Published in final edited form as:
Cancer. 2009 February 15; 115(4): 812–822. doi:10.1002/cncr.24086.

Body mass index and risk of ovarian cancer

Michael F. Leitzmann[1], **Corinna Koebnick**[1,3], **Kim N. Danforth**[2], **Louise A. Brinton**[2], **Steven C. Moore**[1], **Albert R. Hollenbeck**[4], **Arthur Schatzkin**[1], and **James V. Lacey Jr.**[2]

[1]Nutritional Epidemiology Branch, Division of Cancer Epidemiology and Genetics, National Cancer Institute, National Institutes of Health, Department of Health and Human Services, Bethesda, MD

[2]Hormonal and Reproductive Epidemiology Branch, Division of Cancer Epidemiology and Genetics, National Cancer Institute, National Institutes of Health, Department of Health and Human Services, Bethesda, MD

[3]Southern California Permanente Medical Group, Oakland, CA

[4]AARP, Washington, DC

Abstract

Convincing epidemiologic evidence links excess body mass to increased risks of endometrial and postmenopausal breast cancers but the relation of body mass index (BMI) to ovarian cancer risk remains inconclusive. Potential similarities regarding a hormonal mechanism in the etiology of female cancers highlight the importance of investigating associations according to menopausal hormone therapy (MHT) use. However, data addressing whether the relation of BMI to ovarian cancer differs by MHT use are very sparse. We prospectively investigated the association between BMI and ovarian cancer among 94,525 U.S. women, followed from 1996–1997 to December 31, 2003. During 7 years of follow-up, we documented 303 epithelial ovarian cancer cases. As compared with normal weight women (BMI 18.5–24.9 kg/m^2), the multivariate relative risk (MVRR) of ovarian cancer for obese women (BMI ≥30 kg/m^2) in the cohort as a whole was 1.25 (95%-CI=0.93–1.68). Among women who never used MHT, the MVRR for obese versus normal weight women was 1.80 (95%-CI=1.16–2.80). In contrast, no relation between BMI and ovarian cancer was apparent among women who ever used MHT (MVRR=0.96; 95%-CI=0.64–1.43; P-interaction=0.02). Exploratory analyses also suggested a positive association between BMI and ovarian cancer among women without a family history of ovarian cancer (MVRR comparing obese versus normal weight women=1.36; 95%-CI=0.99–1.85), but no relation with BMI was apparent among women with a positive family history of ovarian cancer (MVRR=0.73; 95%-CI=0.34–1.60; P-interaction=0.02). We suspect that obesity is associated with enhanced ovarian cancer risk through a hormonal mechanism.

Introduction

Among gynecological malignancies, ovarian cancer is the most fatal, with a 5-year survival rate of 37% (1). Although ovarian cancer etiology remains incompletely understood, parity and oral contraceptive use are related to decreased ovarian cancer risk, while family history of ovarian cancer and menopausal hormone therapy (MHT) use are associated with increased risk (2–4).

In addition to those factors, excess body weight may play a role in the etiology of ovarian cancer. A recent meta-analysis reported a 16% increased risk of ovarian cancer for adult overweight (body mass index (BMI) 25–29.9 kg/m^2) and a 30% increased risk for adult obesity (BMI ≥30 kg/m^2) when compared with normal weight (18.5–24.9 kg/m^2) (5). It has been hypothesized that in postmenopausal women, adiposity enhances ovarian cancer risk

partly through the mitogenic effects of excess endogenous estrogens synthesized in the adipose tissue via aromatization of androgens (6). According to that hypothesis, a positive association between adiposity and ovarian cancer is expected to be more evident among MHT non-users. In contrast, the relation of adiposity to ovarian cancer is expected to be weaker among MHT users who already exhibit high circulating estrogen levels via an exogenous source. This type of interaction between adiposity and MHT has been shown previously for female cancers, including ovarian cancer (6), endometrial cancer (7), and breast cancer (8).

In a large prospective study with comprehensive data on MHT use and family history of ovarian cancer, we examined BMI in relation to ovarian cancer risk. We investigated whether the association with BMI was stronger in women who never used MHT. Because ovarian carcinogenesis has a strong hereditary component (9), we also addressed whether the relation of adiposity to ovarian cancer varied according to family history of ovarian cancer.

Methods

Study population

The NIH-AARP Diet and Health Study was established in 1995–1996 when 566,402 AARP (formerly known as the American Association of Retired Persons) members aged 50 to 71 years and residing in one of six U.S. states (CA, FL, LA, NJ, NC, and PA) or two metropolitan areas (Atlanta, GA, and Detroit, MI) completed and returned a mailed questionnaire on body weight, height, medical history, and diet (10). A second questionnaire that included more detailed information on family history of cancer and MHT was mailed to baseline questionnaire respondents within six months and was returned by 59.5% of participants. The Special Studies Institutional Review Board (IRB) of the U.S. National Cancer Institute approved the study.

Population for analysis

To incorporate the detailed data on family history of cancer and hormone therapy, our analysis included the 138,057 potentially eligible women who returned the second questionnaire. We excluded women with previously diagnosed cancer other than non-melanoma skin cancer before baseline (n=9,171 women, including 1,572 cases of ovarian cancer), those with bilateral oophorectomy (n=27,908), women with unknown oophorectomy status (n=2,164), subjects who were underweight (BMI<18.5 kg/m^2; n=1,540) or extremely obese (BMI>65.0 kg/m^2; n=46), and those with missing information on baseline weight or height (n=2,703). After exclusions, the analytic cohort included 94,525 women.

Cohort follow-up

Study participants were followed by regular matching of the cohort database to the National Change of Address database maintained by the U.S. Postal Service and through processing of undeliverable mail, other address update services, and directly from participants. Vital status was ascertained by linkage to the Social Security Administration Death Master File. Follow-up searches of presumed deaths in the National Death Index (NDI) Plus provided verification and information on cause of death. For matching purposes, we have virtually complete data on first and last name, address history, gender, and date of birth. Social Security number is available for 85% of our cohort.

Ovarian cancer ascertainment

Linkage to state cancer registries was used to identify epithelial ovarian cancer cases. The cancer registry ascertainment area was recently expanded by three states (TX, AZ, and NV) to capture cancer cases occurring among participants who moved to those states during follow-up. The North American Association of Central Cancer Registries (NAACCR) certifies all eleven cancer registries serving our cohort (11). A validation study comparing registry findings to self-reports and medical records showed that approximately 90% of cancer cases in our cohort are validly identified (12).

During follow-up, we documented 303 ovarian cancer cases. Cancers were identified by anatomic site and histologic code using the International Classification of Disease for Oncology (ICD-O, second and third editions) (13). The endpoint considered was epithelial ovarian cancer (ICD-O C56.9). We also conducted a subanalysis using ovarian cancer mortality as an endpoint.

Statistical analysis

Each participant accrued follow-up time beginning at the scan date of the second questionnaire and ending at the date of diagnosis of epithelial ovarian carcinoma, move out of the registry ascertainment area, death, or the end of follow-up on December 31, 2003, whichever occurred first. Participants were divided into three BMI categories corresponding to definitions of normal weight (18.5–24.9 kg/m^2), overweight (25.0–29.9 kg/m^2), and obesity (≥30.0 kg/m^2) (14). The group of subjects with a BMI of 18.5–24.9 kg/m^2 served as the reference group.

We used Cox regression (15) to estimate hazard ratios and 95% confidence intervals (CI) of ovarian cancer using person-time as the time scale and adjusting for age, race/ethnicity, family history of ovarian cancer in a first or second degree relative, family history of breast cancer in a first or second degree relative, duration of oral contraceptive use, MHT, and physical activity. We tested for and found no departures from the proportional hazards assumption. Tests of linear trend were conducted by modeling the median values of BMI categories as a single continuous variable, the coefficient for which was evaluated using a Wald test.

We examined whether MHT use modified the BMI and ovarian cancer relation by entering the cross product term for BMI (three categories) and MHT use (never, ever) along with the main effects terms for each. The statistical significance of the latter was evaluated using a likelihood-ratio test. We used the same approach to evaluate effect modification by hysterectomy status and family history of ovarian cancer. We also considered the main effects of BMI at age 18 years and the interactions of BMI at age 18 years with MHT, hysterectomy status, and family history of ovarian cancer.

Results

At baseline in 1996–1997, one-third (32.4%) of participants were overweight and nearly one-fourth (22.0%) were obese. Most women were Caucasian, postmenopausal, and in their low 60s at study onset. Ovarian cancer was positively associated with MHT use and family history of ovarian cancer; inversely associated with oral contraceptive use, parity, and non-Caucasian race/ethnicity; and not associated with age at menarche, age at natural menopause, or hysterectomy. Postmenopausal women with hysterectomy were more likely to report MHT than postmenopausal women with an intact uterus.

We examined baseline characteristics among normal weight, overweight, and obese women to assess the potential for confounding (Table 1). Compared with women who were normal

weight at baseline, overweight or obese women less frequently used MHT, were less likely to report a history of oral contraceptive use, and had an earlier age at menarche. In contrast, overweight or obese women had a slightly later age at menopause, had greater parity, were more likely to have had a hysterectomy, and more frequently reported a family history of ovarian cancer than normal weight women. Similar patterns were observed with BMI at age 18 years with the exceptions of parity and hysterectomy, for which inverse relations with BMI at age 18 years were seen. The correlation coefficient between BMI at baseline and BMI at age 18 years was modestly positive (r=0.33).

During 638,510 person-years of follow-up from 1996–1997 through 2003, we documented 303 incident cases of epithelial ovarian cancer, of which 157 were serous, 13 were mucinous, 1 was borderline, 20 were endometroid, 12 were clear cell, and 100 were other ovarian adenocarcinomas.

BMI at baseline

In age-adjusted analysis, BMI showed a weak positive association with ovarian cancer (RR comparing obese with normal weight women=1.14; 95%-CI=0.86–1.51) (Table 2). The relation was slightly strengthened after multivariate adjustment (RR=1.26; 95%-CI=0.94–1.68). Most of the difference between the age-adjusted and multivariate risk estimates was due to including MHT in the model. To determine whether larger BMI conferred greater risk, we compared women with BMI>35.0 kg/m^2 with normal weight women. The multivariate RR was 1.38 (95%-CI=0.92–2.09), suggesting a further increase in ovarian cancer risk with more extreme levels of adiposity, albeit at the expense of less precision of the risk estimate.

We observed a positive relation of BMI to ovarian cancer among women who never used MHT (multivariate RR comparing obese with normal weight women=1.83; 95%-CI=1.18–2.84). In contrast, no association between BMI and ovarian cancer was evident for ever users of MHT (RR for obese vs. normal weight women=0.96; 95%-CI=0.65–1.43). The test for interaction between BMI and MHT was statistically significant (P-value=0.02). Among ever users of MHT, relations of BMI to ovarian cancer were similarly null for the subgroup of women with estrogen-only use (multivariate RR comparing obese with normal weight women=1.17; 95%-CI=0.87–1.57) and the group with estrogen plus progestin use (corresponding multivariate RR=1.01; 95%-CI=0.69–1.47). When we repeated our analysis among women who never used MHT, this time focusing on ovarian cancer mortality as an endpoint, the multivariate RR comparing obese with normal weight women was 1.51 (95%-CI=0.91–2.51). There were no cases of ovarian cancer mortality among women with an intact uterus who never used MHT.

We considered whether the observed interaction between BMI and MHT was explained by the underlying effect of hysterectomy, a variable positively linked both to BMI and to MHT. A positive association between BMI and ovarian cancer was seen both among women with hysterectomy (multivariate RR comparing obese to normal weight women=1.49; 95%-CI=0.87–2.58) and among those with an intact uterus (corresponding RR=1.19; 95%-CI=0.85–1.66). The test for interaction revealed no significant difference of the BMI and ovarian cancer relation according to hysterectomy (P-value=0.72). The P value for the three-way interaction between BMI, MHT use, and hysterectomy was not statistically significant (P-value=0.55).

Among the subgroup of women with no family history of ovarian cancer, a suggestive positive relation between BMI and ovarian cancer was noted (multivariate RR comparing obese with normal weight women=1.36; 95%-CI=1.00–1.86). In contrast, no association between BMI and ovarian cancer was apparent for women with a positive family history of

ovarian cancer (corresponding multivariate RR=0.74; 95%-CI=0.34–1.62). The test for interaction between BMI and family history of ovarian cancer was statistically significant (P-value=0.02). The P value for the three-way interaction between BMI, MHT use, and family history of ovarian cancer was not statistically significant (P-value=0.67).

BMI at age 18 years

Both overweight and obesity at age 18 years showed suggestive positive associations with ovarian cancer, and the relation of BMI at age 18 years to ovarian cancer was stronger than that observed with current BMI, although it failed to reach statistical significance (Table 3). As compared with women who were normal weight at age 18 years, the multivariate RRs of ovarian cancer for overweight and obese women were 1.29 (95%-CI=0.82–2.04) and 1.74 (95%-CI=0.86–3.53), respectively. Age-adjusted and multivariate findings were comparable.

Similar to our previous findings with BMI at baseline, the relation of BMI at age 18 years to ovarian cancer was stronger among women who did not use MHT (RR comparing obese to normal weight women=2.55; 95%-CI=1.11–5.83; P-interaction=0.02). Also consistent with our results for BMI at baseline, the association between BMI at age 18 years and ovarian cancer did not vary according to hysterectomy (P-interaction=0.87), and it did not vary further according to the combination of MHT use and hysterectomy (P-interaction=0.19). The relation of BMI to ovarian cancer was suggestively positive for women who had no family history of ovarian cancer (RR comparing obese to normal weight women=2.01; 95%-CI=0.99–4.09). We were unable to conduct a formal test for interaction for the association of obesity at age 18 years and family history in relation to ovarian cancer because there were no ovarian cancer cases who were obese at age 18 years and had a positive family history of ovarian cancer in the current follow-up cycle.

Combination of BMI at baseline and BMI at age 18 years

In analyses of the joint effects of BMI at baseline and BMI at age 18 years, we combined overweight and obese groups to maintain sufficient numbers of cases in each cell. As compared to women who were normal weight at both age 18 years and at study baseline, elevated ovarian cancer risk for women who were consistently overweight or obese at age 18 years and at baseline was particularly apparent for those who never used MHT (multivariate RR=2.99; 95%-CI=1.69–5.29; P-interaction=0.002) and those who had no family history of ovarian cancer (multivariate RR=1.68; 95%-CI=1.05–2.68; P-interaction=0.09) (Table 4).

Adult weight gain

We also evaluated adult weight gain in relation to ovarian cancer. As compared to women with stable weight between age 18 years and study baseline, the multivariate RRs of ovarian cancer for women who gained 4 to 19.9 kilograms and those who gained 20 or more kilograms during that time period were 0.97 (95%-CI=0.69–1.35) and 1.13 (95%-CI=0.79–1.61), respectively. Similarly null associations for adult weight gain were noted within strata of MHT use, hysterectomy, and family history of ovarian cancer (data not shown). Also, the relations of BMI at baseline, BMI at age 18 years, and adult weight gain to ovarian cancer risk were not further modified by the effects of age, race/ethnicity, age at menarche, oral contraceptive use, parity, menopausal status, smoking, and physical activity (all P for interaction>0.05).

Discussion

As observed in numerous previous investigations summarized in a recent meta-analysis of the available literature (5), BMI at baseline was associated with a modest but statistically non-significant increase in risk for ovarian cancer in our cohort as a whole. However, when we examined the relationship of adiposity to ovarian cancer among women who never used MHT, the association became markedly stronger, with risk among obese women increasing nearly 80% compared with normal weight women. In contrast, no association between BMI and ovarian cancer was observed among ever-users of MHT. The interrelations of BMI, MHT use, and ovarian cancer were not explained by the effects of hysterectomy.

Although the exact etiologic pathways are unresolved, the observed risk increase associated with obesity at baseline according to MHT indicates that adiposity may enhance ovarian cancer risk in part through its estrogenic effects. In postmenopausal women, excess body mass leads to increased estrogen synthesis in adipocytes, resulting in higher circulating estrogen levels (16). Estrogen promotes cell growth in ovarian surface epithelial cell cultures (17). Additional mechanisms are possible. High body mass is associated with hyperinsulinemia and, consequently, with higher levels of free circulating insulin-like growth factor (IGF)-1 and androgens. Both IGF-1 and androgens stimulate cell proliferation in ovarian cancer (18). Obesity is also associated with increased levels of serum leptin, which can act as a mitogen and an angiogenic factor (19) and is involved in ovarian folliculogenesis (20).

Data showing effect modification of the association between BMI and ovarian cancer by MHT use are sparse, but our results regarding this issue are similar to another study on this issue, which observed a positive association between BMI and ovarian cancer mortality among women who never used MHT (RR=1.36; 95%-CI=1.12–1.66) but not among women who ever used MHT (RR=0.93; 95%-CI=0.62–1.41) (6). It is worth pointing out that that study (6) differed from ours in that it excluded women with hysterectomy, captured estrogen-only MHT use, and focused on ovarian cancer mortality and not on ovarian cancer incidence. Thus, results are not strictly comparable with those from our study. In contrast to our study, a recent pooled analysis of 12 cohort studies found no effect modification of the BMI and ovarian cancer relation by MHT use, but data were not shown (21).

In exploratory analyses, we found that BMI was associated with increased risk for ovarian cancer particularly among women without a family history of ovarian cancer. Ovarian carcinogenesis has a strong hereditary component (9), a circumstance that may obscure any true association between BMI and ovarian cancer. Previous data regarding potential effect modification of the BMI and ovarian cancer relation by family history of ovarian cancer are limited to one case-control study (22) that reported no statistically significant interaction between these variables (P-interaction=0.35). However, family history of ovarian cancer tends to have a rather low prevalence in the population (approximately 10% in our study), suggesting that observed positive relations of BMI to ovarian cancer seen in numerous previous studies were likely driven by an increased risk with BMI among women without a family history of ovarian cancer.

On the contrary, if hereditary ovarian cancer risk is determined by etiologic pathways that are in part distinct from those related to adiposity's hormonal and metabolic sequelae, then future investigations may confirm that removing the small subset of women with a self-reported positive family history of ovarian cancer bears the potential to uncover a stronger positive relation of BMI to ovarian cancer risk than would be achievable when considering the study population as a whole. Alternatively, the observed interaction of BMI with family

history of ovarian cancer in our analysis may be the result of chance due to multiple comparisons, as we investigated interactions with numerous potential effect modifiers.

We found that the relation of BMI at age 18 years to ovarian cancer risk tended to be stronger than that with BMI at baseline. This is somewhat consistent with the largest such study to date (23) that observed a positive relation of BMI at age 20 years to ovarian cancer risk but found no association with BMI later in life. This suggests that adolescent or young adulthood BMI may potentially be more etiologically relevant for ovarian cancer than current or late-adulthood BMI when examining the potential adverse effects of excess body mass on ovarian cancer risk. Established stronger associations of ovarian cancer with other early-life factors, such as oral contraceptive use and parity, support a latency period of several decades for ovarian cancer development. Given the modest correlation between BMI at age 18 years and BMI at baseline and the fact that those two measures of adiposity represent different periods in life, we speculate that BMI at age 18 years may relate to ovarian carcinogenesis through distinct mechanisms, such as those associated with early age at menarche or the presence of anovulatory cycles.

In our models focusing on the relation of BMI at age 18 years to ovarian cancer, we refrained from adjusting for BMI later in life (at study baseline) because such adjustment alters the interpretation of BMI at age 18 into a measure of weight gain between age 18 and study baseline.

We did address adult weight gain in a separate model and found no association with ovarian cancer, which was perhaps not surprising because BMI at age 18 years and BMI at study baseline were both positively related to ovarian cancer in their own right. Consistent overweight or obesity at age 18 years and study baseline (i.e., during total adulthood), however, appeared to confer risk exceeding that seen with overweight or obesity at age 18 years only or at study baseline only. This suggests that long-term, consistent, excess weight represents a major underlying anthropometric risk factor for ovarian cancer.

Important advantages of our study include its large size, prospective design, sufficient range in BMI levels, and available data on BMI at age 18 years. This allowed us to examine ovarian cancer risk according to various measures and levels of BMI with adequate precision across a number of potentially important effect modifiers.

Adjustment for established ovarian cancer risk factors, such as parity and oral contraceptive use had little impact on the risk estimates. This suggests that confounding by unmeasured or unknown factors associated with both BMI and ovarian cancer does not likely explain the associations we observed.

The current study also has a number of potential limitations. Our measure of BMI was based on self-reported weight and height, and results could have been affected by imprecise anthropometric assessments. However, the correlations between measured and self-reported weight and height (including recalled weight over several decades) have been found to be high, ranging from 0.80 to 0.95 (24). In addition, information on weight and height was reported prior to ovarian cancer diagnosis and therefore, misclassification would likely be non-differential between cases and non-cases. On the other hand, women have a tendency to underestimate their weight and to over report their height, and heavier women underestimate their weight more than lean women (25). Such misclassifications of weight and height would lead to overstated risk estimates.

Insufficient statistical power limited our ability to conduct detailed analyses of adiposity in relation to histologic subtypes of ovarian cancer. Some previous investigations observed a stronger relation of obesity to non-serous cancers than serous cancers (26–29). Future

studies should examine the potential for differential relationships of adiposity to specific histologic subgroups of ovarian cancer.

Because participants in the NIH-AARP study represent mainly Caucasian women who consented to participate in a follow-up study, our results may not apply to all women. Our findings also may not extend to premenopausal women as the vast majority of participants in our study were postmenopausal at baseline.

In conclusion, this study confirms a modest positive relation between BMI and risk for ovarian cancer. Our results also add support to very limited available evidence that the potential adverse effect of excess body mass on ovarian cancer risk is most apparent given a low exposure to exogenous estrogens, as is the case among women who never used MHT. Further studies should test the hypothesis that the relation of BMI to ovarian cancer varies according to MHT use. Such work should help shed further light on the potential metabolic effects of adiposity on ovarian carcinogenesis. We also present evidence from exploratory analyses, requiring confirmation, for a stronger association between BMI and ovarian cancer among women with no family history of ovarian cancer than those with a positive family history. The observed relations of obesity to ovarian cancer risk have relevance for public health programs aimed at reducing obesity in the population.

References

1. Jemal A, Siegel R, Ward E, et al. Cancer statistics, 2008. CA Cancer J Clin. 2008; 58(2):71–96. [PubMed: 18287387]
2. Beral V, Bull D, Green J, Reeves G. Ovarian cancer and hormone replacement therapy in the Million Women Study. Lancet. 2007; 369(9574):1703–10. [PubMed: 17512855]
3. Lukanova A, Kaaks R. Endogenous hormones and ovarian cancer: epidemiology and current hypotheses. Cancer Epidemiol Biomarkers Prev. 2005; 14(1):98–107. [PubMed: 15668482]
4. Beral V, Doll R, et al. Collaborative Group on Epidemiological Studies of Ovarian Cancer. Ovarian cancer and oral contraceptives: collaborative reanalysis of data from 45 epidemiological studies including 23,257 women with ovarian cancer and 87,303 controls. Lancet. 2008; 371(9609):303–14. [PubMed: 18294997]
5. Olsen CM, Green AC, Whiteman DC, et al. Obesity and the risk of epithelial ovarian cancer: a systematic review and meta-analysis. Eur J Cancer. 2007; 43(4):690–709. [PubMed: 17223544]
6. Rodriguez C, Calle EE, Fakhrabadi-Shokoohi D, Jacobs EJ, Thun MJ. Body mass index, height, and the risk of ovarian cancer mortality in a prospective cohort of postmenopausal women. Cancer Epidemiol Biomarkers Prev. 2002; 11(9):822–8. [PubMed: 12223425]
7. Kaaks R, Lukanova A, Kurzer MS. Obesity, endogenous hormones, and endometrial cancer risk: a synthetic review. Cancer Epidemiol Biomarkers Prev. 2002; 11(12):1531–43. [PubMed: 12496040]
8. Modugno F, Kip KE, Cochrane B, et al. Obesity, hormone therapy, estrogen metabolism and risk of postmenopausal breast cancer. International journal of cancer. 2006; 118(5):1292–301.
9. Antoniou A, Pharoah PD, Narod S, et al. Average risks of breast and ovarian cancer associated with BRCA1 or BRCA2 mutations detected in case Series unselected for family history: a combined analysis of 22 studies. Am J Hum Genet. 2003; 72(5):1117–30. [PubMed: 12677558]
10. Schatzkin A, Subar AF, Thompson FE, et al. Design and serendipity in establishing a large cohort with wide dietary intake distributions: the National Institutes of Health-American Association of Retired Persons Diet and Health Study. American journal of epidemiology. 2001; 154(12):1119–25. [PubMed: 11744517]
11. North American Association of Central Cancer Registries (NAACCR). North American Association of Central Disease Registries. NAACCR; 2004. standards for completeness, quality, analysis, and management of data.
12. Michaud DS, Midthune D, Hermansen S, et al. Comparison of cancer registry case ascertainment with SEER estimates and self-reporting in a subset of the NIH-AARP Diet and Health Study. J Registry Management. 2005; 32:70–5.

13. Fritz, AG.; Percy, C.; Jack, A., et al. International classification of diseases for oncology: ICD-O. 3. Geneva, Switzerland: World Health Organization (WHO); 2000.
14. World Health Org. Physical status: the use and interpretation of anthropometry. Geneva, Switzerland: World Heath Organization; 1995. Report No 854
15. Cox DR. Regression models and lifetables. J R Stat Soc (B). 1972; 34:187–220.
16. Carmichael AR, Bates T. Obesity and breast cancer: a review of the literature. Breast. 2004; 13(2): 85–92. [PubMed: 15019686]
17. Syed V, Ulinski G, Mok SC, Yiu GK, Ho SM. Expression of gonadotropin receptor and growth responses to key reproductive hormones in normal and malignant human ovarian surface epithelial cells. Cancer Res. 2001; 61(18):6768–76. [PubMed: 11559549]
18. Risch HA. Hormonal etiology of epithelial ovarian cancer, with a hypothesis concerning the role of androgens and progesterone. Journal of the National Cancer Institute. 1998; 90(23):1774–86. [PubMed: 9839517]
19. Garofalo C, Surmacz E. Leptin and cancer. Journal of cellular physiology. 2006; 207(1):12–22. [PubMed: 16110483]
20. Pralong FP, Gaillard RC. Neuroendocrine effects of leptin. Pituitary. 2001; 4(1–2):25–32. [PubMed: 11824505]
21. Schouten LJ, Rivera C, Hunter DJ, et al. Height, body mass index, and ovarian cancer: a pooled analysis of 12 cohort studies. Cancer Epidemiol Biomarkers Prev. 2008; (17):902–12. [PubMed: 18381473]
22. Peterson NB, Trentham-Dietz A, Newcomb PA, et al. Relation of anthropometric measurements to ovarian cancer risk in a population-based case-control study (United States). Cancer Causes Control. 2006; 17(4):459–67. [PubMed: 16596298]
23. Engeland A, Tretli S, Bjorge T. Height, body mass index, and ovarian cancer: a follow-up of 1. 1 million Norwegian women. Journal of the National Cancer Institute. 2003; 95(16):1244–8. [PubMed: 12928351]
24. Willett, WC. Nutritional Epidemiology. 2. New York: Oxford University Press; 2006.
25. Spencer EA, Appleby PN, Davey GK, Key TJ. Validity of self-reported height and weight in 4808 EPIC-Oxford participants. Public Health Nutr. 2002; 5(4):561–5. [PubMed: 12186665]
26. Beehler GP, Sekhon M, Baker JA, et al. Risk of ovarian cancer associated with BMI varies by menopausal status. J Nutr. 2006; 136(11):2881–6. [PubMed: 17056817]
27. Brinton LA, Sakoda LC, Frederiksen K, et al. Relationships of uterine and ovarian tumors to pre-existing chronic conditions. Gynecol Oncol. 2007; 107(3):487–94. [PubMed: 17825884]
28. Kurian AW, Balise RR, McGuire V, Whittemore AS. Histologic types of epithelial ovarian cancer: have they different risk factors? Gynecologic oncology. 2005; 96(2):520–30. [PubMed: 15661246]
29. Soegaard M, Jensen A, Hogdall E, et al. Different risk factor profiles for mucinous and nonmucinous ovarian cancer: results from the Danish MALOVA study. Cancer Epidemiol Biomarkers Prev. 2007; 16(6):1160–6. [PubMed: 17548679]

Table 1

Baseline characteristics according to BMI at baseline and BMI at age 18 years*

Variable	BMI (kg/m^2)					
	At baseline			At age 18 years		
	<25.0	25.0–29.9	≥30.0	<25.0	25.0–29.9	≥30.0
Participants (n)	43,102	30,610	20,813	77,721	4,993	1,497
Age at baseline (years)	62.4	62.7	62.1	-	-	-
White race/ethnicity (%)	93.6	90.5	88.5	92.4	92.3	90.5
Non-White race/ethnicity (%)	6.4	8.5	11.5	7.6	7.7	9.5
Never use of menopausal hormones (%)	40.1	46.1	55.7	44.4	54.3	59.4
Current or former use of menopausal hormones (%)	59.9	53.9	44.3	55.6	45.7	40.6
Current or former use of estrogen only in women with hysterectomy (%)	74.4	67.4	56.6	36.5	26.3	21.0
Current or former use of estrogen plus progestin in women with intact uteri (%)	41.3	33.7	24.2	68.9	59.2	52.7
Family history of ovarian cancer (%)	9.1	10.4	11.8	10.0	10.4	10.9
Family history of breast cancer (%)	27.9	27.8	27.6	28.2	27.7	25.1
Age at menarche (years)	12.7	12.6	12.3	12.6	12.2	12.1
Premenopausal (%)	4.7	4.5	4.6	4.6	4.7	4.9
Postmenopausal (%)	92.1	92.7	93.1	92.5	93.0	91.9
Natural menopause at <45 years of age (%)	62.8	60.3	59.4	61.6	62.5	62.7
Natural menopause at ≥45 years of age (%)	7.8	7.9	8.0	7.6	8.6	8.2
History of hysterectomy (%)	22.6	25.8	26.6	24.4	23.1	22.3
Age at menopause (years) among women with natural menopause	50.1	50.2	50.2	50.2	50.1	50.1
History of oral contraceptive use (%)	43.1	40.3	36.5	41.5	34.4	31.6
Parity (number of live-born children) among parous women	2.12	2.24	2.28	2.21	2.01	1.78
Physical activity †	57.1	48.3	35.5	50.2	44.2	39.9

*All values (except current age) were directly standardized to the age distribution of the cohort.

†Defined as >3 hours per week of physical activity of at least moderate intensity.

Table 2

Relative risk of ovarian cancer in relation to BMI at baseline in all women and in subgroups of women defined by selected variables

Variable	BMI at baseline (kg/m^2)			P value for test	
	<25.0	25.0–29.9	≥30.0	of trend	of inter-action
All women					
Person-years	291,801	206,936	139,773		
Number of cases	141	86	76		
Age-adjusted RR (95% CI) *	1.0	0.85 (0.65–1.11)	1.14 (0.86–1.51)	0.45	
Multivariate RR (95% CI) †	1.0	0.89 (0.69–1.18)	1.26 (0.94–1.68)	0.16	
Menopausal hormone use					
Never use					
Number of cases	39	43	43		
Multivariate RR (95% CI) †	1.0	1.39 (0.89–2.14)	1.83 (1.18–2.84)	0.007	
Ever use					
Number of cases	102	43	33		
Multivariate RR (95% CI) †	1.0	0.68 (0.48–0.98)	0.96 (0.65–1.43)	0.53	0.02
Hysterectomy					
No					
Number of cases	110	61	53		
Multivariate RR (95% CI) †	1.0	0.85 (0.62–1.17)	1.19 (0.85–1.66)	0.42	
Yes					
Number of cases	31	25	23		
Multivariate RR (95% CI) †	1.0	1.04 (0.62–1.77)	1.49 (0.87–2.58)	0.16	0.72
Combination of menopausal hormone use and hysterectomy					
Never used menopausal hormones					
No hysterectomy					
Number of cases	37	35	36		
Multivariate RR (95% CI) †	1.0	1.24 (0.78–1.97)	1.74 (1.09–2.76)	0.02	
Hysterectomy					
Number of cases	2	8	7		

Variable	BMI at baseline (kg/m^2)			P value for test	
	<25.0	25.0–29.9	≥30.0	of trend	of inter-action
Multivariate RR (95% CI) †	1.0	3.83 (0.82–18.01)	3.81 (0.79–18.34)	0.13	
Ever used menopausal hormones					
No hysterectomy					
Number of cases	73	26	17		
Multivariate RR (95% CI) †	1.0	0.62 (0.39–0.97)	0.77 (0.45–1.31)	0.15	
Hysterectomy					
Number of cases	29	17	16		
Multivariate RR (95% CI) †	1.0	0.82 (0.45–1.49)	1.34 (0.73–2.48)	0.41	0.55
Family history of ovarian cancer					
No					
Number of cases	119	81	67		
Multivariate RR (95% CI) †	1.0	1.02 (0.77–1.36)	1.36 (1.00–1.86)	0.06	
Yes					
Number of cases	22	5	9		
Multivariate RR (95% CI) †	1.0	0.29 (0.11–0.77)	0.74 (0.34–1.62)	0.31	0.02

*RR=relative risk. CI=confidence interval.

†The multivariate model used person-time as the underlying time metric and included the following covariates: age (continuous), race/ethnicity (White; non-White), family history of ovarian cancer (yes; no), family history of breast cancer (yes; no), duration of oral contraceptive use (never or <1 year; 1–9 years; ≥10 years), menopausal hormone therapy (never use of menopausal hormone therapy; ever use of estrogen only; former use of estrogen plus progestin; current use of estrogen plus progestin; other menopausal hormone use), and physical activity (inactive; achievement of either 20 minutes of vigorous exercise three or more times per week or 3 hours of at least moderate intensity activity per week; achievement of both 20 minutes of vigorous exercise three or more times per week and 3 hours of at least moderate intensity activity per week).

Table 3

Relative risk of ovarian cancer in relation to BMI at age 18 years in all women and in subgroups of women defined by selected variables

Variable	BMI at age 18 years (kg/m^2)			P value for test	
	<25.0	25.0–29.9	≥30.0	of trend	of inter-action
All women					
Person-years	525,503	33,473	9,901		
Number of cases	243	20	8		
Age-adjusted RR (95% CI) *	1.0	1.31 (0.83–2.07)	1.79 (0.89–3.64)	0.05	
Multivariate RR (95% CI) †	1.0	1.29 (0.82–2.04)	1.74 (0.86–3.53)	0.07	
Menopausal hormone use					
Never use					
Number of cases	93	15	6		
Multivariate RR (95% CI) †	1.0	2.06 (1.19–3.56)	2.55 (1.11–5.83)	0.001	
Ever use					
Number of cases	150	5	2		
Multivariate RR (95% CI) †	1.0	0.61 (0.25–1.48)	0.90 (0.22–3.64)	0.39	0.02
Hysterectomy					
No					
Number of cases	179	14	6		
Multivariate RR (95% CI) †	1.0	1.19 (0.69–2.07)	1.70 (0.75–3.86)	0.18	
Yes					
Number of cases	64	6	2		
Multivariate RR (95% CI) †	1.0	1.57 (0.68–3.64)	1.84 (0.45–7.53)	0.19	0.87
Combination of menopausal hormone use and hysterectomy					
Never used menopausal hormones					
No hysterectomy					
Number of cases	82	12	4		
Multivariate RR (95% CI) †	1.0	1.88 (1.02–3.44)	1.94 (0.71–5.31)	0.03	
Hysterectomy					
Number of cases	11	3	2		

Variable	BMI at age 18 years (kg/m^2)			P value for test	
	<25.0	**25.0–29.9**	**≥30.0**	**of trend**	**of inter-action**
Multivariate RR (95% CI) †	1.0	3.45 (0.96–12.39)	6.88 (1.52–31.09)	0.003	
Ever used menopausal hormones					
No hysterectomy					
Number of cases	97	2	2		
Multivariate RR (95% CI) †	1.0	0.37 (0.09–1.52)	1.36 (0.34–5.53)	0.51	
Hysterectomy					
Number of cases	53	3	0		
Multivariate RR (95% CI) †	1.0	1.04 (0.33–3.34)	-	-	0.19
Family history of ovarian cancer					
No					
Number of cases	211	18	8		
Multivariate RR (95% CI) †	1.0	1.34 (0.83–2.17)	2.01 (0.99–4.09)	0.03	
Yes					
Number of cases	32	2	0		
Multivariate RR (95% CI) †	1.0	0.96 (0.23–4.00)	-	-	-

*RR=relative risk. CI=confidence interval.

† The multivariate model included the covariates listed in Table 2 footnote.

Table 4

Multivariate relative risk of ovarian cancer in relation to the combination of BMI at baseline and BMI at age 18 years in all women and in subgroups of women defined by selected variables*

BMI (kg/m^2)		RR (95% CI)
All women		
At baseline	At age 18 years	
<25.0	<25.0	1.0 (ref.)
<25.0	≥25.0	1.26 (0.52–1.32)
≥25.0	<25.0	1.01 (0.78–1.30)
≥25.0	≥25.0	1.41 (0.89–2.32)
Women who never used menopausal hormones		
BMI (kg/m^2)		RR (95% CI)
At baseline	At age 18 years	
<25.0	<25.0	1.0 (ref.)
<25.0	≥25.0	1.56 (0.37–6.49)
≥25.0	<25.0	1.46 (0.95–2.24)
≥25.0	≥25.0	2.99 (1.69–5.29)
Women with hysterectomy		
BMI (kg/m^2)		RR (95% CI)
At baseline	At age 18 years	
<25.0	<25.0	1.0 (ref.)
<25.0	≥25.0	-
≥25.0	<25.0	1.05 (0.64–1.73)
≥25.0	≥25.0	2.04 (0.93–4.49)
Women who never used postmenopausal hormones with hysterectomy		
BMI (kg/m^2)	RR (95% CI)	
At baseline	At age 18 years	
<25.0	<25.0	1.0 (ref.)
<25.0	≥25.0	-
≥25.0	<25.0	2.48 (0.54–1.51)
≥25.0	≥25.0	9.41 (1.82–8.55)
Women with no family history of ovarian cancer		
BMI (kg/m^2)		RR (95% CI)
At baseline	At age 18 years	
<25.0	<25.0	1.0 (ref.)
<25.0	≥25.0	1.19 (0.44–3.24)
≥25.0	<25.0	1.11 (0.85–1.47)
≥25.0	≥25.0	1.68 (1.05–2.68)

The reference group are the women who jointly fell into the categories of BMI at baseline<25.0 kg/m^2 and BMI<25.0 kg/m^2 at age 18 years. The multivariate model included the covariates listed in Table 2 footnote.