 weight (kg) / 3,600; ref. 23) Recommended doses of chemotherapy (24) were calculated and contrasted to actual dose received at the first chemotherapy cycle. Less than 90% of ideal dose for any one drug was considered ''underdosing.'' Body surface area calculations were recorded on the chemotherapy charts for only 399 of 688 (58%) of women. Only those with objective recordings were used in the analysis of FCDR. All patients who received high-dose chemotherapy with stem cell or bone marrow transplant were included in the adequate dose group.

Results

For analysis of time to distant recurrence (n = 1,101), the mean age at interview was 42.7 years (range, 23-69 years). Median follow-up was 5 years (range, 0.2-10.8 years). As shown in Table 2, 74% of patients were premenopausal and most women (62%) had received adjuvant chemotherapy, 34% had received adjuvant hormonal therapy, and only 21% had received no adjuvant treatment.

The mean BMI was 24.5 kg/m^2 (range, 14.8-49.1). Approximately 25% (273 of 1,101) of women were classified as overweight (BMI, 25-30 kg/m^2) and 12% (131 of 1,101) as obese (BMI, ≥30 kg/m^2) at diagnosis. Classification as obese versus nonobese based on objective weight recorded in chemotherapy charts, where available, was the same as that based on weight 1 year before diagnosis for 91% of 399 patients (correlation coefficient = 0.8). Participants had a mean 1.5 kg (SD, 5.7 kg) weight gain between 1 year before diagnosis and interview.

Obesity increased with increasing age (P < 0.001) and was associated with increased tumor size (P = 0.002), increased number of involved axillary nodes (P = 0.003), and with being postmenopausal at diagnosis (P < 0.001; Table 2). There was no association between obesity and estrogen or progesterone receptor status overall (P > 0.6), nor in either premenopausal or postmenopausal groups (P > 0.3), or with tumor grade (P = 0.9) or FCDR (P = 0.1). For those who had chemotherapy, a FCDR was not independently associated with prognosis in terms of distant recurrence (P = 0.2) or death (P = 0.5). Although obesity was associated with tamoxifen use (P = 0.006), this was no longer apparent after adjusting for age (P = 0.2).

For both distant recurrence and death as end points, modeling of body size as a categorical and a continuous variable gave no evidence of a linear nor a quadratic association with prognosis. Graphing estimates and 95% confidence intervals (95% CI) for HRs associated with sextiles of BMI (Fig. 1), indicated that risk was elevated in women with very high BMI. Results are therefore reported for obese versus nonobese women.

Table 2. Patient and tumor characteristics according to obesity

Characteristic	Nonobese (BMI ≤ 30) (n = 970), n (%)	Obese (BMI > 30) (n = 131), n (%)	All patients (n = 1,101), n (%)	P* (P_{trend} †)
Treatment				
Chemotherapy	608 (63)	80 (61)	688 (62)	0.8
FCDR ‡	55 (17)	14 (25)	72 (18)	0.1
Tamoxifen	311 (32)	58 (44)	369 (34)	0.006
None	209 (22)	24 (18)	233 (21)	0.4
Age at diagnosis				
<35	180 (19)	14 (11)	194 (18)	
35-39	289 (30)	29 (22)	318 (29)	
40-49	266 (27)	39 (30)	305 (28)	
>50	235 (24)	49 (37)	284 (26)	0.002 (<0.001)
Menopausal status				
Pre	735 (76)	78 (60)	813 (74)	
Post	235 (24)	53 (40)	288 (26)	<0.001
Tumor size (mm)				
≤20	661 (68)	75 (57)	736 (64)	
21-50	228 (24)	41 (31)	269 (24)	
>50	23 (2)	9 (7)	32 (3)	0.002 (0.002)
Unknown	58 (6)	6 (5)	64 (6)	
Tumor grade				
1	146 (15)	20 (15)	166 (15)	
2	361 (37)	48 (37)	409 (37)	
3	382 (39)	53 (40)	435 (40)	0.9 (0.9)
Unknown	81 (8)	10 (8)	91 (8)	
Number of involved axillary nodes				
0	543 (56)	57 (44)	600 (55)	
1-3	259 (27)	40 (31)	299 (27)	
>3	132 (14)	27 (21)	159 (14)	0.02 (0.003)
Unknown	36 (4)	7 (5)	43 (4)	
ER status				
Negative	335 (35)	44 (34)	379 (34)	
Positive	590 (61)	81 (62)	671 (61)	0.8
Unknown	45 (5)	6 (5)	51 (5)	
PR status				
Negative	292 (30)	42 (32)	334 (30)	
Positive	632 (65)	83 (63)	715 (65)	0.7
Unknown	46 (5)	6 (5)	52 (5)	

Abbreviations: ER, estrogen receptor; PR, progesterone receptor.
*P for no association between characteristic and obesity (excluding unknowns).
†Where applicable.
‡FCDR: first cycle dose reduction in adjuvant chemotherapy (<90%) assessed for the 399 women (55 obese and 344 nonobese) for whom dosing information was available.

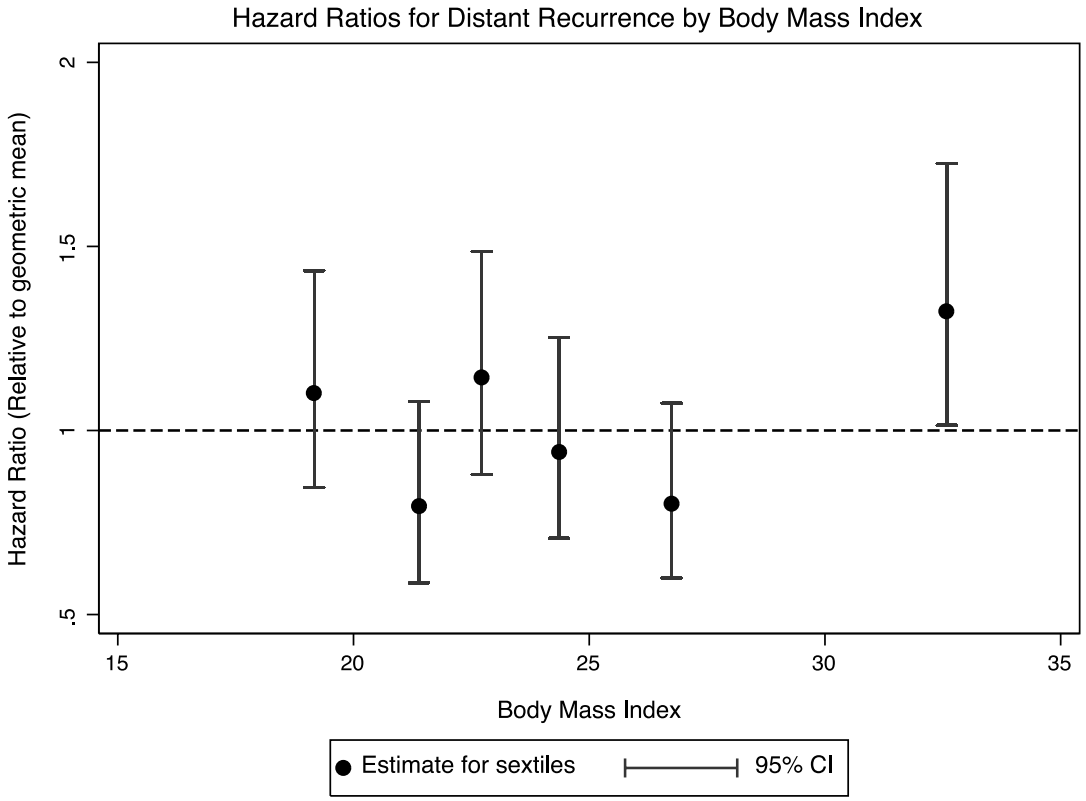

Figure 1. Hazard ratios, relative to geometric mean, for distant recurrence following breast cancer by BMI.

Distant Recurrence. There was a total of 264 events. Obesity was associated with an increased risk of distant recurrence from breast cancer (HR, 1.50; 95% CI, 1.07-2.09; $P = 0.02$). Age, tumor grade, nodal status, and progesterone receptor status (positive) were also found to be independent predictors of recurrence and mortality. After adjustment for the above prognostic factors, obesity remained an independent prognostic factor for disease recurrence (HR, 1.57; 95% CI, 1.11-2.22; $P = 0.02$). In premenopausal women, the adjusted HR was 1.50 (95% CI, 1.00-2.26, $P = 0.06$) and in postmenopausal women it was 2.03 (95% CI, 0.99-4.21, $P = 0.07$).

Mortality. A total of 184 events occurred. Obesity was associated with increased mortality from any cause during the follow-up period (HR, 1.48; 95% CI, 0.99-2.24; $P = 0.06$). Adjusted for other prognostic factors, obesity remained an independent predictor of mortality (HR, 1.56; 95% CI, 1.01-2.40; $P = 0.05$). The adjusted HR was 1.71 (95% CI, 1.05-2.77; $P = 0.04$) in premenopausal women and 0.84 (95% CI, 0.28-2.56; $P = 0.8$) in postmenopausal women. Figure 2 shows the survival curves by obesity status.

The above HR estimates did not differ substantially by hormone receptor status. Obese women had a poorer prognosis in terms of both recurrence and death when the analysis was repeated using only those women for whom objective body size measures were available ($n = 399$). The HR for distant recurrence was 2.18 (95% CI, 1.20-3.95, $P = 0.01$) and 2.30 for death (95% CI, 1.09-4.83, $P = 0.03$). For the premenopausal women in this subgroup, the HR were 2.44 (95% CI, 1.23-4.82, $P = 0.01$) and 2.86 (95% CI, 1.27-6.44, $P = 0.01$) for distant recurrence and death, respectively.

Discussion

In our cohort of newly diagnosed breast cancer patients, deliberately oversampled for early onset and therefore premenopausal disease, obesity was associated with an increased risk of both disease recurrence and death. In the premenopausal group, the HRs for disease recurrence and death were 1.50 (95% CI, 1.00-2.26) and 1.71 (95% CI, 1.05-2.77), respectively. Our finding is consistent with the only other comparably sized, large population-based study of premenopausal women (8), which found an almost identical adjusted HR for mortality.

Interestingly, a clinical trial-based cohort analyzing the efficacy of tamoxifen in both premenopausal and postmenopausal women reported an adverse effect of obesity on mortality with an HR of 1.31, which reduced to 1.2 and became of marginal statistical significance after adjusting for other known prognostic factors. The adverse effect of obesity was apparently independent of menopausal status, but the data were not presented (7). Similarly, another retrospective study of patients enrolled in multiple clinical trials also showed that BMI was an independent but modest prognostic factor (6). In contrast to the previous study, the effect here was stronger for the premenopausal and perimenopausal group, most of whom received chemotherapy without hormonal therapy.

It is unclear why the clinical trial-based cohorts should produce more modest estimates of the effect of obesity on outcome compared with those obtained from population-based studies however, less thorough staging, and the underdosing of chemotherapy in obese patients, all of which are more likely to occur outside a clinical trial context, have been raised as potential reasons (25). However, in our study, we found that obese women were no less likely to receive appropriate adjuvant chemotherapy or to receive more FCDRs. In contrast, FCDR (<85% ideal dose) have been found to be common in obese women in a hospital-based cohort receiving chemotherapy for breast cancer (19). These women were slightly older (mean, 48; range, 25-83 years) than those in our study. In a retrospective multi-institution review of 9,964 women receiving adjuvant chemotherapy between 1989 and 2001, 27% of obese women compared with 11% of overweight

and 9% of healthy weight women had FCDR (<90% ideal dose; $P < 0.001$; ref. 20). In that study, other predictors of FCDR were age of >60 years, presence of a comorbid condition, and women who were diagnosed longer ago. The finding of no difference in FCDR between obese and nonobese women in our study may have been due to insufficient power (only 60% of women could be evaluated for FCDR), the younger age of patients, and the use of a sample group who were more recently diagnosed.

Many smaller studies have analyzed the influence of obesity on outcomes in specifically premenopausal women with breast cancer (refs. 6-16; Table 1). The majority of these did not show any significant association, but all HR point estimates were >1. The definition of obesity also varied between studies (many studies used the upper quartile of BMI in their sample to define obesity rather than the National Centre for Disease Control and Prevention definition), as did the reference groups (i.e., comparison with underweight women rather than nonobese women as in our study).

Traditionally, the adverse effect of obesity on prognosis has been attributed to excessive estrogen (17, 26), and its effect observed to be strongest in the postmenopausal age group. If increased estrogen were the major reason behind the worse outcomes of obese women with breast cancer, one would expect the effect to be stronger in those with estrogen receptor–positive tumors compared with those with estrogen receptor–negative tumors. We found no difference in the effect of obesity on mortality by estrogen receptor status. This result is perhaps not surprising. In premenopausal women, estrogen levels influenced by peripheral aromatization in adipose tissue would presumably be insignificant compared with that produced by functioning ovaries. Other studies have specifically analyzed tumor histopathologic characteristics in relation to obesity in young women and also found varying correlations with hormone receptor status (27-31) but consistent associations with larger tumors and more involved axillary lymph nodes similar to our study (6, 8, 32). However, even after adjustment for these factors, obesity remains a significant predictor of outcome on both estrogen receptor–negative and –positive tumors, suggesting other biological influences apart from estrogen may be responsible for the effect of BMI on prognosis. These mechanisms are unclear; Daling et al. found increased mitotic counts and higher Ki-67 expression in tumors from obese premenopausal women (8); however, our study did not find any associations with BMI and tumor grade.

In obese premenopausal women, the hormonal milieu seems different and obesity has been associated with hyperandrogenism, hyperinsulinemia, and lower serum hormone-binding globulin but unchanged or even decreased estrogens (33). High BMI in early adulthood and premenopausal women has been reported to be inversely related to breast cancer risk (34). A recent study has suggested that hyperinsulinaemia is associated with worse outcomes in breast cancer patients (35, 36). This is perhaps a potential mediator of the adverse effect of obesity in premenopausal breast cancer patients.

Details of reported cause of death were not recorded in our study and death certificates were available for only a limited number of participants; hence, our conclusions apply to all-cause mortality. Previously, it has been noted that obese women have greater all-cause mortality and greater risk of other primary cancers compared with nonobese women (1). However, distant breast cancer recurrence is an excellent surrogate for death from breast cancer, and in our study the risk of distant recurrence was significantly higher in obese compared with nonobese women. Given the age distribution of our sample, it is unlikely that the excess in deaths seen in obese women was contributed to substantially by nonbreast cancer deaths.

Our study relied on self-reported weight estimates (as at 1 year before diagnosis); however, these were found to be highly correlated with actual measured body weights (measured at time of chemotherapy; $r = 0.8$). Cox regression analysis based

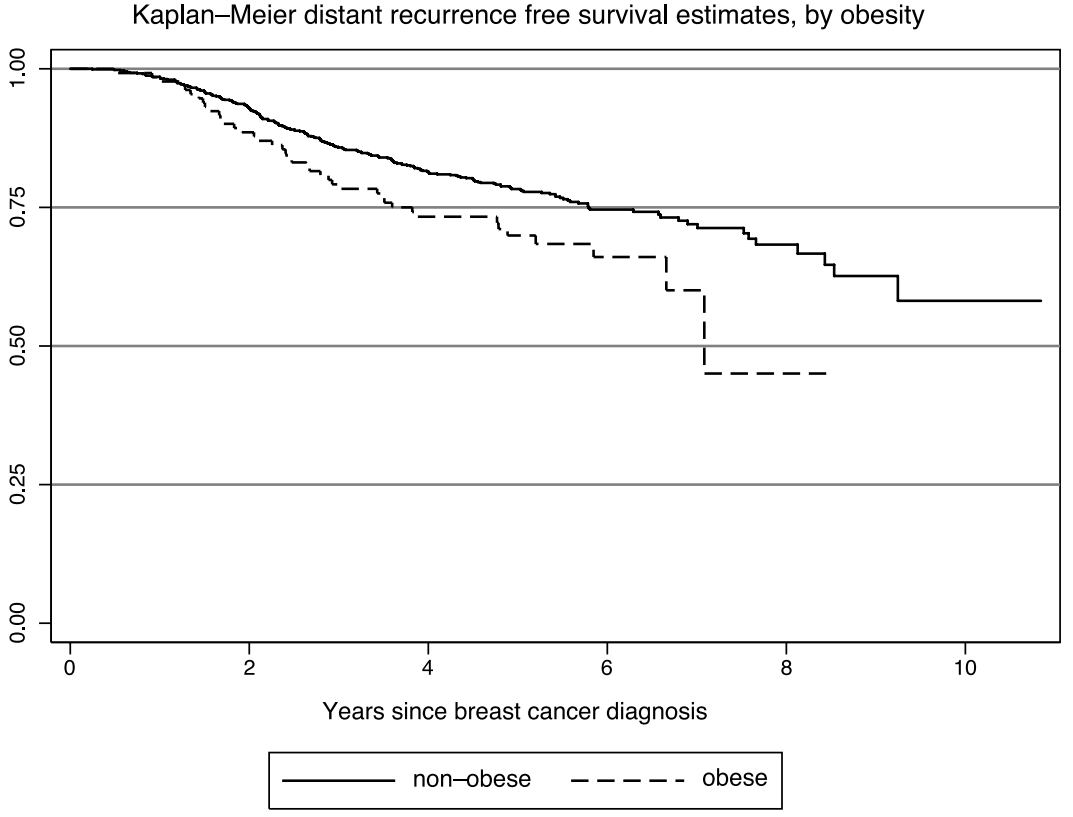

Figure 2. Kaplan–Meier survival estimates of proportion free of recurrence for obese and nonobese women.

on those women who had objective body surface area recorded found the same adverse effect of obesity on prognosis. This lends support to other validation studies that have also shown that self-reported weight is accurate (37). One potential weakness of our study is that we defined obesity in terms of BMI which does not discriminate between fat and lean body mass, the latter of which may be more common in younger compared with older women. There are no other simple anthropometric measurements of obesity however, and BMI is generally accepted to be well correlated with body fat in young women (38, 39).

There was loss of subjects both at recruitment (31%, including 2% deceased) and during follow-up. By left-truncating all subjects at time of recruitment (i.e., accounting for the fact that participation is conditional on survival to recruitment), we have adjusted for any potential survival bias, although our conclusions may not be generalizable to prognosis in the months immediately following breast cancer diagnosis. All women recruited into the ABCFS were included in the analyses of mortality. That mortality and distant recurrence results are consistent suggests that loss of subjects at follow-up did not bias the results. It is possible that those who were not recruited into the ABCFS were more likely to die, because they may have been too ill to enter the study. Our results would be spurious or at least exaggerated if, in addition, obese women were more likely than nonobese women to participate (i.e., if nonobese women with poorer outcomes were underrepresented in the sample analyzed). However, it seems more likely that being obese would be associated with being *less* likely to participate given the association of obesity with comorbidities.

In conclusion, we have shown that obesity is independently associated with poorer breast cancer outcomes overall, and for premenopausal women, in our population-based cohort. This association is not entirely explained by differences in tumor size or nodal status. Physician bias in terms of adjuvant treatment underdosing also did not contribute to the association in our study. Other biological factors apart from estrogen are probably responsible for the association of obesity with unfavorable breast cancer outcomes and remain to be fully elucidated. As obesity, diet, and exercise are potentially modifiable and the prevalence of obesity in western countries remains high and continues to increase, more research into understanding the underlying biological mechanisms and on improving the treatment of obese breast cancer patients diagnosed at any age is warranted.

Acknowledgments

We thank Mandy Muir and Pauline Jacklin for data collection, Maggie Angelakos for data management, Michael Dooley for helpful discussions during the planning phase of the study, and Prue Francis for critical review of an earlier version of the article.

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Cancer Epidemiol Biomarkers Prev 2005;14:1686-1691.