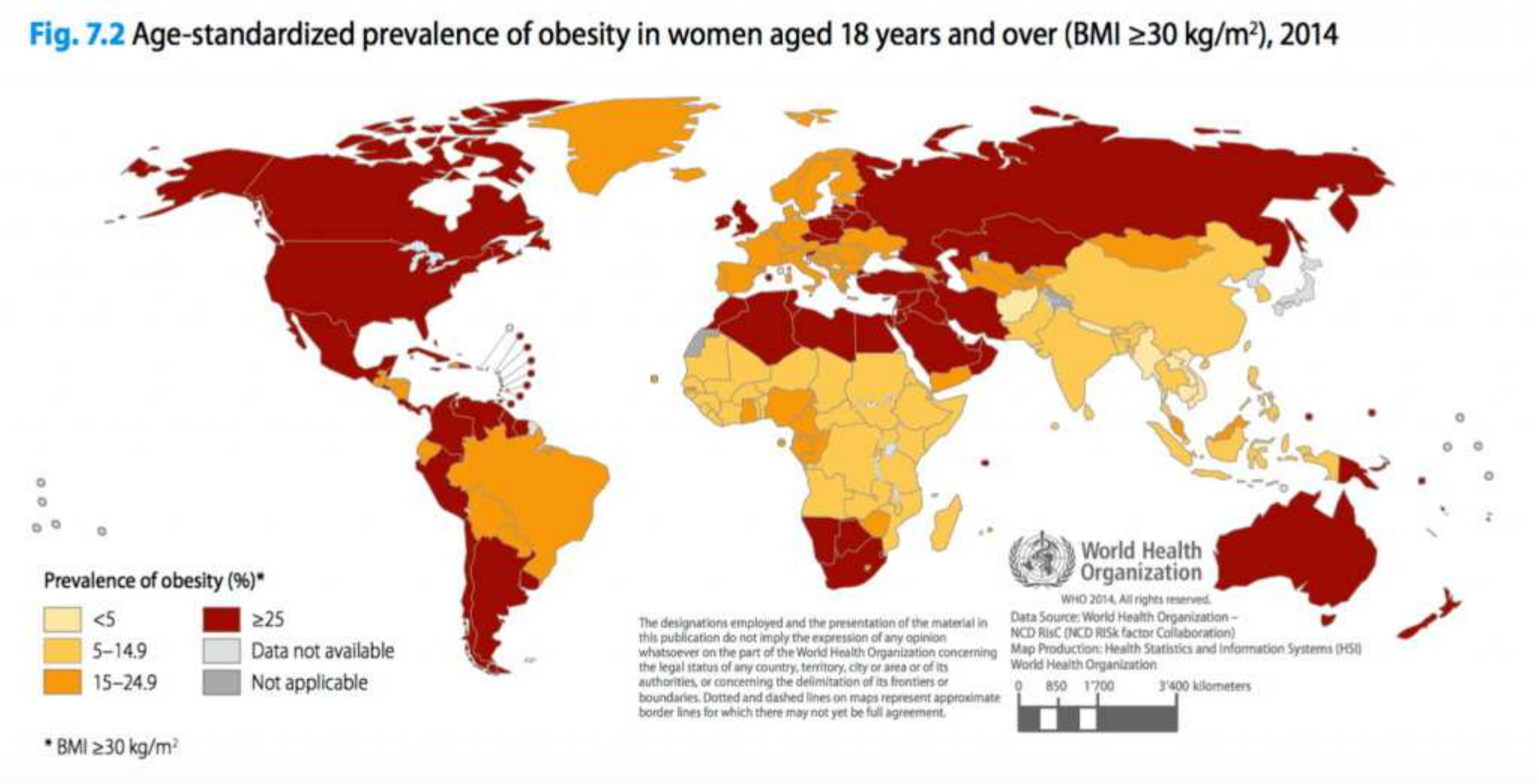
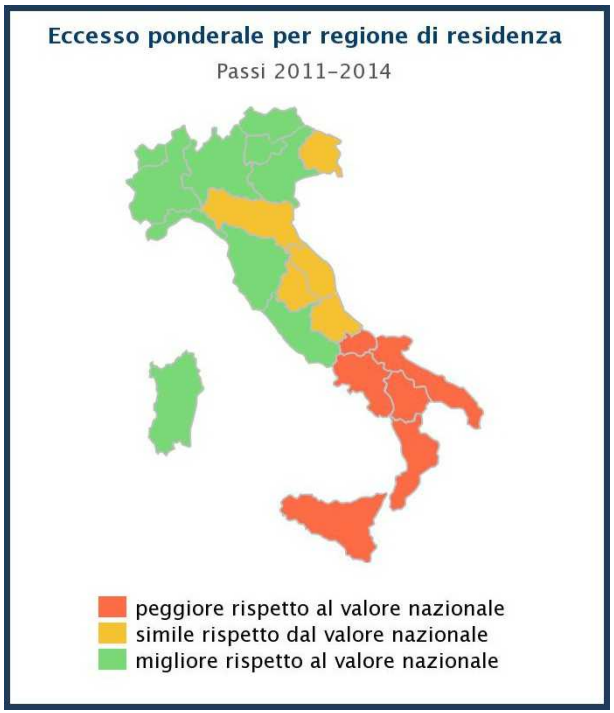
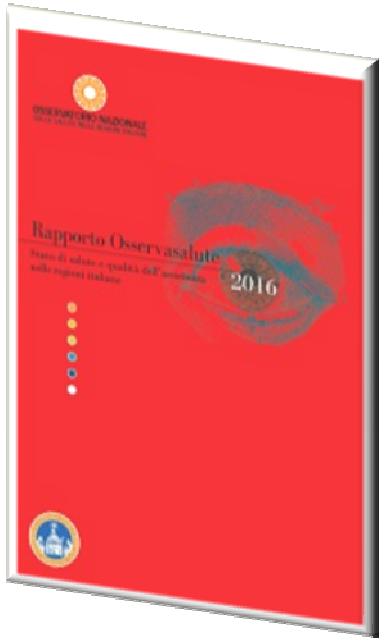
Obesità ed Endometrio

Obesità-Emergenza Mondiale



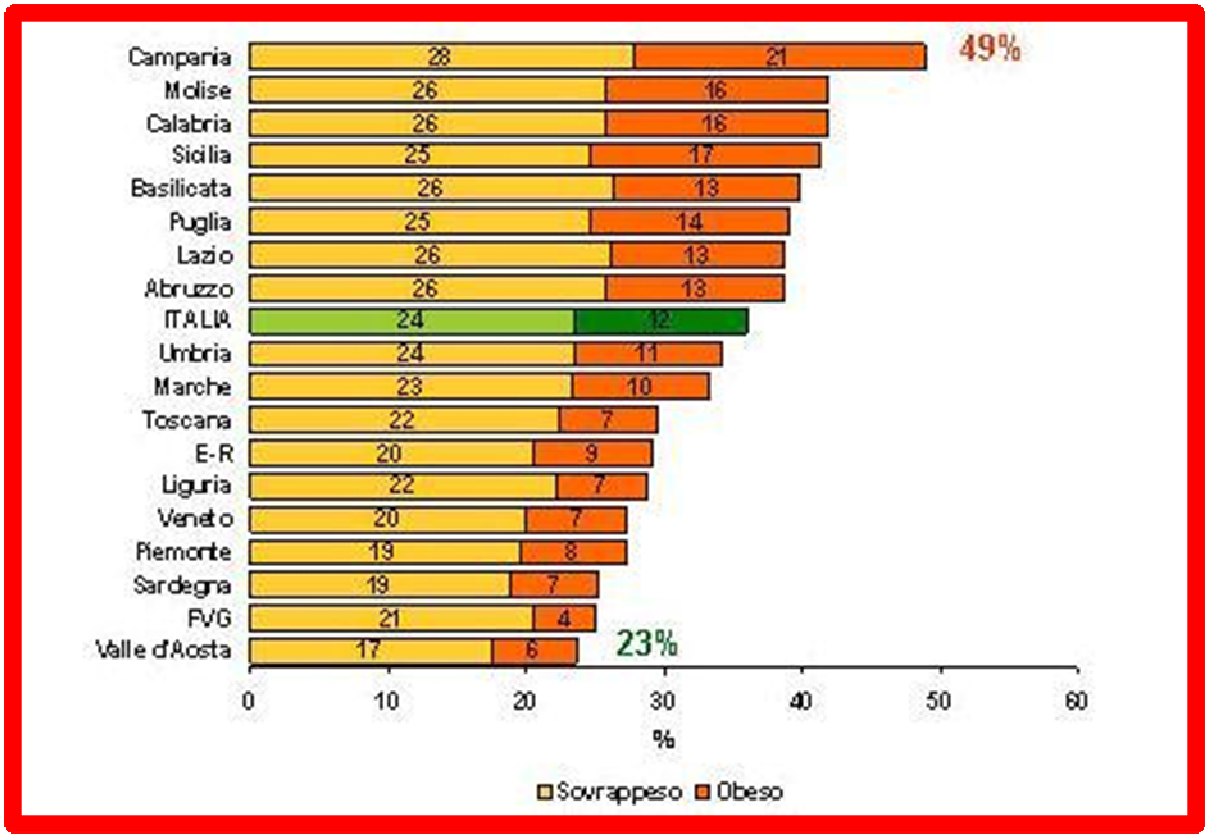
Obesità-Emergenza Nazionale





In Italia, più di un terzo della popolazione adulta (35,3%) è in sovrappeso, mentre una persona su dieci è obesa (9,8%); complessivamente, il 45,1% dei soggetti di età ≥18 anni è in eccesso ponderale

Obesità-Emergenza Campana



Le differenze sul territorio confermano un gap Nord-Sud in cui le Regioni meridionali presentano la prevalenza più alta di persone maggiorenni obese

Body-mass index and incidence of cancer: a systematic review and meta-analysis of prospective observational studies

Andrew G Renehan, Margaret Tyson, Matthias Egger, Richard F Heller, Marcel Zwahlen

Summary

Background Excess bodyweight, expressed as increased body-mass index (BMI), is associated with the risk of some common adult cancers. We did a systematic review and meta-analysis to assess the strength of associations between BMI and different sites of cancer and to investigate differences in these associations between sex and ethnic groups.

Methods We did electronic searches on Medline and Embase (1966 to November 2007), and searched reports to identify prospective studies of incident cases of 20 cancer types. We did random-effects meta-analyses and meta-regression of study-specific incremental estimates to determine the risk of cancer associated with a 5 kg/m² increment in BMI.

Findings We analysed 221 datasets (141 articles), including 282 137 incident cases. In men, a 5 kg/m² increase in BMI was strongly associated with oesophageal adenocarcinoma (RR 1·52, p<0·0001) and with thyroid (1·33, p=0·02), colon (1·24, p<0·0001), and renal (1·24, p<0·0001) cancers. In women, we recorded strong associations between a 5 kg/m² increase in BMI and endometrial (1·59, p<0·0001), gallbladder (1·59, p=0·04), oesophageal adenocarcinoma (1·51, p<0·0001), and renal (1·34, p<0·0001) cancers. We noted weaker positive associations (RR <1·20) between increased BMI and rectal cancer and malignant melanoma in men; postmenopausal breast, pancreatic, thyroid, and colon cancers in women; and leukaemia, multiple myeloma, and non-Hodgkin lymphoma in both sexes. Associations were stronger in men than in women for colon (p<0·0001) cancer. Associations were generally similar in studies from North America, Europe and Australia, and the Asia–Pacific region, but we recorded stronger associations in Asia–Pacific populations between increased BMI and premenopausal (p=0·009) and postmenopausal (p=0·06) breast cancers.

Interpretation Increased BMI is associated with increased risk of common and less common malignancies. For some cancer types, associations differ between sexes and populations of different ethnic origins. These epidemiological observations should inform the exploration of biological mechanisms that link obesity with cancer.

Introduction

Excess bodyweight, whether in people who are overweight (defined as a body-mass index [BMI] of 25 to 29·9 kg/m²) or obese (BMI of 30 kg/m² or greater), is increasingly recognised as an important risk factor for some common cancers.[1,2] Several meta-analyses[3–6] have assessed whether BMI is associated with cancer risk; most have investigated cancer at a particular site in the body. Some have examined the risk of cancer for incremental increases in BMI;[3,4,6,7,8,9,10] others, the risk for overweight and obese categories in comparison with normal weight.[3,5,6,7] Some meta-analyses incorporated results from case-control and cohort studies,[3–5,7,8,9,10] others combined both incident cases and cancer deaths;[3,4,6,7,8] and others included studies that used diagnoses of obesity at discharge from hospital.[3,5,6,7] Comparison of associations across studies, populations, and cancer sites is therefore difficult.

In 2007, the World Cancer Research Fund (WCRF)[1] used a more standardised approach to review the evidence. This report concluded that the evidence that body fatness is associated with increased risk of oesophageal adenocarcinoma, and with cancers of the pancreas, colorectum, postmenopausal breast, endometrium, and kidney is convincing, and that a probably association exists between body fatness and risk of gallbladder cancer.[1] However, several unanswered questions remain, including whether associations hold for less common malignancies, and whether associations differ between sexes and populations of different ethnic backgrounds. Several large cohort studies that were not included in previous reviews, including the Million Women study,[9] studies from different continents,[9,10] and studies of less common malignancies, have been published. We aimed to compare associations across cancer sites, and between sexes and populations to quantify the risk of different cancers associated with an incremental increase in BMI. We used uniform methods and definitions to do a systematic review and meta-analysis of prospective observational studies.

Methods

Search strategy and selection criteria

We systematically searched Medline and Embase (from their commencements to November 2007), with no language restrictions, for studies in humans of the association between bodyweight and cancer

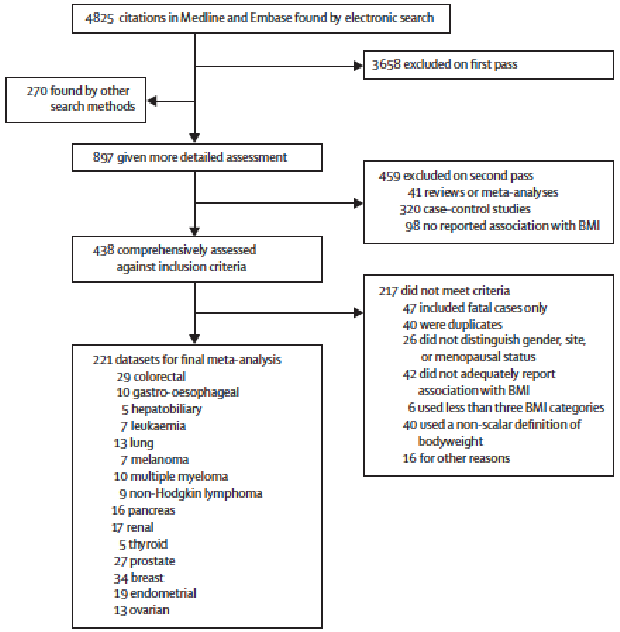


Figure 1: Flow diagram of search strategy and study selection

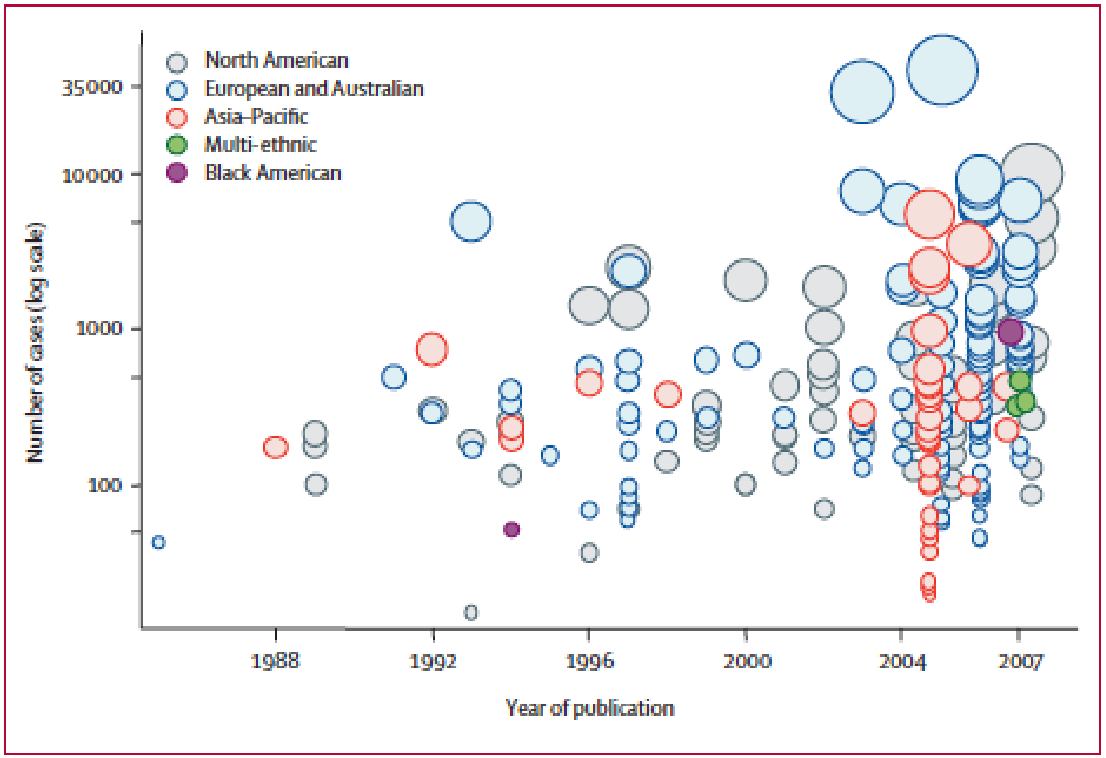


Figure 2: Datasets by year and population group
Size of circle is proportional to sample size.

INCREASED BMI WAS ASSOCIATED WITH SOME CANCERS, BUT NOT OTHERS:

The specifi city of these associations argues against confounding and bias, and for a possible causal link between increased BMI and the risk of developing some cancers. t

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Methods

Search strategy and selection criteria

We systematically searched Medline and Embase (from their commencements to November 2007), with no language restrictions, for studies in humans of the association between bodyweight and cancer incidence

MORE THAN ONE SYSTEM MIGHT AFF ECT THE RISK OF ENDOMETRIAL CANCER: increased oestradiol not only increases endometrial cell proliferation and inhibits apoptosis, but might also stimulate the local synthesis of IGF-I in endometrial tissue. Furthermore, chronic hyperinsulinaemia might promote tumorigenesis in oestrogen-sensitive tissues, since it reduces blood concentrations of sex-hormone-binding globulin, and in turn, increases bioavailable oestrogen

	Number of datasets*	Population group			Number of cases in men	Number of cases in women	Total sample size	Number that measured BMI directly	Median number of potential cancer-specific confounders in analysis	Geometric mean duration of follow-up (years)
		North America	Europe and Australia	Asia-Pacific						
Colorectal cancer†	29	11	12	6			4 833 139	16	2 (0 to 6)	11·0 (9·1–13·3)
Colon					22 440	20 975				
Rectum					14 894	9052				
Gastro-oesophageal cancers†	10	0	8	2			4 673 213	8	2 (1 to 3)	10·8 (7·4–16·0)
Gastric					817	325				
Oesophageal adenocarcinoma					1315	735				
Oesophageal squamous cell carcinoma					6201	1114				
Hepatobiliary cancers†	5	0	3	2			3 319 024	4	1 (1 to 1)	12·7 (7·0–23·1)
Gallbladder					928	1111				
Liver					2039	31				
Leukaemia	7	1	5	1	3371	5317	4 757 649	4	1 (1 to 3)	13·7 (7·7–24·5)
Lung cancer	13	1	8	4	7426	4273	2 649 345	10	3 (1 to 4)	11·9 (8·5–16·6)
Malignant melanoma	7	1	5	1	3492	4786	3 966 859	5	1 (1 to 1)	10·6 (7·1–15·7)
Multiple myeloma	10§	4	4	1	4273	3664	5 171 374	3	1 (1 to 2)	14·6 (10·7–20·0)
Non-Hodgkin lymphoma	9	2	6	1	7041	6248	5 043 747	3	1 (1 to 2)	12·4 (8·6–17·8)
Pancreatic cancer	16‡	4	8	3	2390	2053	3 338 001	6	3 (2 to 5)	9·4 (7·7–11·4)
Renal cancer	17‡	7	7	2	6073	4614	5 473 638	10	2 (1 to 5)	10·6 (8·5–13·3)
Thyroid cancer	5	0	4	1	1212	2375	3 303 073	5	1 (1 to 2)	14·4 (7·2–28·8)
Prostate cancer	27	12	10	5	70 421		3 029 338	14	2 (1 to 3)	10·6 (8·6–13·1)
Breast cancer	34§	12	16	5			2 559 829	15	5·5 (1 to 11)	8·4 (7·1–10·0)
Premenopausal						7930				
Postmenopausal						23 909				
Endometrial cancer	19‡	5	12	1		17 084	3 044 538	12	2 (1 to 6)	10·6 (8·2–13·8)
Ovarian cancer	13	4	7	2		12 208	2 703 734	5	3 (1 to 4)	12·2 (8·8–16·9)

Data are number, median (range), or geometric mean (95% CI). BMI=body-mass index. * Dataset refers to a site-specific cohort per paper. Several papers reported multiple sites. If a paper reported two separate cohorts (e.g. one each for men and women) for the same site, these were counted as two datasets. † These sites were grouped together in the literature search, since site-specific estimates were frequently reported in the same article. ‡ Totals do not equal sum of population groups since they include multiethnic populations: one each for pancreatic, renal, and endometrial cancers. § Totals do not equal sum of populations groups since they include Black American population: one each for multiple myeloma and breast cancer.

Table 1: Baseline characteristics for studies included in meta-analysis

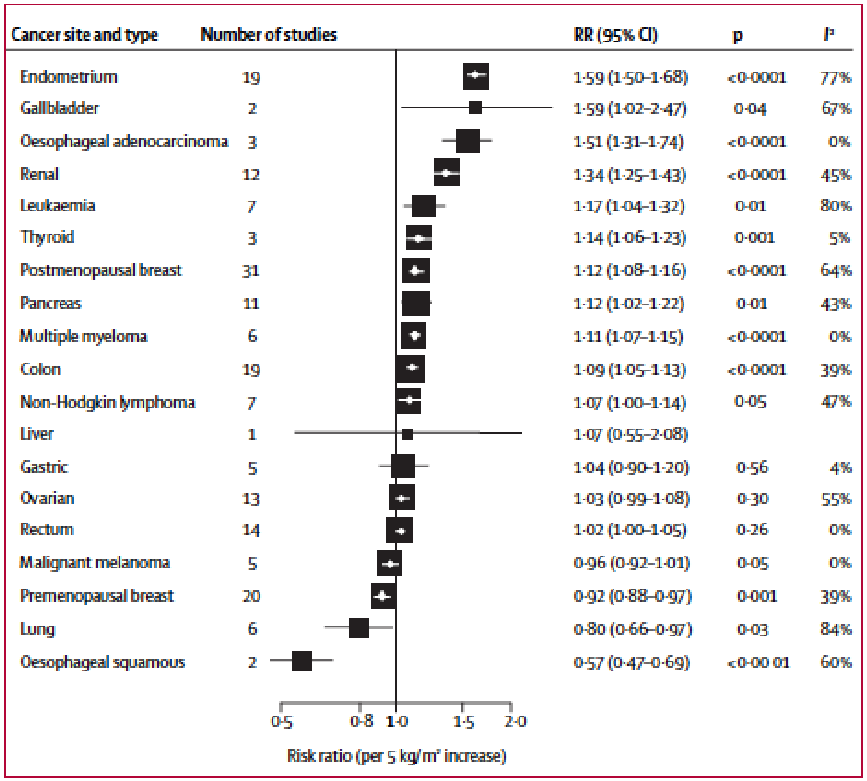

Figure 4: Summary risk estimates by cancer sites in women

Review

Obesity, Endogenous Hormones, and Endometrial Cancer Risk: A Synthetic Review[1]

Rudolf Kaaks,[2] Annekatrin Lukanova, and Mindy S. Kurzer

International Agency for Research on Cancer, 69372 Lyon, France [R. K., A. L.]; Department of Public Health and Clinical Medicine/Nutritional Research, Umeå University Hospital, Sweden [A. L.]; and Department of Food Science and Nutrition, College of Agricultural, Food and Environmental Sciences, College of Human Ecology, St. Paul, Minnesota 55108 [M. S. K.]

Abstract

Endometrial cancer is a disease of the affluent, developed world, where epidemiological studies have shown that ≥40% of its incidence can be attributed to excess body weight. An additional proportion may be because of lack of physical activity. Alterations in endogenous hormone metabolism may provide the main links between endometrial cancer risk, and excess body weight and physical inactivity. Epidemiological studies have shown increased endometrial cancer risks among pre- and postmenopausal women who have elevated plasma androstenedione and testosterone, and among postmenopausal women who have increased levels of estrone and estradiol. Furthermore, there is evidence that chronic hyperinsulinemia is a risk factor.

These relationships can all be interpreted in the light of the "unopposed estrogen" hypothesis, which proposes that endometrial cancer may develop as a result of the mitogenic effects of estrogens, when these are insufficiently counterbalanced by progesterone. In our overall synthesis, we conclude that development of ovarian hyperandrogenism may be a central mechanism relating nutritional lifestyle factors to endometrial cancer risk. In premenopausal women, ovarian hyperandrogenism likely increases risk by inducing chronic anovulation and progesterone deficiency. After the menopause, when progesterone synthesis has ceased altogether, excess weight may continue increasing risk through elevated plasma levels of androgen precursors, increasing estrogen levels through the aromatization of the androgens in adipose tissue. The ovarian androgen excess may be because of an interaction between obesity-related, chronic hyperinsulinemia with genetic factors predisposing to the development of ovarian hyperandrogenism.

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[1] The study was supported by Public Health Service Grants R01 CA81188-01 and R01 CA81200-01 from the National Cancer Institute, and Grant DAMD17-02-1-0422 (to M. K.).
[2] To whom requests for reprints should be addressed, at Hormones and Cancer Group, IARC, 150 cours Albert Thomas, 69372 Lyon, France. Phone: 33-4-72-73-8553; Fax: 33-4-72-73-8361; E-mail: kaaks@iarc.fr.

Introduction

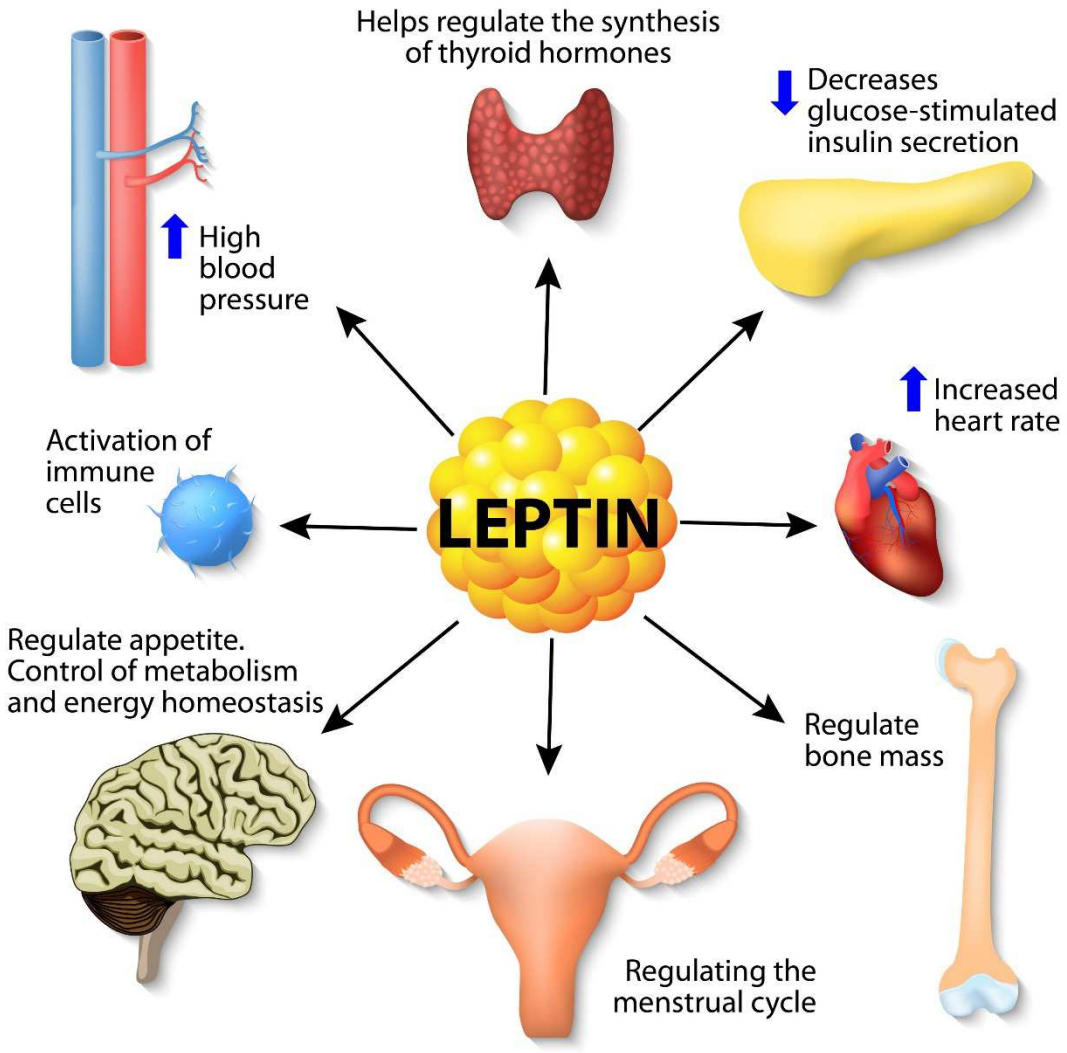
Incidence rates of endometrial cancer are up to 10 times higher in Western, industrialized countries than in Asia or rural Africa (1, 2), and changes in incidence rates over time (3), after industrial development (4), or migration from low-risk to high-risk areas (5–7), have shown that endometrial cancer has strong environmental, *i.e.*, nongenetic, risk factors, which are related to the westernization of lifestyle. These environmental risk factors most likely include low level of physical activity and obesity (4, 5, 8, 9). In different studies, obesity has been associated with a 2–3-fold increase in endometrial cancer risk in both pre- and postmenopausal women (10) and has been estimated to account for ~40% of endometrial cancer incidence in affluent societies (11). Whereas in many studies risk rose approximately linearly with increasing Body Mass Index (BMI),[4] a few studies showed a threshold effect, with an increase only among obese women with a BMI of ~30 kg/m^2 or higher (10). It is possible that this threshold effect might apply especially to endometrial cancer risk among young, premenopausal women (12, 13), and that the more linear increase applies to cancers occurring at a more advanced, postmenopausal age; however, data are insufficient to draw a definite conclusion. Besides excess body weight, epidemiological evidence suggests a possible protective effect of regular physical activity (10), but more studies are needed to confirm this and to estimate more precisely the magnitude of effect.

Although the mechanisms are not understood completely, endogenous hormones appear to play an important role in the development of endometrial cancer. Increased endometrial cancer risk has been associated with early menarche and late menopause, suggesting a relationship of risk with greater lifetime exposure to estrogens at premenopausal levels (3). Other hormone-related factors associated with risk are parity and use of exogenous estrogens for oral contraception or postmenopausal replacement therapy (5, 14–17). Furthermore, risk has been related to plasma concentrations of estrogens, progesterone, androgens, SHBG, and insulin (18–21). It is generally thought that excess weight influences endometrial cancer risk through changes in endogenous hormone metabolism (22, 23).

From a histological and molecular pathology perspective, at least two major types of endometrial tumors can be distinguished. Type I tumors are mostly endometrioid carcinomas, represent up to ~80% of endometrial cancers, and are generally associated with endometrial hyperplasia (15, 24). Type II tumors are more often serous papillary, clear cell, or squamous

[4] The abbreviations used are: BMI, body mass index; SHBG, sex hormone binding globulin; IGF, insulin-like growth factor; SOC, sequential oral contraceptives; COC, combined oral contraceptives; POC, progestogen only oral contraceptives; ERT, estrogen only replacement therapy; SEPRT, sequential estrogen-progestin replacement therapy; CEPRT, combined estrogen-progestin replacement therapy; PCOS, polycystic ovary syndrome; LH, luteinizing hormone; IGFBP, insulin-like growth factor binding protein; E_2, estradiol; E_1, estrone; Δ4-A, Δ4-androstenedione; T, testosterone.

Effetti dell'obesità sulle donne



LEPTIN IS A MAIN PRODUCT OF BODY FAT AND REGULATES THE GONADOTROPHIN SURGE, which initiates the development of pubertal stages

Menarca precoce

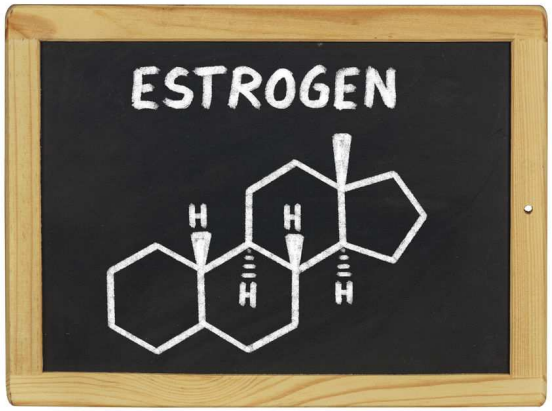
changes in body weight and composition are crucial in regulating pubertal development in women

the age of menarche generally occurs at a younger age in obese girls than in normal-weight girls

Menopausa

The relationship between obesity and reproductive disturbances, and most likely menstruation, appears to be stronger for early-onset Obesity

the onset of ovarian failure and increased production of follicle-stimulating hormone (FSH) at menopause occurs several years earlier in obese than in normal-weight Women



VS

Obesity is associated with ELEVATED LEVELS OF ESTROGEN THROUGH PERIPHERAL CONVERSION OF ANDROGENS TO ESTROGEN, in particular, androstenedione, in adipose tissue by aromatase

Vol. 11, 1531–1543, December 2002 Cancer Epidemiology, Biomarkers & Prevention 1531

Review

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A weighty problem: metabolic perturbations and the obesity-cancer link

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Stephen D. Hursting[*]

Abstract

Obesity is an established risk factor for several cancers, including breast, colon, endometrial, ovarian, gastric, pancreatic and liver, and is increasingly a public health concern. Obese cancer patients often have poorer prognoses, reduced response to standard treatments, and are more likely to develop metastatic disease than normo-weight individuals. Many of the pathologic features of obesity promote tumor growth, such as metabolic perturbations, hormonal and growth factor imbalances, and chronic inflammation. Although obesity exacerbates tumor development, the interconnected relationship between the two conditions presents opportunities for new treatment approaches, some of which may be more successful in obese cohorts. Here, we discuss the many ways in which excess adiposity can impact cancer development and progression and address potential preventive and therapeutic strategies to reduce the burden of obesity-related cancers.

Keywords

adipose tissue; cancer; inflammation; obesity; risk factors

Introduction

In the past three decades, the prevalence of obesity has dramatically increased, with nearly 40% of adults and 20% of children in the USA currently classified as obese, defined as a body mass index (BMI) of ≥30 kg/m^2 [1]. It is estimated that more than 600 million adults are obese and 2.1 billion are overweight worldwide [2]. Aside from biophysical problems such as overexertion of cardiovascular, skeletal, muscular, and respiratory systems, obesity poses as a major risk factor for a plethora of diseases and comorbidities [3], including type II diabetes, cardiovascular disease, hypertension, chronic inflammation, and, the focus of this review, cancer.

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Conflict of interest statement: The authors declare no conflict of interest.

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Obesity, Endogenous Hormones, and Endometrial Cancer Risk: A Synthetic Review[1]

Rudolf Kaaks,[2] Annekatrin Lukanova, and Mindy S. Kurzer

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Abstract

Endometrial cancer is a disease of the affluent, developed world, where epidemiological studies have shown that ≥40% of its incidence can be attributed to excess body weight. An additional proportion may be because of lack of physical activity. Alterations in endogenous hormone metabolism may provide the main links between endometrial cancer risk, and excess body weight and physical inactivity. Epidemiological studies have shown increased endometrial cancer risks among pre- and postmenopausal women who have elevated plasma androstenedione and testosterone, and among postmenopausal women who have increased levels of estrone and estradiol. Furthermore, there is evidence that chronic hyperinsulinemia is a risk factor. These relationships can all be interpreted in the light of the "unopposed estrogen" hypothesis, which proposes that endometrial cancer may develop as a result of the mitogenic effects of estrogens, when these are insufficiently counterbalanced by progesterone. In our overall synthesis, we conclude that development of ovarian hyperandrogenism may be a central mechanism relating nutritional lifestyle factors to endometrial cancer risk. In premenopausal women, ovarian hyperandrogenism likely increases risk by inducing chronic anovulation and progesterone deficiency. After the menopause, when progesterone synthesis has ceased altogether, excess weight may continue increasing risk through elevated plasma levels of androgen precursors, increasing estrogen levels through the aromatization of the androgens in adipose tissue. The ovarian androgen excess may be because of an interaction between obesity-related, chronic hyperinsulinemia with genetic factors predisposing to the development of ovarian hyperandrogenism.

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Introduction

Incidence rates of endometrial cancer are up to 10 times higher in Western, industrialized countries than in Asia or rural Africa (1, 2), and changes in incidence rates over time (3), after industrial development (4), or migration from low-risk to high-risk areas (5–7), have shown that endometrial cancer has strong environmental, *i.e.*, nongenetic, risk factors, which are related to the westernization of lifestyle. These environmental risk factors most likely include low level of physical activity and obesity (4, 5, 8, 9). In different studies, obesity has been associated with a 2–3-fold increase in endometrial cancer risk in both pre- and postmenopausal women (10) and has been estimated to account for ~40% of endometrial cancer incidence in affluent societies (11). Whereas in many studies risk rose approximately linearly with increasing Body Mass Index (BMI),[4] a few studies showed a threshold effect, with an increase only among obese women with a BMI of ~30 kg/m^2 or higher (10). It is possible that this threshold effect might apply especially to endometrial cancer risk among young, premenopausal women (12, 13), and that the more linear increase applies to cancers occurring at a more advanced, postmenopausal age; however, data are insufficient to draw a definite conclusion. Besides excess body weight, epidemiological evidence suggests a possible protective effect of regular physical activity (10), but more studies are needed to confirm this and to estimate more precisely the magnitude of effect.

Although the mechanisms are not understood completely, endogenous hormones appear to play an important role in the development of endometrial cancer. Increased endometrial cancer risk has been associated with early menarche and late menopause, suggesting a relationship of risk with greater lifetime exposure to estrogens at premenopausal levels (5). Other hormone-related factors associated with risk are parity and use of exogenous estrogens for oral contraception or postmenopausal replacement therapy (5, 14–17). Furthermore, risk has been related to plasma concentrations of estrogens, progesterone, androgens, SHBG, and insulin (18–21). It is generally thought that excess weight influences endometrial cancer risk through changes in endogenous hormone metabolism (22, 23).

From a histological and molecular pathology perspective, at least two major types of endometrial tumors can be distinguished. Type I tumors are mostly endometrioid carcinomas, represent up to ~80% of endometrial cancers, and are generally associated with endometrial hyperplasia (15, 24). Type II tumors are more often serous papillary, clear cell, or squamous

[4] The abbreviations used are: BMI, body mass index; SHBG, sex hormone binding globulin; IGF, insulin-like growth factor; SOC, sequential oral contraceptives; COC, combined oral contraceptives; POC, progestogen only oral contraceptives; ERT, estrogen only replacement therapy; SEPRT, sequential estrogen-progestin replacement therapy; CEPRT, combined estrogen-progestin replacement therapy; PCOS, polycystic ovary syndrome; LH, luteinizing hormone; IGFBP, insulin-like growth factor binding protein; E_2, estradiol; E_1, estrone; Δ4-A, Δ4-androstenedione; T, testosterone.

- Aumento Estrogeni
- Diminuzione SHBG
- Diminuzione LH
- Diminuzione Estradiolo
- Diminuzione Inibina B

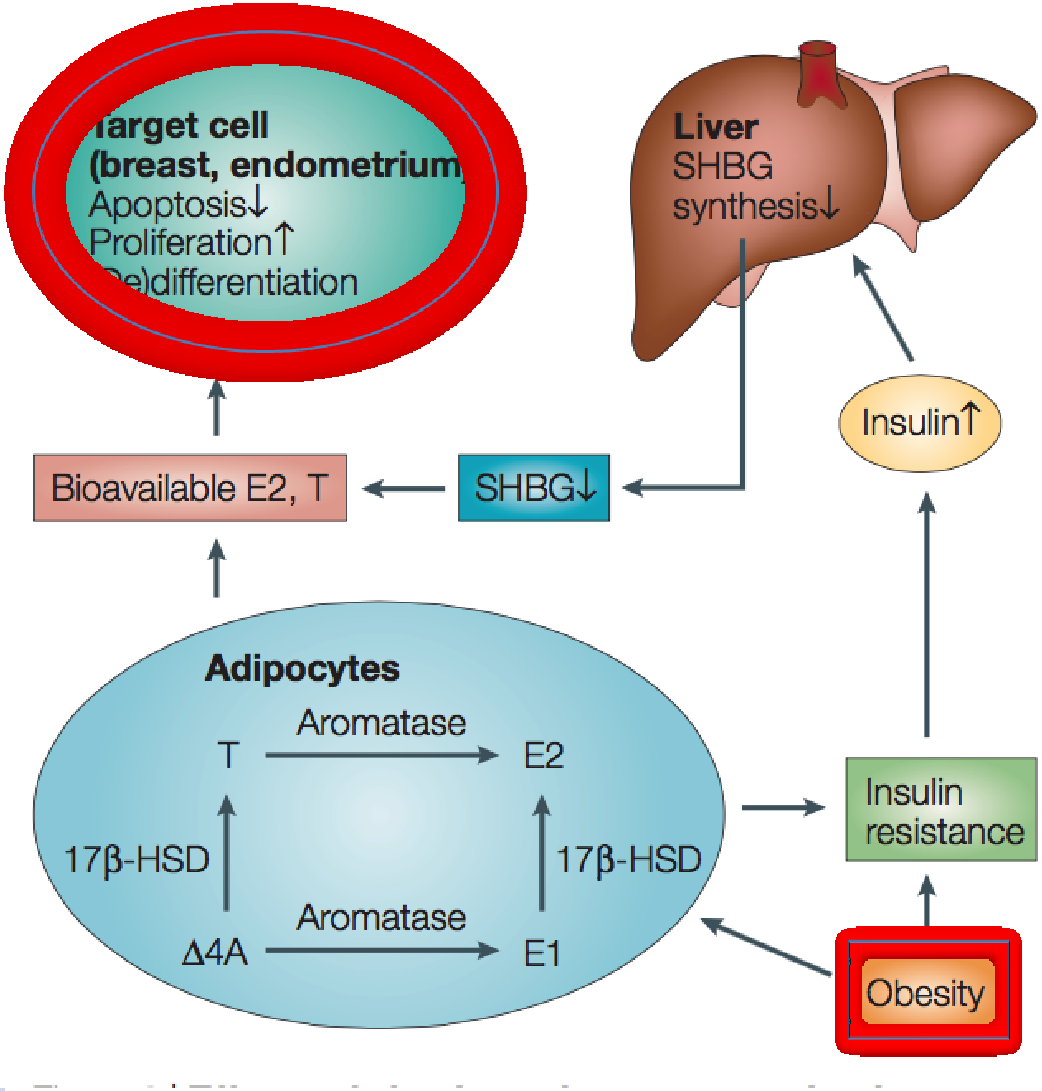

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Table 2 | **Associations of obesity with selected hormones and proteins**

Hormone or binding globulin	Obesity versus normal weight
Insulin	Increased levels with obesity
IGF1	Non-linear relation, with peak levels in people with BMIs of 24–27 kg/m^2
Free IGF1	Increased levels with obesity
IGFBP1	Decreased levels with obesity
IGFBP3	Increased levels with obesity or no observed effect
SHBG	Decreased levels with obesity
Total testosterone	Decreased levels with obesity (men); no observed effect (women); increased levels with obesity (premenopausal women with polycystic ovary syndrome)
Free testosterone	No observed effect or decreased levels with obesity (men); increased levels with obesity (women)
Total oestradiol	Increased levels with obesity (men and postmenopausal women); no observed effect (premenopausal women)
Free oestradiol	Increased levels with obesity (men and postmenopausal women); no observed effect (premenopausal women)
Progesterone	No observed effect or decreased levels with obesity in women with a susceptibility to develop ovarian hyperandrogenism (premenopausal women only)

BMI, body mass index; IGF1, insulin-like growth factor 1; IGFBP, IGF-binding protein; SHBP, sex-hormone-binding globulin.

IR and hyperinsulinemia hypothesis

DE GRUYTER Horm Mol Biol Clin Invest 2015; 21(1): 75–87

Valentina Vicennati*, Silvia Garelli, Eleonora Rinaldi, Sara Rosetti, Guido Zavatta, Uberto Pagotto and Renato Pasquali

Obesity-related proliferative diseases: the interaction between adipose tissue and estrogens in post-menopausal women

Abstract: Epidemiological studies have shown that overweight and cancer are closely related, even though obesity alone does not apparently heighten cancer risk by the same amount. Given the low overall risk of all cancers with obesity, it is unlikely that obesity alone causes cancer, but should instead be considered as a tumor promoter. There are three main hypotheses that could explain how obesity might contribute to cancer development and growth: the inflammatory cytokines from adipose tissue hypothesis, the insulin resistance and hyperinsulinemia hypothesis, and the unopposed estrogen cancer hypothesis. The link between obesity and cancer is that adipocytes constitute a major component of the tumor microenvironment for breast and abdominally metastasizing cancers, promoting tumor growth. This review will mainly focus attention on the relationship between adipose tissue, estrogens, and cancer risk.

Keywords: adipose tissue; estrogens; cancer.

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Introduction

It has been estimated that about 20% of all cancers are caused by excess weight [1], and the Million Women Study has shown that approximately half can be attributed to obesity in postmenopausal women [2]. There is a direct association between excess weight and cancer, even though obesity alone, apparently, does not heighten cancer risk in all tissues by the same amount [1–7].

A systematic review and meta-analysis of prospective observational studies [5] has demonstrated that the obesity and cancer association is sex specific and this remains mostly true for different geographic populations. However, cancer risk in obesity is different between ethnic groups [5]. Common cancers in obese people are predominantly endometrial, esophageal adenocarcinoma, colorectal, postmenopausal breast, prostate, and renal [6, 7]. Less common malignancies associated with obesity are malignant melanoma, thyroid cancers [8], leukemia, non-Hodgkin's lymphoma, and multiple myeloma [9].

There are many examples showing the relationship between obesity and carcinogenesis: weight accumulation with age is linked to an increase in postmenopausal breast cancer risk in women who do not follow a menopausal hormone therapy regimen [10]. In addition, cohort studies have shown that breast cancer risk was lowered by 50% in women who intentionally underwent weight loss higher than 10 kg after menopause [11].

In addition, the Swedish Obese Subjects (SOS) study, a large prospective study, which established that bariatric surgery achieves an average of 20 kg weight reduction in obese patients with a body mass index (BMI) higher than 40 kg/m². That matched the surgery group with untreated morbidly obese women, which reported a significant reduction in cancer incidence in association with substantial weight loss on a follow-up longer than 10 years [12].

Apart from BMI [13–18], different body fat distribution seems to be linked to cancer risk. The Framingham Heart Study has shown that visceral adiposity is associated with cancer after adjustment for clinical risk factors and generalized adiposity [19]. As for mortality, a longitudinal study in US women has shown that waist circumference and waist-to-hip ratio are strongly and positively associated with cancer mortality, independently of BMI [20].

Apart from these epidemiological studies, the other link between obesity and cancer is that adipocytes constitute a major component of the tumor microenvironment

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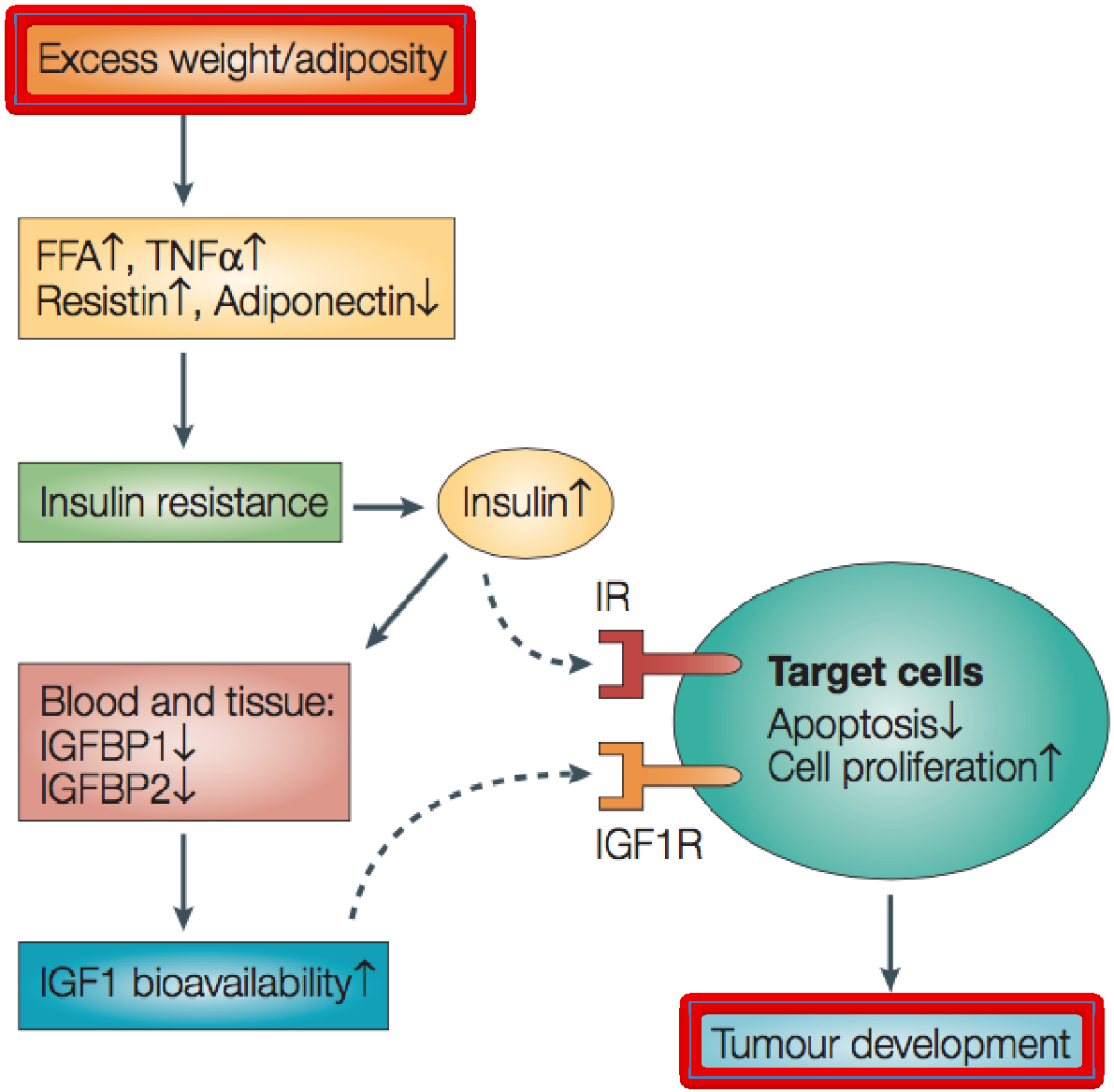

The unopposed estrogen cancer hypothesis

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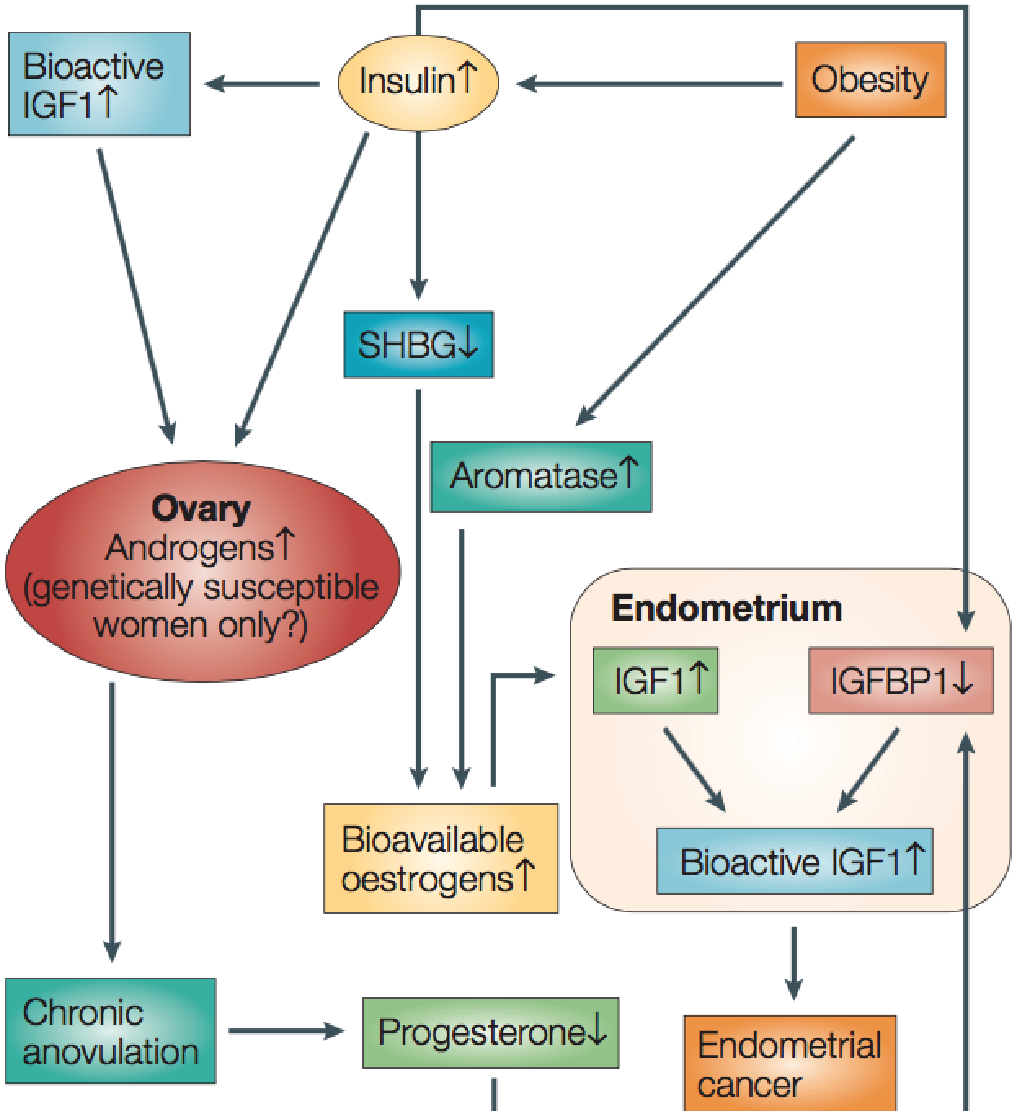
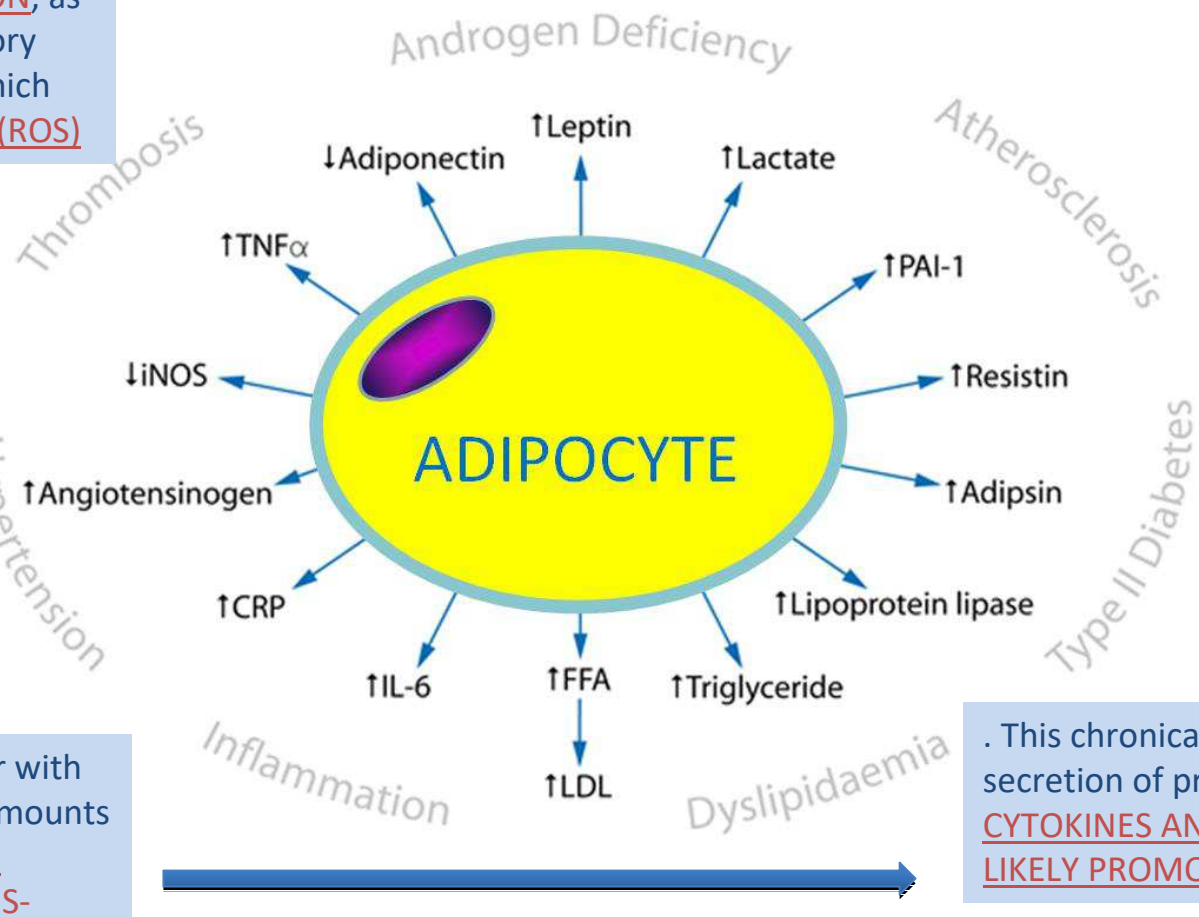


Inflammatory cytokines from adipose tissue hypothesis

Adipose tissue in obesity is in a state of LOW-GRADE CHRONIC INFLAMMATION, as shown by the presence of inflammatory cells (lymphocytes, macrophages), which generate REACTIVE OXYGEN SPECIES (ROS)

THESE ROS HAVE MITOGENIC PROPERTIES at low concentrations and they could be considered tumor promoter

The inflammatory cells, together with adipocytes, secrete significant amounts of ADIPOKINES AND CYTOKINES, IMPLICATED IN TUMOR PROGRES-SION



. This chronically increased systemic secretion of pro-inflammatory CYTOKINES AND ROS IN OBESITY LIKELY PROMOTES TUMORIGENESIS

Best Practice & Research Clinical Obstetrics and Gynaecology 29 (2015) 516–527

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7

Obesity and menstrual disorders

Mourad W. Seif, PhD FRCOG [a, b, *], Kathryn Diamond, MRCOG [a], Mahshid Nickkho-Amiry, MBChB PhD [a, b]

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[b] University of Manchester, Manchester, UK

THE PREVALENCE OF MENSTRUAL CYCLE IRREGULARITIES WAS 8.4% IN WOMEN WHO WERE 74% OVERWEIGHT, as opposed to 2.6% in women who were <20% overweight .

15% OVERWEIGHT WAS ASSOCIATED WITH A SIGNIFICANTLY HIGHER CHANCE OF HAVING A MENSTRUAL CYCLE LONGER THAN 43 DAYS .

the association between body fat distribution and menstrual cycle disturbances in 11,791 women was examined . In that study, the relative risk (RR) of oligomenorrhoea in woman with upper body fat predominance was 3.15 ($P < 0.001$) compared with women with lower body fat predominance

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EXCLUSION OF PREGNANCY is essential in women presenting with oligomenorrhoea or amenorrhoea

The plan of investigation will be structured aiming to explore the cause in a systematic approach, investigating THE HYPOTHALAMIC EPITUITARY E OVARIAN AXIS AND AIMING TO EXCLUDE PITUITARY ADENOMAS AND HYPERPROLACTINAEMIA AND PRIMARY OVARIAN FAILURE.

In addition, other causes of obesity with oligomenorrhoea/amenorrhoea should be considered and investigated such as ADRENAL AND THYROID DYSFUNCTION

who are of reproductive age, before a management plan is formulated and TREATMENT OPTIONS ARE CONSIDERED.

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Management of HMB in obese women

7

Obesity and menstrual disorders

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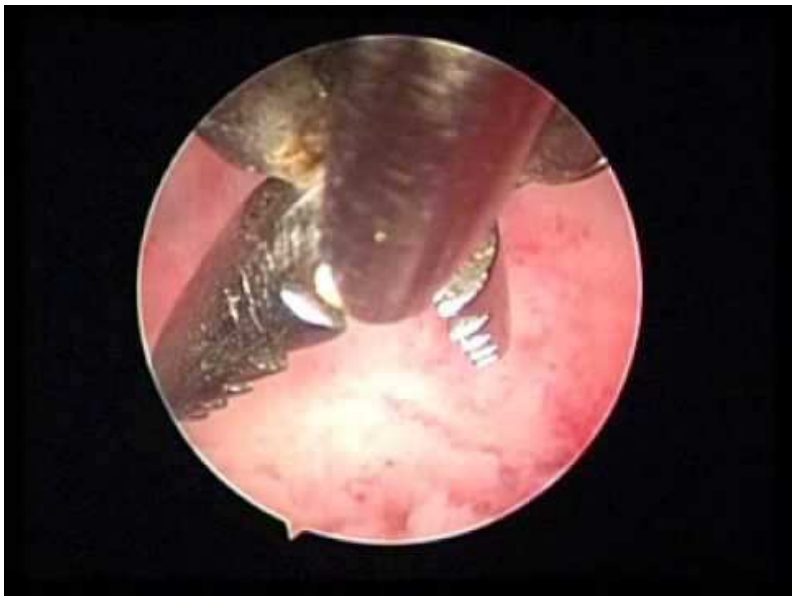
Table 1
Summary of the efficacy of different treatment modalities for heavy menstrual bleeding (HMB) in obese women.

Treatment	Effectiveness in obese women	Side effects/challenges
Combined oral contraceptive pill (COCP)	Effective regardless of weight with regard to cycle control and endometrial protection	Additional increased risk of venous thrombosis. Avoid in those with BMI >35 and multiple cardiovascular
Progestogen-releasing intrauterine device (LNG-IUS)	Longer time to achieve amenorrhoea in obese women. Associated with less patient satisfaction	May be technically difficult to insert
Progestogen-only pill (POP)	Same efficacy as in non-obese women.	Unpredictable bleeding patte
Depot-medroxyprogesterone acetate (DPMA) injection	Reduced efficacy if given subcutaneously	Possibility of further weight gain in already obese women
Progestogen-only implant	Theoretical need for early replacement	Unpredictable bleeding pattern
Endometrial ablation	Same efficacy as in non-obese women for first-generation techniques. No studies to date on second-generation techniques.	Associated risk of endometrial hyperplasia must be excluded prior to ablation. Unsuitable fo women planning for pregnancy
Hysterectomy	Same efficacy as in non-obese women. Laparoscopic approach should be the preferred option when appropriate.	Increased risk of surgical and anaesthetic complications particularly if associated with co-morbidities.



Clinical practice guidelines

on the management of abnormal uterine bleeding

In premenopausal women recommend endometrial biopsy to exclude EH and EC.

Iperplasia endometriale

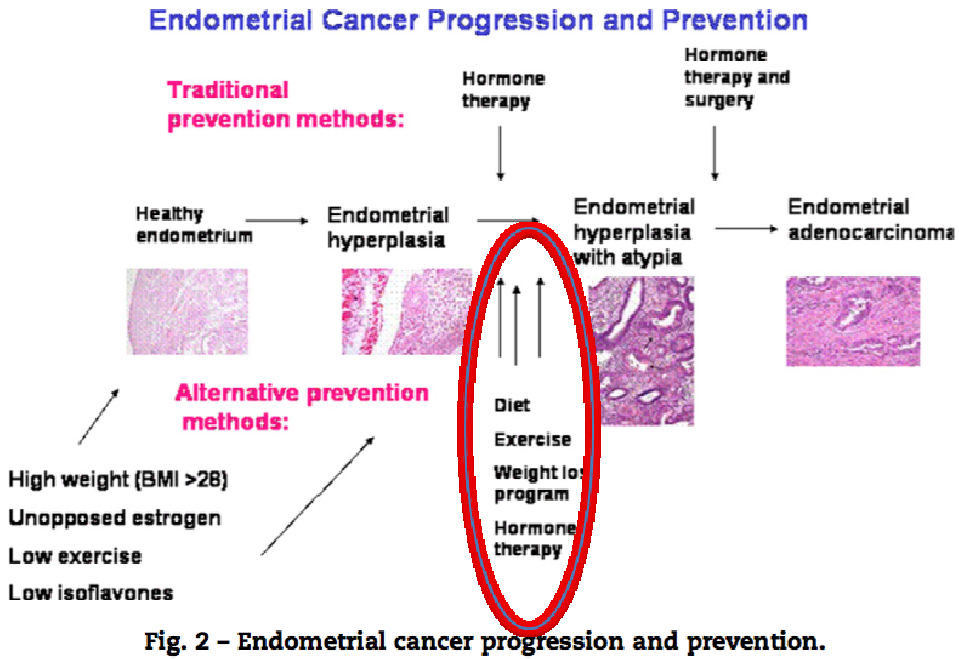


Fig. 2 – Endometrial cancer progression and prevention.

Endometrial hyperplasia, an overgrowth or thickening of the uterine lining, can be the first warning sign of the pathological process eventually leading to endometrial carcinoma

EUROPEAN JOURNAL OF CANCER 44 (2008) 1632–1644

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Review

Endometrial hyperplasia, endometrial cancer and prevention: Gaps in existing research of modifiable risk factors

Faina Linkov[a], Robert Edwards[b], Judith Balk[b], Zoya Yurkovetsky[a], Barbara Stadterman[a], Anna Lokshin[a], Emanuela Taioli[a,c,*]

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[b]Magee-Womens Hospital of UPMC Health System, 300 Halket Street, Pittsburgh, PA 15213, United States
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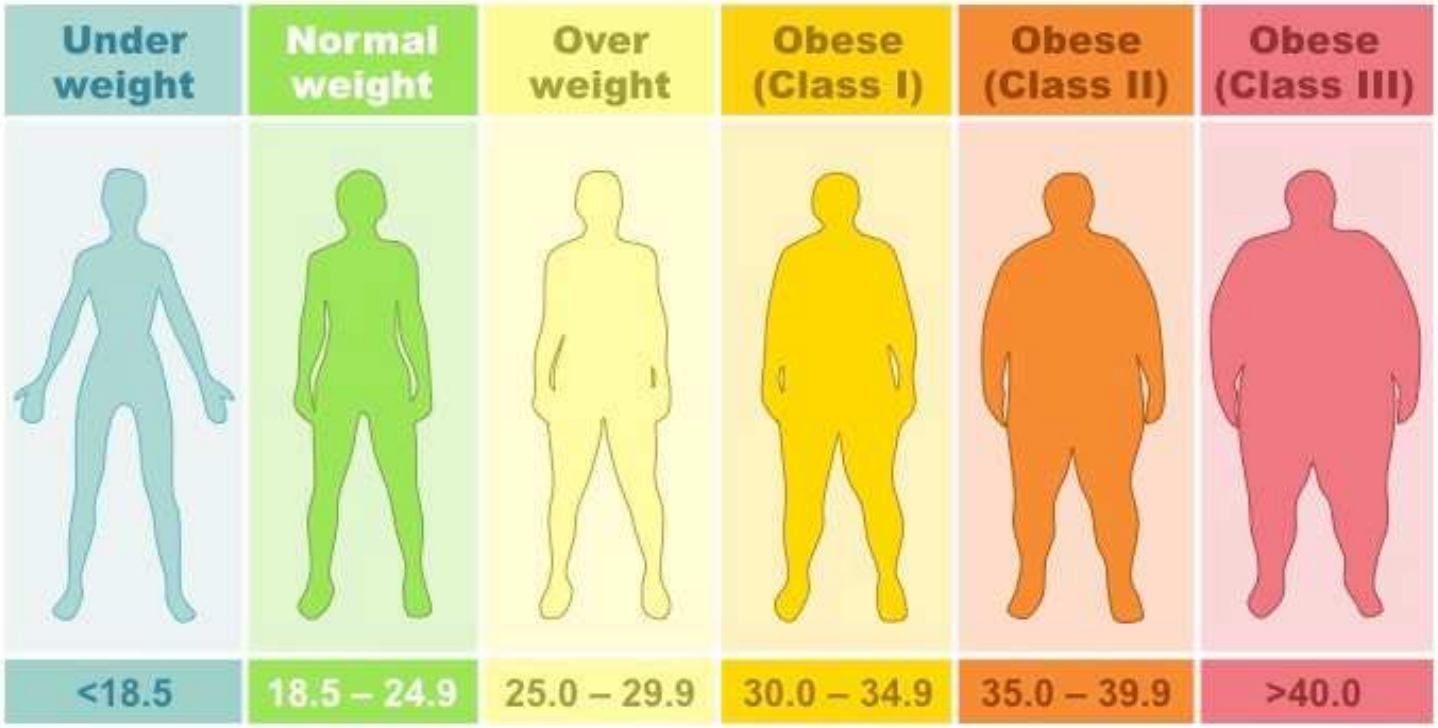
Table 1 – Summary of review studies on EC modifiable risk factors

Risk factor	Author (reference)	Number of studies evaluated, countries	Number of cases	Study type	Contrast	Relative risk (RR) or Odds Ratio (OR) (95% confidence interval (CI))	Findings
Physical activity	Voskuil[16]	Ten cohort studies, 24 case control studies from 11 countries	15,236	Review of cohort and case case control studies	Most active versus least active	OR (OR) 0.73 (0.62–0.86)	Inverse association endometrial cancer/ high level of physical activity
Consumption of animal food	Bandera[77]	Three cohort studies and 16 case control studies from 11 countries	12,901	Meta analysis of cohort and case control studies	Intake frequency: high versus low intake	Meat OR 1.26 (1.03–1.54) Red meat OR 1.51 (1.19–1.93)	Increased risk endometrial cancer with meat consumption
Consumption of fruits and vegetables	Bandera[21]	One cohort and 16 case control studies from 10 countries	10,158	Meta analysis of cohort and case control studies	Intake frequency: high versus low intake	Vegetables OR 0.71 (0.55–0.91) Cruciferous vegetables OR 0.85 (0.74–0.97) Fruits OR 0.97 (0.92–1.02)	Decreased risk of endometrial cancer with consumption of fruits and vegetables
Body mass index (BMI)	Renehan[58]	Nineteen cohort and case control studies from North America, Europe, Australia and Asia-Pacific	17,084	Meta analysis	Effects across BMI ranges	RR 1.59, $p < 0.0001$	Increased risk endometrial cancer with every 5 kg/m^2 increase
Obesity endogenous hormones	Kaaks[8]	Over 200 articles reviewed	N/A	Review article	Several types of hormones; Excess weight versus normal weight	N/A	unopposed oestrogen hypothesis, increased
Exogenous and endogenous hormones	khmedhanov[59]	One hundred and fifty articles; three cohort studies on oestrone levels examined in detail	Three hundred and thirty-two cases (in 3 cohort studies)	Review article	High hormone level versus low hormone level	OR up to 3.8 (1.7–8.4) for high oestrone level	Increased risk of endometrial cancer with increased circulating levels of oestrogenic hormones



- The inclusion of BMI as a risk factor in the updating of clinical guidelines related to the diagnosis and management of abnormal uterine bleeding in premenopausal women

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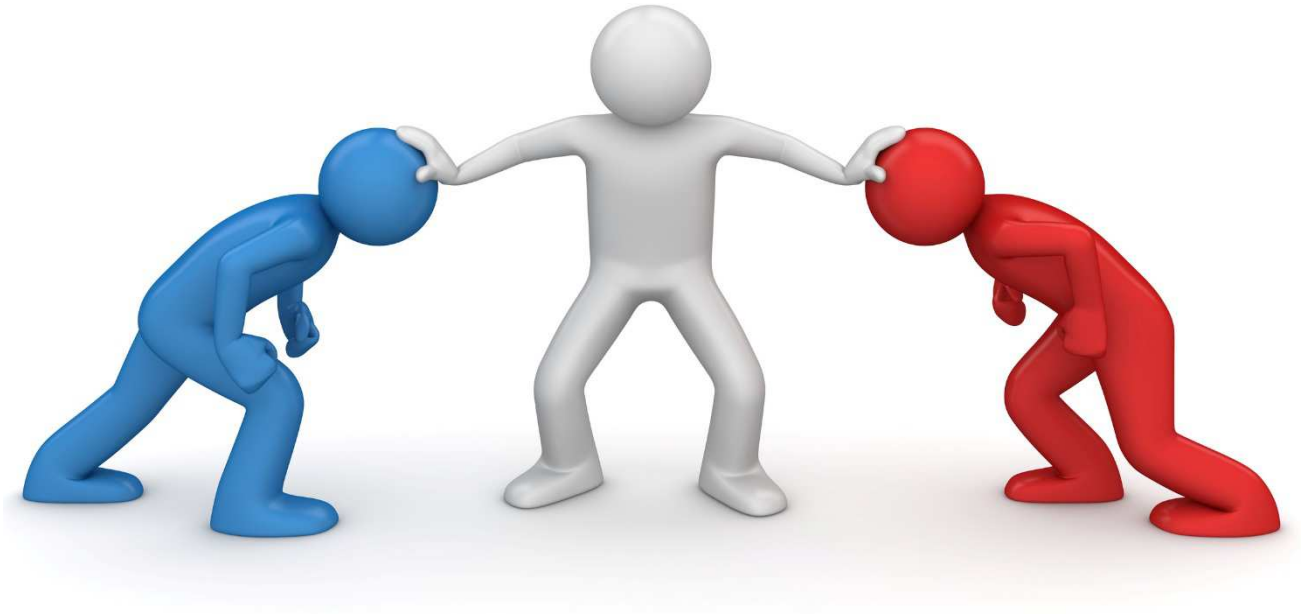
[c]*Department of Epidemiology, University of Pittsburgh Graduate School of Public Health, United States*

Table 2 – Overview of conventional therapies for endometrial hyperplasia and endometrial cancer

Condition	Commonly recommended therapies
Endometrial hyperplasia	Progesterone, medroxyprogesterone acetate, megestrol acetate, levonorgestrel, progestin-containing intrauterine device (IUD)
Endometrial hyperplasia with atypia	Hysterectomy High-dose continuous progestin therapy daily (medroxyprogesterone acetate, megestrol acetate) and repeat biopsies for women who want to retain fertility
Endometrial cancer	Total abdominal hysterectomy, bilateral salpingo-oophorectomy and evaluation for metastatic disease Radiation therapy (for patients whose cancers have progressed beyond stage IB (International Baccalaureate) grade 2)

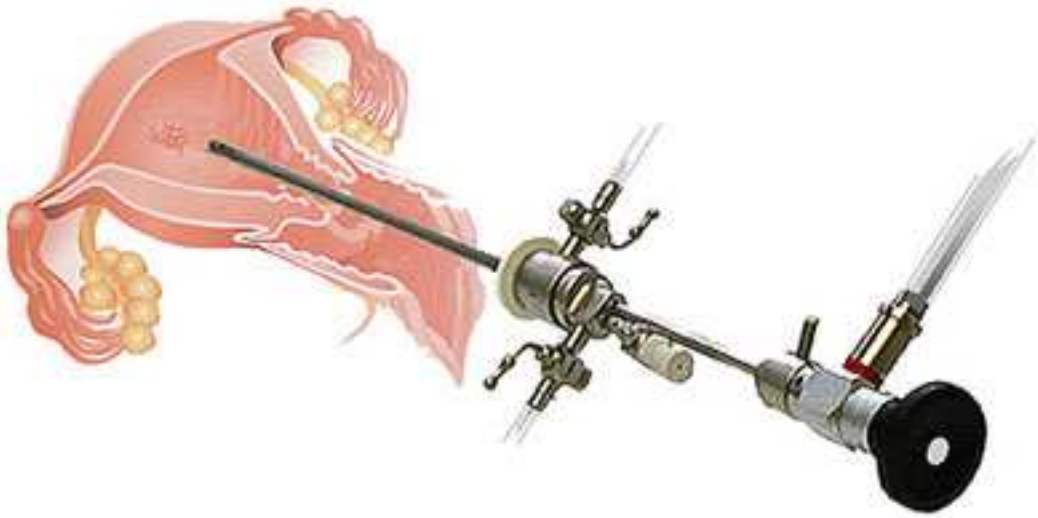
Diagnosi

US vs MRI



Diagnosi

Isteroscopia diagnostica con biopsia



Trattamento conservativo

Gynécologie Obstétrique Fertilité & Sénologie 45 (2017) 112–118

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Point de vue d'expert

Traitement conservateur des hyperplasies atypiques et cancers de l'endomètre et préservation de la fertilité

Fertility-sparing management of endometrial cancer and atypical hyperplasia

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Trattamento conservativo

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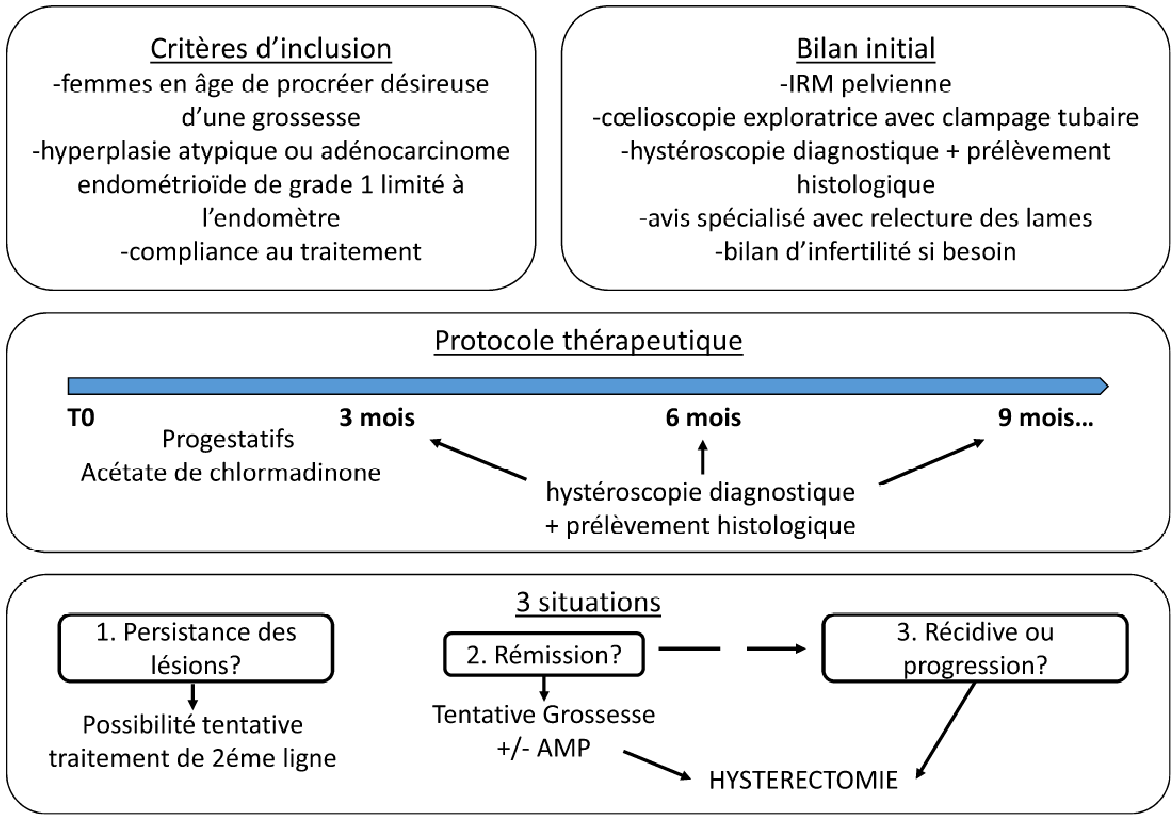

Fig. 1. Principes du traitement conservateur des hyperplasies atypiques et cancer de l'endomètre.

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CLINICAL ARTICLE

Oncologic and reproductive outcomes after fertility-sparing management with oral progestin for women with complex endometrial hyperplasia and endometrial cancer

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Progestotherapy

ABSTRACT

Objective: To investigate the oncologic and reproductive outcomes after progestin treatment of complex endometrial hyperplasia (CEH) and grade 1 endometrial carcinoma (EC). *Methods:* In a retrospective study, data were obtained for patients aged 20–42 years with CEH or grade 1 EC at presumed stage IA (without myometrial invasion) who wished to preserve fertility and were treated at the Peking Union Medical College Hospital, China, between January 1, 2000, and December 31, 2011. Patients had received oral medroxyprogesterone acetate (200–500 mg/day) or megestrol acetate (160–480 mg/day) for at least 6 months. Response to progestin treatment was assessed histologically. *Results:* Among 53 included patients, 39 (74%) achieved complete response after a median period of 6 (3–24) months. Complete response was less frequent among obese than nonobese patients (4/12 [33%] vs 35/41 [85%]; $P = 0.001$). Disease recurrence was recorded in 10 (26%) patients with complete response; the 5-year recurrence-free survival rate was 71%. Among the 31 patients who retained a desire to conceive, 17 (52%) became pregnant. *Conclusion:* Fertility-sparing management with oral progestin is effective. Obesity is associated with a lower probability of long-term success.

1. Introduction

Endometrial carcinoma (EC) is the most common cancer of the female genital tract in high-income countries [1,2], and is also becoming increasingly frequent in China [3]. Its precursor, complex endometrial hyperplasia (CEH), is found in 50–10% of all premenopausal women presenting with abnormal uterine bleeding worldwide [4,5]. For patients with EC or CEH, hysterectomy with or without bilateral salpingo-oophorectomy is the gold-standard treatment. Nevertheless, this treatment can be unacceptable to patients who still wish to conceive; a conservative, fertility-sparing approach should therefore be considered in this population.

EC and CEH usually occur due to unopposed estrogen stimulation [6]. Because well-differentiated EC tends to retain estrogen and progesterone receptors [7], hormone (progestin) therapies have been previously used in the treatment of this disease [8]. However, it has been reported that some patients show little response to progestin and can even progress during treatment [8–11]. Thus, a re-evaluation of the safety of progestin therapy and the identification of features that predict treatment success would greatly benefit this population.

The objective of the present study was to assess the efficacy and relevant prognostic factors of progestin treatment in Chinese patients with a diagnosis of CEH or grade 1 EC at presumed stage IA (without myometrial invasion).

2. Materials and methods

A retrospective study was undertaken using data for patients with EC or CEH and of childbearing age who were managed with oral progestin fertility-sparing treatment between January 1, 2000, and December 31, 2011, at the Peking Union Medical College Hospital, China. Patients' eligibility for oral progestin treatment included: age of 20–42 years, with a strong desire for fertility preservation and pathologic endometrium results of grade 1 EC or CEH; expression of progestin receptors (PgRs) in the endometrium; no evidence of myometrial invasion (evaluated by transvaginal ultrasonography and pelvic magnetic resonance imaging [MRI]); and presumed stage IA disease on the basis of the 1988 staging system of the International Federation of Gynecology and Obstetrics. All the patients treated with oral progestin during this time period were included in the present study except four cases lost to follow-up. The body mass index (BMI, calculated as weight in

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ONCOLOGY

Reproductive and oncologic outcomes after progestin therapy for endometrial complex atypical hyperplasia or carcinoma

Rashmi Kudesia, MD; Tomer Singer, MD; Thomas A. Caputo, MD; Kevin Michael Holcomb, MD; Isaac Kligman, MD; Zev Rosenwaks, MD; Divya Gupta, MD

OBJECTIVES: This study evaluated fertility and oncological outcomes in women with complex atypical hyperplasia (CAH) or nonmyoinvasive grade 1 endometrioid endometrial carcinoma (EM) who desired fertility-sparing therapy.

STUDY DESIGN: The retrospective cohort study included women younger than 45 years with CAH or EM who desired fertility-sparing treatment at our institution. Only patients for whom both oncological treatment and pregnancy outcomes were available were included. Statistical analyses were performed using a Fisher exact test, Pearson χ^2 test, and Spearman rank correlation test, as appropriate.

RESULTS: Seventy-five patients were identified, and 23 (13 CAH, 10 EM) met the inclusion criteria. All 23 patients had at least 1 prior pregnancy. Treatment was split between oral progesterone only (38.5% CAH, 40% EM), levonorgestrel intrauterine device only (30.8% CAH, 20% EM), and both (30.8% CAH, 40% EM). After a median follow-up of 13 months (range, 3–74 months), 9 patients (46.2% CAH, 30% EM, $P = .39$) had persistent/progressive disease. Eight patients (30.8% CAH, 40% EM, $P = .69$) ultimately had a hysterectomy, and 3 of these (13.0%) were found to have persistent/progressive disease. Median time from diagnosis to hysterectomy was 13 months (range, 4–56 months). Fourteen of the 23 patients utilized assisted reproductive techniques (60.9%); 12 underwent IVF and 2 chose a gestation carrier. Seven clinical intrauterine pregnancies (30.4%) resulting in 6 live births (26.1%) were found in the entire cohort.

CONCLUSION: Fertility-sparing treatment for CAH and grade 1 endometrial cancer is feasible with progestin therapy and leads to clinically meaningful rates of pregnancy in young women who desire fertility.

Key words: endometrial cancer, endometrial hyperplasia, fertility-sparing treatment, progestin therapy

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In the United States, endometrial cancer is the most common gynecological malignancy and accounts for 6% of all cancers in women, with a 2.5% lifetime risk.[1] In 2013, the National Cancer Institute estimates 49,560 new cases in the United States and 8190 deaths.[2] The majority of patients are postmenopausal, and the average age of diagnosis is 61 years.

However, grade 1 endometrioid endometrial cancer (EM) or its precursor lesion, complex atypical hyperplasia (CAH), can still affect premenopausal women, particularly those with risk factors of obesity, polycystic ovarian syndrome, and infertility. Some of these women desire retention of fertility, in which case, standard surgical treatment, comprising hysterectomy, bilateral salpingo-oophorectomy, and lymph node dissection, is unacceptable. As this situation becomes more common with increasing rates of obesity and delayed childbearing, there is a greater need for fertility-sparing treatments.[3,4]

Options for patients with EM or CAH who desire fertility preservation include the following: egg/embryo freezing prior to hysterectomy, progestin treatment followed by use of assisted reproductive technologies (ART), or hysterectomy with lymph node dissection and preservation of ovaries with the future use of a gestational carrier.

Progestin therapy is most commonly used to allow a disease-free window in which to attempt pregnancy. This approach has been evaluated and found viable in small studies[5-12] and literature

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The authors report no conflict of interest.

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Original Article

Fertility preserving treatment with hysteroscopic resection followed by progestin therapy in young women with early endometrial cancer

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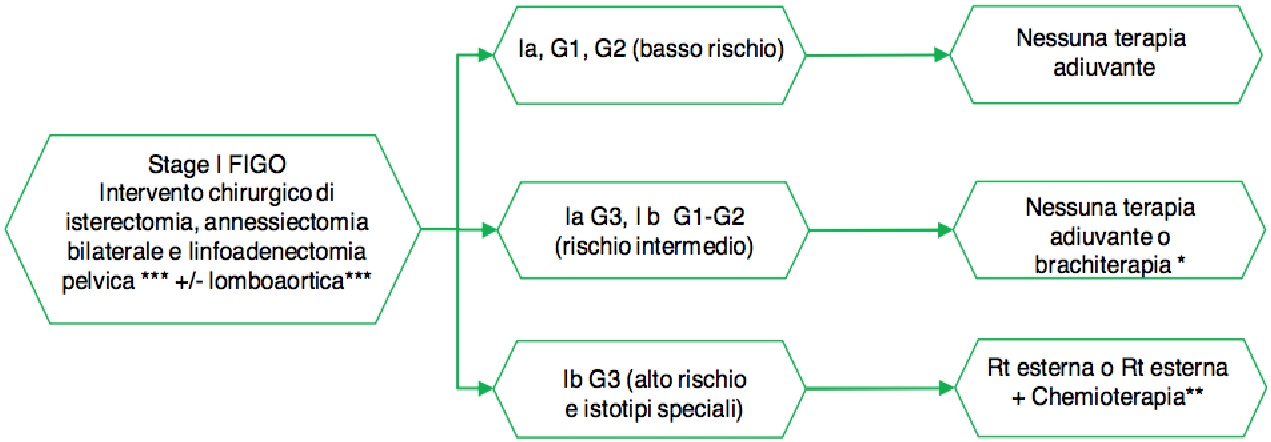
Trattamento radicale

TRATTAMENTO: STADIO I

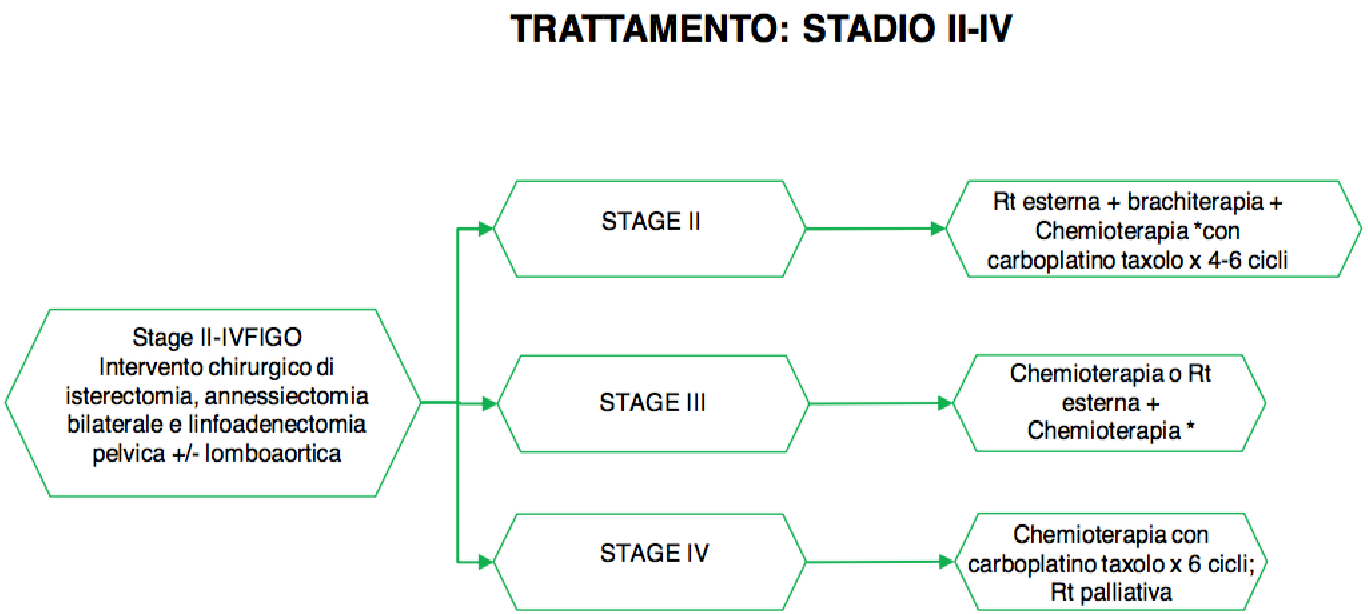


*in particolare la brachiterapia viene proposta in presenza di eta'> 60 anni, infiltrazione miometriale >50% e G3 (rischio intermedio-alto);

** Impiego adiuvante della chemioterapia con carboplatino e taxolo in aggiunta alla radioterapia con livello di evidenza positivo debole; forza della raccomandazione C; negli istotipi speciali anche in assenza di definitive evidenze la chemioterapia è consigliata

*** solo nell'alto rischio

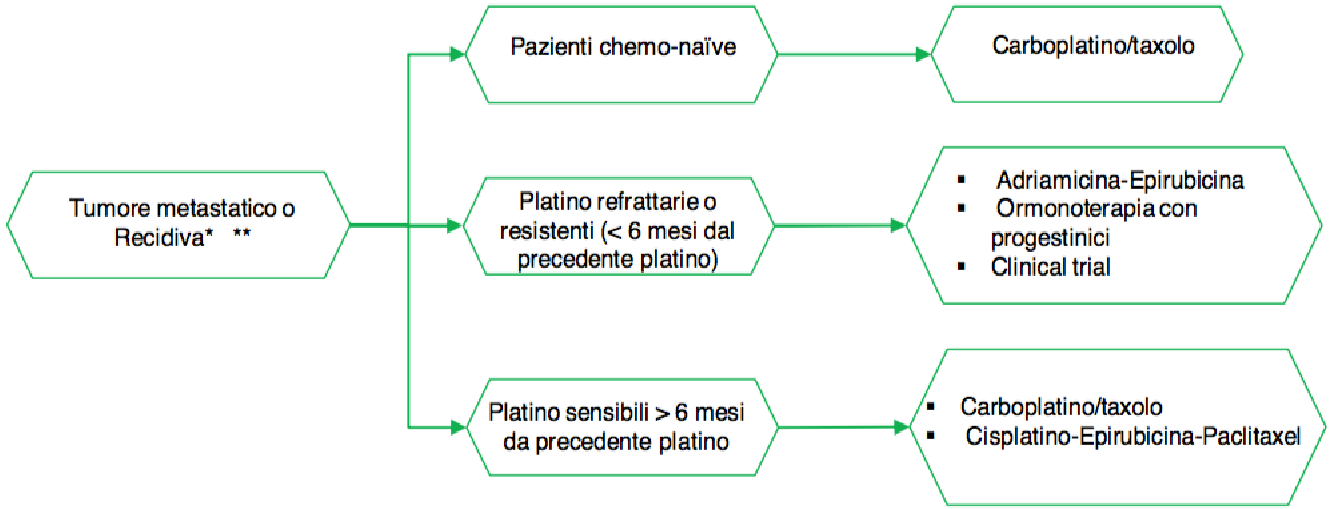
Trattamento radicale



*Impiego adiuvante della chemioterapia in aggiunta alla radioterapia; livello di evidenza positivo debole; forza della raccomandazione B

Trattamento radicale

TRATTAMENTO: STADIO III-IV



* in caso di lesione asportabile e ripresa di malattia > 6 mesi dal trattamento primario considerare chirurgia della recidiva;

**in caso di ripresa di malattia in pazienti non precedentemente radiotrattate o in presenza di lesione fuori dal campo della precedente radioterapia, considerare trattamento RT

Costi

Obermair *et al. Gynecologic Oncology Research and Practice* (2016) 3:1
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Gynecologic Oncology Research and Practice

RESEARCH Open Access

Surgical safety and personal costs in morbidly obese, multimorbid patients diagnosed with early-stage endometrial cancer having a hysterectomy

Andreas Obermair[1,2,8*], Donal J. Brennan[3], Eva Baxter[4], Jane E. Armes[5], Val Gebski[6] and Monika Janda[7]

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Difficoltà chirurgica nella paziente obesa

Impact of body mass index and operative approach on surgical morbidity and costs in women with endometrial carcinoma and hyperplasia

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Table 2
30-day complications stratified by body mass index and surgical approach (N = 1112).

Complication type	All patients				Open abdominal surgery				Minimally invasive surgery			
	BMI				BMI				BMI			
	≤29 n = 385 n (%)	30–39 n = 406 n (%)	≥40 n = 321 n (%)	p	≤29 n = 156 n (%)	30–39 n = 156 n (%)	≥40 n = 129 n (%)	p	≤29 n = 229 n (%)	30–39 n = 250 n (%)	≥40 n = 192 n (%)	p
Wound infections	13 (3%)	12 (3%)	22 (7%)	0.02	8 (5%)	8 (5%)	18 (14%)	0.006	5 (2%)	4 (2%)	4 (2%)	0.89
Venous thrombo-embolism	1 (0.3%)	1 (0.2%)	8 (3%)	0.002	1 (1%)	1 (1%)	6 (5%)	0.02	0 (0%)	0 (0%)	2 (1%)	0.08
Cardiac	6 (2%)	8 (2%)	6 (2%)	0.90	5 (3%)	3 (2%)	2 (2%)	0.60	1 (0.4%)	5 (2%)	4 (2%)	0.27
Respiratory	12 (3%)	12 (3%)	16 (5%)	0.28	10 (6%)	8 (5%)	10 (8%)	0.66	2 (1%)	4 (2%)	6 (3%)	0.21
Stroke	1 (0.3%)	2 (1%)	0 (0%)	0.45	1 (1%)	1 (1%)	0 (0%)	0.66	0 (0%)	1 (0.4%)	0 (0%)	0.43
Other infections	8 (2%)	5 (1%)	6 (2%)	0.63	6 (4%)	1 (1%)	5 (4%)	0.14	2 (1%)	4 (2%)	1 (1%)	0.52
Hematoma/hemorrhage	10 (3%)	8 (2%)	8 (3%)	0.82	5 (3%)	4 (3%)	7 (5%)	0.41	5 (2%)	4 (2%)	1 (1%)	0.37
Acute renal failure	4 (1%)	7 (2%)	5 (2%)	0.70	4 (3%)	4 (3%)	3 (2%)	0.99	0 (0%)	3 (1%)	2 (1%)	0.27
Shock	4 (1%)	3 (1%)	2 (1%)	0.81	3 (2%)	2 (1%)	2 (2%)	0.90	1 (0.4%)	1 (0.4%)	0 (0%)	0.67
Fluid/electrolyte imbalances	14 (4%)	18 (4%)	11 (3%)	0.75	7 (5%)	11 (7%)	9 (7%)	0.57	7 (3%)	7 (3%)	2 (1%)	0.35
Other surgical complications	33 (9%)	32 (8%)	31 (10%)	0.69	21 (14%)	21 (14%)	19 (15%)	0.94	12 (5%)	11 (4%)	12 (6%)	0.69
Overall complication rate	73 (19%)	76 (19%)	75 (23%)	0.23	45 (29%)	48 (31%)	50 (39%)	0.18	28 (12%)	28 (11%)	25 (13%)	0.84
Number of complications per patient												
0	312 (81%)	330 (81%)	(246) (77%)	0.048	111 (71%)	108 (69%)	79 (61%)	0.03	201 (88%)	222 (89%)	167 (87%)	0.74
1	55 (14%)	55 (14%)	46 (14%)		31 (20%)	34 (22%)	28 (22%)		24 (11%)	21 (8%)	18 (9%)	
2	6 (2%)	15 (4%)	19 (6%)		4 (3%)	12 (8%)	14 (11%)		2 (1%)	3 (1%)	5 (3%)	
≥ 3	12 (3%)	6 (2%)	10 (3%)		10 (6%)	2 (1%)	8 (6%)		2 (1%)	4 (2%)	2 (1%)	

BMI, body mass index (Kg/m^2).

Limited Public Knowledge of Obesity and Endometrial Cancer Risk

What Women Know

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OBJECTIVE: To estimate if women in the general population are aware of the relationship between obesity and cancer risk, and to identify groups who may benefit from educational programs.

METHODS: A self-administered survey was distributed to women in the Houston community. The questions were taken from a bank of validated questions published by the Center for Disease Control, Behavioral Risk Factor Surveillance System, and the Harvard Forums on Health Survey. Demographic information and participant knowledge of obesity-related cancer risk was collected. Logistic regression and Cochran-Armitage tests for trend were use to assess the association between predictor variables and knowledge.

RESULTS: One thousand five hundred forty-five women completed the survey; 28% were normal weight (body mass index [BMI] less than 25 kg/m²), 24% were overweight (BMI 25–30 kg/m²), and 45% were obese (BMI at least 30 kg/m²). Fifty-eight percent (95% confidence interval 56–61%) were not aware that obesity increased risk for endometrial cancer. There was no difference in knowledge of endometrial cancer risk associated with any of the demographic characteristics studied. Black women were the most likely to respond that they did not know about the relationship between obesity and cancer. There was no association between personal weight and knowledge of obesity-associated risk.

CONCLUSION: There is limited knowledge of the relationship between obesity and cancer risk, particularly among black women. Patient education regarding these risks may increase awareness of the relationship between obesity and endometrial cancer among women.

(Obstet Gynecol 2008;112:835–42)

LEVEL OF EVIDENCE: III

See related article on page 899.

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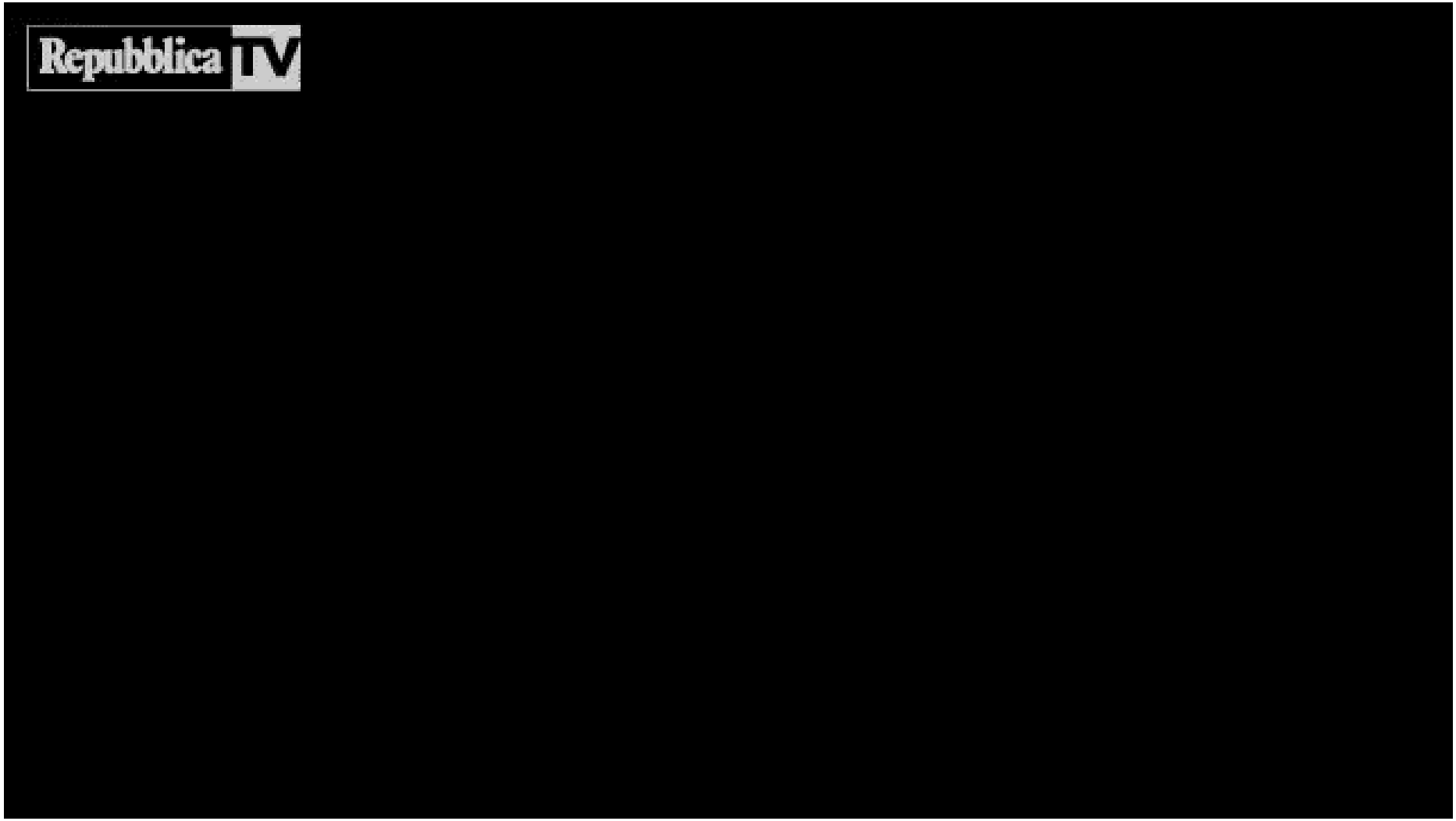
The prevalence of overweight and obese Americans has continued to rise over the last 3 decades. In 2003 to 2004, 66% of adults in the United States were either overweight or obese (body mass index [BMI] 25 kg/m² or higher), an increase from only 47% in 1960.[1] This increase in the prevalence of obesity has been shown to be particularly important in women and in minority groups. Black and Hispanic women have been shown to have the highest weight accumulation when compared with either white women or men.[2] In addition, black women are projected to have the highest increase in obesity based on current growth rates.[3]

It is well known that obesity increases risk for multiple medical problems, including type 2 diabetes mellitus, hypertension, coronary heart disease, hypercholesterolemia, and respiratory complications, including obstructive sleep apnea, and osteoarthritis.[4] Recently, several studies have shown that obesity also increases risk for certain types of cancer. Women who are obese have been shown to have significantly higher rates of endometrial, breast, and colon cancer when compared with nonobese women.[5,6] Endometrial cancer has the highest association with obesity, with a relative risk (RR) of 4.0 in women with a BMI 32 kg/m² or higher and 6.0 in women with a BMI 35 kg/m² or higher when compared with women with a BMI less than 23

THIS STUDY PROVIDES CONTINUED EVIDENCE OF THE GAP IN KNOWLEDGE WITHIN THE GENERAL POPULATION REGARDING THE HEALTH RISKS, AND IN PARTICULAR THE CANCER RISKS, ASSOCIATED WITH OBESITY.

In 2001 the U.S. Department of Health and Human Services and the Surgeon General made a call to action to prevent and decrease overweight and obesity, in an effort to fight the growing issue of obesity in the United States.

The prevention of childhood obesity was made a priority, and efforts were made to target lower socioeconomic and minority population groups who were thought to be at highest risk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