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Association of Nongenetic Factors With Breast Cancer Risk in Genetically Predisposed Groups of Women in the UK Biobank Cohort.

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The association between noninherited factors, including lifestyle factors, and the risk of breast cancer (BC) in women and the association between BC and genetic makeup are only partly characterized. A study using data on current genetic stratification may help in the characterization. Objective: To examine the association between healthier lifestyle habits and BC risk in genetically predisposed groups. Design, Setting, and Participants: Data from UK Biobank, a prospective cohort comprising 2728 patients with BC and 88 489 women without BC, were analyzed. The data set used for the analysis was closed on March 31, 2019. The analysis was restricted to postmenopausal white women. Classification of healthy lifestyle was based on Cancer Research UK guidance (healthy weight, regular exercise, no use of hormone replacement therapy for more than 5 years, no oral contraceptive use, and alcohol intake <3 times/wk). Three groups were established: favorable (≥4 healthy factors), intermediate (2-3 healthy factors), and unfavorable (≤1 healthy factor). The genetic contribution was estimated using the polygenic risk scores of 305 preselected single-nucleotide variations. Polygenic risk scores were categorized into 3 tertiles (low, intermediate, and high). Main Outcomes and Measures: Cox proportional hazards regression was used to assess the hazard ratios (HRs) of the lifestyles and polygenic risk scores associated with a malignant neoplasm of the breast. Results: Mean (SD) age of the 2728 women with BC was 60.1 (5.5) years, and mean age of the 88 489 women serving as controls was 59.4 (4.9) years. The median follow-up time for the cohort was 10 years (maximum 13 years) (interquartile range, 9.44-10.82 years). Women with BC had a higher body mass index (relative risk [RR], 1.14; 95% CI, 1.05-1.23), performed less exercise (RR, 1.12; 95% CI, 1.01-1.25), used hormonal replacement therapy for longer than 5 years (RR, 1.23; 95% CI, 1.13-1.34), used more oral contraceptives (RR, 1.02; 95% CI, 0.93-1.12), and had greater alcohol intake (RR, 1.11; 95% CI, 1.03-1.19) compared with the controls. Overall, 20 657 women (23.3%) followed a favorable lifestyle, 60 195 women (68.0%) followed an intermediate lifestyle, and 7637 women (8.6%) followed an unfavorable lifestyle. The RR of the highest genetic risk group was 2.55 (95% CI, 2.28-2.84), and the RR of the most unfavorable lifestyle category was 1.44 (95% CI, 1.25-1.65). The association of lifestyle and BC within genetic subgroups showed lower HRs among women following a favorable lifestyle compared with intermediate and unfavorable lifestyles among all of the genetic groups: women with an unfavorable lifestyle had a higher risk of BC in the low genetic group (HR, 1.63; 95% CI, 1.13-2.34), intermediate genetic group (HR, 1.94; 95% CI, 1.46-2.58), and high genetic group (HR, 1.39; 95% CI, 1.11-1.74) compared with the reference group of favorable lifestyle. Intermediate lifestyle was also associated with a higher risk of BC among the low genetic group (HR, 1.40; 95% CI, 1.09-1.80) and the intermediate genetic group (HR, 1.37; 95% CI, 1.12-1.68). Conclusions and Relevance: In this cohort study of data on women in the UK Biobank, a healthier lifestyle with more exercise, healthy weight, low alcohol intake, no oral contraceptive use, and no or limited hormonal replacement therapy use appeared to be associated with a reduced level of risk for BC, even if the women were at higher genetic risk for BC.

Association of Circulating Progesterone With Breast Cancer Risk Among Postmenopausal Women.

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The role of endogenous progesterone in the development of breast cancer remains largely unexplored to date, primarily owing to assay sensitivity limitations and low progesterone concentrations in postmenopausal women. Recently identified progesterone metabolites may provide insights as experimental data suggest that 5α-dihydroprogesterone (5αP) concentrations reflect cancer-promoting properties and 3α-dihydroprogesterone (3αHP) concentrations reflect cancer-inhibiting properties. Objective: To evaluate the association between circulating progesterone and progesterone metabolite levels and breast cancer risk. Design, Setting, and Participants: Using a sensitive liquid chromatography-tandem mass spectrometry assay, prediagnostic serum levels of progesterone and progesterone metabolites were quantified in a case-cohort study nested within the Breast and Bone Follow-up to the Fracture Intervention Trial (n = 15 595). Participation was limited to women not receiving exogenous hormone therapy at the time of blood

sampling (1992-1993). Incident breast cancer cases (n = 405) were diagnosed during 12 follow-up years and a subcohort of 495 postmenopausal women were randomly selected within 10-year age and clinical center strata. Progesterone assays were completed in July 2017; subsequent data analyses were conducted between July 15, 2017, and December 20, 2018. Exposures: Circulating concentrations of pregnenolone, progesterone, and their major metabolites. Main Outcomes and Measures: Development of breast cancer, with hazard ratios (HRs) and 95% CIs was estimated using Cox proportional hazards regression adjusted for key confounders, including estradiol. Evaluation of hormone ratios and effect modification were planned a priori. Results: The present study included 405 incident breast cancer cases and a subcohort of 495 postmenopausal women; the mean (SD) age at the time of the blood draw was 67.2 (6.2) years. Progesterone concentrations were a mean (SD) of 4.6 (1.7) ng/dL. Women with higher circulating progesterone levels were at an increased risk for breast cancer per SD increase in progesterone levels (HR, 1.16; 95% CI, 1.00-1.35; P = .048). The association with progesterone was linear in a 5-knot spline and stronger for invasive breast cancers (n = 267) (HR, 1.24; 95% CI, 1.07-1.43; P = .004). Among women in the lowest quintile (Q1) of circulating estradiol (<6.30 pg/mL) elevated progesterone concentrations were associated with reduced breast cancer risk per SD increase in progesterone levels (HR, 0.38; 95% CI, 0.15-0.95; P = .04) and increased risk among women in higher quintiles of estradiol (Q2-Q5; ≥6.30 pg/mL) (HR, 1.18; 95% CI, 1.04-1.35; P = .01; P = .04 for interaction). Conclusions and Relevance: In this case-cohort study of postmenopausal women, elevated circulating progesterone levels were associated with a 16% increase in the risk of breast cancer. Additional research should be undertaken to assess how postmenopausal breast cancer risk is associated with both endogenous progesterone and progesterone metabolites and their interactions with estradiol.

Ovarian removal at or after benign hysterectomy and breast cancer: a nationwide cohort study.

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PURPOSE: Large-scale population-based registry studies investigating the risk of breast cancer after removal of both ovaries at hysterectomy for benign conditions in women with no known genetic predisposition to cancer are needed. We aimed to perform such a study taking into account the age at surgery status and use of hormone replacement therapy (HRT). METHODS: Within the female population of Denmark born 1937-1996, we evaluated breast cancer incidence after unilateral or bilateral oophorectomy concomitant with or after benign hysterectomy in comparison with no surgery and with hysterectomy alone using health registry data during 1978-2016. In a subpopulation followed from 1996, the analyses were stratified according to use of HRT. RESULTS: We found a reduced risk of breast cancer among women aged < 45 years at bilateral oophorectomy compared with women with hysterectomy alone (HR = 0.78; 95% CI 0.66, 0.92), whereas slightly increased risks were seen in women above 50 years. In the subpopulation, non-users of HRT aged ≥ 50 years at oophorectomy had a HR of 0.74 (95% CI 0.56, 0.98) for breast cancer after bilateral oophorectomy compared with hysterectomy alone. CONCLUSIONS: Our large-scale study covering four decades provides evidence that bilateral oophorectomy performed at young age in women with benign indications for hysterectomy is associated with a reduction in breast cancer risk. The finding of a negative association at older ages in women not using HRT deserves further attention.

Review: Sex-Specific Aspects in the Bariatric Treatment of Severely Obese Women.

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This systematic literature review aims to point out sex-specific special features that are important in the bariatric treatment of women suffering from severe obesity. A systematic literature search was carried out according to Cochrane and Preferred Reporting Items for Systematic review and Meta-Analysis Protocols (PRISMA-P) guidelines. After the literature selection, the following categories were determined: sexuality and sexual function; contraception; fertility; sex hormones and polycystic ovary syndrome; menopause and osteoporosis; pregnancy and breastfeeding; pelvic floor disorders and urinary incontinence; female-specific cancer; and metabolism, outcome, and quality of life. For each category, the current status of research is illuminated and implications for bariatric treatment are determined. A summary that includes key messages is given for each subsection. An overall result of this paper is an understanding that sex-specific risks that follow or result from bariatric surgery should be considered more in aftercare. In order to increase the evidence, further research focusing on sex-specific differences in the outcome of bariatric surgery and promising treatment approaches to female-specific diseases is needed. Nevertheless, bariatric surgery shows good

potential in the treatment of sex-specific aspects for severely obese women that goes far beyond mere weight loss and reduction of metabolic risks.

Graves' disease and vertebral fracture: possible pathogenic link in postmenopausal women.

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BACKGROUND AND OBJECTIVE:Thyrotoxicosis is associated with accelerated bone turnover and increases the risk of fractures and osteoporosis. Graves' disease is the most common cause of hyperthyroidism. However, studies that examined risk factors associated with fragility fractures only in patients with Graves' disease are limited. Here we investigated whether the risk of vertebral fracture (VF) of postmenopausal Graves' disease patients is high and tried to identify the risk factors for VF in that population. DESIGN AND METHODS: Forty-three postmenopausal women with Graves' disease were enrolled. Physical and biochemical indices, thyroid indices, and bone mineral density (BMD) were measured, and lateral X-rays were obtained to evaluate VFs. Age- and sex-matched healthy individuals were enrolled as the control group (n=86). RESULTS: The prevalence of VFs (35% vs. 17%, $p < 0.05$), osteoporosis (63% vs. 33%, $p < 0.01$), and severe osteoporosis (40% vs. 17%, $p < 0.01$) was significantly higher in the Graves' disease group. Although there was no significant difference in either thyroid hormone levels or the positive ratio of thyroid antibodies, the prevalence of thyroid stimulating antibody (TSAb) was significantly higher in Graves' disease patients with VF compared to without (100% vs. 68%, $p < 0.05$). Multivariate logistic regression analyses adjusted for age identified Graves' disease as being associated with the presence of VFs (OR 2.72, 95% CI 1.13 - 6.54, $p < 0.05$) in postmenopausal women. CONCLUSIONS:Postmenopausal Graves' disease patients had high risks of VF and severe osteoporosis. TSAb could be involved as a risk factor for VF in postmenopausal Graves' disease.

Comparison of the Efficacy of Tibolone and Transdermal Estrogen in Treating Menopausal Symptoms in Postmenopausal Women.

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OBJECTIVES: This study aimed to compare the efficacy of tibolone and transdermal estrogen in treating menopausal symptoms in postmenopausal women with an intact uterus. METHODS: Overall, 26 women consumed tibolone orally and 31 women received transdermal estrogen gel mixed with progestogen. The menopause rating scale (MRS) was used to assess their menopausal symptoms at their first outpatient visit and 6 months later. RESULTS: The transdermal estrogen group showed significant improvements in more items of the MRS questionnaire. There was a favorable change in body weight in the transdermal estrogen group compared with that in the tibolone group. Depressive mood, irritability, physical and mental exhaustion, sexual and bladder problems, and joint and muscular discomfort improved only in the transdermal estrogen group, whereas heart discomfort and vaginal dryness improved only in the tibolone group. Nevertheless, the intergroup differences in each item were insignificant after adjusting for body mass index and hypertension, which differed before treatment. CONCLUSIONS: Both the therapeutic options improved menopausal symptoms within 6 months of use. However, transdermal estrogen appeared to be more effective in preventing weight gain in menopausal women than tibolone.