HHS Public Access

Author manuscript

Gynecol Oncol. Author manuscript; available in PMC 2021 September 13.

Published in final edited form as:

Gynecol Oncol. 2020 July ; 158(1): 123–129. doi:10.1016/j.ygyno.2020.04.700.

Cardiometabolic comorbidities and epithelial ovarian cancer risk among African-American women in the African-American Cancer Epidemiology Study (AACES)

Jeanine N. Staples, M.D.[1], **Lauren C. Peres, Ph.D.**[2], **Fabian Camacho, M.S.**[3], **Anthony J. Alberg, Ph.D.**[4], **Elisa V. Bandera, Ph.D.**[5], **Jill Barnholtz-Sloan, Ph.D.**[6], **Melissa L. Bondy, Ph.D.**[7], **Michele L. Cote, Ph.D.**[8], **Ellen Funkhouser, Ph.D.**[9], **Patricia G. Moorman, Ph.D.**[10], **Edward S. Peters, Sc.D.**[11], **Ann G. Schwartz, Ph.D.**[8], **Paul D. Terry, Ph.D.**[12], **Joellen M. Schildkraut, Ph.D.**[13]

[1]Division of Gynecology Oncology, Department of Obstetrics and Gynecology, University of Virginia, Charlottesville, VA, USA

[2]Department of Cancer Epidemiology, H. Lee Moffitt Cancer Center and Research Institute, Tampa, Florida, USA

[3]Department of Public Health Sciences, University of Virginia, Charlottesville, Virginia, USA

[4]Department of Epidemiology and Biostatistics, Arnold School of Public Health, University of South Carolina, Columbia, SC, USA

[5]Department of Population Science, Rutgers Cancer Institute of New Jersey, New Brunswick, New Jersey, USA

[6]Department of Population and Quantitative Health Sciences and Case Comprehensive Cancer Center, Case Western Reserve University School of Medicine, Cleveland, OH, USA

[7]Cancer Prevention and Population Sciences Program, Baylor College of Medicine, Houston, Texas, USA

[8]Karmanos Cancer Institute, Wayne State University School of Medicine, Detroit, MI, USA

[9]Division of Preventive Medicine, University of Alabama at Birmingham, Birmingham, Alabama, USA

Corresponding Author: Jeanine N. Staples MD MPH, Division of Gynecologic Oncology, Department of Obstetrics and Gynecology, University of Virginia Health 35 System, Box 800712, Charlottesville, VA 22908, Telephone: (434) 924-8703, js6qf@hscmail.mcc.virginia.edu.

Author contributions: Data acquisition: AA, MB, EB, PM, JMS, EF, J B-S, EP, AS, MC, PT, SC. Data Management/Data analysis: JNS, LA, FW, FC. Manuscript preparation: JNS, JMS, PM, EB, AA, J B-S. All authors read and approved the final manuscript.

CRediT Author Statement

Author contributions: Data acquisition: AA, MB, EB, PM, JMS, EF, J B-S, EP, AS, MC, PT, SC. Data Management/Data analysis: JNS, LA, FW, FC.

Manuscript preparation: JNS, JMS, PM, EB, AA, J B-S. All authors read and approved the final manuscript.

Conflict of interest: The authors declare that they have no competing interests.

[10]Department of Community and Family Medicine, Duke University Medical Center, Durham, NC, USA

[11]Epidemiology Program, Louisiana State University Health Sciences Center School of Public Health, New Orleans, Louisiana, USA

[12]Department of Medicine, University of Tennessee Medical Center – Knoxville, Knoxville, Tennessee, USA

[13]Emory University Rollins School of Public Health, Atlanta, GA, USA

Abstract

Background: Studies that have examined the association between cardiovascular comorbidities and epithelial ovarian cancer (EOC) have yielded inconsistent results. It remains unknown whether cardiometabolic disease is associated with EOC in African American (AA) women, who have a higher prevalence of cardiovascular disease and lower risk of EOC than White women. Here, we estimate the effect of cardiovascular comorbid conditions and EOC risk among AA women.

Methods: Data were available from 593 ovarian carcinoma patients and 752 controls enrolled in the African American Cancer Epidemiology Study (AACES). Participants were asked to self-report a history of hypertension, hyperlipidemia, and diabetes and any current medication use. The relationship between hypertension, hyperlipidemia, diabetes, and medications taken for these conditions was determined using multivariate logistic regression.

Results: Hypertension was associated with an increased risk (adjusted odds ratio (aOR)=1.32, 95% confidence interval (CI)=1.01, 1.73), whereas diabetes and hyperlipidemia were associated with a decreased risk (aOR=0.67, 95% CI=0.49, 0.91 and aOR=0.61, 95% CI=0.47, 0.80, respectively) of EOC. Use of anti-diabetic medication was inversely associated with EOC risk, as was use of lipid lowering medications (in the overall study population), which were predominantly statins. Among women with hypertension, use of anti-hypertensive medications was inversely associated with EOC risk, with associations that were most pronounced for diuretics, ARBs and ACE inhibitors.

Conclusion: Hypertension was associated with an increased EOC risk in this patient population, whereas an inverse association was observed for diabetes and hyperlipidemia. The decreased risk of EOC identified with use of anti-hypertensive, anti-diabetes or lipid-lowering medications could have implications for risk reduction strategies.

Keywords

Ovarian cancer risk; disparities; cardiovascular disease

Introduction

Ovarian cancer is the most lethal of all gynecological malignancies. The Surveillance, Epidemiology, and End Results (SEER) Program estimates 22,530 new cases will be diagnosed in 2019 and 13,980 thousand women will die from the disease [1]. The age-adjusted incidence rate is highest among White women (12.1 per 100,000), followed by Hispanics (10.3), Asian/Pacific Islanders (9.4), and African American (AA) women (9.2)

[2]. The observed variability of incidence rates between racial/ethnic sub-groups is likely multifactorial, but the current literature evaluating these differences is somewhat limited. Further research on etiologic risk factors for ovarian cancer is necessary, particularly among minority women who are underrepresented in epidemiological studies.

The impact of cardiometabolic disease and use of various cardiometabolic agents on risk of epithelial ovarian cancer (EOC) has previously been explored, but data is limited and somewhat inconsistent. Hypertension and diabetes are perhaps the most studied, given the relatively high prevalence among the general population (33% and 10%, respectively [3]). Studies evaluating the association between hypertension and EOC risk have had mixed findings [4–7]. Investigators have shown that certain anti-hypertensive agents may be positively associated with EOC risk, while others are not [4]. The Nurses Health Study (NHS) showed a positive association between use of thiazide diuretics and EOC, yet no associations were observed for beta-blockers or ace-inhibitors [4]. In a meta-analysis of 19 observational studies, women with diabetes had a modest increased risk of ovarian cancer [8]. Additionally, recent data suggests a weak positive association between hyperlipidemia and EOC risk [5, 7]. Although statins have been suggestively inversely associated with risk, no association has been identified between biguanide (metformin) use and EOC risk [9, 10].

It remains unknown whether cardiometabolic disease or medication use is associated with risk of EOC in AA women, who generally have a higher prevalence of diabetes and cardiovascular disease than Whites [3]. The goal of the present study is to investigate the potential influence of cardiometabolic co-morbidities and their associated medication use on EOC risk among AA women.

Methods

Study Design and Participants

AACES is a population-based case–control study of self-identified AA women with incident invasive EOC in 11 geographic locations in the United States (Alabama, Georgia, Illinois, Louisiana, Michigan, New Jersey, North Carolina, Ohio, South Carolina, Tennessee, and Texas). Institutional review board approval was obtained from the University of Virginia School of Medicine and all participating institutions. The methods used in AACES have been previously described [11] and are briefly reported here. Cases were identified using rapid case ascertainment through cancer registries, hospitals, and gynecologic oncology clinics. Inclusion criteria for cases included self-identified AA women, between 20 and 79 years of age, and diagnosed with histologically confirmed incident EOC between December 1, 2010 and December 31, 2015. Controls were identified using random digit dialing and were frequency-matched to cases by 5-year age categories and geographic location. Controls were eligible if they self-identified as AA and excluded if they had a previous diagnosis of EOC or if they had a prior bilateral oophorectomy. Cases and controls completed a baseline telephone survey including detailed questions on demographics; reproductive, gynecologic, and medical history; exogenous hormone use; personal and family history of cancer; and lifestyle characteristics including smoking, alcohol consumption and physical activity.

Exposures

Participants were asked to self-report a history of hypertension, hyperlipidemia, or diabetes mellitus and the age at diagnosis for each condition. Women who reported a comorbidity diagnosis after the reference date (cases: diagnosis of EOC; controls: time of interview) were categorized as not having the disease (n=7 women with diabetes, 9 women with hyperlipidemia and 15 women with hypertension). Participants were also asked to report any medication use, as well as duration and indication of use, at the time of the interview. The names of each drug were reviewed and categorized by mechanism of action (Supplementary Table 1). Women reporting use of combination medications (e.g., diuretic and calcium channel blocker) were categorized as use of both types.

Statistical Analysis

Characteristics of cases and controls were compared using chi-square and t-tests. Multivariable logistic regression was used to calculate odds ratios (ORs) and 95% confidence intervals (CIs) for the association between each comorbidity and their medications with risk of EOC. All models were adjusted for study site, age (continuous), parity (0, 1–2, >2 live births), family history of breast or ovarian cancer in a first degree relative (yes/no), duration of oral contraceptive pill (OCP) use (continuous), education (graduated high school, some education after high school, college graduate) and body mass index (<25, 25–30, 30–35, 35–40, >40 kg/m^2). For the models evaluating each comorbidity and EOC risk, we provide an additional model adjusted for the presence of the other co-morbidities (e.g., for the association between diabetes and EOC risk, hypertension and hyperlipidemia were included as covariates in the model). We also assessed whether a combination of comorbid conditions was associated with EOC risk (e.g., HTN and HLD, HTN and DM). For the models evaluating medication use and EOC risk, ORs were calculated among the entire study population and also among the women with that specified comorbidity. All analyses were repeated, restricted to the most common histotype, high-grade serous carcinoma (HGSC). We also assessed interactions between each comorbidity and their associated medication use with EOC risk. All analyses were conducted using SAS version 9.4.

Results

Characteristics of the cases and controls are found in Table 1. Significant differences in the distribution of EOC risk factors such as parity, BMI, OC use, and family history of breast or ovarian cancers are observed by case-control status.

When controlling for the presence of other co-morbidities, hypertension is associated with an increased risk of EOC, OR=1.32 (95% CI= 1.01, 1.73) (Table 2). The association appears to significantly weaken over time, with women who have hypertension for <10 years conferring a stronger risk (OR=1.59, 95% CI= 1.17, 2.16) than those with hypertension for 10 years or longer (OR=1.10, 95% CI= 0.81, 1.50) (P=0.02 for comparison of ORs). Conversely, hyperlipidemia or diabetes is associated with a decreased EOC risk, OR=0.61 (95% CI= 0.47, 0.80) and OR=0.67 (95% CI= 0.49, 0.91), respectively. No differences were observed by duration of diabetes or hyperlipidemia. Among the study population, 13.8% of

cases (N=53) and 12.5% of controls (N=94) were diagnosed with all three co-morbidities. A diagnosis of all three comorbidities is associated with a decreased EOC risk, OR=0.58 (95% CI= 0.38, 0.89), suggesting that the impact of hyperlipidemia and diabetes outweigh the risk impact of hypertension when all three are present. When restricting to HGSC, the ORs for hypertension, diabetes and hyperlipidemia were similar to that of all EOC (Supplementary Table 2), but the association diminishes for those with hypertension for 10 years or longer (OR=0.93, 95% CI=0.65, 1.34).

Among the entire study population, a suggestive inverse association is present between ever use of any anti-hypertensive medication and EOC risk, OR=0.79 (95% CI=0.62, 1.02), while among women with hypertension this association is more pronounced, OR=0.43 (95% CI=0.28, 0.66) (Table 3). Indications for use of anti-hypertension medication among women who do not have hypertension include anxiety, cardiac arrythmia, peripheral edema and congestive heart failure. Among women with hypertension, use of diuretics, angiotensin-converting-enzyme (ACE) inhibitors and angiotensin receptor blockers (ARBs) was associated with a decreased EOC risk, while no association was present for calcium channel blockers (CCB) or beta blockers (BB). There were 23 cases and 33 controls who used anti-hypertensive medication for indications other than hypertension, which was associated with an increased risk (OR = 1.36, 95% CI 0.72, 2.54) compared to the inverse association for anti-hypertensive medication use among hypertensive patients (OR = 0.46, 95% CI 0.30, 0.71, interaction p=0.006, Table 4).

Among the study population, ever use of any anti-diabetes medication is associated with a decreased risk of EOC (OR=0.58, 95% CI 0.42, 0.79). Use of anti-diabetes medications among non-diabetics is rare (N=8 cases and N=6 controls) and limited to biguanide (metformin) use for other diseases related to insulin-resistance (eg. PCOS and fatty liver disease). Among women with diabetes, the reduced risk of EOC with use of anti-diabetes medication is even more pronounced (OR=0.47, 95% CI 0.26–0.86). Women with untreated diabetes made up 28% of cases and 17% of controls. Use of metformin is associated with a decreased risk of EOC (OR=0.63, 95% CI 0.43, 0.93). A suggestive, but not statistically significant, inverse association for use of insulin and sulfonylurea was also present (OR=0.66, 95% CI 0.37, 1.16 and OR=0.82, 95% CI 0.47, 1.42, respectively). An interaction between use of medication and presence of diabetes with EOC risk was observed (p=0.007, Table 4). Ever use of any lipid lowering medication is associated with a decreased risk of EOC in the study population (OR=0.52, 95% CI 0.39, 0.69), which is largely driven by statins (OR=0.55, 95% CI 0.41, 0.73). Although use of non-statin lipid lowering medications was rare (n=18), an inverse association with EOC risk was observed (OR=0.25, 95% CI 0.07, 0.84). No interaction was observed between use of medication and presence of hyperlipidemia with EOC risk (p= 0.825, Table 4). Again, restricting to HGSC revealed results similar to the overall findings (Supplemental Table 3).

Discussion

In the largest case-control study of AA women with EOC, we found that hypertension is associated with an increased EOC risk, yet among hypertensive women, ever use of any anti-hypertensive medication is associated with a decreased EOC risk. Due to the common

nature of polytherapy for hypertension, we evaluated specific medications and observed that use of diuretics, ARBs and ACE inhibitors were all associated with a decreased risk of EOC, while CCB and BB use did not show an effect. Race is an explicit branch-point in the treatment algorithm for hypertension. Diuretics or CCB are recommended for monotherapy in AA individuals without chronic kidney disease (CKD), whereas ACE-I should be used in AA with CKD and proteinuria because of the higher incidence of end-stage renal disease in AA patients [12, 13]. One could argue that diuretics should be prioritized as initiating treatment over CCB among AA, particularly among those who may be at increased risk for EOC. While the impact of CCB on EOC risk did not reach statistical significance, there was a borderline positive association with risk among the study population.

In the Nurses' Health Study (NHS) [4], hypertension was not associated with EOC risk, yet current use of any anti-hypertensive medication was associated with a slightly increased risk, primarily driven by use of thiazide diuretics. Furthermore, CCBs were associated with a decreased risk in the NHS. Findings from our study directly conflict to those of the NHS, potentially as a consequence of evaluating a different patient population. With 97% White enrollment in the NHS [14], there is a notable lack of diversity in the NHS study population. Moreover, the prevalence of hypertension among women in the NHS study was lower than that of our study population (33% in NHS vs. 56% among controls and 65% among cases in AACES). Additionally, use of anti-hypertension medication use was 36% in the NHS compared to 55% in AACES. Perhaps the most substantial difference between AACES and NHS is the study design and data collection procedures. As NHS is a cohort study with continuous biennial follow-up, a history of anti-hypertensive medication use prior to diagnosis could be determined. In AACES, medication use was defined at the time of the questionnaire, coinciding with diagnosis and interview. Thus, AACES was able to evaluate the association between "current use" and EOC risk. Furthermore, other studies have reported findings consistent with the present study. Bjorge, et al found that among 287,320 women from Austria, Norway and Sweden, hypertension was associated with a slightly increased risk of ovarian cancer, particularly among endometrioid tumors [7]. More recently, a large SEER-Medicare case-control study including 298,728 women found that hypertension was associated with a modest increased risk for ovarian cancer [5].

The precise mechanism underlying the association between hypertension and EOC risk is not clear. In studies with animal models, hypertension may result in abnormal proliferation and a defective growth stimulatory-inhibitory control [15]. High blood pressure does appear to increase the risk of other types of cancer, but more research is needed to clarify the association between hypertension and ovarian cancer [16]. Furthermore, teasing out the interaction between hypertension and use of anti-hypertensive medications is paramount to better understand the complex relationship with EOC risk. We found that among women with hypertension, use of anti-hypertensive medication is inversely associated with risk of EOC. This offers a potential explanation to the diminishing association between hypertension and EOC over time. We found that women who have had hypertension for <10 years have a more pronounced positive association (OR=1.59) than those who had hypertension for 10 years or longer (OR=1.10). Prolonged use of anti-hypertensive medication may potentially play a role in combating the pro-inflammatory and pro-stimulatory state of hypertension.

Beta-blockers are perhaps the most studied anti-hypertensive medication from an epidemiologic standpoint. Pre-clinical evidence shows that continuous adrenergic activation can promote ovarian cancer growth and metastasis [17]. Thus, the anti-adrenergic nature of beta-blockers has been a topic of interest with respect to improving survival outcomes. In perhaps the largest study examining this topic to date, including 1425 patients with ovarian cancer, beta blockers were associated with better survival [18]. Hefner and Csef further explored this in 2017 with a confirmatory qualitative systematic review [19]. Subsequent studies have shown that beta-blockers do not influence the prognosis of patients with epithelial ovarian cancer [20]. Few studies, however, have looked at the relationship between beta blockade and ovarian cancer risk. NHS found no association between beta-blocker use and risk of developing ovarian cancer, which is consistent with our findings [4].

In the present study, we found that hyperlipidemia was associated with a decreased risk of EOC, and among the entire study population, ever use of any lipid-lowering medication was also inversely associated with risk. Hyperlipidemia may cause increased tumor angiogenesis, reduced apoptosis and increased tumor cell proliferation due to its effect on various signaling pathways [21] and relevant proteins, such as cell survival kinase Akt [22]. When compared to healthy controls, aberrant lipid metabolism has been detected in ovarian cancer patients during early and late stages of disease, including patients with recurrent disease [23, 24]. While a number of epidemiologic studies have shown differing associations between cholesterol and cancer risk by cancer site and sex [16], our findings are consistent with a large longitudinal cohort study that found patients with hyperlipidemia have a 33% decreased risk of breast cancer [25]. Other studies have shown a modest increased EOC risk among women with hyperlipidemia (5, 7). Treatment with lipid-lowering medications may contribute to the observed decreased risk of EOC among women with hyperlipidemia in the present study. While a significant interaction was not identified between hyperlipidemia and use of lipid-lowering medications, among women with hyperlipidemia, use of any lipid-lowering medication was associated with a 33% decreased risk of EOC. These findings are consistent with the New England Case Control (NEC) Study, including 2,040 cases with EOC and 2,100 frequency-matched controls, who found that women who used statins had a 32% lower risk of ovarian cancer compared to non-users [26]. Basic science research suggests that statins' inhibition of HMG-CoA reductase leads to reduced levels of mevalonate and its downstream products which are critical for cellular functions related to cell cycle progression [27]. Thus, disruption of these processes could theoretically suppress tumor initiation, growth and metastasis [27]. This warrants future investigation of the potentially beneficial effect of these medications on women at risk for EOC.

Several underlying mechanisms by which diabetes and carcinogenesis may be linked have been proposed. Exposure to chronic hyperglycemia may induce formation of reactive oxygen species, reduce tumor suppression from AMP-activated protein kinase, and lead to the accumulation of advanced glycation end products that modulate the mitogenic NF–kB pathway [28, 29, 30]. Hyperglycemia also reduces IGF binding protein, resulting in higher exposure to growth-stimulating IGF-I and IGF-II [30]. As such, most studies have shown a weak positive association between circulating insulin levels and ovarian cancer risk [10]. However, in Michels et al, an impaired fasting glucose was associated with a decreased risk of ovarian cancer, which is consistent with our findings [5]. While we found that

diabetes was associated with a decreased risk of EOC, there was a significant interaction between diabetes and medication use suggesting that women without diabetes who took diabetes medications had a borderline positive association with EOC risk, while an inverse association was present for women who had diabetes and took diabetes medications. This finding highlights the importance of medication use in modifying risk. The antitumor effect of metformin is thought to be related to a reduction of insulin and insulin-like growth factor.

Our study has many strengths including a large sample size, population-based study, and detailed information on use of different classes of medications and known ovarian cancer and cardiometabolic risk factors. Furthermore, this is the first study to evaluate these associations among AA women. However, there are limitations to consider. Presence of comorbidities was based on self-report; however, there is data to suggest a moderate overall concordance between patient self-reports and claims records for clinical diagnosis and substantial concordance for medication use [32]. Any misclassification errors due to under-reporting of comorbidity diagnoses would likely attenuate the association with EOC risk. A detailed history of prior medication use was not available in this study and remains an important area of investigation for future studies. Individuals who engage in the health care system and attempt to manage their disease with medications may differ from those who do not engage. The present study did not have information on medication compliance or the extent of cardiometabolic disease severity or control. Thus, we cannot assume that medication use (or report thereof) implies regular engagement in the health system, compliance, or adequate disease control. Although this is the largest case-control study of EOC in African-American women, there were relatively small numbers of women in certain strata of medication use, potentially impacting our power to detect an association.

In summary, this study population of AA women had a high prevalence of cardiometabolic conditions. We observed that hypertension is associated with an increased risk of EOC among AA women, and hyperlipidemia and diabetes both confer a decreased risk. Moreover, our observation of inverse associations with EOC risk for use of medications for each comorbidity highlights the need for further research to examine the mechanisms underlying this finding and demonstrates the importance of adequate management of these chronic conditions.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgements:

We acknowledge the AACES interviewers, Christine Bard, LaTonda Briggs, Whitney Franz (North Carolina), and Robin Gold (Detroit). We also acknowledge the individuals responsible for facilitating case ascertainment across the 10, including Christie McCullum-Hill (Alabama); Rana Bayakly, Vicki Bennett, Judy Andrews, and Debbie Chambers (Georgia); the Louisiana Tumor Registry; Lisa Paddock and Manisha Narang (New Jersey); Diana Slone, YingliWolinsky, Steven Waggoner, Anne Heugel, Nancy Fusco, Kelly Ferguson, Peter Rose, Deb Strater, Taryn Ferber, Donna White, Lynn Borzi, Eric Jenison, Nairmeen Haller, Debbie Thomas, Vivian von Gruenigen, Michele McCarroll, Joyce Neading, John Geisler, Stephanie Smiddy, David Cohn, Michele Vaughan, Luis Vaccarello, Elayna Freese, James Pavelka, Pam Plummer, William Nahhas, Ellen Cato, John Moroney, Mark Wysong, Tonia Combs, Marci Bowling, Brandon Fletcher (Ohio); Susan Bolick, Donna Acosta, Catherine Flanagan (South Carolina); Martin Whiteside (Tennessee) and Georgina Armstrong and the Texas Registry, Cancer Epidemiology and Surveillance Branch, Department of State Health Services.

Funding: The AACES study was funded by NCI (CA142081-01A1). Additional support was provided by Metropolitan Detroit Cancer Surveillance System (MDCSS) with federal funds from the National Cancer Institute, National Institute of Health, Dept. of Health and Human Services, under Contract No. HHSN261201000028C and the Epidemiology Research Core, supported in part by NCI Center Grant (P30CA22453) to the Karmanos Cancer Institute, Wayne State University School of Medicine.

References

[1]. Siegel RL, Miller KD and Jemal A (2019), Cancer statistics, 2019. CA A Cancer J Clin, 69: 7–34. doi:10.3322/caac.21551

[2]. Howlader N, Noone AM, Krapcho M, Miller D, Brest A, Yu M, Ruhl J, Tatalovich Z, Mariotto A, Lewis DR, Chen HS, Feuer EJ, Cronin KA (eds). SEER Cancer Statistics Review, 1975–2016, National Cancer Institute. Bethesda, MD, https://seer.cancer.gov/csr/1975_2016/, based on November 2018 SEER data submission, posted to the SEER web site, April 2019

[3]. Mozaffarian D, Benjamin EJ, Go AS, et al.Heart disease and stroke statistics--2015 update: A report from the American Heart Association. Circulation2015; 131: e29–e322. [PubMed: 25520374]

[4]. Huang T, Poole EM, Eliassen AH, Okereke OI, Kubansky LD, Sood AK Forman JP, Tworoger SS. Hypertension, use of antihypertensive medications, and risk of epithelial ovarian cancer. Int J Cancer2016; 139:291–299. [PubMed: 26934358]

[5]. Michels KA, McNeel TS, Trabert B. Metabolic syndrome and risk of ovarian and fallopian tube cancer in the United States: An analysis of linked SEER-Medicare data. Gynecol Oncol201911; 155(2):294–300. [PubMed: 31495456]

[6]. Soler M, Chatenoud L, Negri E, Parazzini F, Franceschi S, La Vecchia C. Hypertension and hormone-related neoplasms in women. Hypertension19998; 34(2):320–325. [PubMed: 10454461]

[7]. Bjorge T, Lukanova A, Tretli S, Manjer J, Ulmer H, Stocks T, Selmer R, Nagel G, Almquist M, Concin H, Hallmans G, Jonsson H, et al.Metabolic risk factors and ovarian cancer in the Metabolic Syndrome and Cancer project. Int J Epidemiol. 2011; 40:1667–77. [PubMed: 21984693]

[8]. Lee JY, Jeon I, Kim JW, Song YS, Yoon JM, Park SM. Diabetes mellitus and ovarian cancer risk : a systematic review and meta-analysis of observational studies. Int J Gynecol Cancer32013; 23(3):402–12. [PubMed: 23354371]

[9]. Khan MS, Fatima K, Rameez. Impact of statins on risk and survival of ovarian cancer. J Gynecol Oncol. 2015; 26(3):240–241. doi:10.3802/jgo.2015.26.3.240 [PubMed: 26197861]

[10]. Urpilainen E, Marttila M, Hautakoski A, Arffman M, Sund R, Ilanne-Parikka P, Arima R, Kangaskokko J, Puistola U, Läärä E, Hinkula MThe role of metformin and statins in the incidence of epithelial ovarian cancer in type 2 diabetes: a cohort and nested case–control study. BJOG2018; 125: 1001–1008. [PubMed: 29412502]

[11]. Schildkraut JM, Alberg AJ, Bandera EV, Barnholtz-Sloan J, Bondy M, Cote ML, et al.A multi-center population-based case-control study of ovarian cancer in African-American women: the African American Cancer Epidemiology Study (AACES). BMC Cancer2014; 14:688. [PubMed: 25242549]

[12]. Group ACR. Major outcomes in high-risk hypertensive patients randomized to angiotensin-converting enzyme inhibitor or calcium channel blocker vs diuretic: The Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT). JAMA. 2002; 288:2981–2997. [PubMed: 12479763]

[13]. Wright JT Jr., Bakris G, Greene T, et al.Effect of blood pressure lowering and antihypertensive drug class on progression of hypertensive kidney disease: results from the AASK trial. JAMA. 2002;288:2421–2431. [PubMed: 12435255]

[14]. Bao Y, Bertoia ML, Lenart EB, et al.Origin, methods, and evolution of the three Nurses' Health studies. Am J Public Health. 2016; 106(9):1573–1581. [PubMed: 27459450]

[15]. Hadrava V, Tremblay J PAbnormalities in growth characteristics of aortic smooth muscle cells in spontaneously hypertensive rats. Hypertension1989; 13: 589–597. [PubMed: 2786847]

[16]. Radišauskas R, Kuzmickienė I, Milinavičienė E, Everatt R. Hypertension, serum lipids and cancer risk: a review of epidemiological evidence. Medicina (2016); 52: 89–98 [PubMed: 27170481]

[17]. Tang J, Li Z, Lu L, Cho CH. B-Adrenergic system, a backstage manipulator regulating tumour progression and drug target in canacer therapy. Semin Cancer Biol. 2013; 23(6 pt B):533–542. [PubMed: 24012659]

[18]. Watkins J L, Thaker P H, Nick A M. et al.Clinical impact of selective and nonselective beta-blockers on survival in patients with ovarian cancer. Cancer. 2015; 121:3444–3451. [PubMed: 26301456]

[19]. Hefner J, Csef H. The Clinical Relevance of Beta Blockers in Ovarian Carcinoma: A Systematic Review. Geburtshilfe Frauenheilkd. 201610; 76(10): 1050–1056. [PubMed: 27761025]

[20]. Heitz F, Hengsbach A, Harter P, Traut A, Ataseven B, Schneider S, Prader S, Kurzeder C, Sporkmann M, du Bois A. Intake of selective beta blockers has no impact on survival in patients with epithelial ovarian cancer. Gynecol Oncol. 20171;144(1):181–186. [PubMed: 27863705]

[21]. Mondul AM, Weinstein SJ, Virtamo J, Albanes D. Serum total and HDL cholesterol and risk of prostate cancer. Cancer Causes Control2011;22(11):1545–52. [PubMed: 21915616]

[22]. Oh HY, Lee EJ, Yoon S, Chung BH, Cho KS, Hong SJ. Cholesterol level of lipid raft micro domains regulates apoptotic cell death in prostate cancer cells through EGFR-mediated Akt and ERK signal transduction. Prostate2007;67:1061–9. [PubMed: 17469127]

[23]. Xiao Y; Chen Y; Kennedy AW; Belinson J; Xu YEvaluation of plasma lysophospholipids for diagnostic significance using electrospray ionization mass spectrometry (ESI-MS) analyses. Ann. N. Y. Acad. Sci. 2000, 905, 242–259. [PubMed: 10818458]

[24]. Xu Y; Shen Z; Wiper DW; Wu M; Morton RE; Elson P; Kennedy AW; Belinson J; Markman M; Casey GLysophosphatidic acid as a potential biomarker for ovarian and other gynecologic cancers. JAMA1998, 280, 719–723. [PubMed: 9728644]

[25]. Carter PR, Uppal H, Chandran S, Bainey KR, Potluri R, Algorithm for Comorbidities, Associations, Length of Stay and Mortality (ACALM) Research Unit, 3106 Patients with a diagnosis of hyperlipidaemia have a reduced risk of developing breast cancer and lower mortality rates: a large retrospective longitudinal cohort study from the UK ACALM registry, European Heart Journal, Volume 38, Issue suppl_1, August 2017, ehx504.3106, 10.1093/eurheartj/ehx504.3106.

[26]. Akinwunmi B, Vitonis AF, Titus L, Terry KL, Cramer DW. Statin therapy and association with ovarian cancer risk in the New England Case Control (NEC) study. Int J Cancer2019;144(5):991–1000. [PubMed: 30006925]

[27]. Wong WW, Dimitroulakos J, Minden MD, Penn LZ. HMG-CoA reductase inhibitors and the malignant cell: the statin family of drugs as triggers of tumor-specific apoptosis. Leukemia2002;16:508–19. [PubMed: 11960327]

[28]. Becker S,Dossus L, Kaaks R. Obesity related hyperinsulinaemia and hyperglycaemia and cancer development. Arch Physiol Biochem2009;115:86–96. [PubMed: 19485704]

[29]. Ramasamy R, Yan SF, Schmidt AM. RAGE: therapeutic target and biomarker of the inflammatory response—the evidence mounts. J Leukoc Biol2009;86:505–12. [PubMed: 19477910]

[30]. Chakrabarty S, Kondratick L. Insulin-like growth factor binding protein-2 stimulates proliferation and activates multiple cascades of the mitogen-activated protein kinase pathways in NIH-OVCAR3 human epithelial ovarian cancer cells. Cancer Biol Ther2006;5:189–97. [PubMed: 16357519]

[31]. Zi F, Zi H, Li Y, He J, Shi Q, Cai Z. Metformin and cancer: An existing drug for cancer prevention and therapy. Oncol Lett. 2018;15(1):683–690. doi:10.3892/ol.2017.7412 [PubMed: 29422962]

[32]. Wu CS, Lai MS, Gau SS, Wang SC, Tsai HJConcordance between patient self-reports and claims data on clinical diagnoses, medication use, and health system utilization in Taiwan. PloS ONE. 2014;9:e112257. doi: 10.1371/journal.pone.0112257. [PubMed: 25464005]

Table 1.

Characteristics of AACES Participants

Participant characteristics	Case (n=593) Mean (SD) or n (%)	Control (n=752) Mean (SD) or n (%)	p-value
Age, years[a]			
Continuous	58.10 (10.9)	54.98 (11.67)	<0.0001
<50	124 (20.9)	201 (26.7)	
50–60	201 (33.9)	281 (37.4)	
60–70	171 (28.8)	195 (25.9)	
>70	97 (16.4)	75 (10.0)	0.001
BMI, kg/m^2			
Continuous	32.76 (8.39)	31.95 (8.13)	0.08
<25	86 (14.6)	141 (18.8)	
25 – 30	155 (26.3)	198 (26.4)	
30 – 35	171 (29.0)	189 (25.2)	
35 – 40	84 (14.3)	123 (16.4)	
>40	93 (15.8)	100 (13.3)	
Missing	4	1	0.11
Parity			
Continuous	2.27 (1.82)	2.3 (1.6)	0.74
0 births	109 (18.4)	96 (12.8)	
1–2 births	248 (42.0	342 (45.6)	
>2 births	234 (39.6)	312 (41.6)	
Missing	2	2	0.02
Duration of OCP use, months			
Continuous	43.31 (67.82)	53.19 (70.2)	0.01
Never	209 (35.3)	182 (24.4)	
≥ 1 to <60 months	214 (36.1)	315 (42.2)	
≥60 months	169 (28.6)	250 (33.5)	
Missing	1	5	0.01
Income			

	Case (n=593)	Control (n=752)	
Participant characteristics	**Mean (SD) or n (%)**	**Mean (SD) or n (%)**	**p-value**
<$25,000	241 (45.3)	320 (44.1)	
≥$25,000	291 (54.7)	405 (55.9)	
Missing	61	27	0.68
Education			
High school or less	266 (44.9)	281 (37.7)	
Some post-high school	143 (24.1)	211 (28.1)	
College graduate	184 (31.0)	260 (34.6)	0.02
Menopausal status			
Pre-	81 (13.7)	140 (18.6)	
Peri-	71 (12.0)	86 (11.4)	
Post-	440 (74.3)	526 (69.9)	
Missing	1	0	0.05
Family history of breast or ovarian cancer			
Yes	157 (26.5)	134 (17.8)	
No	436 (73.5)	618 (82.2)	0.0001
Tubal ligation			
Yes	209 (35.2)	302 (40.2)	
No	384 (64.8)	450 (59.8)	0.07
Smoking status			
Never	328 (55.5)	437 (58.1)	
Past	176 (23.4)	167 (22.2)	
Current	60 (10.2)	148 (19.7)	
Missing	2	0	<0.0001
History of DM			
Yes	130 (21.9)	176 (23.4)	
No	463 (78.1)	576 (76.6)	
Age at DM diagnosis, years	51.5 (12.6)	49.7 (11.9)	0.20
Use of anti-DM meds			
Yes	101 (17.0)	152 (20.2)	
No	492 (83.0)	600 (79.8)	0.14

Participant characteristics	Case (n=593) Mean (SD) or n (%)	Control (n=752) Mean (SD) or n (%)	p-value
History of HLD			
Yes	195 (32.9)	279 (37.1)	
No	398 (61.1)	473 (62.9)	0.11
Age at HLD diagnosis, years	52.3 (11.3)	51.8 (11.0)	0.65
Use of anti-HLD meds			
Yes	127 (21.4)	207 (27.5)	
No	466 (78.6)	545 (72.5)	0.01
HTN at diagnosis			
Yes	388 (65.4)	422 (56.1)	
No	205 (34.6)	329 (43.78	
Missing	0	1	0.0005
Age at HTN diagnosis, years	47.6 (12.0)	45.6 (12.02)	0.02
Use of anti-HTN meds			
Yes	326 (55.0)	411 (54.6)	
No	267 (45.0)	341 (45.4)	0.91
Stage			
1	131 (23.7)		
2	53 (9.6)		
3	320 (58.0)		
4	48 (8.7)		
Missing	41		
Histology	41		
HGSC	385 (65.6)		
LGSC	19 (3.24)		
Endometrioid	53 (9.03)		
Clear cell	23 (3.92)		
Mucinous	22 (3.75)		
Other	85 (14.5)		

Abbreviations: AACES = African American Cancer Epidemiology Study; BMI = body mass index; OCP = Oral Contraceptive Pill; HTN = hypertension; HLD = hyperlipidemia; DM = diabetes; HGSC = high-grade serous carcinoma; LGSC = low-grade serous carcinoma

[a] Age at diagnosis for cases and age at the time of interview for controls.

Table 2:

Estimated ORs and 95% CIs for the association of Hypertension, Hyperlipidemia, Diabetes and EOC Risk *

	Cases	Controls		
Comorbidity	**n(%)**	**n(%)**	**OR (95% CI)** [a]	**OR (95% CI)** [b]
History of HTN				
No	205 (34.6)	330 (43.9)	1.00 (Referent)	1.0 (Referent)
Yes	388 (65.4)	422 (56.1)	1.11 (0.86, 1.83)	1.32 (1.01, 1.73)
Duration of HTN				
Never diagnosed	205 (34.6)	330 (43.9)	1.00 (Referent)	1.0 (Referent)
<10 years	187 (31.5)	184 (24.5)	1.33 (0.99, 1.79)	1.59 (1.17, 2.16)
≥ 10 years	201 (33.9)	238 (31.6)	0.92 (0.68, 1.24)	1.10 (0.81, 1.50)
History of DM				
No	463 (78.1)	576 (76.6)	1.00 (Referent)	1.00 (Referent)
Yes	130 (21.9)	176 (23.4)	0.63 (0.47, 0.84)	0.67 (0.49, 0.91)
Duration of DM				
Never diagnosed	463 (78.1)	576 (76.6)	1.00 (Referent)	1.00 (Referent)
<10 years	70 (11.8)	102 (13.6)	0.64 (0.45, 0.92)	0.68 (0.48, 0.98)
≥ 10 years	60 (10.1)	74 (9.8)	0.61 (0.41, 0.92)	0.66 (0.44, 1.00)
History of HLD				
No	398 (67.1)	473 (62.9)	1.00 (Referent)	1.00 (Referent)
Yes	195 (32.9)	279 (37.1)	0.60 (0.46, 0.77)	0.61 (0.47, 0.80)
Duration of HLD				
Never diagnosed	398 (67.1)	473 (62.9)	1.00 (Referent)	1.00 (Referent)
<10 years	114 (19.2)	183 (24.3)	0.58 (0.43, 0.79)	0.59 (0.44, 0.80)
≥ 10 years	81 (13.7)	96 (12.7)	0.63 (0.44, 0.90)	0.64 (0.44, 0.93)
Combination				
None	101 (26.2)	246 (32.7)	1.00 (Referent)	
HTN only	118 (30.6)	157 (20.9)	1.16 (0.84, 1.61)	
HLD only	15 (3.9)	55 (7.3)	0.35 (0.19, 0.65)	
DM only	5 (1.3)	17 (2.3)	0.26 (0.09, 0.74)	
HTN & HLD	62 (16.1)	118 (15.7)	0.67 (0.46, 0.99)	

Comorbidity	Cases n(%)	Controls n(%)	OR (95% CI)[a]	OR (95% CI)[b]
HTN & DM	28 (7.3)	53 (7.0)	0.63 (0.38, 1.05)	
HLD & DM	3 (0.8)	12 (1.6)	0.40 (0.14, 1.14)	
HTN, HLD & DM	53 (13.8)	94 (12.5)	0.58 (0.38, 0.89)	

EOC: epithelial ovarian cancer; OR: odds ratio; CI: confidence interval; HTN: hypertension; HLD: hyperlipidemia; DM: diabetes mellitus; OCP: oral contraceptive pill; BMI: body mass index

[*] Among cases, presence of HTN, DM, or HLD must precede cancer diagnosis. Cases that developed these co-morbidities after their cancer diagnosis were not included as having HTN, DM, or HLD.

[a] Models adjusted for age, site, parity, family history, OCP use, BMI and education

[b] Models adjusted for age, site, parity, family history, OCP use, BMI, education and presence of the other co-morbidities

Table 3:

Estimated ORs and 95% CIs for the association of medication use & EOC risk

	Cases n(%)	Controls n(%)	OR (95% CI)	Cases n(%)	Controls n(%)	OR (95% CI)
	Overall (N=1345)			Women with hypertension (N=810)		
Anti-Hypertensive Medication Use						
Never use	267 (45.0)	341 (45.4)	1.00 (Referent)	85 (21.9)	44 (10.4)	1.00 (Referent)
Current use[a]	326 (55.0)	411 (54.6)	0.79 (0.62, 1.02)	303 (78.1)	378 (89.6)	0.43 (0.28, 0.66)
Beta-Blocker	112 (18.9)	147 (19.5)	1.09 (0.80, 1.50)	109 (28.1)	133 (31.5)	1.07 (0.76, 1.50)
CCB	140 (23.6)	141 (18.7)	1.31 (0.96, 1.78)	135 (34.8)	139 (32.3)	1.07 (0.77, 1.49)
Diuretics	128 (21.6)	213 (28.3)	0.58 (0.43, 0.78)	118 (30.4)	195 (46.2)	0.49 (0.35, 0.68)
ARBs	75 (12.6)	109 (14.5)	0.67 (0.47, 0.96)	71 (18.3)	106 (25.1)	0.50 (0.34, 0.74)
ACE Inhibitors	104 (17.5)	136 (18.1)	0.75 (0.54, 1.03)	98 (25.3)	129 (30.6)	0.59 (0.42, 0.85)
				Women with diabetes (N=306) [b]		
Anti-Diabetes Medication Use						
Never use	492 (83.0)	600 (79.8)	1.00 (Referent)	37 (28.50	30 (17.0)	1.00 (Referent)
Current use[a]	101 (17.0)	152 (20.2)	0.58 (0.42, 0.79)	93 (71.5)	146 (83.0)	0.47 (0.26, 0.86)
Insulin	23 (3.9)	36 (4.8)	0.66 (0.37, 1.16)	23 (17.7)	35 (19.9)	0.69 (0.36, 1.33)
Biguanide	66 (11.1)	103 (13.7)	0.63 (0.43, 0.93)	63 (48.5)	99 (56.2)	0.67 (0.40, 1.10)
Sulfonylurea	27 (4.5)	43 (5.7)	0.82 (0.47, 1.42)	22 (16.9)	43 (24.4)	0.70 (0.38, 1.31)
				Women with hyperlipidemia (N=474)		
Lipid Lowering Medication Use						
Never use	466 (78.6)	545 (72.5)	1.00 (Referent)	80 (41.0)	96 (34.4)	1.00 (Referent)
Current use[a]	127 (21.4)	207 (27.5)	0.52 (0.39, 0.69)	115 (59.0)	183 (65.6)	0.67 (0.44, 1.01)
Statin	124 (20.9)	196 (26.1)	0.55 (0.41, 0.73)	113 (57.9)	173 (62.0)	0.72 (0.47, 1.08)
Other	4 (0.7)	14 (1.9)	0.25 (0.07, 0.84)	3 (1.5)	13 (4.7)	0.23 (0.06, 0.92)

OR: odds ratio; CI: confidence interval; EOC: epithelial ovarian cancer; CCB: calcium channel blocker; ARBs: angiotensin II receptor blockers; ACE: angiotensin-converting-enzyme; OCP: oral contraceptive pill; BMI: body mass index.

ORs for individual drug classes are controlled for age, site, parity, family history, OCP use, education, BMI as well as use of any other medication in that disease specific category.

[a]Current use indicates use of any medication in the allotted category.

[b] Firth regression was used for all ORs included under 'Women with diabetes'

Table 4:

Estimated ORs and 95% CIs for the evaluation of interaction between each comorbidity and associated medication use

	Cases n(%)	Controls n(%)	OR (95% CI)	Interaction p-value
Diagnosed with Hypertension				
No hypertensive drug use	85 (14.3)	44 (5.8)	1.00 (Referent)	
Hypertension drug use	303 (51.1)	378 (50.3)	0.46 (0.30, 0.71)	
No Hypertension				
No hypertensive drug use	182 (30.7)	297 (39.5)	1.00 (Referent)	
Hypertension drug use	23 (3.9)	33 (4.4)	1.36 (0.72, 2.54)	0.006
Diagnosed with Diabetes				
No diabetic drug use	37 (6.2)	30 (4.0)	1.00 (Referent)	
Diabetic drug use	93 (15.7)	146 (19.4)	0.47 (0.26, 0.86)	
No Diabetes				
No diabetic drug use	455 (76.7)	570 (75.8)	1.00 (Referent)	
Diabetic drug use	8 (1.3)	6 (0.8)	2.89 (0.90, 9.25)	0.007
Diagnosed with Hyperlipidemia				
No Hyperlipidemia drug use	80 (13.5)	96 (12.8)	1.00 (Referent)	
Hyperlipidemia drug use	115 (19.4)	183 (24.3)	0.63 (0.41, 0.96)	
No Hyperlipidemia				
No Hyperlipidemia drug use	386 (65.1)	449 (59.7)	1.00 (Referent)	
Hyperlipidemia drug use	12 (2.0)	24 (3.2)	0.57 (0.26, 1.25)	0.83

Model is controlled for age, site, parity, family history, OCP use, education, and BMI, and presence of the other comorbidities. Use of anti-hypertensive medications occurred in 23 cases and 33 controls without hypertension. Use of anti-diabetes medications occurred in 8 cases and 6 controls without diabetes. Use of anti-hyperlipidemia medications occurred in 12 cases and 24 controls without hyperlipidemia.