Relation between obesity and the oestrogen receptor status of breast cancer

David Pisani, Etienne Mark Paris, Gordon Caruana Dingli

Abstract

Introduction: Obesity is a growing problem in the Western world. Correlations have been found between increasing body mass index (BMI) and breast cancer. The objectives were to establish whether a relationship exists between BMI and breast cancer and to investigate any association between BMI and tumour oestrogen receptor expression.

Method: Clinical and socio-demographic details (age, menopausal status, height and weight) of a sample of women with breast cancer operated in 2010 were collected, dividing the group into oestrogen receptor positive (ER+) and negative (ER–) subgroups. The average BMI of each subgroup was compared to the mean BMI of a sample of the general Maltese female population obtained from the European Health Examination Survey 2010 Report (Pilot Study) by virtue of an ANOVA test. Subsequently, the relations between oestrogen receptor expression and each of menopausal status, age and BMI were statistically analysed using chi-squared analysis and two-sample t-tests.

Results: A total of 103 patients were studied. 72 patients (age range: 40 – 90 years) had ER+ malignancy and 31 patients (29 – 81 years) had ER- malignancy. The mean BMI's of the ER+ and ER- subgroups were 30.1 and 27.1 respectively, while that of the female general population (29 – 90 years) was 28.4. Analysis revealed a significant difference between the BMI's of the ER+ and ER- subgroups ($p < 0.05$) but no difference between each receptor subgroup and the general population. Neither menopausal status nor age was found to correlate with positive oestrogen receptor expression.

Conclusions: Women with ER+ malignancy tended to be significantly more obese than those with ER- breast cancer. However, neither subgroup had a mean BMI significantly different from that of the general population.

David Pisani MD*
Doctor of Medicine and Surgery
Mater Dei Hospital
Msida, Malta
pisanidavid@gmail.com

Etienne Mark Paris MD
Doctor of Medicine and Surgery
Mater Dei Hospital
Msida, Malta

Gordon Caruana Dingli MD, LRCP (Edin), LRCS (Edin), LRCP&S (Glasg), FRCS (Edin), FRCP RCP&S (Glasg)
Consultant General and Breast Surgeon
Head of Breast Clinic at
Mater Dei Hospital
Senior Lecturer at University of Malta
Medical School
Msida, Malta

*Corresponding Author

Introduction

Obesity is a growing problem in Western developed countries. According to data from the European Health Interview Survey, published by Eurostat in November 2011, Malta ranked second, after the UK, in the prevalence of obesity in females, with 21.1% of women having a BMI over 30.[1] Research has long since demonstrated a relationship between obesity and various forms of malignancy, including colon cancer, endometrial cancer, renal cell carcinoma and oesophageal adenocarcinoma.[2, 3] In addition to this, several studies have also shown a strong correlation between body mass and postmenopausal breast cancer.[4-6] Moreover, it has been confirmed that overweight women with breast cancer have a poorer prognosis than thinner women,[7] with obese patients having a 46% increase in the risk of metastatic disease, roughly twice the risk of recurrence over a 5-year period and a 60% risk of death over a 10-year period.[3]

Our study aimed to establish whether the relationship between body mass and breast cancer also holds true in the Maltese populace, given the high prevalence of overweight and obese individuals. Moreover, we attempted to find an association between obesity and the oestrogen receptor status of the breast neoplasia.

Methodology

We performed a hospital-based retrospective study on a number of breast cancer patients seen by one of two surgical firms at Mater Dei Hospital Breast Clinic, Malta. Following acquisition of appropriate hospital approval, 103 histologically confirmed breast cancer cases were ascertained between the 1st of January 2010 and the 31st of December 2010. Eligible cases had to be females with a Maltese citizenship. For each case, various anthropomorphological details, including age, height, weight and menopausal status, were obtained from patient hospital records, and the BMI was then calculated by dividing the weight (in kilograms) by the height squared (in squared metres).

The sample was then divided into two groups; those patients with ER+ and those with ER– malignancies. This data was subsequently compared with the average BMI of a sample of the Maltese female population, obtained from the European Health Examination Survey 2010 Report (Pilot Study),[8] taking only those females aged between 29 and 90 years (the same age range as the breast cancer patient sample), in order to investigate whether significant differences exist between the BMIs of the general Maltese female population, the ER+ sample and the ER– sample.

Using appropriate statistical tests, the relationship between tumour oestrogen receptor expression and each of menopausal status, age and BMI was subsequently analysed.

Results

A summary of the BMI data in the histologically confirmed breast cancer cases and the general population is shown in *Table 1*. *Chart 1* compares the BMI distributions of the ER+ and ER– groups respectively.

By virtue of an Analysis of Variance (ANOVA) test, the mean BMIs of the ER+ sample, the ER– sample and the general population were compared in order to ascertain whether breast cancer patients in each subgroup were significantly more obese than the Maltese female general population. A significant difference was found between the three distributions (p=0.0246). Post hoc Tukey testing demonstrated a significant difference (at the 95% significance level) between the BMIs of the ER+ and ER– groups only, but no significant difference between each breast cancer subgroup individually and the general population.

Table 2 divides each oestrogen receptor subgroup according to menopausal status. The correlation between oestrogen receptor status and menopausal status was explored using a χ^2-test. The resulting p-value for this analysis was 0.0820, suggesting that there is no correlation between oestrogen receptor status and menopausal status at the 95% significance level.

A correlation between oestrogen receptor status and age was sought using a two-sample t-test with equal variance and this yielded a p-value of 0.0448, signifying that patients with ER– breast cancer tend to be younger than those with ER+ cancer. Using the same test, correlation between BMI and oestrogen receptor status yielded a p-value of 0.0116. This implies that both relations are significant at the 95% significance level, the latter correlation being considerably stronger.

Since age is a potential confounding variable in the relationship between the oestrogen receptor status of breast cancer and BMI, multivariate linear regression analysis was carried out in order to account for differences in age. The results are shown in *Table 3*. The results demonstrate a p-value of 0.011 for the oestrogen receptor status / BMI relationship and 0.700 for the age / BMI relationship, therefore reaching the conclusion that age does not significantly confound the relationship between tumour oestrogen receptor expression and BMI. Hence, positive oestrogen receptor status remains significantly associated with increasing BMI, even when adjusted for age.

Discussion

The study concluded a number of points in relation to breast cancer in the Maltese population. Firstly, Maltese women with breast cancer were found to be neither more nor less obese than the general female population. However, those women with ER+ malignancy are significantly more obese than those with ER- breast cancer.

Breast cancer is by far the commonest malignancy in females in Malta, with the incidence rate approaching 1 case per 1,000 people.[9] Obesity has been strongly linked with breast cancer in numerous studies,[2-6, 10] such that the observed rises in incidence in breast cancer might well be linked to the dramatic increases in the number of overweight and obese individuals.[11] Data from the European Health Interview Survey 2008 revealed that in Malta, 28.4% of females over the age of 15 years were overweight and 20.6% were obese,[12] while the European Health Examination Survey 2010 report revealed that in females over the age of 18 years, 25.6% were overweight but 32.0% were obese.[8] This demonstrates a very high and ever increasing prevalence of obesity in the Maltese Islands.

However, why this study demonstrated no statistically significant difference between the BMIs of the European Health Interview Survey 2010 sample, the ER+ sample and the ER– sample is not clear. One possibility is that the sample size is too small to detect the difference. Another possibility is that since the prevalence of obesity is so high in Malta, it is difficult to detect a difference between the overweight / obese and the normal weight population since the risk factor being studied (i.e. obesity) is not present in only a small minority of the population.

Table 1: *Summary of BMI data in histologically confirmed breast cancer cases and general population*

	Sample Size	Mean BMI (kg/m²)	Standard Deviation	95% Confidence Intervals
ER+	72	30.1	5.61	28.8 – 31.4
ER–	31	27.1	4.91	25.3 – 28.9
General Maltese Female Population	89	28.4	5.43	26.4 – 27.3

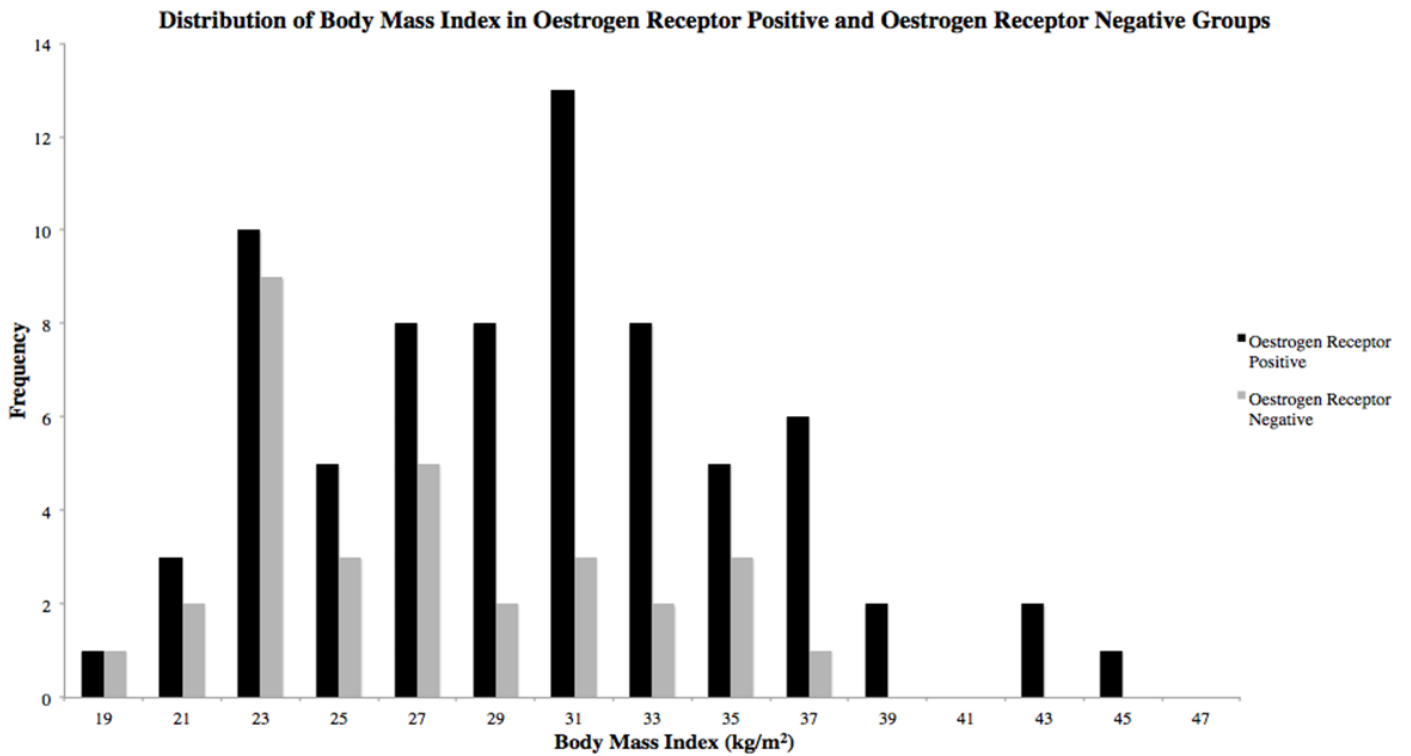*Figure 1*: *BMI distributions in ER+ and ER– breast cancer groups*

Table 2: Menopausal status of breast cancer cases

	Premenopausal	Postmenopausal
ER+	14 (19.4%)	58 (80.6%)
ER–	11 (35.5%)	20 (64.5%)

Table 3: Multivariate analysis of oestrogen receptor status, BMI and age

BMI	Coefficient	Standard Error	t	p>|t|	95% Confidence Intervals
Oestrogen Receptor	3.081	1.192	2.590	0.011	0.717 – 5.446
Age	- 0.018	0.048	- 0.390	0.700	- 0.113 – 0.076
Constant (alpha)	28.168	2.875	9.800	0.000	22.463 – 33.872

In addition to this, the incidence of breast cancer in Malta is relatively low compared to that of other countries like Belgium and France, where the incidence rates are roughly 140 cases per 100,000 people,[9] and this may make finding a relationship between breast cancer and obesity all the more difficult.

The relationship between obesity and ER+ malignancy holds true in Malta. This relationship has been demonstrated repeatedly in other studies.[11, 13-15] The pathogenesis linking obesity and ER+ breast cancer is not completely clear. In post-menopausal women, oestrogen is largely produced by adipose tissue, which possesses the enzyme aromatase, which can synthesize oestrone.[16] Obese individuals have higher levels of circulating oestrogens and reduced levels of the steroid carrier sex hormone-binding globulin.[7] The high blood free oestrogen levels may be associated with increased, and possibly aberrant, division of breast epithelial cells. However, how, and even if, this high level of oestrogen results in anomalous oestrogen receptor expression on breast cancer cells remains unclear. It is likely that other adipocytokines apart from oestrogen are involved in the pathogenesis.[7]

This study demonstrated no association between positive oestrogen receptor status and menopausal status but showed an association between increasing age and positive oestrogen receptor expression. Clark, McGuire and Osborne found a similar result in almost 3,000 women with primary breast cancer, showing that when patient age and menopausal status were analysed together, the primary determinant of positive oestrogen receptor status was age.[17] Other studies, however, demonstrated that post-menopausal women had a greater tendency for developing ER+ disease.[18, 19] The positive correlation of oestrogen receptor status with age may stem, in part, from the correlation between age and an increasing BMI, with the European Health Interview Survey (2008) and the European Health Examination Survey (2010) demonstrating increasing BMI with age in the Maltese population.[8, 12]

The fact that a small sample size was taken is a significant limitation of this study, as is the fact that the heights and weights of the sample of patients taken were obtained from the patient records rather than being measured directly. In addition, the impact of other potentially confounding variables (for example,

nulliparity, use of the oral contraceptive pill and smoking) were not investigated. Finally, the fact that BMI was taken as a measure of obesity may in itself be a limitation since BMI does not always correlate with body fat content.

Conclusion

Maltese women with ER+ tumours have been found to be significantly more obese than those with ER– tumours but neither group was found to be significantly more or less obese than the general population. Positive oestrogen receptor expression correlated with obesity, with obese women being more at risk of developing ER+ malignancy.

Conflict of Interest Statement

The authors declare no potential conflicts of interest.

References

1. European Health Interview Survey. Between 8% and 25% of adults are obese across Member States. No systematic differences between women and men. [Internet]. Eurostat 2011 [cited 2012, February 3]. Available from: http://epp.eurostat.ec.europa.eu/cache/ity_public/3-24112011-bp/en/3-24112011-bp-en.pdf.
2. Parkin DM, Boyd L. Cancers attributable to overweight and obesity in the UK in 2010. Br J Cancer. 2011;105(S2):S34-S37.
3. Sinicrope FA. Obesity and Breast Cancer Prognosis: Weight of the Evidence. J Clin Oncol. 2011;29:4-7.
4. Msolly A, Gharbi O, Mahmoudi K, Limem S, Hochlef M, Ben Ahmed S. Association between Body Mass Index and Risk of Breast Cancer in Tunisian Women. Ann Saudi Med. 2010;31:393-97.
5. Shu XO, Jin F, Dai Q, Shi JR, Potter JD, Brinton LA, et al. Association of Body Size and Fat Distribution with Risk of Breast Cancer Among Chinese Women. Int. J. Cancer. 2001;94:449-55.
6. Singh P, Kapil U, Shukla NK, Deo SVS, Dwivedi SN. Association of Overweight and Obesity with Breast Cancer in India. Indian J Community Med. 2011;36:259-62.
7. McTiernan A, Rajan B, Tworoger SS, Irwin M, Bernstein L, Baumgartner R, et al. Adiposity and Sex Hormones in Postmenopausal Breast Cancer Survivors. J Clin Oncol. 2003;21:1961-66.
8. Department of Health in the Ministry of Health, the Elderly and Community Care. The European Health Examination Survey Pilot Study 2010. [Internet]. Directorate for Health Information and Research [cited 2012, April 4]. Available from: https://ehealth.gov.mt/download.aspx?id=7693
9. Ferlay J, Parkin DM, Steliarova-Foucher E. Estimates of Cancer Incidence and Mortality in Europe in 2008. Eur J Cancer. 2010;46:765-81.
10. Bodmer A, Castiglione-Gertsch M, Pralong F and Zaman K. Breast Cancer and Obesity, A Dangerous Relation. Rev Med Suisse. 2012;23:1101-04.
11. Gompel A, Pichard C, Plu-Bureau G, Neves Castro M. Insulin Resistance, Obesity and Breast Cancer Risk. Maturitas. 2008;60:19-30.
12. Department of Health in the Ministry of Health, the Elderly and Community Care. The European Health Interview Survey 2008. [Internet]. Directorate for Health Information and Research [cited 2012, June 27]. Available from: https://ehealth.gov.mt/download.aspx?id=3177
13. Bernstein L, Carpenter CL, Enger SE, Paganini-Hill A, Ross RK. Body Size, Physical Activity, and Breast Cancer Hormone Receptor Status: Results from Two Case-Control Studies. Cancer Epidemiol Biomarkers Prev. 2000;9:681.
14. Eskelinen M, Männistö S, Pietinen P, Pyy M, Palmgren J, Uusitupa M. Body-Size Indicators and Risk of Breast Cancer According to Menopause and Oestrogen-Receptor Status. Int J Cancer. 1996;68:8-13.
15. Lahmann PH, Hoffman K, Allen N, van Gils CH, Khaw KT. Body Size and Breast Cancer Risk: Findings from the European Prospective Investigation into Cancer and Nutrition (EPIC). Int J Cancer. 2004;111:762-71.
16. Lupattelli G, Mannarino E, Ronti T. The Endocrine Function of Adipose Tissue: An Update. Clin Endocrinol (Oxf). 2006;64:355-65.
17. Clark GM, McGuire WL, Osborne CK. Correlations between Oestrogen Receptor, Progesterone Receptor and Patient Characteristics in Human Breast Cancer. JCO. 1984;2:1102-09.
18. Anderson WF, Brawley OW, Chatterjee N, Ershler WB. Oestrogen Receptor Breast Cancer Phenotypes in the Surveillance, Epidemiology and End Results Database. Breast Cancer Res Treat. 2002;76:27-36.
19. Cox EB, Leight GS, McCarty Sr KS, McCarty Jr KS, Silva JS, Wells SA. Relationship of Age and Menopausal Status to Oestrogen Receptor Content in Primary Carcinoma of the Breast. Ann Surg. 1983;197:123-7.