



Impact of weight change and weight cycling on risk of different subtypes of endometrial cancer

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Abstract *Aim:* Obesity is an established risk factor for endometrial cancer. Associations tend to be stronger for the endometrioid subtype. The role of adult weight change and weight cycling is uncertain. Our study aimed to determine whether there is an association between different adult weight trajectories, weight cycling and risk of endometrial cancer overall, and by subtype.

Methods: We analysed data from the Australian National Endometrial Cancer study, a population-based case-control study that collected self-reported information on height, weight at three time points (age 20, maximum and 1 year prior to diagnosis [recent]), intentional weight loss/regain (weight cycling) from 1398 women with endometrial cancer and 1538 controls. Odds ratios (OR) and 95% confidence intervals (CI) were calculated using multivariable logistic regression analysis.

Results: Relative to women who maintained a stable weight during adulthood, greater weight gain after the age of 20 was associated with increased risk of endometrial cancer (OR for gain 40+kg all subtypes 5.3, 95% CI 3.9–7.3; endometrioid 6.5, 95% CI 4.7–9.0). The strongest associations were observed among women who were continually overweight from the age of 20 (all subtypes OR 3.6, 95% CI 2.6–5.0). Weight cycling was associated with increased risk,

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particularly among women who had ever been obese (OR 2.9 95% CI 1.8–4.7), with ~3-fold risks seen for both endometrioid and non-endometrioid tumour subtypes. Women who had intentionally lost weight and maintained that weight loss were not at increased risk.

Conclusion: These results suggest that higher adult weight gain, and perhaps weight cycling, independently increase the risk of endometrial cancer, however women who lost weight and kept that weight off were not at increased risk.

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1. Introduction

Endometrial cancer currently ranks as the most common gynaecological malignancy in the developed world, and in 2008, approximately 288,000 new endometrial cancers were diagnosed worldwide.¹ Incidence rates of this cancer have been increasing over the last few decades, particularly among postmenopausal women, and it has been hypothesised that one of the main contributing factors is increasing prevalence of obesity.² Obesity, a condition associated with the production of sex hormones in adipose tissue particularly after menopause, is now considered by the World Cancer Research Fund and the American Institute for Cancer Research to be a convincing cause of endometrial cancer.³ The rapidly increasing prevalence of obesity forewarns that endometrial cancer will become a more important public health problem in future years, with some predicting a rise in incidence of 50–100% in the next 20 years.^{4–6}

Obese women have an approximately 3-fold increased risk of developing endometrial cancer compared with non-obese women, and current estimates suggest up to 45% of endometrial cancers can be attributed to excess body fat.^{7,8} Although current weight and adult weight gain are associated with substantial increases in risk, relatively little is known about the effects of weight loss on endometrial cancer risk.^{9–11} It has been difficult to delineate the effect of weight loss on endometrial cancer risk because intentionally losing weight and keeping it off is relatively uncommon and, in addition, it is difficult to distinguish between intentional and non-intentional weight loss. It is also difficult to separate the effects of weight change from those of current weight.¹²

Weight cycling, repeated cycles of weight loss followed by regain, has been associated with the redistribution of body fat from peripheral to central locations and with replacement of lean body mass by fat mass.^{13,14} Weight cycling is also thought to promote excessive weight gain. This raises the possibility that weight cycling may be associated with even further increased risk of endometrial cancer, however to date a positive association has only been reported in one of the four previous studies that have investigated this issue.^{10,15–17}

Furthermore, most previous studies have considered endometrial cancer as a single entity, and it is thus currently unclear if obesity, adult weight change or weight

cycling affects risk of the major subtypes of endometrial cancer differentially. Endometrial cancers are broadly classified into two main groups^{18,19}; type I tumours (predominately low grade endometrioid cancers) are associated with endometrial hyperplasia and comprise 80–90% of all sporadic endometrial cancers, with the remaining 10–20% grouped as type II tumours. Type II tumours include uterine papillary serous and clear cell carcinomas. Very little is currently known about their aetiology, although limited data suggest they may not be as strongly related to oestrogenic stimuli, including obesity.^{20–22}

The aim of the current study was to examine the role of obesity, and in particular clarify the roles of adult weight change and weight cycling in the aetiology of endometrial cancer, overall and for the two main subtypes.

2. Materials and methods

2.1. Study participants

The Australian National Endometrial Cancer study (ANECS) was an Australia-wide, population-based, case-control study of endometrial cancer. The study methods have been described in detail elsewhere.²³ Briefly cases were women aged 18–79 years, with newly diagnosed, histologically confirmed, epithelial endometrial cancer diagnosed between July 2005 (May 2005 in Queensland) and December 2007. Of 2707 women identified, 394 women were excluded because they could not be contacted ($n = 66$), their physicians refused permission to contact them ($n = 108$), or because of language difficulties, mental incapacity, or they were too sick ($n = 220$). The remaining 2313 women were invited to participate and, of these, 1497 (65%) agreed to take part in the study. We excluded 39 women (not primary epithelial endometrial cancer; diagnosed outside the study period), leaving a final sample of 1458 eligible women, 1398 (96%) of whom completed an interview.

Cases were compared to control women without endometrial cancer, sampled in two groups, using identical methods. The first group of controls was recruited between 2005 and 2007 specifically for the ANECS study. The women were randomly selected from the Australian electoral role (enrolment to vote in Australia is compulsory) to match the state of residence and age

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