Title

Incidence and risk factors for lower limb lymphedema associated with endometrial cancer: Results from a prospective, longitudinal cohort study.

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1 **ABSTRACT**

2 **Background**

3 Evidence on the incidence and risk factors for lower limb lymphedema (LLL) associated with endometrial
4 cancer is limited. Our objective was to use data from a prospective, longitudinal gynaecological cancer
5 cohort study to determine LLL incidence up to 24 months post-diagnosis of endometrial cancer and to
6 explore the relationship between personal and treatment-related factors and risk of developing LLL.

7
8 **Methods**

9 Women recently diagnosed with endometrial cancer (n=235) were evaluated at regular intervals post-
10 diagnosis (up to 3-monthly) using bioimpedance spectroscopy (BIS) and self-reported leg swelling (SRLS).

11
12 **Results**

13 Incidence of LLL at 24 months post-diagnosis was 33% and 45% according to BIS and SRLS, respectively.
14 When analyses were restricted to obese women, incidence at 24 months post-diagnosis increased to 67%
15 (BIS) and 54% (SRLS). Following adjusted analyses, higher body mass index was associated with higher odds
16 of baseline lymphedema (BIS: OR 1.91, 95% CI 1.47-2.49, p<0.01; SRLS: OR 1.06, 95% CI 1.00-1.12, p<0.01)
17 and LLL incidence by 24 months post-diagnosis (BIS: OR 1.29, 95% CI: 0.99-1.68, p=0.055; SRLS: OR 1.06,
18 95% CI 1.02-1.11, p=0.008). According to SRLS, presence of comorbidities was also associated with baseline
19 lymphedema (OR: 1.43, 95% CI: 1.15-1.78, p=0.001), and more extensive lymph node dissection (OR 1.06,
20 95% CI: 1.01-1.12, p=0.026) and receipt of chemotherapy (OR: 2.65, 95% CI: 1.12-6.29, p=0.027) were
21 identified as risk factors for lymphedema incidence.

22
23 **Conclusions**

24 These findings suggest that LLL following endometrial cancer is common, particularly in women with high
25 body mass index, or comorbidities, and those requiring more extensive lymph node dissection or
26 chemotherapy. Future studies should examine the potential of weight loss intervention as a strategy to
27 reduce LLL incidence.

28

INTRODUCTION

Endometrial cancer is the most common gynecological cancer in developed countries [1]. Its primary treatment comprises hysterectomy and bilateral salpingo-oophorectomy with or without pelvic and para-aortic lymphadenectomy. While endometrial cancer treatment is associated with relatively favourable survival outcomes (5-year relative survival following endometrial cancer is 81%; mean 5-year survival for all-cancers combined is 67% [2]), unfortunately it is also associated with morbidity, particularly the presence of lower limb lymphedema (LLL) [3].

LLL is characterised by abnormal swelling of the legs and/or lower trunk caused by the accumulation of extracellular fluid (ECF). Reported prevalence of LLL following endometrial cancer varies between 0% [4] and 50% [5], with differences in methods and timing of assessment, and study design (cross-sectional or retrospective cohort studies using practitioner observation or self-report of lymphedema), contributing to the inconsistent findings. Gynecological cancer patients with LLL report higher unmet needs, greater financial burden and lower quality of life than those who do not have LLL [6, 7].

Surgical lymphadenectomy is considered the most significant risk factor for developing lymphedema in other cancer cohorts [8, 9]. In women with endometrial cancer the data is less clear, however, there is some evidence to suggest lymphadenectomy may also increase risk [10, 11]. Investigation into other potential risk factors suggests receipt of radiotherapy [6, 12-17], chemotherapy [6], presence of comorbidities [18], the use of nonsteroidal anti-inflammatory drugs pre-diagnosis [6] and reduced physical activity levels [19] may increase risk of LLL, although findings are limited and lack consistency. Further, given the high prevalence of obesity in the endometrial cancer population [20], and the known relationship between obesity and lymphedema [21], it is unclear to what extent obesity may mediate the relationship between LLL development and other potential risk-factors in this specific patient group. To reduce disease-related burden it is essential to improve understanding of the prevalence and incidence of LLL associated with endometrial cancer and characteristics which increase one's risk.

Accurate identification of LLL and its risk factors are influenced by the measurement method and diagnostic criteria used [22]. To date, LLL measurement methods have included self-report assessment of symptoms [17, 23], circumferential measurement of leg size [15], and clinical diagnosis [11, 12, 18], with the latter method typically underestimating incidence [6]. Bioimpedance spectroscopy (BIS) is a method which evaluates ECF by measuring tissue resistance to the flow of electric current [24]. BIS has high specificity [25], high intra- and inter-rater reliability [26] and is a sensitive measure for early detection of upper-limb unilateral lymphedema [27]. Recent work by Steele and colleagues [28, 29] identified normative values for arm-to-leg ratios of ECF and identification of diagnostic criteria for uni- or bilateral LLL in conditions such as endometrial cancer [29]. These normative data studies have therefore enabled us to explore prevalence, cumulative burden and cumulative incidence of lymphedema, as determined by BIS and self-report, using data from a prospective, cohort study of women with endometrial cancer, and to explore whether these differed by body mass index. This study also aimed to identify treatment, disease or behavioural risk factors associated with LLL in this cohort.

MATERIALS AND METHODS

The Lymphedema Evaluation in Gynecological cancer Study (LEGS) was a prospective, longitudinal study examining lymphedema in 408 Australian women with gynecological cancer. Data contributed by women diagnosed with endometrial cancer have been examined in this report (n=235). Ethical approval was received from hospital Human Research Ethics Committees (approval numbers: 2008000211, 2007/168, 200842, 1189A/P, 08/16, 10/14, 10/10/RPAH/28).

Procedure

Detailed description of the study design and LEGS protocol have been published previously [30, 31]. In summary, women were eligible to participate in LEGS if they were 18 years or older, were diagnosed with gynecological cancer between June 2008 and February 2011 and received treatment at one of six participating hospitals in Queensland, Australia. Women were excluded if they were pregnant (contraindicated for BIS), could not provide informed consent, or were not likely to return to their treating hospital for outpatient follow-up. Baseline assessment was conducted prior to surgery and definitive cancer diagnosis for all eligible, consenting women and included participants completing a questionnaire describing their demographics, behavioural characteristics and comorbidities, and objective and self-reported assessment of lymphedema. Details of endometrial cancer diagnosis and treatment were extracted from each participant's medical record. Participants were prospectively followed and evaluated at subsequent hospital visits with review schedules differing between hospitals. To accommodate this variation, follow-up assessments were grouped into phases: 6 weeks to 3 months; 6 to 12 months; and, 15 to 24 months.

The primary outcome of this study was LLL, as assessed objectively using BIS (although those with a pacemaker, allergies against adhesive electrodes or extensive internal metal plates were ineligible for BIS assessment) and via self-reported leg swelling (SRLS). BIS measurements were taken for each limb using the ImpediMed SFB7 device according to the standard ImpediMed protocol (ImpediMed Ltd., Brisbane). The participant assumed a supine position with legs apart. For any given measure, two measurement electrodes were placed at either end of the arm or leg (i.e., wrist for arm measures and ankle for leg measures) with a current drive electrode placed at the base of the middle finger or toe, respectively, and another placed on the ipsilateral or contralateral foot or hand, respectively. Impedance of ECF (R_0) in each limb segment was then measured and the resistance (R_0) recorded. To determine those who did and who did not have lymphedema, R_0 values were then used in the following predictive equations [29]:

Dominant side of the body:

$$\text{predictor} = -18.41 + 5.58(\text{arm } R_0/\text{leg } R_0) - 0.45(\text{male}=1 | \text{female}=0) + 0.03(\text{age}) + 0.24(\text{BMI})$$
$$\text{probability} = \exp(\text{predictor}) / (1 + \exp(\text{predictor}))$$
$$\text{probability} > 0.045 = \text{lymphedema}$$

Non-dominant side of the body:

$$\text{predictor} = -18.59 + 6.11(\text{arm } R_0/\text{leg } R_0) - 0.44(\text{male}=1 | \text{female}=0) + 0.02(\text{age}) + 0.24(\text{BMI})$$
$$\text{probability} = \exp(\text{predictor}) / (1 + \exp(\text{predictor}))$$
$$\text{probability} > 0.042 = \text{lymphedema}$$

SRLS was assessed by asking participants to respond with "yes", "no" or "unsure" to whether they had experienced swelling in their right leg, left leg, or both legs in the past three months (or past 6 weeks for the first time this question was asked post-surgery). For each data collection period, if a participant responded yes to having swelling in either the right or left leg, they were classified as 'yes' to having SRLS at that time.

Additional information including histological type, stage of disease, type of surgery, number of lymph nodes removed, type of treatment, and baseline body mass index (BMI) was collected from medical records. Education level, income, employment status, marital status, children in care, presence of additional comorbidities and physical activity levels were collected via a participant-completed questionnaire at baseline.

Data analysis

Descriptive statistics were used to summarize participant characteristics. Lymphedema data using BIS and SRLS measurements respectively, established point prevalence, cumulative burden and cumulative incidence were estimated. Point prevalence was calculated by counting the number of women with any evidence of lymphedema at each phase of assessment, using all available data at that phase. Cumulative burden was calculated by counting the number of women who reported swelling up to and including each phase of assessment, irrespective of baseline symptoms, using all available data (that is, those with missing data contributed to the denominator). Cumulative incidence was calculated by counting the number of women with newly developed lymphedema after baseline divided by the number of women providing data at baseline and at least one other relevant time point (that is, cases excluded from numerator and denominator were those with lymphedema present at baseline, with missing data at baseline, or with baseline data but no follow up data).

Characteristics associated with prevalence of LLL at baseline and characteristics predictive of LLL incidence at 24 months were assessed using univariable and multivariable logistic regression analyses, respectively. Variables in final models included age, as well as those characteristics which retained statistical or clinically significant (ORs that are <0.6 or >1.5) associations in either the BIS or SRLS model. All analyses were performed using SPSS version 25.

RESULTS

BIS data and self-reported lymphedema data were available from 171 and 227 women, respectively. Characteristics of the women who provided BIS and self-reported data were similar in terms of demographic and medical characteristics (Table 1), with approximately 70% diagnosed with stage I disease, 50% receiving laparoscopic surgery with an average of seven nodes dissected and $>80\%$ overweight or obese. Women missing all follow up data (and hence excluded from analyses) had mostly similar characteristics to those who provided follow up data, except they tended to be older, have lower BMI and more frequently experienced a relapse of their cancer. Those missing SRLS follow up data also had a higher treatment-related burden than those providing follow up data (Supplementary Table 1).

Point prevalence (Table 2): according to BIS assessment, point prevalence of lymphedema in either leg at baseline (prior to definitive endometrial cancer diagnosis and treatment) was 71% and varied between 71-77% between baseline and 24-months post-diagnosis. Of those with evidence of LLL, 85-93% had evidence of bilateral lymphedema according to BIS. When prevalence was examined according to BMI status, 0%, 50% and 97% of those at normal weight, overweight and obese had lymphedema at baseline, respectively. Point prevalence of SRLS ranged between 15% (baseline) and 38% (at 24-months post-diagnosis). Point prevalence of SRLS between baseline and 24-months post-diagnosis was consistently higher for women with $\text{BMI} \geq 30 \text{ kg/m}^2$ (20.5-46.7%) compared with women with $\text{BMI} < 30 \text{ kg/m}^2$ (3.1-36.7%).

Cumulative burden (Table 2): by 24-months post-diagnosis, according to BIS, 80% of women had evidence of LLL. When stratified by BMI categories, 18%, 76% and 100% of normal weight, overweight and obese women had evidence of LLL by 24-months post-diagnosis, respectively. Cumulative burden of SRLS at 24-months post-diagnosis was also high (52%). However, the relationship between BMI and cumulative burden of SRLS at 24-months post-diagnosis was less clear, although burden was still highest in the obese group (61%).

Cumulative incidence (Table 2): of the women with no evidence of LLL at baseline according to BIS, 33% subsequently developed LLL by 24-months post-diagnosis (was 15%, 56% and 67% for those in the normal weight, overweight and obese category, respectively). According to SRLS, incidence by 24-months post-diagnosis was 45% (with no trends for increasing incidence with increasing BMI category).

Characteristics associated with lymphedema: findings from unadjusted analyses of baseline lymphedema and lymphedema incidence by 24 months post-diagnosis (according to BIS and SRLS) and associated personal, diagnosis, treatment and behavioural characteristics are presented in Supplementary Table 2. According to statistical significance or clinically important ORs unadjusted analyses suggest that there may be a relationship between employment, children in care, stage of disease, number of comorbidities, BMI and physical activity levels and baseline lymphedema. Age, income, children in care, number of comorbidities, physical activity levels, chemotherapy, number of lymph nodes dissected and BMI were also identified as potential risk factors for lymphedema incidence according to unadjusted analyses. Table 3 presents those characteristics that were included in the final models and demonstrate that higher body mass index (for BIS and SRLS) was associated with higher odds of baseline lymphedema and risk of LLL at 24-months post-diagnosis. Higher number of comorbidities was also associated with baseline SRLW. Odds of having baseline LLL were reduced in those who participated in sufficient levels of weekly physical activity; although while the association was clinically relevant, results were not supported statistically. In addition to BMI, more extensive lymph node dissection and receipt of chemotherapy were also identified as risk factors for LLL at 24-months post-diagnosis according to SRLS. These same factors were also potential risk factors for LLL incidence according to BIS, but this model had more limited power and findings were not supported statistically.

DISCUSSION

This longitudinal study shows that, according to BIS, 70% of women had abnormal increases in extracellular fluid in one or both lower limbs already before receiving any treatment for endometrial cancer, while LLL point prevalence between six weeks and 24-month post-diagnosis was 73-77%. When BMI was taken into account, point prevalence between baseline to 24 months post-diagnosis ranged between 4-14%, 50-60% and 95-96% for those in the healthy weight, overweight and obese categories, respectively. While LLL burden was lower according to SRLS compared with BIS, point prevalence of SRLS ranged between 24-38% from baseline to 24 months post-diagnosis. At any point in time, higher proportions of obese women self-reported leg swelling (21-47%) compared with those in the healthy weight or overweight category (3-37% and 5-21%, respectively). By 24 months post-diagnosis, 81% and 52% of women had experienced LLL as assessed via BIS or SRLS, respectively. Furthermore, post-treatment, 33% and 45% of women developed LLL according to BIS and SRLS, respectively. These prevalence, burden and incidence data highlight that LLL is very common for women receiving treatment for endometrial cancer.

Our findings show that new cases continued to present through to final assessment at 24 months post-diagnosis. Specifically, overall and when assessed using BIS and SRLS, incidence increased from 22-33% and 18-45%, respectively, between six weeks through to 24 months post-diagnosis. This observation differs from those in the unilateral breast cancer setting, where incidence tends to plateau around 12-18 months post-diagnosis [32, 33]. As such, these incidence findings, together with the high prevalence data, underscore the potential value that could be gained through providing awareness education and prospective surveillance of lower limb lymphedema for all women with endometrial cancer at least up until 24 months post-diagnosis. Further, the potential gains from implementing evidence-based risk reduction and management strategies, such as BMI reduction, are high.

Identifying lymphedema prevention and management strategies requires an understanding of potential risk factors. Lymphedema is most commonly regarded as a consequence of treatment for cancer [9]. However, in our analyses, many women already had signs of extracellular fluid accumulation in the legs *before* starting treatment (70%), with approximately 50% and nearly 100% of those overweight and obese, respectively, showing evidence of abnormal increases in one or both legs. While our self-reported lymphedema findings were lower (14% reported SRLS at baseline), to our knowledge these baseline rates are higher than any previously reported.

In addition to higher BMI, more extensive lymph dissection and receipt of chemotherapy were also identified as risk factors for the development of LLL. Specifically, with every one additional lymph node dissected, LLL risk increased by 6%, and those who received chemotherapy had 1.7-2.7 increased odds of developing LLL. Lymph node dissection has long been considered a primary risk factor for the development of secondary lymphedema. Further, a systematic review and meta-analysis exploring risk factors for unilateral arm lymphedema associated with breast cancer, found receipt of adjuvant therapy, including radiotherapy or chemotherapy, as risk factors with 'moderate level of evidence', defined as having consistent findings in at least 75% of studies, including at least one high quality study [9]. Although more limited by the quantity and quality of original research, a review which specifically focused on exploring incidence and risk factors of LLL following gynecologic cancer also found extent of lymphadenectomy and receipt of chemotherapy or radiation therapy as risk factors. The mechanisms by which chemotherapy may increase risk of lymphedema are currently unknown. Nonetheless, given that chemotherapy is a systemic therapy, it seems plausible that it may increase lymph load either directly or indirectly (e.g., due to impact on both healthy and malignant cells) thereby increasing LLL risk. The odds of LLL according to either BIS or SRLS were 1.4 times higher for those receiving external brachytherapy. However, these ORs neither met our predefined clinically relevant threshold (<0.6 or ≥ 1.5) nor were supported statistically, and they remained unchanged in adjusted analyses. The strong relationship we observed between obesity and lymphedema, alongside the high rates of obesity ($>80\%$ with BMI >15) may have made it particularly difficult to detect other risk factors, such as radiation therapy. As such, future research that continues to explore relationships between treatment or personal characteristics and LLL will need to consider and account for obesity rates in sample size calculations and any subsequent statistical analyses, including assessment of potential confounding and/or effect modification by BMI.

The high prevalence of baseline extracellular fluid increases identified by BIS may reflect oedema from obesity itself [34, 35], and/or the presence of venous insufficiency or lymphatic dysfunction that may or may not be associated with endometrial cancer or another comorbidity. Excluding obesity, our sample experienced a mean of two other comorbidities, many of which have also been associated with increases in extracellular fluid, such as renal and cardiac conditions [36-38]. However, higher BMI was also identified as a risk factor for developing lymphedema post-endometrial cancer. As such, it is clear that women with endometrial cancer, in particular overweight and obese women with comorbidities, represent a group in high need of lymphedema risk reduction strategies and assistance with lymphedema management.

Alongside increased BMI, unadjusted and adjusted analyses suggested that insufficient levels of physical activity (that is, participating in less than 150 minutes of physical activity per week) may have been associated with higher odds of baseline lymphedema (according to both BIS and SRLS, although results were not supported statistically). There is consistent evidence in support of physical activity intervention for those with cancer, including improved management of chronic disease and comorbidities, fitness, function, and quality of life [39]. Higher rates of physical activity post-endometrial cancer have also been associated with reductions in all-cause mortality by 52% [40]. Further, physical activity has been linked with

lower risk of lymphedema and improved management [41, 42], and is crucial in the management and prevention of sarcopenia obesity [43]. Given the high rates of obesity (and likely sarcopenic obesity), comorbidities, and lymphedema identified in our sample of women with endometrial cancer, it seems plausible that physical activity intervention for all, alongside weight management for those who are overweight and obese, has significant potential for improving the lives of women diagnosed with endometrial cancer.

The differences and similarities observed between our BIS and SRLS results are noteworthy. BIS is used to detect higher than normal extracellular fluid in the lower limbs which may or may not be detectable by the patient. In contrast, SRLS reflects patient perceptions which may be influenced by changes in physical appearance or symptoms (such as tightness, redness, poor range of movement). A lower point prevalence and cumulative burden identified via SRLS compared with BIS may reflect the more sensitive nature of BIS previously identified [24]. It also seems plausible that given the presence of multiple comorbidities for the majority of our sample, sensitivity of identifying changes in symptoms that reflect lymphedema may be less in this cohort compared with other cancer cohorts (e.g., women with unilateral breast cancer). An exception to this pattern was noted for the group with normal/underweight BMI who had higher rates of SRS compared with BIS identification. Lymphedema may have a different subjective presentation in this group which has not been previously explored. Compared with BIS, when assessed by SRLS, point prevalence showed a more consistent trend towards an increase across timepoints, irrespective of BMI groups. This reflects a more commonly reported pattern and may reflect the dominance of self-report data in previous research rather than BIS assessed lymphedema. Of note though, the particularly high prevalence of lymphedema at baseline according to BIS leaves little room for increases over time according to this method of assessment.

In contrast to the differences in prevalence and cumulative burden findings, incidence by 24 months post-diagnosis was similar between the two methods, with 33-45% of new cases of lymphedema presenting. Incidence is higher than what has been observed in the upper-limb breast cancer setting (33-45% vs 20% [44]) but sits within the range found in previous gynecological studies [45]. Further, both methods demonstrated the clear relationship between lymphedema and obesity, including higher BMI as a risk factor for lymphedema post-endometrial cancer diagnosis. Additional strengths of this study include the prospective design and use of an objective and self-report method of assessing lymphedema. However, while the sample size is larger than any other previous prospective investigation assessing lymphedema using BIS in an endometrial cancer cohort, the high incidence of lymphedema at baseline meant that the sample contributing to risk factor analysis was small, limiting our power to detect contributing risk factors. Nonetheless, our sample of women with endometrial cancer were generally representative of the wider endometrial cancer population.

In summary, findings show that lymphedema is a prevalent and important issue for women with endometrial cancer, worthy of baseline assessment, prospective follow up and early intervention. When assessing lymphedema, researchers and clinicians should consider the need for comprehensive objective- and self-report assessment and should account for the role of BMI as a risk factor for lymphedema.

Conflict of interest

The authors do not have any conflict of interest to disclose.

1

2 **Authors Contribution**

3 Authors AO, MJ, DV, LW, HRH and SH led study design, implementation and data collection of the LEGS
4 study. AP led all components of this manuscript with oversight in all aspects from SH and particular
5 assistance from DV in data analysis and reporting. All authors contributed to the interpretation and
6 reporting of the results and approved the final version of the manuscript.

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Table 1: Participant demographic, clinical and treatment characteristics

Characteristics	Bioimpedance Spectroscopy (n=171)	Self-Report (n=227)
Age (years)		
Mean (SD)	60.16 (9.5)	62.08 (10.1)
Range	35-79	34-90
Age category, N (%)		
<60 years	86 (50.3)	98 (43.3)
≥60 years	85 (49.7)	129 (56.8)
Body mass index (kg/m ²), Mean (SD)		
Total sample	34.0 (9.3)	33.80 (8.9)
Category:		
<25 kg/m ²	28 (16.4)	37 (16.3)
25-29.99 kg/m ²	38 (22.2)	48 (21.2)
≥30 kg/m ²	105 (61.4)	142 (62.6)
Number of comorbidities (excluding obesity)		
Mean (SD)	2.45 (2.05)	2.30 (1.91)
Range	0-10	1-10
Histological type, N (%)		
Adenocarcinoma ^a	127 (74.3)	169 (74.4)
Stage, N (%)		
I	121 (70.8)	160 (70.5)
II	21 (12.3)	24 (10.6)
III	17 (9.9)	26 (11.5)
IV	8 (4.7)	13 (5.7)
Missing	4 (2.3)	4 (1.8)
Surgery, N (%)		
Laparoscopy	90 (52.6)	122 (53.7)
Laparotomy (midline incision)	64 (37.4)	82 (36.1)
Laparotomy (lower transverse incision)	15 (8.8)	18 (7.9)
Other/missing	2 (1.2)	5 (2.1)
Lymph node dissection, N (%)		
Yes	79 (46.2)	110 (48.5)
Pelvic	73 (42.7)	103 (45.4)
Aortic	13 (7.6)	21 (9.3)
Total lymph nodes dissected, mean (SD)	7.2 (7.6)	7.6 (8.0)
Chemotherapy, N (%)		
Yes	42 (24.6)	56 (24.7)
Radiotherapy: External beam, N (%)		
Yes	47 (27.5)	60 (26.4)
Radiotherapy: Intracavity brachytherapy, N (%)		
Yes	21 (12.3)	25 (11.0)
Relapse during study, N (%)		
Yes	23 (13.5)	33 (14.5)

^a Histological type for all other cases included squamous cell carcinoma, adenosquamous carcinoma, serous carcinoma and unspecified

Table 2: Point prevalence, cumulative burden and cumulative incidence of lymphedema

	Time of Assessment, N (%)			
	Baseline	6 wks–3 months	6–12 months	15–24 months
Point prevalence^a				
Bioimpedance spectroscopy				
Total sample (n=171)	108/153 (70.6)	70/96 (72.9)	101/132 (76.5)	104/141 (73.8)
BMI <25 (n=28)	1/27 (3.7)	1/13 (8.0)	3/22 (13.6)	2/22 (9.1)
BMI ≥25–<30 (n=38)	16/32 (50.0)	15/26 (57.7)	18/28 (64.3)	21/35 (60.0)
BMI ≥30 (n=105)	91/94 (96.8)	54/57 (94.7)	80/82 (97.6)	81/84 (96.4)
Self-report leg swelling				
Total sample (n=227)	29/200 (14.5)	46/209 (22.0)	69/203 (34.0)	74/194 (38.1)
BMI <25 (n=37)	1/32 (3.1)	5/32 (15.6)	11/33 (36.7)	10/30 (33.3)
BMI ≥25–<30 (n=48)	2/41 (4.9)	6/47 (12.8)	9/44 (20.5)	7/42 (16.7)
BMI ≥30 (n=142)	26/127 (20.5)	35/130 (26.9)	49/126 (38.9)	57/122 (46.7)
Cumulative burden^b				
Bioimpedance spectroscopy				
Total sample (n=171)		121/163 (74.2)	132/168 (78.6)	138/171 (80.7)
BMI <25 kg/m ² (n=28)		2/28 (7.1)	5/28 (17.9)	5/28 (17.9)
BMI ≥25–<30 kg/m ² (n=38)		22/35 (62.9)	26/37 (70.3)	29/38 (76.3)
BMI ≥30 kg/m ² (n=105)		97/100 (97.0)	101/103 (98.1)	104/105 (99.0)
Self-report				
Total sample (n=227)		60/219 (27.4)	96/227 (42.3)	117/227 (51.5)
BMI <25 kg/m ² (n=37)		5/34 (14.7)	13/37 (35.1)	17/37 (46.0)
BMI ≥25–<30 kg/m ² (n=48)		7/47 (14.9)	13/48 (27.1)	13/48 (27.1)
BMI ≥30 kg/m ² (n=142)		48/138 (34.8)	70/142 (49.3)	87/142 (61.3)
Cumulative incidence^c				
Bioimpedance spectroscopy (either leg)				
Total sample (n=171)		5/22 (22.7)	11/39 (28.2)	15/45 (33.3)
BMI <25 kg/m ² (n=28)		1/11 (9.1)	4/24 (16.7)	4/26 (15.4)
BMI ≥25–<30 kg/m ² (n=38)		4/10 (40.0)	6/13 (46.2)	9/16 (56.3)
BMI ≥30 kg/m ² (n=105)		0/1 (0.0)	1/2 (50.0)	2/3 (66.7)
Self-report (n=227)				
Total sample		129/162 (17.9)	58/166 (34.9)	77/171 (45.0)
BMI <25 kg/m ² (n=37)		4/29 (13.8)	11/29 (37.9)	14/31 (45.2)
BMI ≥25–<30 kg/m ² (n=48)		5/39 (12.8)	9/39 (23.1)	10/41 (24.4)
BMI ≥30 kg/m ² (n= 142)		20/94 (21.28)	38/98 (38.78)	53/99 (53.5)

^a Point prevalence = number of women with any evidence of lymphedema at that phase of assessment/ total cases with data at that phase of assessment; ^b Cumulative burden = number of women reporting swelling at or before the phase of assessment/ number of women providing data at one or more time points; ^c Cumulative incidence = number of women with newly developed lymphedema after baseline/ number of women providing data at baseline and at least one other relevant time point (cases excluded from numerator and denominator were those with lymphedema present at baseline, with missing data at baseline, or with baseline data but no follow up data).

Table 3: Characteristics associated with lymphedema at baseline and predictive of lymphedema incidence by 24 months post diagnosis, as determined by multivariable logistic regression analysis*

	Bioimpedance Spectroscopy			Self-reported leg swelling		
	n	OR (95%CI)	p value	n	OR (95%CI)	p value
Characteristics associated with lymphedema at baseline						
Age (years)	153	1.06 (0.99-1.44)	0.106	199	1.01 (0.96-1.07)	0.589
Number of comorbidities (excluding obesity)	153	0.99 (0.69-1.43)	0.956	199	1.43 (1.15-1.78)	0.001
Body mass index (kg/m ²)	153	1.91 (1.47-2.49)	0.001	199	1.06 (1.00-1.12)	0.041
Physical activity						
Sedentary or insufficiently active (REF)	68	1.00		91	1.00	
Sufficiently active	85	0.38 (0.10-1.40)	0.145	108	0.68 (0.28-1.63)	0.383
Characteristics predictive of lymphedema incidence at 24 months post-diagnosis ^b						
Age (years)	36	1.10 (0.99-1.23)	0.067	128	1.01 (0.97-1.06)	0.509
Body mass index (kg/m ²)	36	1.29 (0.99-1.68)	0.055	128	1.06 (1.02-1.11)	0.008
Number of lymph node dissected	36	1.06 (0.92-1.21)	0.434	128	1.06 (1.01-1.12)	0.026
Chemotherapy (yes)	12	1.72 (0.28-10.47)	0.558	33	2.65 (1.12-6.29)	0.027

OR=odds ratio; CI= confidence interval; REF= referent category. *Sample contributing to the lymphedema at baseline analysis and lymphedema incidence at 24 months post-diagnosis analysis were those who contributed to point prevalence calculations (table 2) and those who contributed to lower limb lymphedema incidence calculations (table 2), respectively, and for whom we had data for all variables included in the final model (those variables presented in table above).