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History of hypertension, heart disease, and diabetes and ovarian cancer patient survival: evidence from the ovarian cancer association consortium

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Abstract

Purpose—Survival following ovarian cancer diagnosis is generally low; understanding factors related to prognosis could be important to optimize treatment. The role of previously diagnosed comorbidities and use of medications for those conditions in relation to prognosis for ovarian cancer patients has not been studied extensively, particularly according to histological subtype.

Methods—Using pooled data from fifteen studies participating in the Ovarian Cancer Association Consortium, we examined the associations between history of hypertension, heart disease, diabetes, and medications taken for these conditions and overall survival (OS) and progression-free survival (PFS) among patients diagnosed with invasive epithelial ovarian carcinoma. We used Cox proportional hazards regression models adjusted for age and stage to estimate hazard ratios (HRs) and 95% confidence intervals (CIs) overall and within strata of histological subtypes.

Results—History of diabetes was associated with increased risk of mortality (n = 7,674; HR = 1.12; 95% CI = 1.01–1.25). No significant mortality associations were observed for hypertension (n = 6,482; HR = 0.95; 95% CI = 0.88–1.02) or heart disease (n = 4,252; HR = 1.05; 95% CI = 0.87–1.27). No association of these comorbidities was found with PFS in the overall study population. However, among patients with endometrioid tumors, hypertension was associated with lower risk of progression (n = 339, HR = 0.54; 95% CI = 0.35–0.84). Comorbidity was not associated with OS or PFS for any of the other histological subtypes. Ever use of beta blockers, oral antidiabetic medications, and insulin was associated with increased mortality, HR = 1.20; 95% CI = 1.03–1.40, HR = 1.28; 95% CI = 1.05–1.55, and HR = 1.63; 95% CI = 1.20–2.20, respectively. Ever use of diuretics was inversely associated with mortality, HR = 0.71; 95% CI = 0.53–0.94.

Conclusions—Histories of hypertension, diabetes, and use of diuretics, beta blockers, insulin, and oral antidiabetic medications may influence the survival of ovarian cancer patients. Understanding mechanisms for these observations could provide insight regarding treatment.

Keywords

Ovarian cancer prognosis; Hypertension; Diabetes; Medications; Mortality; Beta blockers

Introduction

Ovarian cancer is the fifth most common cause of cancer deaths among females [1] and the most lethal among gynecological cancers [2]. Despite all the advances in treatment of patients with ovarian cancer, survival has not improved considerably over the past several decades [3]. Older age, higher stage of disease, poor differentiation of tumor, and the presence of residual disease after cytoreductive surgery are well-established clinical characteristics associated with poor prognosis [4, 5].

It is crucial to understand the role of additional factors related to ovarian cancer prognosis including factors that, unlike clinical characteristics, are potentially modifiable and might contribute to changing the course of ovarian cancer and improve survival. Among potential factors related to ovarian cancer survival, the role of previously existing comorbidities may be of importance. In particular, hypertension and diabetes are of interest in that these are among the most prevalent diseases [6]. Presence of these conditions could influence prognosis directly, perhaps by affecting cancer cell biology or by increasing production of growth factors influencing the evolution of cancer cells as a result of prolonged exposure to hyperglycemia among patients with pre-existing diabetes [7]. The presence of hypertension, diabetes, and their possible complications, such as diabetes-associated neuropathy, myocardial infarction, or heart failure, could affect prognosis indirectly by altering patients' ability to tolerate chemotherapy or to receive less invasive surgery [7] or less aggressive treatment [8].

Use of medications commonly prescribed for hypertension and other cardiovascular conditions, such as beta adrenergic receptor blockers (beta blockers), may also have a direct impact on prognosis by limiting the growth of ovarian tumors. In preclinical studies, ovarian tumors tend to express adrenergic receptors; activation of these receptors may lead to the

production of growth factors and result in faster growth and increased invasiveness of the tumors [9, 10]. Beta blockers can bind to adrenergic receptors and have been shown to decrease invasiveness of ovarian cancer cells in vitro [10].

Epidemiologic evidence regarding the relationship of concurrent morbidities and the associated use of medications with survival of ovarian cancer patients is limited and not consistent. Increased blood pressure and diabetes were found to be associated with increased mortality in some studies [7, 11–13] but not all [11, 14, 15]. Also, in studies that combined hypertension and diabetes or diabetes only in a comorbidity index, either no association was observed [16, 17] or increased mortality risk was associated with the presence of comorbidities [18, 19]. Finally, the use of beta blockers has been found to be related to improved prognosis of ovarian cancer patients in some studies [20, 21] but not all [22, 23].

There is evidence that the risk factors for ovarian cancer differ by histologic subtype [24]. However, existing studies on the presence of comorbidities and survival of ovarian cancer patients have not examined risk by histotype. Moreover, very few studies have examined the influence of medications prescribed for these comorbid conditions on ovarian cancer outcomes both as independent predictors and as potential effect modifiers of the associations between comorbidities and prognosis. Utilizing pooled data from thirteen case–control studies and two case-only studies, we investigated the association between history of hypertension, heart disease, and diabetes as well as medications commonly prescribed for these conditions with survival outcomes among patients diagnosed with invasive epithelial ovarian cancer.

Materials and methods

Data collection

Data were obtained from thirteen case–control and two case-only ovarian cancer studies participating in the Ovarian Cancer Association Consortium (OCAC). In all of the studies except AOV, participants provided informed consent, and the study protocols of each study were approved by the institutional review boards (IRBs) at the corresponding institutions. For AOV, consent was waived by the IRB since, in this particular study, a retrospective chart review was utilized as a method of data collection.

Characteristics of these participating studies including study names, location, dates of enrollment, methods of data collection and of determination of the history of hypertension, heart disease, and diabetes, and prevalence of these conditions are provided in Table 1. Data collection methods varied among the study sites and included interviewer-administered interviews conducted either in-person or by telephone, self-completed questionnaires, and/or medical record reviews.

Collection of data regarding comorbidities also differed among the studies. Some sites had specific question phrasing for disease diagnosis by physician or other health care professional (CON, DOV, GER, and HAW for diabetes, HOP for hypertension and diabetes, MAL for heart disease and diabetes, NCO, NJO, and NTH). Other studies asked about ever having the disease (AUS- for diabetes, JPN, NEC, and WOC). In some studies, comorbidity

data were collected by medical record abstraction (AOV for hypertension and diabetes, HAW for hypertension and heart disease, and LAX, HOP, and NTH for all diseases of interest). For AUS, history of hypertension and heart disease was determined based on the answer to an initial question on history of diseases requiring medical care. For MAL, history of hypertension was determined based on the answer to a question on ever usage of antihypertensive medications.

In addition to heterogeneity in data collection and disease status determination methods, studies also differed in their definitions of heart disease and diabetes. For instance, heart disease was defined as angina or myocardial infarction in JPN; cardiovascular disease, coronary artery disease, atherosclerosis, history of heart attack or stroke, heart failure, or heart valve problems for LAX; myocardial infarction in MAL; unspecified heart disease in NJO; heart attack, angina, or coronary artery disease in NEC; myocardial infarction or congestive cardiac insufficiency in NTH; and coronary artery disease in WOC studies.

For diabetes, seven study centers obtained information about general history of the disease (AOV, DOV, GER, JPN, MAL, NJO, WOC), while eight studies elicited data regarding both insulin-dependent diabetes and non-insulin-dependent diabetes (NEC) or data regarding diabetes treated with insulin or with oral medications or diet (AUS, CON, HAW, HOP, NCO, NTH, and LAX).

In the following studies, ages at the time of diagnosis of conditions of interest were recorded: AUS, DOV, GER, HAW, HOP, LAX, NCO, NEC, NJO, and NTH for hypertension; AUS, HOP, JPN, LAX, MAL, NEC, NJO, NTH, and WOC for heart disease; AUS, CON, DOV, GER, HAW, HOP, LAX, MAL, NCO, NEC, NJO, and NTH for diabetes. Because of the nature of data collection, the data regarding these diseases included conditions developed both prior and after being diagnosed with ovarian cancer.

Detailed information on ever use of medications, specifically the names of ever used medications, was collected by AUS, NEC, and NJO. HOP and NTH provided information on categories of medication use, beta blockers for HOP, diuretics for NTH, and any antihypertensive medications use for both HOP and NTH. In the CON study, data were obtained regarding insulin use, and in CON and HAW regarding oral antidiabetic medications use.

Prior to statistical analysis, data were cleaned, harmonized, and checked for inconsistencies. For the purpose of harmonization, we defined history of heart disease as having any type of heart condition as determined by each of the study sites. History of diabetes was defined as either having a history of diabetes or ever use of oral antidiabetic medications or insulin.

For the studies that provided information on medication use, medications were divided into the following categories: angiotensin-converting enzyme (ACE) inhibitors, beta blockers, calcium channel blockers, diuretics, oral antidiabetic medications, and insulin. Medications typically prescribed for hypertension were also combined to define a single variable of any use of antihypertensive medications.

From the participants (N = 12,511 patients), we excluded women diagnosed with non-epithelial (N = 140) or non-invasive (N = 2,520) tumors and those who were not followed for survival outcomes (N = 332). The final study population included 9,519 patients diagnosed with either ovarian (N = 8,904), fallopian (N = 171), or peritoneal (N = 444) cancer. After additional exclusion of patients with missing information on hypertension, heart disease, or diabetes, and, for diabetes, exclusion of patients who reported history of either gestational or borderline diabetes, our analytic dataset included 6,482 patients with available information on hypertension status (yes/no), 4,252 patients with available information on heart disease (yes/no), and 7,674 patients with available information on history of diabetes (yes/no).

After categorizing medication intake, we found the number of patients with data on the use of antihypertensive or antidiabetic medications (yes/no) as follows: 1,500 patients for ACE inhibitors, 2,294 patients for beta blockers, 1,594 patients for calcium channel blockers, 1,728 patients for diuretics, 2,670 patients for any antihypertensive medications, 1,685 patients for oral antidiabetic medications intake, and 2,001 patients for insulin.

Statistical analysis

We used Cox proportional hazards models to estimate hazard ratios (HRs) and the corresponding 95% confidence intervals (CIs) for associations for each comorbidity and for the use of each type of medication with ovarian cancer survival outcomes in the pooled sample. Overall survival (OS) was calculated from the date of diagnosis to the earlier of date of death or end of follow-up. Progression-free survival (PFS) was defined as the time period from the date of diagnosis to the date when progression status (persistence, recurrence, or death) was determined, or to the end of follow-up for patients without any progression. Progression was ascertained according to the OCAC guidelines that instructed OCAC studies' principal investigators to determine progression based on clinical, biochemical (CA-125), or radiological assessment. While information on OS was provided by all of the study sites included in the present analysis, information on time to progression was provided only by the AUS, HAW, JPN, HOP, LAX, MAL, NCO, and NEC studies. Using data from only these studies reduced the study population to 2,868 patients with information on hypertension status (yes/no), 2,493 patients with information on heart disease status (yes/no), and to 3,129 patients with information on diabetes status (yes/no).

All statistical models were adjusted for age at ovarian cancer diagnosis (continuous) and cancer stage (localized, regional, or distant). These two variables were selected a priori because of their known strong influence on the survival of ovarian cancer patients [49–51]. Models were additionally evaluated for confounding by each of the following variables: race (white/non-white), body mass index (BMI: 18.5 to <25 kg/m^2/25 to <30 kg/m^2/≥30 kg/m^2), education (high school or less/higher than high school), family history of breast or ovarian cancer (no/yes/unknown), menopausal status (premenopausal/postmenopausal), parity and breastfeeding status (never pregnant/pregnant but not breastfed/breastfed), any regular use of genital powder (no/yes), history of hysterectomy (no/yes), ever use of oral contraceptives (no/yes), history of tubal ligation (no/yes), tumor grade (well differentiated/moderately differentiated/poorly differentiated/undifferentiated/unknown), tumor histology (high grade

serous/low grade serous/mucinous/endometrioid/clear cell/other), and the presence of gross disease after cytoreductive surgery (none/any residual disease). Inclusion of any of these potential confounders did not change the observed age- and stage-adjusted measures of association by more than 10%. Therefore, none of these covariates were included in the final models.

We first calculated study-specific HRs and 95% CIs. We examined statistical heterogeneity among study-specific HRs using I^2 statistics and Cochran's Q-statistic [52]. No appreciable heterogeneity among study-specific HRs was observed (data not shown). Therefore, we estimated pooled age- and stage-adjusted HRs and 95% CIs and reported these results herein.

To better understand the potential role of prediagnostically developed conditions, we additionally examined the duration of history of hypertension, heart disease, and diabetes prior to ovarian cancer diagnosis in relation to risk of death. The durations of the comorbidity variables were calculated by subtracting age at the time of the condition diagnosis from the age at the time of diagnosis with ovarian cancer. The duration variables were then dichotomized using various cut-points: 5 years, 10 years, and the median values of disease duration, 9.5 years for hypertension, 7 years for heart disease, and 8 years for diabetes.

Patients with no history of the comorbidity under consideration were selected as the referent category in analyses conducted to assess the association between comorbidities and survival outcomes, and patients with no reported use of the specific medication of interest were selected as the referent category when examining the associations between medications use and OS and PFS. To account for the possibility of variation in confounders among the sites, we additionally adjusted each of the models for study site. In the models for the associations between medications intake and survival outcomes, we additionally adjusted for the use of each of the groups of antihypertensive or antidiabetic medications.

In an attempt to assess the independent role of each comorbidity or combination of comorbidities on patients' survival, we created a composite variable that was categorized based on the number of comorbidities that the patient had. This variable had the following categories: having no hypertension, heart disease, and diabetes (referent); hypertension only; heart disease only; diabetes only; hypertension and diabetes; hypertension and heart disease; diabetes and heart disease; and hypertension, diabetes, and heart disease.

To explore the role of diabetes severity on the survival of ovarian cancer patients, we also created an additional composite variable with the following categories: no diabetes (referent); diabetes with no reported antidiabetic medication use; and diabetes with reported use of antidiabetic medications. We used these newly created composite variables in the Cox proportional hazards models to explore their association with OS.

Further, we examined whether associations for the presence of comorbidity or medication use with survival endpoints differed in strata of main histotypes, high-grade serous, low-grade serous, mucinous, endometrioid, and clear cell carcinomas. Associations were also examined according to strata of BMI ($18.5\ kg/m^2 < BMI < 25.0\ kg/m^2$ vs. $BMI \geq 25.0\ kg/$

m^2), age at ovarian cancer diagnosis (<65 vs. ≥65 years), and stage of disease (local/regional vs. distant). Presence of multiplicative interaction was determined by including product terms between the exposures of interest and potential effect modifiers (weight status, age at diagnosis, stage of disease, and study site) and utilizing likelihood ratio statistics to assess the significance of these terms.

As a part of an additional stratified analysis, we separately explored the associations between hypertension and OS by history of diabetes and ever use of medications prescribed for hypertension including beta blockers, ACE inhibitors, calcium channel blockers, and diuretics. For diabetes, we also examined the associations with OS stratified by history of hypertension. For hypertension, we conducted a separate analysis for subjects with interview year prior to the year of 2003 versus from 2003 onward to reflect changes in the guidelines for prevention and management of hypertension over time [53]. For beta blockers, we examined the associations separately among users of non-selective and selective beta blockers.

To further examine the role of antihypertensive medications on mortality, we repeated analyses with referent group being never use of any antihypertensive medication. Also, for each group of antihypertensive medications, we restricted analyses to individuals with hypertension. In addition, we incorporated left truncation in all of the models to account for time between the date of ovarian cancer diagnosis and date of the interview and the inability to enroll women who had died prior to the recruitment date.

Additional analyses were performed to address the possibility of misclassification of the tumor histotypes, specifically high-grade endometrioid tumors. Since pathological review of tumors obtained from all patients was performed only in a subset of included studies (AOV, CON, HAW, HOP, NCO, NEC, NJO, LAX, and WOC), we attempted to address the possibility of misclassification of high-grade endometrioid tumors [54] by reclassifying them as high-grade serous tumors if endometrioid tumors' grade was ≥ G3 [55] and repeating analyses with updated classification of endometrioid and high-grade serous tumors. All statistical tests were two-sided; p values < 0.05 were considered significant.

Results

In this sample of ovarian cancer patients, the prevalence of hypertension, heart disease, and diabetes were 25.9, 3.9, and 8.3%, respectively. Across the studies, the prevalence of hypertension ranged from 7.8 to 40.7%, heart disease from 0.7 to 10.1%, and diabetes from 1.6 to 16.6% (Table 1). Median survival times were 67.9 and 73.7 months for patients with and without hypertension, 61.7 and 72.6 months for patients with and without diabetes, and 54 and 68.4 months for patients with and without heart disease, respectively.

Distributions of the descriptive characteristics among those with and without the diseases of interest are shown in Table 2. Patients with a history of hypertension, heart disease, or diabetes were significantly more likely to be older, less educated, and postmenopausal, and to have a higher BMI and a history of hysterectomy compared to patients without the condition.

History of hypertension was not associated with risk of death among these women with ovarian cancer, HR = 0.95; 95% CI = 0.88–1.02 (Table 3). However, we observed an inverse association between hypertension and OS among those with duration of hypertension more than 5 years, HR = 0.88; 95% CI = 0.79–0.98, whereas in women with hypertension duration of five or fewer years there was no association, HR = 0.93; 95% CI = 0.80–1.07. Similar associations were observed when 10 years and 9.5 years were used as cut-points for the hypertension duration variable. No significant associations were found between history of hypertension and risk of death for each histotype, most likely due to lack of power (Table 3). The associations were not appreciably different in strata of stage, age, overweight status, presence of diabetes, reported use of antihypertensive medications, or year of interview (results not shown).

Among the studies that provided information on progression, no association was observed between history of hypertension and PFS, HR = 0.98; 95% CI = 0.88–1.10 (Table 4). However, when the analysis was stratified by the main histotypes, decreased risk of progression was associated with hypertension among patients diagnosed with endometrioid tumors, HR = 0.54; 95% CI = 0.35–0.84. No association was found between hypertension and PFS for the other histological subtypes.

We did not observe any association between history of heart disease and any of the survival outcomes. Also, no association was found in the analyses stratified by the same study subgroups reported above for hypertension.

History of diabetes was associated with increased risk of death among these patients with ovarian cancer, HR = 1.12; 95% CI = 1.01–1.25 (Table 3). No association was observed between history of diabetes and PFS in the overall sample. The estimated associations did not change appreciably in analyses stratified by histotype, overweight status, age, stage, or history of hypertension.

When examining the association between a composite variable representing different combinations of comorbidities reported by the patients, we observed that being diagnosed with hypertension only was inversely associated with mortality, HR = 0.83; 95% CI = 0.75–0.93 (results not shown). Having any other combinations of these comorbidities was not associated with death. When exploring the role of diabetes severity in relation to OS, we also observed an increased risk of mortality among those who reported use of any antidiabetic medications, HR = 1.30; 95% CI = 1.07–1.56 (results not shown). At the same time, history of diabetes with no reported antidiabetic medications use was positively but non-significantly associated with mortality, HR = 1.13; 95% CI = 0.78–1.64.

When we examined the use of medications for hypertension, heart disease, and diabetes in relation to OS and PFS, we observed that the use of beta blockers, oral antidiabetic medications, and insulin was associated with increased risk of mortality, HR = 1.20; 95% CI = 1.03–1.40, HR = 1.28; 95% CI = 1.05–1.55, and HR = 1.63; 95% CI = 1.20–2.20, respectively (Table 5). The associations were similar between those who reported the use of selective and non-selective beta blockers, although the individual HRs did not reach statistical significance (results not shown). Use of ACE inhibitors, calcium channel blockers,

and diuretics was associated with decreased risks of mortality for which only diuretics reached statistical significance, HR = 0.71; 95% CI = 0.53–0.94 (Table 5). Additional adjustment for other medications of interest did not appreciably change the observed HRs, nor did stratification by any of the potential effect modifiers. Additional adjustment for study site did not change the observed HRs nor did reclassification of high-grade endometrioid carcinomas into high-grade serous ovarian cancer. For antihypertensive medications, changing the referent group into never use of any medication or limiting the analysis to individuals with hypertension also did not produce a substantial change in the observed HRs. None of the product terms between the exposures of interest and potential effect modifiers that were included in the models were significant.

Discussion

Ovarian cancer is an important public health problem partly because of its high rate of mortality. However, because it is a relatively infrequent disease, large studies are difficult to accomplish. Pooling of samples, such as that in this OCAC consortium, is critical to understanding factors related to survival. In this large sample of patients with invasive ovarian cancer, we observed higher risk of death among women with history of diabetes compared to women with no history of this disease. We also observed an inverse association between history of hypertension and PFS among women diagnosed with endometrioid ovarian carcinoma. Finally, reduced mortality was seen among those with longer duration of hypertension prior to diagnosis with ovarian cancer.

Various biological mechanisms have been proposed to explain the influence of concurrent health conditions on the prognosis of ovarian cancer patients. For example, chronic exposure to hyperinsulinemia, which is common among older patients diagnosed with diabetes, may lead to the activation of the Ras–MAPK and PI 3-K–mTOR pathways which can play roles in tumor cell proliferation and cancer progression [56, 57]. Hyperglycemia, which is also common among patients with diabetes, can promote the growth of tumor cells which use glucose as a source of energy necessary for their increased metabolism [58]. Several studies that have evaluated the role of diabetes in relation to survival among ovarian cancer patients have shown a significantly increased risk of death among women with this concurrent condition [7, 11–13]. Our results provide additional evidence for the role of diabetes as an independent factor affecting prognosis. It is important to note, however, that the strength of association observed in our study was lower than that observed by others. Such heterogeneity may have resulted in a higher probability of underreported diabetes among the studies that were based on self-report, while most of the previously conducted studies were based on data from medical records abstraction.

To our knowledge, this study is the first to evaluate the association between history of hypertension and survival outcomes among ovarian cancer patients specifically within strata of histological subtypes. In one prospective study, an inverse association was observed between increased blood pressure and OS among women diagnosed with ovarian cancer [15]. Conversely, one retrospective study failed to find an association between history of hypertension and survival [11]. Our observation of an inverse association between history of hypertension and risk of ovarian cancer progression among patients diagnosed with

endometrioid tumors could potentially be explained by the underlying biology of this particular subtype. It has been speculated that endometrioid ovarian tumors originate from endometrial cells that reach the ovaries through retrograde flow of menstrual tissue [59]. For endometrial cancer, there is evidence of reduced mortality associated with a history of hypertension [60, 61]. The published literature that notes this association is lacking in tested biological mechanisms. The authors of both of these studies of endometrial cancer hypothesized that antihypertensive treatment might be responsible for the reduced risk of mortality. In our study, we only observed the association with PFS and not with OS. We also did not find that the association was stronger among those using any of the antihypertensive medications. Unfortunately, due to limited power, we were not able to examine the association between hypertension and survival in strata of antihypertensive medications intake additionally stratified by histological subtype. It is plausible that antihypertensive medications could have a differential effect on a hormonal admixture in the patient's body and may influence the tumor microenvironment differently depending on the histotype. This finding could have important clinical implications and should be further examined in future studies.

Contrary to what was observed in two preclinical studies [9, 10], in our study, there was no inverse association between the use of beta blockers and survival. Results similar to ours have been observed in some [22, 23] but not in other studies [20, 21, 62]. Studies that found no benefit of beta blockers use in relation to survival assessed the exposure including usage during the prediagnostic period. Studies that observed a beneficial role of beta blockers relied on the assessment of use during the post-diagnostic period which could have been affected by immortal person-time bias [63]. In our study, the use of beta blockers was primarily prediagnostic which would have avoided this bias. We also did not observe any substantial difference between mortality HRs according to selectivity of the beta blockers.

In contrast to our results for beta blockers, the findings for diuretics, ACE inhibitors, and calcium channel blockers suggest a beneficial role of these medications in relation to ovarian cancer survival. Our finding of an inverse relationship between history of hypertension and OS among those with hypertension only and among those with longer duration of hypertension prior to ovarian cancer diagnosis also suggests a potentially beneficial role of longer exposure to these antihypertensive medications. While this study is not able to disentangle the mechanisms for these associations, perhaps the use of diuretics, ACE inhibitors, calcium channel blockers, and beta blockers differentially alters the milieu within the tumor microenvironment, although the mechanisms of the latter are unclear.

It is also important to note that our findings are not consistent with the results of a recently published study by Huang et al. [64] that reported an increased risk of ovarian cancer among users of diuretics and no association for use of beta blocker. The appearance of the discrepancy in findings for ovarian cancer risk and survival could be because diuretics may have different influence on the processes of ovarian cancer initiation and progression. It could also be because of differences in populations that realize the protective benefit of diuretics and those that develop ovarian cancer in spite of the protective benefits of diuretics.

Finally, while an earlier study demonstrated that antidiabetic medications, metformin in particular, were associated with improved ovarian cancer survival [58], we found that intake of oral antidiabetic medications was associated with increased risk of death, HR = 1.28; 95% CI = 1.05–1.55. In our study, we were not able to examine the metformin association separately from that of the other oral antidiabetic drugs because of the relatively small number of patients who reported taking metformin. The increased risk of death among those who reported taking oral antidiabetic medications observed in our study could be explained by the fact that the use of these medications may be associated with more severe disease compared to those who did not report taking these medications. Our observation of increased mortality among diabetic patients using antidiabetic medications further supports this speculation.

In the analysis of our results, the strengths and weaknesses of the study need to be considered. The main advantage of the current study is its large sample size that allowed the examination of associations by histological subtypes of ovarian cancer as well as of the roles of potential effect modifiers, including the use of antihypertensive medications. We were also able to determine an impact of hypertension and diabetes on survival rather than only an association between a combined index of comorbidity and ovarian cancer survival as has been done in earlier studies.

There are also limitations of this study that are important to consider. Although almost all of our contributing data came from case–control studies, differences in methods existed between them. In particular, exposure assessments differed between the studies, including the year of the assessment. Practice patterns and treatment strategies for hypertension have changed over time [65]. We tried to address this situation by stratifying patients according to year of interview, prior to 2003 compared to 2003 and thereafter, when the guidelines for prevention and management of hypertension had changed [53]. There was no appreciable change in the results in the two time periods. Another limitation is that we were not able to restrict our analyses to cases who died of ovarian cancer since, in our study population, the information on cause of death was available for a limited number of patients. However, among cases with a known cause of death, 94.5% of patients died from ovarian cancer, which is very similar to the percentage of cases who died of this disease reported in other OCAC survival studies [66, 67]. Therefore, we could assume that, for OS, our results approximate ovarian cancer survival fairly well.

A further limitation is that, while we had information regarding the presence of comorbidities, we did not have data regarding disease severity. For instance, diabetes, particularly type II diabetes, is a heterogeneous disease comprising various degrees of hyperglycemia and resistance to insulin [68]. Our necessarily simplified dichotomization of exposures could have attenuated the estimates of underlying associations. Although we attempted to address this limitation by creating a composite variable representing diabetes severity, we were still not able to capture the complexity of this particular disease. Additionally, we utilized self-report of disease status or information obtained from medical records rather than direct physiologic measures of blood pressure or of fasting glucose. Self-report of co-occurring diseases could have resulted in some exposure misclassification, though likely of non-differential nature. Moreover, some residual confounding may be

possible because of our inability to assess the influence of post-diagnostic treatment of ovarian cancer patients. Even though the recommended initial chemotherapy regimen is standard [69], therapy may be individualized based on clinical characteristics of the patients and response to treatment. We were also not able to account for the possible use of additional medications as prophylactic measures to prevent complications of chemotherapy, particularly thromboembolic events. There could also be residual confounding because unmeasured factors could have a different impact among various histologic subtypes [70]. This confounding could have been explained in these subtype-specific results [70]. Finally, our findings could be the result of multiple testing.

In summary, we found that history of diabetes was associated with increased risk of death among ovarian cancer patients. This finding contributes to the current knowledge of the role of diabetes in influencing the prognosis of ovarian cancer patients [7, 11, 13]. This observation may be particularly important in the context of a growing number of individuals with diabetes, a disease that may affect the treatment of ovarian cancer. Moreover, our observation of an inverse association between history of hypertension and risk of progression among patients with endometrioid ovarian carcinomas suggests the importance of further studies to examine the mechanisms underlying this finding and investigate the difference of tumor microenvironment among various histologic subtypes. Understanding of the mechanisms for these observations could provide insight regarding treatment. More importantly, integration of the full clinical profile for ovarian cancer patients may be essential in understanding the factors related to their overall morbidity and mortality.

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Table 1

Characteristics of studies included in the analysis, Ovarian Cancer Association Consortium

Study acronym	Study name	Study location, year of diagnosis	Data collection method	Average age at diagnosis with OVCA, years	Median time of follow-up (range of follow-up) in days	History of hypertension determination	Patients with hypertension, (%)	History of heart disease determination	Patients with heart disease, *n* (%)	History of diabetes determination	Patients with diabetes, *n* (%)
AOV [25, 26]	Alberta ovarian tumor types study	Canada 1978–2010	MRR	56.8	1,496 (1–9,834)	MRR: reporting of disease	187 (33%)	–	–	MRR: reporting of disease	66 (11.7%)
AUS [27]	Australian ovarian cancer study	Australia 2002–2006	Self-completed questionnaire	59.4	1,664 (9–3,672)	Q: disease requiring regular medical care	141 (12.1%)	Q: disease requiring regular medical care	8 (0.7%)	Q: ever having condition	72 (5.9%)
CON [28]	Connecticut ovarian cancer study	USA Connecticut 1998–2003	Inperson interview	59.3	2,268 (150–3,947)	–	–	–	–	Q: disease diagnosed by physician	18 (4.6%)
DOV [29, 30]	Disease of the ovary and their evaluation study	USA: Washington 2002–2005 (DOV) 2006–2009 (DVE)	In-person interview	56.1	1,550 (243–4,043)	Q: disease diagnosed by physician or other health care professional	222 (31.7%)	–	–	Q: disease diagnosed by physician or other health care professional	69 (9.8%)
GER [31]	German ovarian cancer study	Germany 1993–1996	Self-administered questionnaire	56.9	1,464.5 (18–6,060)	Q: disease diagnosed by physician	66 (28.3%)	–	–	Q: disease diagnosed by physician	18 (7.7%)
HAW [32, 33]	Hawaii ovarian cancer study	USA: Hawaii 1993–2008	In-person interview	56.8	2,738 (143–7,662)	MRR: reporting of disease	146 (40.7%)	–	–	Q: disease diagnosed by physician	61 (12.3%)
HOP [34]	Hormones and ovarian cancer prediction study	USA: Pennsylvania, Ohio, and New York 2003–2009	In-person interview and MRR	60.3	1,809 (40–3,982)	Q: disease diagnosed by physician MRR: reporting of disease	264 (36.6%)	MRR: reporting of disease	49 (7.3%)	Q: disease diagnosed by physician MRR: reporting of disease	120 (16.6%)
JPN [35]	Hospital-based research program at Aichi cancer center	Japan 2001–2005	In-person interview	53.5	1,121.5 (43–3,396)	Q: ever having disease	5 (7.8%)	Q: ever having disease	2 (3.1%)	Q: ever having disease	1 (1.6%)
LAX	Women's cancer program at the Samuel Oschin comprehensive cancer institute	USA: California 1989–present	MRR	58.4	1,483 (11–8,239)	MRR: reporting of disease	94 (28.9%)	MRR: reporting of disease	16 (4.9%)	MRR: reporting of disease	22 (6.8%)
MAL [36, 37]	Malignant ovarian cancer study	Denmark 1994–1999	In-person interview	59.3	1,349 (5–6,208)	Determined based on medication intake reported during interview	93 (16.9%)	Q: disease diagnosed by physician	10 (1.8%)	Q: disease diagnosed by physician	19 (3.0%)
NCO [38, 39]	North Carolina ovarian cancer study	USA: North Carolina 1999–2008	Self-completed questionnaire	57.2	1,567 (93–4,506)	Q: disease diagnosed by physician	120 (38.1%)	–	–	Q: disease diagnosed by physician	88 (9.4%)

Study acronym	Study name	Study location, year of diagnosis	Data collection method	Average age at diagnosis with OVCA, years	Median time of follow-up (range of follow-up) in days	History of hypertension determination	Patients with hypertension, (%)	History of heart disease determination	Patients with heart disease, *n* (%)	History of diabetes determination	Patients with diabetes, *n* (%)
NEC [40, 41]	New England case–control study of ovarian cancer	USA: New Hampshire and Massachusetts 1992–2003	In-person interview	55.4	2,815 (70–7,709)	Q: ever having disease	136 (16%)	Q: Ever having disease	39 (4.6%)	Q: ever having disease	31 (3.7%)
NJO [42–44]	New Jersey ovarian cancer study	USA: New Jersey 2002–2008	Phone interview	56.3	2,373 (165–4,085)	Q: disease diagnosed by health care professional	72 (30.4%)	Q: disease diagnosed by health care professional	16 (6.8%)	Q: disease diagnosed by health care professional	22 (9.3%)
NTH [45, 46]	Nijmegen ovarian cancer study	Netherlands 1989–2006	MRR	54.6	3,510 (349–8,739)	Q: disease diagnosed by physician	83 (33.6%)	Q: disease diagnosed by physician MRR	10 (4.1%)	Q: disease diagnosed by physician MRR	26 (10.7%)
WOC [47, 48]	Warsaw ovarian cancer study	Poland 1997–2010	Self-administered questionnaire	53.5	1,168 (13–4,825)	Q: ever having disease	49 (32.9%)	Q: ever having disease	15 (10.1%)	Q: ever having disease	5 (3.4%)

OVCA ovarian cancer, *Q* questionnaire, *MRR* medical records reviews

Table 2

Characteristics of ovarian cancer patients by hypertension, heart disease, and diabetes status, Ovarian Cancer Association Consortium

Covariate	History of hypertension			History of heart disease			History of diabetes		
	Yes *n* = 1678	No *n* = 4804	*p* value[a]	Yes *n* = 165	No *n* = 4087	*p* value[a]	Yes *n* = 638	No *n* = 7036	*p* value[a]
Age at diagnosis with ovarian cancer, mean (SD)	62.1 (10.5)	55.5 (11.2)	<0.001	66.5 (10.0)	57.3 (11.5)	< 0.001	60.4 (10.6)	57.1 (11.4)	< 0.001
Race, *n* (%)									
White	1,336 (84.6)	4,159 (90.9)	<0.001	153 (93.3)	3,813 (94.3)	0.59	478 (78.1)	5,989 (88.9)	< 0.001
Non-white	243 (15.4)	417 (9.1)		11 (6.7)	231 (5.7)		134 (21.9)	746 (11.1)	
Body mass index (kg/m^2), *n* (%)									
18.5 to <25	349 (28.0)	1,996 (51.8)	<0.001	47 (35.9)	1,670 (47.1)	0.02	100 (19.8)	2,791 (48.3)	< 0.001
25 to <30	382 (30.7)	1,102 (28.6)		42 (32.1)	1,061 (29.9)		142 (28.1)	1,672 (29.0)	
≥30	514 (41.3)	755 (19.6)		42 (32.1)	815 (23.0)		263 (52.1)	1,312 (22.7)	
Education, *n* (%)									
High school or less	735 (51.2)	1,923 (45.1)	<0.001	89 (60.1)	1,949 (50.1)	0.02	292 (52.0)	2,915 (46.7)	0.02
More than high school	702 (48.8)	2,339 (54.9)		59 (39.9)	1,941 (49.9)		270 (48.0)	3,332 (53.3)	
Family history of breast or ovarian cancer, *n* (%)									
No	343 (20.4)	1,033 (21.5)	0.60	54 (32.7)	1,137 (27.8)	0.39	148 (23.2)	1,748 (24.8)	0.21
Yes	317 (18.9)	875 (18.2)		30 (18.2)	789 (19.3)		136 (21.3)	1,308 (18.6)	
Unknown	1,018 (60.7)	2,896 (60.3)		81 (49.1)	2,161 (52.9)		354 (55.5)	3,980 (56.6)	
Menopausal status, *n* (%)									
Premenopausal	250 (15.4)	1,596 (34.3)	<0.001	13 (8.0)	1,194 (29.8)	< 0.001	105 (17.0)	2,045 (29.8)	< 0.001
Postmenopausal	1,377 (84.6)	3,057 (65.7)		149 (92.0)	2,811 (70.2)		415 (83.0)	4,809 (70.2)	
Parity and breastfeeding, *n* (%)									
Never pregnant	269 (19.2)	978 (23.2)	<0.001	26 (18.7)	752 (20.4)	0.61	122 (21.8)	1,300 (20.8)	0.11
Pregnant but not breastfed	497 (35.4)	1,192 (28.2)		47 (33.8)	1,105 (30.0)		208 (37.1)	2,104 (33.6)	
Breastfed	639 (45.5)	2,053 (48.6)		66 (47.5)	1,831 (49.7)		231 (561)	2,857 (45.6)	
Genital powder use, *n* (%)									
No	395 (49.1)	1,162 (44.9)	0.03	42 (46.2)	969 (39.1)	0.18	160 (49.1)	1,649 (46.9)	0.45
Yes	409 (50.9)	1,427 (55.1)		49 (53.8)	1,507 (60.9)		166 (50.9)	1,917 (53.1)	
Hysterectomy, *n* (%)									
No	1,061 (66.4)	3,523 (76.2)	<0.001	106 (71.6)	3,099 (80.5)	0.01	401 (65.5)	5,066 (74.5)	< 0.001

Covariate	History of hypertension			History of heart disease			History of diabetes		
	Yes n = 1678	No n = 4804	p value[a]	Yes n = 165	No n = 4087	p value[a]	Yes n = 638	No n = 7036	p value[a]
Yes	537 (33.6)	1,099 (23.8)		42 (28.4)	752 (19.5)		211 (34.5)	1,731 (25.5)	
Ever use of oral contraceptives, n (%)									
No	676 (49.1)	1,725 (41.5)	<0.001	101 (68.7)	1,712 (45.6)	< 0.001	254 (46.4)	2,672 (43.3)	0.16
Yes	702 (50.9)	2,429 (58.5)		46 (31.3)	2,039 (54.4)		293 (53.6)	3,497 (56.7)	
Tubal ligation, n (%)									
No	1,237 (84.8)	3,560 (83.1)	0.13	134 (84.8)	3,300 (84.2)	0.83	447 (79.1)	5,288 (83.0)	0.02
Yes	221 (15.2)	722 (16.9)		24 (15.2)	621 (15.8)		118 (20.9)	1,086 (17.0)	
Stage, n (%)									
Localized	280 (16.7)	841 (17.5)	0.08	32 (19.4)	637 (15.6)	0.42	107 (16.8)	1,223 (17.4)	0.06
Regional	347 (20.7)	1,034 (21.5)		28 (17.0)	792 (19.4)		136 (21.3)	1,433 (20.4)	
Distant	1,019 (60.7)	2,875 (59.9)		105 (63.6)	2,636 (64.5)		380 (59.6)	4,300 (61.1)	
Unknown	32 (1.9)	54 (1.1)		0 (0)	22 (0.5)		15 (2.4)	80 (1.1)	
Grade, n (%)									
Well differentiated	207 (12.3)	666 (13.9)	0.002	16 (9.7)	518 (12.7)	0.06	91 (14.3)	896 (12.7)	0.28
Moderately differentiated	369 (22.0)	973 (20.3)		36 (21.8)	912 (22.3)		139 (21.8)	1,494 (21.2)	
Poorly differentiated	758 (45.2)	2,353 (49.0)		97 (58.8)	2,359 (57.7)		285 (44.7)	3,422 (48.6)	
Undifferentiated	103 (6.1)	261 (5.4)		6 (3.6)	47 (1.2)		37 (5.8)	415 (5.9)	
Unknown	241 (14.4)	551 (11.5)		10 (6.1)	251 (6.1)		86 (13.5)	809 (11.5)	
Histology, n (%)									
High grade serous	687 (45.9)	2,112 (48.0)	0.10	92 (58.2)	2,180 (55.3)	0.39	257 (45.1)	3,094 (48.1)	0.47
Low grade serous	63 (4.2)	215 (4.9)		3 (1.9)	227 (5.8)		30 (5.3)	293 (4.6)	
Mucinous	97 (6.5)	312 (7.1)		10 (6.3)	235 (6.0)		33 (5.8)	442 (6.9)	
Endometrioid	295 (19.7)	775 (17.6)		26 (16.5)	574 (14.6)		109 (19.1)	1,146 (17.8)	
Clear cell	143 (9.6)	455 (10.3)		9 (5.7)	285 (7.2)		60 (10.5)	661 (10.3)	
Other	211 (14.1)	536 (12.2)		18 (11.4)	444 (11.3)		81 (14.2)	790 (12.3)	
Presence of gross disease after cytoreductive surgery, n (%)									
No	336 (48.8)	1,006 (47.3)	0.49	41 (48.8)	1,105 (47.7)	0.85	116 (43.8)	1,256 (45.2)	0.67
Yes	352 (51.2)	1,120 (52.7)		43 (51.2)	1,210 (52.3)		149 (56.2)	1,526 (54.8)	

Numbers may not add up due to missing observations

[a] p value for χ^2 test for categorical variables and t test for age at diagnosis variable

Table 3

History of hypertension, heart disease, and diabetes and risk of death among epithelial ovarian cancer patients, Ovarian Cancer Association Consortium

	History of hypertension				History of heart disease				History of diabetes			
	Dead	**Alive**	**HR (95% CI)[a]**	***p* value**	**Dead**	**Alive**	**HR (95% CI)[a]**	***p* value**	**Dead**	**Alive**	**HR (95 %CI)[a]**	***p* value**
Overall sample												
History of disease												
No	2,655	2,149	1.00 (ref)		2,441	1,646	1.00 (ref)		3,995	3,041	1.00 (ref)	
Yes	982	696	0.95 (0.88–1.02)	0.16	115	50	1.05 (0.87–1.27)	0.63	394	244	1.12 (1.01–1.25)	0.03
Duration of disease[b,c]												
None	2,655	2,149	1.00 (ref)		2,441	1,646	1.00 (ref)		3,995	3,041	1.00 (ref)	
≤5 years	189	122	0.93 (0.80–1.07)	0.30	25	5	1.27 (0.85–1.88)	0.24	113	74	1.17 (0.97–1.41)	0.10
>5 years	418	307	0.88 (0.79–0.98)	0.02	30	15	0.96 (0.67–1.37)	0.81	184	95	1.13 (0.98–1.31)	0.10
p for trend			0.01				0.84				0.04	
High grade serous												
History of disease												
No	1,545	567	1.00 (ref)		1,633	547	1.00 (ref)		2,293	801	1.00 (ref)	
Yes	513	174	0.99 (0.90–1.10)	0.93	79	13	1.04 (0.82–1.30)	0.77	202	55	1.06 (0.92–1.23)	0.41
Low grade serous												
History of disease												
No	117	98	1.00 (ref)		122	105	1.00 (ref)		161	132	1.00 (ref)	
Yes	35	28	0.73 (0.49–1.09)	0.12	1	2	0.40 (0.05–2.91)	0.37	19	11	1.14 (0.71–1.85)	0.58
Mucinous												
History of disease												
No	94	218	1.00 (ref)		68	167	1.00 (ref)		134	308	1.00 (ref)	
Yes	41	56	0.98 (0.66–1.45)	0.93	6	4	2.62 (1.07–6.40)	0.04	13	20	1.41 (0.79–2.54)	0.25
Endometrioid												
History of disease												
No	225	550	1.00 (ref)		175	399	1.00 (ref)		349	797	1.00 (ref)	
Yes	89	206	0.80 (0.62–1.03)	0.09	11	15	1.18 (0.63–2.22)	0.60	36	73	1.18 (0.84–1.67)	0.34
Clear cell												
History of disease												

	History of hypertension				History of heart disease				History of diabetes			
	Dead	**Alive**	**HR (95% CI)[a]**	***p* value**	**Dead**	**Alive**	**HR (95% CI)[a]**	***p* value**	**Dead**	**Alive**	**HR (95 %CI)[a]**	***p* value**
No	175	280	1.00 (ref)		110	175	1.00 (ref)		256	405	1.00 (ref)	
Yes	59	84	1.08 (0.79–1.46)	0.64	4	5	1.77 (0.63–4.96)	0.28	24	36	0.98 (0.64–1.49)	0.92

[a]Models adjusted for age at diagnosis and stage of disease

[b]Based on information from AUS, DOV, GER, HAW, HOP, LAX, NCO, NEC, NJO, and NTH for hypertension; AUS, HOP, JPN, LAX, MAL, NEC, NJO, NTH, and WOC for heart disease; AUS, CON, DOV, GER, HAW, HOP, LAX, MAL, NCO, NEC, NJO, and NTH for diabetes

[c]Numbers do not add up to the total number of patients due to missing observations

Table 4

History of hypertension, heart disease, and diabetes and risk of progression among epithelial ovarian cancer patients, Ovarian Cancer Association Consortium

	History of hypertension				History of heart disease				History of diabetes			
	Progression				Progression				Progression			
	Yes	No	HR (95% CI)[a,b]	*p* value	Yes	No	HR (95% CI)[a,b]	*p* value	Yes	No	HR (95% CI)[a,b]	*p* value
Overall sample												
History of disease												
No	1,489	692	1.00 (ref)		1,663	744	1.00 (ref)		1,961	902	1.00 (ref)	
Yes	472	215	0.98 (0.88–1.10)	0.71	58	28	0.99 (0.75–1.30)	0.93	190	76	1.03 (0.88–1.21)	0.71
Duration of disease[c]												
None	1,489	692	1.00 (ref)		1,663	744	1.00 (ref)		1,961	902	1.00 (ref)	
≤5 years	79	35	1.05 (0.83–1.33)	0.70	8	2	1.12 (0.50–2.51)	0.78	55	20	1.14 (0.85–1.52)	0.39
>5 years	212	99	0.98 (0.84–1.14)	0.80	7	4	1.11 (0.53–2.34)	0.78	86	35	1.03 (0.81–1.29)	0.85
p for trend			0.87				0.71				0.64	
High grade serous												
History of disease												
No	975	219	1.00 (ref)		1,121	244	1.00 (ref)		1,291	274	1.00 (ref)	
Yes	379	60	1.10 (0.96–1.26)	0.16	52	7	1.09 (0.82–1.45)	0.56	121	20	1.16 (0.96–1.42)	0.13
Low grade serous												
History of disease												
No	80	44	1.00 (ref)		88	56	1.00 (ref)		102	56	1.00 (ref)	
Yes	20	17	0.89 (0.52–1.52)	0.67	1	1	2.27 (0.28–18.46)	0.44	11	9	0.69 (0.34–1.43)	0.32
Mucinous												
History of disease												
No	34	85	1.00 (ref)		38	87			45	105	1.00 (ref)	
Yes	11	22	1.29 (0.60–2.77)	0.52	0	4	–	–	2	6	2.91 (0.63–13.37)	0.17
Endometrioid												
History of disease												
No	109	137	1.00 (ref)		118	156	1.00 (ref)		143	203	1.00 (ref)	

	History of hypertension				History of heart disease				History of diabetes			
	Progression				Progression				Progression			
	Yes	No	HR (95% CI)[a,b]	*p* value	Yes	No	HR (95% CI)[a,b]	*p* value	Yes	No	HR (95% CI)[a,b]	*p* value
Yes	32	61	0.54 (0.35–0.84)	0.01	1	10	0.19 (0.03–1.36)	0.10	13	19	0.86 (0.48–1.54)	0.61
Clear cell												
History of disease												
No	170	98	1.00 (ref)		67	89	1.00 (ref)		78	117	1.00 (ref)	
Yes	64	26	0.92 (0.47–1.81)	0.81	1	3	1.14 (0.16–8.35)	0.90	10	9	1.90 (0.42–1.96)	0.80

[a]Models adjusted for age at diagnosis and stage of disease

[b]Based on data from AUS, HAW, JPN, LAX, MAL, NCO, and NEC

[c]Data provided by AUS, HAW, HOP, LAX, NCO, and NEC for hypertension; AUS, JPN, HOP, LAX, MAL, and NEC for heart disease; AUS, HAW, HOP, LAX, MAL, NCO, and NEC for diabetes

Table 5

Association between intake of antihypertensive and antidiabetic medications and risk of death and progression among epithelial ovarian cancer patients, Ovarian Cancer Association Consortium

Medications	Dead	Alive	HR (95% CI)[a,b]	Progression	No progression	HR (95% CI)[c]
Angiotensin-converting enzyme inhibitor						
No	875	558	1.00 (ref)	425	270	1.00 (ref)
Yes	36	31	0.87 (0.62–1.23)	16	12	1.24 (0.74–2.07)
Beta blocker						
No	1,169	807	1.00 (ref)	787	384	1.00 (ref)
Yes	219	99	1.20 (1.03–1.40)	161	66	1.11 (0.93–1.32)
Calcium channel blocker						
No	879	565	1.00 (ref)	426	201	1.00 (ref)
Yes	103	47	0.84 (0.68–1.03)	64	23	0.93 (0.70–1.24)
Diuretic						
No	905	718	1.00 (ref)	424	201	1.00 (ref)
Yes	52	53	0.71 (0.53–0.94)	7	2	1.14 (0.54–2.42)
Any antihypertensive medications						
No	1,108	904	1.00 (ref)	731	369	1.00 (ref)
Yes	415	243	1.00 (0.89–1.13)	281	109	1.10 (0.95–1.28)
Oral antidiabetic medications						
No	763	719	1.00 (ref)	449	208	1.00 (ref)
Yes	117	86	1.28 (1.05–1.55)	85	37	0.97 (0.77–1.23)
Insulin						
No	1,023	915	1.00 (ref)	475	221	1.00 (ref)
Yes	44	19	1.63 (1.20–2.20)	27	8	1.18 (0.80–1.75)

[a]Models adjusted for age at diagnosis and stage of disease

[b]Data provided by AUS, NEC, and NJO for ACE inhibitors and calcium channel blockers; AUS, HOP, NEC, and NJO for beta blockers; AUS, NEC, NJO, and NTH for diuretics; AUS, HOP, NEC, NJO, and NTH for all hypertensive medications; HAW, HOP, NEC, NJO, and NTH for oral antidiabetic medications; CON, HAW, HOP, NEC, NJO, and NTH for insulin

[c]Data provided by AUS and NEC for ACE inhibitors, calcium channel blockers, beta blockers, diuretics, all hypertensive medications; HAW and NEC for oral antidiabetic medications and insulin