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Risk of Epithelial Ovarian Cancer in Relation to Use of Antidepressants, Benzodiazepines, and Other Medications Acting on the Central Nervous System

by

Sascha Dublin

A dissertation submitted in partial fulfillment

of the requirements for the degree of

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Abstract

Risk of Epithelial Ovarian Cancer in Relation to Use of Antidepressants, Benzodiazepines, and Other Medications Acting on the Central Nervous System

by Sascha Dublin

Chairperson of the Supervisory Committee:
Professor Noel S. Weiss
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An increased risk of ovarian cancer among users of antidepressants, benzodiazepines, and certain other medications affecting the central nervous system has been hypothesized based on prior laboratory and epidemiologic research. We examined these associations in a case-control study. We identified 314 members of a health maintenance organization who were diagnosed with epithelial ovarian cancer between 1981-1997, were ages 35-79 at diagnosis, and had at least four years of prior membership. Using membership and billing records, up to four controls were matched to each case on calendar year, age, and length of membership (n=790). Information regarding medication use was obtained from the institution's computerized pharmacy database, while information regarding other characteristics was obtained through medical record review.

We found that compared to controls, cases were slightly less likely to have filled two antidepressant prescriptions in a six-month period (adjusted odds ratio [OR] 0.71, 95% confidence interval [CI] 0.47-1.05) or to have used an antidepressant continuously for six months or longer (OR 0.64, 95% CI 0.36-1.15). Cases were less likely than controls to have filled two benzodiazepine prescriptions in six months (OR 0.70, 95% CI 0.47-1.04) or to have

used benzodiazepines continuously for six months or longer (OR 0.53, 95% CI 0.15-1.87). There was no evidence that risk of ovarian cancer increased with increasing number of prescriptions filled or pills dispensed for either antidepressants or benzodiazepines. There was no association between risk of ovarian cancer and use of medications acting via pathways involving serotonin/norepinephrine, dopamine and/or norepinephrine (DA/NE), or gamma-aminobutyric acid (GABA).

In conclusion, our findings do not support an association between increased risk of epithelial ovarian cancer and use of antidepressants, benzodiazepines, or certain other medications acting on the central nervous system.

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INTRODUCTION

Epidemiology of ovarian cancer

The incidence of ovarian cancer in the United States is 14.6 per 100,000 women.[1] It generally has a poor prognosis, with a relative survival of only 42% five or more years after diagnosis.[1] Since ovarian cancer produces few symptoms until late in the course of disease, it is often diagnosed at an advanced stage, which carries a particularly poor prognosis. Between 1989-95, 60% of incident cases of invasive ovarian cancer were diagnosed after distant disease was already present.[1] There are three major histologic categories of ovarian cancer—germ cell, stromal, and epithelial—which vary in their mean age of onset and associated risk factors, suggesting distinct etiologic pathways. In Europe and North America, over 90% of ovarian cancers are of epithelial origin.[2]

The etiologies of epithelial ovarian cancer are not well understood. Epidemiologic evidence suggests that risk increases in parallel with lifetime number of ovulations. This idea is supported by the fact that increasing parity and use of oral contraceptives, both of which suppress ovulation, have consistently been found to be associated with decreased risk of this cancer. Studies examining these associations have been reviewed by Weiss et al.[3]

There are several possible mechanisms by which ovulation, or physiological events associated with ovulation, could increase a woman's risk of ovarian cancer. During the menstrual cycle, the elevated gonadotropin levels which stimulate follicular development (a pre-requisite for ovulation to occur) could lead to increased cell proliferation, either through direct stimulation of epithelial cells or via heightened production of estrogen and/or estrogen precursors. This increased proliferation could eventually result in malignant transformation.

This hypothesis has been discussed at length by Cramer and Welch[4] and, more recently, by Risch.[5]

Under this hypothesis, one might expect higher levels of gonadotropins such as follicle stimulating hormone (FSH) and luteinizing hormone (LH) to be associated with an increased risk of ovarian cancer. However, in a nested case-control study, Helzlsouer et al. reported associations in the opposite direction.[6] Women who later developed ovarian cancer had lower levels of FSH at entry into the study compared to matched controls (mean level 16.3 IU/L for 31 cases compared to 17.9 IU/L for 62 controls, p=0.04). This relationship was seen for both pre- and post-menopausal subjects. Risk of ovarian cancer appeared to decrease with increasing levels of both FSH and LH, although the trend was statistically significant only for FSH.

At first glance, these results seem inconsistent with the findings expected according to the gonadotropin hypothesis. However, it may be that the time period at which gonadotropin levels were measured in this study is not the etiologically relevant time period. Women who developed ovarian cancer had a mean age of 53 at study entry and were diagnosed an average of 8 years later. If exposure to gonadotropins earlier in reproductive life (e.g. age 20-40) were the etiologically important exposure, then that exposure would not have been captured for most study subjects. Alternatively, it may be that there is a threshold level above which gonadotropins stimulate ovarian cells, and that once this threshold is reached the absolute gonadotropin level is not important. If this were the case, then it might be more relevant to ascertain whether a woman has experienced long periods of gonadotropin suppression (such as those resulting from pregnancy or oral contraceptive use) rather than to measure her absolute gonadotropin levels at a single point in time. In summary, while the results of Helzlsouer et al. do not support the gonadotropin hypothesis, they do not provide strong evidence against it.

An alternative hypothesis postulates that ovulation increases the risk of ovarian cancer via the accompanying disruption of the ovarian epithelial lining. This disruption likely results in increased cell proliferation, necessary to heal the ovulatory "wound", which could in turn create a greater potential for malignant transformation. Furthermore, it has been suggested that the formation of epithelial inclusion cysts, which may be associated with ovulation, may expose epithelial cells to high levels of hormones produced in the ovarian stroma, ultimately increasing the risk of malignancy.[4,5]

Antidepressants and Benzodiazepines

In 1995, Harlow et al. reported findings from a case-control study suggesting that women who had used antidepressants or benzodiazepines were at increased risk of developing epithelial ovarian cancer.[7] The increase in risk associated with use of these drugs was approximately two-fold. These results, and those from other epidemiologic studies that followed, will be discussed in greater detail below.

There are several major classes of antidepressants. A description of these drugs and their mechanisms of action can be found in Richelson et al.[8] The earliest available antidepressants fell into two main categories: the monoamine oxidase (MAO) inhibitors and the tricyclic antidepressants (TCAs). MAO inhibitors, available since 1959, include the drugs tranylcypromine sulfate (sold as Parnate) and phenelzine sulfate (Nardil). They inhibit an enzyme, monoamine oxidase, that breaks down neurotransmitters such as serotonin, norepinephrine, and dopamine. When this enzyme is inhibited, higher levels of neurotransmitters are available for release into the synaptic clefts between neurons in the brain. However, MAO inhibitors also block enzymes that break down chemicals found in certain foods, potentially leading to dangerous side effects. As a result, they are currently

recommended as drugs of last resort, for patients who are not responsive to other types of antidepressants.[8]

The TCAs, which are named based on their three-ring chemical structure, became available in 1959 with the introduction of imipramine (Tofranil). Other widely used TCAs include amitriptyline (sold as Elavil or Endep) and doxepin (sold as Adapin or Sinequan), introduced in 1961 and 1969 respectively. Antidepressants in this class are thought to work by blocking molecular pumps on presynaptic neurons that remove neurotransmitters from the synaptic cleft. When these pumps are blocked, neurotransmitters remain in the synaptic cleft instead of being taken back up by presynaptic cells, and so neurotransmitter levels in the synaptic cleft increase. These re-uptake pumps are specific for certain neurotransmitters (for instance, serotonin, dopamine, or norepinephrine). Most of the TCAs affect the re-uptake of more than one neurotransmitter. However, various TCAs block different pumps to differing degrees. For instance, one TCA may block re-uptake of norepinephrine more strongly, while another may block re-uptake of serotonin more strongly. While the TCAs differ in their selectivity and in their relative potencies, these differences do not seem to be correlated with differences in efficacy.[8]

TCAs also bind to receptors for other important chemical messengers in the body, such as histamine and acetylcholine, sometimes with greater potency than they bind to the re-uptake pumps described above. Their effects as antihistaminic and anticholinergic agents are responsible for a number of unpleasant side effects, including drowsiness, weight gain, dry mouth, and constipation. Certain TCAs are so potent as histamine receptor antagonists that they are increasingly being used to treat allergic symptoms.[8]

Until 1980, these two types of antidepressants (MAO inhibitors and TCAs) were the only types available. During the 1980's, several other antidepressants became available which

did not fall neatly into existing categories. Maprotiline (sold as Ludiomil), introduced in 1980, has a four-ring (tetracyclic) structure. Like the TCAs, it is thought to act by blocking re-uptake of neurotransmitters from the synaptic cleft. In 1981, trazodone (Desyrel) was introduced, and in 1985 bupropion (Welbutrin) became available. Both are considered "atypical" antidepressants.[8]

In 1987, with the introduction of fluoxetine (Prozac), a new class of antidepressants became available: the selective serotonin re-uptake inhibitors, or SSRIs. This group also includes the drugs paroxetine (Paxil) and sertraline (Zoloft). Like the TCAs, these drugs are thought to act by blocking neurotransmitter re-uptake and thus increasing synaptic neurotransmitter levels. However, unlike the TCAs, these drugs are highly selective for serotonin re-uptake pumps, with a potency for blocking serotonin re-uptake that is 20-70 fold higher than their potency for blocking norepinephrine re-uptake.[8] The SSRIs have fewer side effects than the TCAs and for this reason have largely eclipsed the TCAs since their introduction in the late 1980s.

Benzodiazepines are not used to treat depression but rather for a number of conditions including anxiety, insomnia, and muscle spasm. They act through an entirely different pathway than those described above. Descriptions of their presumed mechanism of action can be found in pharmacology textbooks.[9] The predominant hypothesis is that benzodiazepines act by binding to a type of receptor for gamma-aminobutyric acid (GABA), the main inhibitory neurotransmitter, and enhancing GABA's effects. $GABA_A$ receptors, a subtype found in the brain, are ligand-gated channels through which chloride can enter the neuron. It is thought that by binding to $GABA_A$ receptors, benzodiazepines amplify the chloride flow that occurs when GABA binds. The inflow of negative charge makes the neuron less likely to become

depolarized and, ultimately, to fire. Since benzodiazepines have no direct effect on chloride flows, their effects are limited by the amount of GABA that is present.[9]

Animal Studies and Possible Biological Mechanisms

Results from some animal studies support a possible association between antidepressant use and risk of cancer. Studies have reported that antidepressants accelerate the growth of tumors in rodents, including melanoma, fibrosarcoma, and mammary tumors[10] as well as colon cancer.[11] In one study, fluoxetine promoted the growth of preneoplastic lesions in the liver following exposure to aflatoxin B_1.[12] Studies have examined drugs in the tricyclic family, desipramine[11] and amitriptyline,[10] as well the selective serotonin re-uptake inhibitor fluoxetine.[10,12] Tumor promotion was seen in animal models involving exposure to carcinogens as well as those involving transplants of tumor cells into healthy animals.

Several different mechanisms could be responsible for tumor promotion by antidepressants. LaBella and Brandes have proposed that these drugs act via an intracellular histamine receptor associated with the anti-estrogen binding site (AEBS) to modulate the interaction between histamine and cytochrome P-450 enzymes and, ultimately, to perturb levels of a variety of small molecules that serve as signals for growth and differentiation.[13] Alternatively, Wright et al. have suggested that antidepressants act as tumor promoters by inhibiting apoptosis, a mechanism of programmed cell death that is thought to be important in controlling the growth of cells that could give rise to tumors.[14] In their experiments, clinically relevant levels of amitriptyline suppressed or even entirely blocked apoptosis induced by a variety of triggers including ultraviolet light, tumor necrosis factor and the anticancer agent vinblastine.[14]

It has also been proposed that, by altering neurotransmitter levels in the brain, antidepressants may affect gonadotropin levels and ultimately lead to increased stimulation of ovarian cells, thus increasing women's risk of ovarian cancer.[15] This hypothesis finds support from animal studies that suggest that neurotransmitters such as serotonin and dopamine influence gonadotropin levels. In one study, intraperitoneal administration of 5-HTP (a precursor of serotonin) to prepubertal female rats resulted in increased serum levels of FSH and LH after 30 minutes.[16] Intraperitoneal administration of serotonin to female goldfish increased gonadotropin levels for up to 2 hours after administration in fish at varying gonadal stages.[17] If similar effects occur in adult women, then this could provide one possible mechanism by which antidepressants which block the re-uptake of serotonin could increase the risk of ovarian cancer. **(other citations? should I elaborate on this further?)**

The mechanism by which benzodiazepine use might influence the development of ovarian cancer is unclear. Benzodiazepines exert their clinically useful effects (reduction of anxiety, induction of sleep, etc.) via receptors in the central nervous system. In addition to these central receptors, a peripheral benzodiazepine receptor (PBR) has been identified that is widely distributed in tissues throughout the body. The PBR has been the subject of a number of review articles.[18,19] It has been hypothesized that this receptor may regulate cell growth and proliferation. Some researchers have reported that, at micromolar concentrations, peripheral-type ligands inhibit cell growth and proliferation.[20,21] However, at lower concentrations these ligands may have stimulatory effects. Ikezaki and Black have reported that, at nanomolar concentrations, ligands that bind to the PBR stimulate cell growth and DNA synthesis in cultured cells from brain tumors and in 3T3 fibroblasts.[22] It is not clear what the implications of these results are with regard to the benzodiazepines that are used clinically. Some, but not all, of these drugs act on peripheral as well as central-type receptors. For instance, diazepam

binds to both central and peripheral-type receptors. In contrast, clonazepam binds strongly to central receptors but has almost no affinity for peripheral-type receptors.[18,23]

It has also been suggested that benzodiazepines may affect the risk of ovarian cancer through effects on the hypothalamic-pituitary-gonadal axis.[7]. Harlow and Cramer initially proposed that by inducing microsomal enzymes in the liver, benzodiazepines might increase the rate of estrogen metabolism, leading to more rapid breakdown of serum estradiol and, ultimately, to increased gonadotropin levels. In turn, these elevated gonadotropin levels could lead to increased stimulation of ovarian cells.[7] However, the evidence that benzodiazepines induce hepatic enzymes comes from experiments in which rodents were given doses much higher than those used in clinical settings.[24-26] For instance, Kitagawa et al. administered temazepam to rats and mice at doses ranging from 120 to 1000 mg/kg/day,[25] which is equivalent to doses of 7,200 to 60,000 mg for a 60 kilogram woman. In contrast, a typical clinical dosage would be between 7.5 and 30 mg.[9] It is unclear whether benzodiazepines also induce hepatic enzymes at clinically relevant levels. Fukazawa et al. observed that chronic administration of 2.5 mg/kg/day of bromazepam, about 10 times the typical clinical dose, did not affect liver weight, activity of hepatic enzymes, or the rate of elimination of bromazepam from the blood in mice administered this dosage for up to 21 days.[26]

Additional mechanisms by which benzodiazepines might influence risk of ovarian cancer involve potential effects on endogenous steroid levels. Studies have demonstrated that exogenous benzodiazepines such as diazepam can act via peripheral benzodiazepine receptors to stimulate steroidogenesis, including progesterone synthesis, in cell types including Leydig and granulosa cells.[23,27] For instance, Amsterdam et al. reported that treatment with diazepam significantly increased progesterone synthesis in granulosa cells derived from rat ovaries.[27]

Specific central-type benzodiazepines such as clonazepam did not stimulate progesterone synthesis in these experiments.

Krueger, Papadopoulos, and others have argued that benzodiazepines' effect on steroidogenesis occurs at an early stage, possibly involving the translocation of cholesterol from the outer to the inner mitochondrial membrane.[23,28] If so, these drugs could have wide-ranging effects on the synthesis of many steroids, including estrogen, progesterone, and testosterone. It is unclear what effect such changes might have on women's risk of ovarian cancer. If the increase in steroidogenesis resulted in increased production of estrogens, this could down-regulate gonadotropin levels, ultimately leading to decreased stimulation of the ovary and perhaps a decreased risk of ovarian cancer. In addition, Risch has proposed that decreased progesterone levels could be associated with increased risk of ovarian cancer.[5] This suggests another putative mechanism by which use of benzodiazepines might lead to a reduced risk of ovarian cancer. On the other hand, Risch has suggested that increased levels of testosterone and other androgens may increase women's risk of ovarian cancer.[5]

In summary, while laboratory research provides some intriguing possibilities for mechanisms by which benzodiazepines might alter risk of ovarian cancer, there is no definitive evidence supporting an association in either direction.

Epidemiologic Studies of Medications acting on the Central Nervous System and Risk of Ovarian Cancer

In 1995, Harlow et al. reported findings from a case-control study suggesting that women who had used certain psychotropic drugs were at increased risk of developing epithelial ovarian cancer.[7] Among women with ovarian cancer, 4.0% reported past use of antidepressants compared to 2.2% of women without cancer who were sampled from the underlying population

(OR 2.1, with 95% confidence limits from 0.9-4.8). Since Harlow's cases included women diagnosed between 1978-81 and 1984-7, and since the first selective serotonin re-uptake inhibitor was not introduced until 1987, any association with antidepressants seen in this study can be attributed to the tricyclic antidepressants rather than to the SSRIs. The drugs categorized as antidepressants in this study also included an MAO inhibitor, phenelzine, as well as lithium and Mellaril (an antipsychotic). However, usage of these three drugs is generally rare and would be unlikely to make a substantial contribution to the association.

In addition, women with epithelial ovarian cancer reported greater use of benzodiazepines prior to diagnosis compared to controls (8.9% vs. 5.3%; OR 1.8, 95% CI 1.0-3.1).[7] For both antidepressants and benzodiazepines, the association with increased risk was seen only for use prior to age 50 and beginning more than 10 years prior to cancer diagnosis. To examine the possibility that the observed associations could have been due to recall bias, rather than to a causal relationship between use of these medications and ovarian cancer, Harlow et al. examined other classes of medications as well and found no overall association between reported use and cancer risk. However, the study lacked information regarding daily dosage and duration of use, and so the authors were unable to examine the relationship between ovarian cancer risk and increasing levels of exposure.

In a study conducted several years later,[15] Harlow et al. examined a wider variety of drugs that act on the central nervous system, including amphetamines, barbiturates, anticonvulsants, antipsychotic agents, and non-benzodiazepine sedatives as well as antidepressants and benzodiazepines. Women with ovarian cancer were more likely to report at least 6 months' use of any of these drugs (17.6%, compared to 12.6% of controls; OR 1.4, 95% CI 1.0-2.0). The association was seen only for invasive ovarian cancer, not borderline tumors, and was strongest for premenopausal use and use of at least 2 years' duration. In addition,

women with ovarian cancer were more likely to report past use of each individual class of drugs compared to controls. Among cases, 7.1% had used antidepressants for at least 6 months compared to 5.2% of controls, while 6.6% had used sedatives (benzodiazepines or other types) compared to 5.2% of controls.[15] This study included cases diagnosed between 1992-7. This means that, prior to diagnosis, study subjects would have had access to many antidepressants that had not been available for use by subjects in Harlow et al.'s initial study.[7] Drugs that would have been available to subjects in the second study but not the initial study include the SSRIs fluoxetine, sertraline, and paroxetine as well as the atypical antidepressants trazodone and bupropion. Thus, the particular antidepressants used by subjects in Harlow's second study may have been considerably different than those used by subjects in Harlow's initial study.

In the second study,[15] Harlow et al. performed further analyses after grouping the drugs according to presumed mechanisms of action (independent of therapeutic class or indication for use). An increased risk of ovarian cancer was seen only for drugs believed to act via pathways involving gamma-aminobutyric acid (GABA) (OR 1.3, 95% CI 0.8-2.1) and dopamine or norepinephrine (DA/NE) (OR 2.4, 95% CI 1.1-5.2). The GABA-ergic category included benzodiazepines as well as meclizine, barbiturates, carbamazepine, meprobamate, and phenytoin. The DA/NE category included three antidepressants (desipramine, nortriptyline, and bupropion), none of which had been used by any of the subjects in Harlow's initial study, as well as other drugs including amphetamines. No increased risk was observed for drugs thought to operate via serotoninergic or mixed serotonin/norepinephrine pathways (OR 0.9, 95% CI 0.5-1.8). This category contained several antidepressants used by women in Harlow's first study (amitriptyline, imipramine, and phenelzine), as well as the SSRIs fluoxetine, sertraline, and paroxetine and the atypical antidepressant trazodone, none of which was on the market at the

time of Harlow's initial study. Harlow et al. did not report what proportion of the drugs in the serotoninergic category consisted of the older versus the newer medications.

It is difficult to compare the results of Harlow et al.'s second study[15] with those reported in the initial study[7] because the particular drugs used differ so greatly, due to time trends in the availability of various antidepressants. Of the 11 antidepressants used by subjects in the second study,[15] only three were also used by subjects in the initial study. All three of these older medications were assigned to the serotoninergic group in the second study, for which no association with ovarian cancer was seen (OR 0.9, 95% CI 0.5-1.8).[15] In this respect, the findings from the second study conflict somewhat with those reported in Harlow's initial study, which reported an increased risk among women who had used antidepressants (OR 2.1, 95% CI 0.9-4.8).[7] Considering benzodiazepine use, the findings of these two studies also conflict somewhat. In the second study,[15] benzodiazepines were classified in the group of drugs acting via GABA-ergic pathways, for which the OR was 1.3 (95% CI 0.8-2.1).[15] This is lower than the OR for benzodiazepine use reported in Harlow's initial study (OR 1.8, 95% CI 1.0-3.1).[7] However, since the GABA-ergic grouping used in Harlow's second study contained a number of drugs other than benzodiazepines, some of which are likely to have been widely used (meprobamate and meclizine), it is difficult to know whether it is really appropriate to compare these odds ratios.

One other study has examined the relationship between benzodiazepine use and risk of ovarian cancer.[29] Using data from a hospital-based case-control study, Rosenberg et al. reported that women with ovarian cancer were equally likely as controls to report "sustained" use of benzodiazepines, defined as use at least four times per week for one month or more beginning more than two years prior to the time of hospital admission: "sustained" use was reported by 4.2% of cases, compared to 5.5% of controls with other cancers (OR 0.9, 95% CI

0.6-1.4). There was no evidence of an increased risk among women whose use had begun 10 or more years prior to admission (OR 1.2, 95% CI 0.6-2.6). Women with at least five years of sustained benzodiazepine use were actually at decreased risk of ovarian cancer (RR 0.3, 95% CI 0.1-0.9). Women reporting "recent" benzodiazepine use (defined as use exclusively within the two years prior to admission) were at increased risk of ovarian cancer, with OR 2.1 (95% CI 1.4-3.1), but the interpretation of this association is ambiguous because the cancer could already have been present at the time of drug use. It is possible that increased use of benzodiazepines in this more recent time period could have resulted from early symptoms of cancer, rather than being an etiologically relevant exposure. While the results reported above come from analyses comparing women with ovarian cancer to controls with other types of cancer, Rosenberg et al. reported that similar results were found with non-cancer controls.

In summary, results from these three studies are inconclusive. While Harlow's initial study[7] reported increased risk of epithelial ovarian cancer associated with both antidepressants and benzodiazepines, Harlow's second study[15] reported no association between ovarian cancer risk and use of serotoninergic drugs, a grouping which contained several of the antidepressants used by subjects in Harlow's first study as well as a number of antidepressants that had not been available during the time period of Harlow's first study. However, in the second study,[15] Harlow et al. did observe an elevated risk for drugs acting via pathways involving dopamine and/or norepinephrine, a grouping that contained two tricyclic antidepressants as well as amphetamines and other drugs. None of the drugs in this grouping had been used by any subjects in Harlow's initial study,[7] and so these results cannot be compared to prior findings.

In Harlow's second study, a modestly elevated risk (OR 1.3, 95% CI 0.8-2.1) was seen for use of drugs presumed to act via GABA-ergic pathways (the group including benzodiazepines as well as barbiturates and anticonvulsants, among other drugs).[15] In contrast,

Rosenberg et al. found no association between sustained use of benzodiazepines and risk of ovarian cancer (OR 0.9, 95% CI 0.6-1.4).[29]

These studies had a number of methodological differences that could account for their different conclusions, including differences in subject selection and exposure ascertainment. For both studies, Harlow's controls came from the general population, while Rosenberg used hospitalized controls. About two-thirds of Rosenberg's controls had primary cancers other than those included in the case groups, including cancer of the pancreas, bladder, bone/connective tissue, kidney/kidney pelvis, stomach, leukemia, esophagus, or vulva. The other one-third were admitted for acute nonmalignant disorders for which the authors felt hospitalization would be obligatory (such as appendicitis or ectopic pregnancy).

Considering exposure ascertainment, Rosenberg et al. asked specifically about history of benzodiazepine use and gathered detailed information about frequency and duration of use as well as dosage.[29] In contrast, Harlow's initial publication[7] combined data from two studies, one of which obtained information about benzodiazepines and antidepressants in a very broad and non-specific way: subjects were first asked about use of hormonal medications and then about use of "any other medications" (430 subjects). However, the second study which provided data for this publication asked specifically about use of tranquilizers and antidepressants. This study contributed 474 subjects, or slightly more than half of the total. The failure to ask directly about use of the drugs of interest puts a greater burden on study subjects, in terms of effort and ability to remember past medication usage. This could have enhanced recall bias in Harlow's initial study, in that cases might be more likely to recall and report in detail their past medication use. It is unclear in what way subjects were asked about past use of medications in the study providing the data for Harlow's second publication.[15]

Limitations of Prior Studies

As discussed above, the three studies published to date have provided conflicting information about possible relationships between use of antidepressants, benzodiazepines, and risk of epithelial ovarian cancer. Thus, further research is needed to clarify the nature of these associations.

In addition, these studies have important limitations. One limitation concerns selection of an appropriate control group. While Harlow's studies were population-based,[7,15] Rosenberg et al. relied on hospital-based controls,[29] some of whom were patients with other types of cancer and some who were admitted for acute conditions. This hampers interpretation of their findings, since hospitalized controls may not be representative of the underlying population from which ovarian cancer cases arose. If use of benzodiazepines affects the likelihood of developing cancer at other sites, or of being admitted to the hospital for certain acute conditions, then the findings of this study could be biased.

Furthermore, all three studies gathered information about drug exposure solely through in-person interviews conducted after subjects were diagnosed with cancer. This approach raises the possibility of recall bias. Women who have been diagnosed with cancer may be more likely to recall any past use of prescription drugs, because they may have been reviewing their personal history for any unusual occurrences that might explain why they developed cancer. In addition, there could be reporting bias. Since use of psychotropic drugs may be considered stigmatizing, women in the general population may be inclined to underreport any such use. If cases are motivated to report their past use more honestly than controls, this discrepancy could create an apparent elevation in risk associated with use of these drugs.

Furthermore, exposure data gathered through interviews may be subject to nondifferential misclassification. It may be difficult for women to remember the details of

prescription drug use from the distant past, particularly drug names and dosages. In one study that investigated the accuracy of self-reported medication usage,[30] only 85% of subjects who had filled multiple prescriptions for non-steroidal anti-inflammatory drugs (NSAIDS) recalled any usage in a telephone interview. 30% of subjects who had filled one or more NSAID prescriptions recalled the drug name accurately. When asked about name and dose, only 15% of study subjects recalled both of these accurately. Among women who had used estrogen continuously for 90 or more days, 78% percent recalled the name accurately, while 26% recalled both name and dose. Accuracy of recall went down as time elapsed since medication use increased, with 46% of NSAID users accurately recalling drug name after 2-3 years compared to 22% after 7-11 years.[30] The authors concluded that medication histories obtained through interview are likely to be incomplete.

Reliance on in-person interviews could also result in selection bias, particularly for a disease such as epithelial ovarian cancer which is often rapidly fatal. The potential for selection bias can be seen by considering the second study by Harlow et al.[15] Of 1080 potentially eligible cases, the investigators were able to interview 615 (about 57%). Of those who were not interviewed, 93 had died prior to contact; 60 could not be located; 136 refused to participate (which may have been due to severity of illness, among other factors); and for an additional 126 women, the physician refused permission to contact, either because she was severely ill or because of family circumstances. It seems possible that women with the most advanced disease were the least likely to be included in this study. If use of any of the drugs under study were associated with severity of disease—perhaps through a direct effect on prognosis or through an association with health-care-seeking behavior, which could perhaps affect the likelihood of early diagnosis—then the exclusion of cases with more severe disease could bias the results.

We had the opportunity to examine the association between use of prescription drugs and risk of epithelial ovarian cancer using data from the automated pharmacy database established by Group Health Cooperative (GHC), a large health maintenance organization (HMO) in the Seattle/Puget Sound area. This approach offers several advantages. First, because exposure information is recorded prior to cancer diagnosis, the potential for recall and reporting bias is eliminated. Second, this database can provide detailed and accurate information about prescription drug use, particularly about exact drug names and dosages, which may be difficult to remember long after use occurred. Finally, this approach greatly diminishes selection bias, since pharmacy information is available for women independent of the severity of their disease. In addition, the use of data from an HMO allowed us to select controls who were likely to be representative of the underlying population from which ovarian cancer cases arose. This was possible because GHC, like other health care plans, maintains administrative databases enumerating their members.

These advantages motivated us to conduct a population-based case-control study in the setting of this large HMO to examine possible associations between use of antidepressants, benzodiazepines, and other drugs acting on the central nervous system and risk of epithelial ovarian cancer.

METHODS

Overview

We conducted a population-based case-control study to examine possible associations between epithelial ovarian cancer and the use of antidepressants, benzodiazepines, and other medications acting on the central nervous system. Our source population consisted of female members of Group Health Cooperative (GHC), a large health maintenance organization with more than 450,000 members in the Seattle-Puget Sound area. Using the GHC Cancer Registry, we identified women aged 35-79 years who were diagnosed with epithelial ovarian cancer between March 1, 1981 and June 30, 1997 (cases). Controls were randomly selected from the population of women who were GHC members within a year of the time a case was diagnosed, and they were individually matched to cases on age and length of GHC membership. Information on use of prescription drugs came from GHC's computerized pharmacy database, while information on other characteristics was obtained through medical record review. We compared the proportion of cases with past use of these medications to the proportion of controls with such use to determine whether there was any association between use of these medications and risk of epithelial ovarian cancer.

Case ascertainment

We identified cases using the Cancer Surveillance System of Western Washington (CSS), a population-based cancer registry participating in the Surveillance, Epidemiology and End Results (SEER) program. Table 1 depicts the selection and exclusion criteria used to identify eligible cases. Between March 1, 1981 and June 30, 1997, there were 400 cases of epithelial ovarian cancer among female members of Group Health Cooperative aged 35-79. To

minimize problems with missing data, we limited our study to the 334 (84%) who had been members of GHC for at least four years prior to diagnosis. One woman was excluded during this step because of inadequate information regarding dates of enrollment. In addition, we excluded two women who had gaps in membership totaling at least half of the time after their original date of enrollment and nine more who had gaps of two or more years during the time that the pharmacy database was in existence (because of concerns about matching cases to controls adequately). This left 323 women. Three additional women were not utilizing GHC clinics but instead lived in rural areas where they received care from individual providers who contracted with GHC. Since these women lived far from GHC pharmacies (which are located at GHC clinics), it seems unlikely that they would have filled prescriptions there, and so we excluded them. There were also three women with invalid information about home clinic, indicating one of the following possibilities: missing information in the computer files; the woman was receiving care from contract providers in outlying areas (see above); or her chart was never created. These women were excluded from the study. In addition, one woman was excluded because of ambiguities regarding her age (possibly off by as much as 20 years). Another potential case was excluded due to ambiguities in SEER regarding tumor site, while one more was inadvertently excluded due to a programming error. After all exclusions were applied, there were 314 women eligible for study. Of these, 260 had invasive disease, while 54 had tumors of borderline malignant potential. There were 100 cases with local disease (SEER Stage 1; 31.9%), 22 (7.0%) with regional disease (SEER Stage 2), 182 (58.0%) with distant disease (SEER Stage 3), and 10 (3.2%) with unknown stage.

For four women with epithelial ovarian cancer, no chart was available for review because it had been lost or destroyed. These women were included in the study because we anticipated that information about their use of prescription drugs would still be available

through the computerized pharmacy database. However, because we had no information about covariates for these women, they were excluded from any analyses that adjusted for factors other than age, length of GHC membership, and calendar year.

Cases were assigned a "reference date" of 1.5 years prior to cancer diagnosis. Information about prescription drug use and other characteristics of interest was only obtained prior to the reference date, in order to increase the likelihood that exposures occurred prior to the onset of disease.

Control selection

Controls were selected from among women aged 35-79 years who were members of Group Health Cooperative within a year of the date that the corresponding case was diagnosed. We attempted to obtain at least two controls per case. Controls were individually matched to cases on age and length of GHC membership. Potential controls were excluded if they had undergone bilateral oophorectomy prior to the corresponding case's date of diagnosis or if they had undergone hysterectomy and had unknown ovarian status. Information on these procedures was obtained through computerized ICD-9 codes for hospital procedures, available since the mid-1980's, and through medical record review. We did not allow women who later developed ovarian cancer to be selected as controls in this study, nor did we allow women to be selected as a control more than once.

Controls were obtained in two ways. First, a number of controls were available for whom chart review had already been performed as part of a study of myocardial infarction and stroke. The study methodology has been described previously.[31] These controls were only available for certain years (reference dates 7/86 through 12/94, corresponding to cases with diagnosis dates from 1/88 to 6/96). In the original study, they were frequency-matched to the

myocardial infarction and stroke cases by age and calendar year and ranged in age from 40 to 79, with a median age of 70. In addition, they were required to be post-menopausal. For our study of ovarian cancer, where existing controls were not available, new controls were obtained by sampling from GHC's membership and billing records.

Use of existing controls

We had access to information on 2241 existing controls whose charts had been reviewed for the study described above.[31] These women had already been assigned a "reference date" for the purposes of chart review. We excluded women with a history of bilateral oophorectomy (518 women) or prior hysterectomy with unknown ovarian status (60 women). We also required that these controls be enrolled in GHC at their "pseudo-diagnosis" date (defined as 1.5 years after their reference date); that any gaps in GHC membership sum to less than half of the time after initial enrollment; and that there not be gaps in GHC membership summing to two or more years during the period that the pharmacy database was in existence. After these exclusions, there were 1494 potential controls available for matching. For 459 of these women (31%), both hysterectomy and oophorectomy status were unknown, but these women were still considered eligible, and 116 actually were selected to be controls. We allowed these women to be eligible because we felt that the likelihood that they had undergone bilateral oophorectomy was small. First, bilateral oophorectomy is uncommon. In a 1982 survey of women age 25-74, 9.9% reported having undergone bilateral oophorectomy.[32] Among women age 50-74 (a group more comparable in age to the existing controls available to us) the proportion was 18.3%. Second, it may be that this information is more likely to be missing from the medical record for women who have not undergone these operations, and thus women with missing information may be even less likely to have undergone these procedures.

Furthermore, we were concerned about the possibility of introducing bias by excluding women because they were missing this information, which could have been an indication that they rarely sought health care or that they had other medical conditions severe enough to preclude routine pelvic or other examination. In either case, the reason they were lacking this information might have affected their likelihood of using prescription drugs, the exposure of interest in this study.

We matched existing controls to cases based on reference date (within one year), age (by decade), and length of GHC membership (within one year). After attempting to identify up to two existing controls for each case, we allowed up to two additional existing controls to be assigned to each case, yielding as many as four controls for some cases. In total, we obtained 400 controls from this source.

Identification of new controls

For cases who had not yet been assigned two controls, we sampled from the GHC membership and billing database. These newly ascertained controls were randomly selected from among women who were members of GHC at the time their matched case was diagnosed. They were assigned the same diagnosis and reference dates as their case and were individually matched to cases based on age at diagnosis or "pseudo-diagnosis" dates (by 5-year intervals) and length of GHC membership (within 6 months). Women were excluded if they had gaps in membership totaling at least half of the time after initial enrollment or if they had gaps during the time of the computerized pharmacy database totaling 2 or more years. During the sampling process, we identified up to 5 potential controls per case.

We used medical record review to determine whether these controls had undergone bilateral oophorectomy. For 3 women the relevant portion of the medical record was

unavailable, having been lost or destroyed. These women were excluded because we could not verify their ovarian status. There were 44 women who had undergone bilateral oophorectomy, while 40 had undergone hysterectomy and had unknown ovarian status. An additional 15 women were found to have gaps in enrollment necessitating their exclusion. There were 4 women living in outlying areas where they received care from individual providers who contracted with GHC, instead of through GHC clinics. Since they would not have had access to a GHC pharmacy, they were excluded, as we would be missing all exposure information. One woman was excluded because of conflicting information regarding her age (possibly off by 10 years).

In total, after all exclusions were applied, 390 eligible controls were obtained in this way.

Data collection

As described above, women with epithelial ovarian cancer were assigned a "reference date" 1.5 years prior to the date of diagnosis. Existing controls had already been assigned a reference date when their chart review was conducted for the original study, and newly ascertained controls were assigned the same reference date as their matched case. For all subjects, information on exposures and potential confounding factors was collected only up to the reference date.

Information on the use of antidepressants, benzodiazepines, and other drugs was obtained from the GHC computerized pharmacy database, in existence since March 1977. For each prescription, this database includes the date filled, quantity dispensed, dosage, and formulation. Prescribing instructions are available for many but not all prescriptions. We did not attempt to collect information on past prescription drug use from the medical chart,

particularly use that occurred prior to joining GHC, because this information is not routinely collected in the course of medical care and, if present, may be selectively recorded.

Information on other characteristics was obtained from chart review, including demographic characteristics (race and marital status), behavioral characteristics (smoking), and reproductive characteristics (parity, age at menarche and menopause, and use of oral contraceptives). We collected information about height and weight as well as history of gynecologic surgeries (hysterectomy, oophorectomy, and tubal ligation).

For cases and newly ascertained controls, the following rules were used in ascertaining characteristics from chart review. For height, we recorded the earliest height from a physical examination conducted when the woman was at least 21 years of age. If no physical exam height was available, the value was taken from the earliest self-report (for example, the initial application for GHC membership) or radiology slip. For weight, we used the most recent weight from a physical examination, unless there was a self-reported or radiology weight that was at least 6 months more recent, in which case the more recent weight was used.

For cases and newly-identified controls, chart review was conducted by three trained abstractors, two of whom were registered nurses. Charts with ambiguous information about ovarian status or use of hormone replacement therapy around the time of menopause were reviewed by the study manager. Approximately 10% of charts were double-abstracted as part of ongoing training and quality assurance, and data were double-entered to minimize errors at the time of data entry.

There were several variables for which information was not obtained in comparable ways for existing controls compared to cases and newly-identified controls. First, when the original chart review was conducted for existing controls, no information was gathered about whether women had undergone tubal ligation. This information was obtained in the chart

reviews performed for cases and newly-identified controls. Secondly, information about hysterectomy status was sought for existing controls only during some of the years that the study of myocardial infarction and stroke was conducted, and thus many of these women are classified as having unknown hysterectomy status. This information was sought for all cases and newly-identified controls, and as a result a much smaller number of these women are classified as having unknown hysterectomy status. Finally, there were subtle differences in the rules used to determine history of oral contraceptive use. Among the existing controls, some women with no explicit mention of oral contraceptive use in the chart were classified as never-users (for instance, if they had been members for a long time without any mention of oral contraceptive use, or if the chart mentioned that they were using some other form of birth control). In contrast, for cases and newly-identified controls, women were only classified as never-users if the chart explicitly stated that they had never used oral contraceptives or if they had undergone tubal ligation, hysterectomy, or menopause prior to 1960 (when oral contraceptives first became available). Thus, for variables regarding tubal ligation, hysterectomy, and oral contraceptive use, comparisons between existing controls and cases are not appropriate.

Initially, we attempted to create a variable to measure oral contraceptive use among cases and newly-identified controls that would be as similar as possible to the variable measuring oral contraceptive use among existing controls. For this preliminary variable, women with oral contraceptive use lasting at least 6 months were classified as ever-users, while women with less than 6 months of use mentioned in the chart were classified as never-users. Women who were known to have used oral contraceptives but for unknown duration were classified as ever-users. As described above, women were classified as never-users if there was no mention of oral contraceptive use in the chart and they had undergone tubal ligation, hysterectomy, or menopause prior to 1960 (16 cases and 24 controls).

After comparing newly-identified controls with existing controls regarding prevalence of oral contraceptive use, we determined that the variables measuring oral contraceptive use remained too disparate for valid comparisons to be made between cases and existing controls. Since we would be unable to use these data for existing controls, we decided to make some minor changes in the oral contraceptive use variable for cases and newly-identified controls. In creating the final variable, we classified women as ever-users if they had used oral contraceptives for at least two months. If the chart indicated that a woman had used oral contraceptives but her duration of use was unknown, then her oral contraceptive use was classified as unknown (19 cases and 29 controls).

Creation of Exposure Variables

To identify prescriptions for drugs of interest, we began by examining GHC's lists of therapeutic classes to find classes which included drugs acting on the central nervous system. Classes that we felt were likely to include drugs of interest in this study included the following: anticonvulsants; antinauseant antihistamines (the class containing meclizine); anorexics/analeptics (the class containing amphetamines); and psychotherapeutics, particularly those labeled as antianxiety medications, benzodiazepines, tricyclic antidepressants, tricyclic-phenothiazine combinations, miscellaneous antidepressants, and monoamine oxidase inhibitors. Based on pharmacy data from our study subjects, we then listed all drugs used by women in this study that fell within the therapeutic classes we had identified. We used these drug lists to identify individual drugs of interest.

After identifying particular drugs of interest, we created a number of variables to measure sustained exposure to benzodiazepines, antidepressants, and other drugs acting on the central nervous system. First, we created variables to indicate whether a woman ever filled two

prescriptions for antidepressants or benzodiazepines within a six-month period. For antidepressants, women were required to have filled two prescriptions for the same drug (although they could be for different strengths or formulations) within six months. We applied this criterion because it is quite common for patients to switch or discontinue use of antidepressants early in treatment due to side effects, and so we felt that prescriptions for two different antidepressants might not represent continuous use. In contrast, for benzodiazepines, we considered use to be continuous even if the prescriptions were for different drugs within the class, because we felt that it was much less likely that patients would have switched drugs or discontinued a benzodiazepine prescription early due to side effects.

In addition, we created variables to gauge the likelihood that a woman had used a drug continuously for at least six months. Again, individual antidepressants were considered to be different drugs, while all benzodiazepines were grouped together. When dosing instructions were available (e.g. "take three pills per day"), we divided the quantity of pills prescribed by the number of pills intended to be taken each day to estimate the number of days that prescription would have been expected to last, which is sometimes referred to as the "runout". For a large proportion of prescriptions (37.0% for benzodiazepines and 36.9% for antidepressants), no dosing instructions were available. In these cases, we assumed daily use of one pill per day.

Next, for each prescription, we divided the number of days the prescription would have been expected to last (the "runout") by the actual days elapsed to the next prescription to determine whether use was likely to have been continuous. We wanted to take imperfect compliance into account in calculating whether a prescription would have been likely to last until the date the next prescription was filled. On the assumption of 75% compliance, we required a ratio of at least 0.75 expected days/actual days for use to be considered continuous. In other words, we allowed people to be up to 33.3% overdue in refilling a prescription. The

duration of a prescription was considered to be either the expected days based on dosing instructions or the actual elapsed days to the next prescription, whichever was smaller. This duration was summed across prescriptions that were considered to have been continuous to obtain the maximum duration for each episode of use. For the final prescription in an episode, we used the number of days the prescription would have been expected to last (based on dosing instructions) as the duration of the prescription. If a woman had at least one episode of use that included at least two prescriptions and that had a calculated duration of at least 180 days, she was considered to have used that drug continuously for six months or longer. A single prescription for more than 180 pills was not considered to constitute six months' use.

In addition, we created variables to measure total cumulative exposure to the drugs of interest. We calculated women's total number of prescriptions in each major group (antidepressants vs. benzodiazepines) as well as total number of pills dispensed. In this case, prescriptions for different antidepressants were added to obtain the final number. In calculating the total number of pills prescribed, we did not take into account the dosing instructions indicating how many pills were intended to be taken each day.

Based on the findings of a 1998 paper by Harlow et al.,[15] we also examined a wider variety of drugs that act on the central nervous system, including anticonvulsants (phenytoin and carbamazepine), lithium, amphetamines, buspirone (used to treat anxiety), meprobamate (a non-benzodiazepine tranquilizer), barbiturates (phenobarbitol, secobarbital, and pentobarbitol), and meclizine (an antihistamine used to treat motion sickness and vertigo). We made use of Harlow's grouping system, which classified each drug as operating through pathways involving primarily GABA; DA/NE; or serotoninergic or mixed serotonin and NE pathways. There were six drugs used by our subjects that were not used by any of Harlow's subjects and thus were not included in Harlow's grouping scheme: the antidepressants maprotiline, amoxapine,

protriptyline, and tranylcypromine; and the barbiturates secobarbitol and pentobarbitol. We assigned tranylcypromine, an MAO inhibitor, to the serotoninergic group because phenelzine (another MAO inhibitor) had been placed in this group. We assigned secobarbitol and pentobarbitol to the GABA-ergic group, the group to which phenobarbitol had been assigned. For maprotiline, amoxapine, and protriptyline, we used data on their relative potencies at blocking re-uptake of dopamine, serotonin, and norepinephrine to assign them to the group that seemed most appropriate.[8] Ultimately, all three were placed in the DA/NE group.

For these analyses, we classified women as having had two prescriptions in six months for a given group if they had two prescriptions for an individual drug (regardless of dose or formulation) belonging to that group within a 6-month period. The variables for at least 6 months of continuous use were, as above, based on total duration of continuous prescriptions for a single drug. As before, benzodiazepines were all treated as the same drug for the purposes of these variables. Also, we created variables to measure total cumulative exposure to drugs acting through each major pathway. We calculated women's total number of prescriptions in each major group (serotoninergic, GABA-ergic, or DA/NE) as well as total number of pills dispensed for drugs in a group. In this case, prescriptions for different drugs within a major group were added to obtain the final number of prescriptions. In calculating the total number of pills prescribed, we did not take into account the dosing instructions indicating how many pills were intended to be taken each day.

Statistical Analysis

We wanted to determine whether newly-identified controls were comparable to existing controls in terms of their demographic and reproductive characteristics. Because these groups differed substantially in age, we calculated age-adjusted distributions for these variables using

the direct method[33] before comparing the two groups. Women under 50 were excluded from all of these calculations because there were only three existing controls in this age group. We used the age distribution of newly-identified controls as the standard for adjustment (with age grouped as 50-59, 60-64, 65-69, 70-74, and 75-79 years). To obtain age-adjusted proportions, we first obtained age-stratified distributions for each variable for each group of women. Then we multiplied the proportion of women in a given age stratum with a certain value for a characteristic by the proportion of newly-identified controls in that age stratum. We added that product to the comparable product for the next age stratum, and so on. The sum of these products across all age strata is the age-adjusted proportion of women with that value for that characteristic for that particular group of controls. These calculations were performed in Microsoft Excel.

In addition, we wanted to determine whether there were differences in the distribution of exposure variables between newly-identified controls and existing controls. Again, we used the direct method to adjust for age, as described above. We concluded that distributions of the exposure variables were similar enough between the two control groups that it was appropriate to combine them.

To examine the association between risk of ovarian cancer and use of antidepressants, benzodiazepines, and other medications of interest, we compared the proportion of ovarian cancer cases who had used a certain medication prior to reference date with the proportion of controls with such use. Except where noted, conditional logistic regression was used to estimate odds ratios (ORs) and 95% confidence intervals (CIs) after adjustment for the matching variables age, reference date, and length of GHC membership (by matched sets). The likelihood ratio test was used to determine statistical significance.

We performed subgroup analyses limited to cases and newly-identified controls to examine whether adjustment for tubal ligation or oral contraceptive use altered these associations. Existing controls were excluded from these analyses because data on these variables was not gathered (tubal ligation) or was not gathered in a comparable way (oral contraceptive use). Because of the large proportion of women with missing values for oral contraceptive use, we did not use conditional logistic regression for analyses that included this variable. Instead, we used unconditional logistic regression and adjusted for age as a continuous variable. We compared the odds ratios obtained for the variables measuring medication use before and after adjustment for oral contraceptive use (grouped as ever/never), to see if the odds ratios changed substantially.

Because our initial results indicated that women with epithelial ovarian cancer (cases) had received fewer prescriptions from GHC pharmacies prior to reference date compared to controls, we performed analyses to determine whether adjustment for number of prescriptions altered our risk estimates. In these models, we adjusted for the total number of prescriptions for drugs other than the exposure of interest (as a continuous variable). For instance, in logistic regression models examining the effects of antidepressant use, we adjusted for total number of prescriptions for drugs other than antidepressants.

We used logistic regression models to test whether there was a trend toward increasing risk with increasing number of prescriptions filled or pills dispensed. These analyses were limited to women who had ever used the medication under study. Because of the large number of women who were excluded (due to never having used these medications), we did not use conditional logistic regression for these analyses but rather unconditional logistic regression with adjustment for age as a continuous variable. To test for trend, we used a model that included the variable of interest (pill count or prescription count) as a grouped linear variable,

categorized as shown in the results tables. In some cases we used a grouping scheme developed a priori (e.g. 1, 2-4, 5+ prescriptions), while in other cases we developed groupings based on the tertiles of the distribution among controls who had ever used the medication being examined. We used the likelihood ratio test to compare the model containing age and the grouped linear variable with the nested model that included only age to determine the significance level of these tests.

We repeated our primary analyses looking only at the 260 women with invasive disease and their matched controls. We also looked separately at women with mucinous tumors, women with non-mucinous epithelial tumors, women with local disease (SEER Stage 1), women with distant disease (SEER Stage 3), women under 50 years of age at diagnosis, women 50 or older at diagnosis, white women, and parous women. For the analyses limited to white women and parous women, the use of conditional logistic regression would have resulted in the loss of a large number of women from the model, and so in these cases we used unconditional logistic regression and adjusted for age as a continuous variable. We examined the effects of adjusting for reference date in addition to age and concluded that this did not substantially alter our risk estimates.

RESULTS

We wanted to determine whether newly-identified controls (those who had their medical records reviewed specifically for this study) were comparable to existing controls (those whose records were reviewed for a previous study[31]) in terms of their demographic and reproductive characteristics. Selected characteristics of these two groups are shown in Table 2. The existing controls were older than the newly-identified controls, with 44.3% of existing controls aged 70 or older compared to 11.3% of newly-identified controls. This reflects the fact that the existing controls were selected for a study of risk factors for myocardial infarction and stroke, diseases that predominantly affect older individuals, and also that the study for which they were chosen was limited to postmenopausal women. Because of the difference in age, we calculated age-adjusted distributions for other demographic and reproductive variables (Table 2).

Existing controls were available only for the reference years 1986-1994, while newly-identified controls were selected across all reference years (1979-1995). As noted in the Methods section, the "reference year" was set 1.5 years prior to the date of diagnosis for cases, and information about prescription drug use and other covariates was only obtained up until the reference date. A similar date was assigned to newly-identified controls.

The two groups of controls were generally similar in terms of marital status. Existing controls were somewhat more likely to be widowed (17.5% vs. 10.8% of newly-identified controls, before age-adjustment). However, this was reversed after age-adjustment (Table 2). There were substantial differences between the two groups in terms of smoking status. Although a similar proportion of women in each group were classified as current or past smokers (Table 2), existing controls were much more likely to be classified as never smokers

(27.4% vs. 8.1%, after age-adjustment) and less likely to be classified as unknown (1.5% vs. 12.2%) or as not current NOS (not otherwise specified; 31.9% vs. 41.0%). The discrepancies in smoking status suggest that different assumptions may have been used during chart review, particularly because of the substantial differences in the proportion of unknown values.

The two groups of controls were similar in terms of race, with about 70% being white and about 20% in each group having unknown race (Table 2). The groups had similar distributions for parity as well, one of the characteristics most consistently associated with risk of ovarian cancer. However, for another important reproductive characteristic, oral contraceptive use, the two control groups looked very different. Among newly-identified controls, 42.8% had unknown oral contraceptive use, compared to only 11.5% of existing controls. This difference, which was not attenuated by adjustment for age, reflects the fact that different assumptions were used in conducting chart review for these two groups of controls (see Methods section). Because the charts of cases were reviewed using the same rules and assumptions as the newly-identified controls, we concluded that it would not be appropriate to include existing controls in any analyses examining past use of oral contraceptives.

Information about tubal ligation was obtained only for newly-identified controls. Information on hysterectomy status was obtained for existing controls only in certain years. This explains the substantial differences seen in Table 2, where it can be seen that 59.5% of existing controls have unknown hysterectomy status compared to only 2.3% of newly-identified controls. Adjustment for age did not ameliorate this discrepancy.

On average, newly-identified controls had filled fewer prescriptions at GHC pharmacies prior to reference date. Their median number of prescriptions filled per year was 6.7, and the mean was 10.4 with 95% confidence limits from 9.3-11.5. In contrast, existing controls had a median of 8.7 and a mean of 11.9 (95% CI 10.8-13.1). After adjustment for age, the two groups

looked more similar, with means of 12.2 and 10.2 respectively. However, further adjustment for reference date resulted in a greater discrepancy, with newly-identified controls filling an average of 12.8 prescriptions per year compared to 9.6 per year for existing controls.

After examining the distributions of demographic and reproductive characteristics for the two control groups shown in Table 2, we concluded that it was appropriate to combine these groups for most variables, with the exceptions being smoking status, oral contraceptive use, history of tubal ligation, and hysterectomy status. Thus, Table 3a depicts selected characteristics of cases compared to all controls for all other reproductive and demographic characteristics of interest. Table 3b depicts selected characteristics of cases compared to newly-identified controls for the four variables for which the two control groups differed the most: smoking status, oral contraceptive use, history of tubal ligation, and hysterectomy status.

As can be seen from Table 3a, the group of all controls was slightly older than the cases (for example, 28.0% of all controls were 70 years of age or older, compared to 22.0% of cases). This can be explained by the fact that a relatively greater number of existing controls was allowed to be matched to each case, and these controls were on average older than the newly-identified controls. Overall, cases and controls were similar with respect to reference year and length of GHC enrollment, other matching variables.

Cases and controls were generally similar with respect to marital status, although a higher proportion of cases were divorced (14.3%, compared to 8.2% of all controls; see Table 3a). In terms of race, cases and controls were quite similar. Cases were more likely to be nulliparous (16.9%, compared to 11.4% of controls). A similar proportion of cases and controls had unknown parity.

Compared to controls, cases had filled fewer prescriptions per year at GHC pharmacies prior to reference date (Table 3a). For cases, the median number of prescriptions filled per year

was 6.6, compared to 7.7 for the group of all controls. The means for these groups were 10.3 (95% CI 9.0-11.5) and 11.2 (95% CI 10.4-12.0) respectively. These differences diminished after adjustment for age (Table 3a).

Table 3b shows a comparison of cases with newly-identified controls for those demographic and reproductive variables which differed between the two control groups. In terms of smoking status, cases and newly-identified controls were generally similar, although cases were slightly less likely to be current smokers (15.0%, vs. 20.0% of newly-identified controls). Cases were more likely never to have used oral contraceptives (31.5%, compared to 15.6% among newly-identified controls). The proportion of women with unknown values for oral contraceptive use was similar in the two groups (43.0% vs. 50.3%). Cases were less likely to have undergone tubal ligation compared to newly-identified controls. A similar proportion of women in each group had ever undergone hysterectomy.

Study subjects had received prescriptions for a wide variety of drugs that act on the central nervous system. Table 4 shows the number of prescriptions filled by controls as well as the number of controls who had filled prescriptions for individual drugs, with drugs grouped into major therapeutic classes (antidepressants, benzodiazepines, antipsychotic agents, and other/miscellaneous). Among the antidepressants, the most commonly used drug was doxepin, which accounted for about one-third of all antidepressant prescriptions, with 724 prescriptions filled by 88 women. Other commonly used antidepressants were amitriptyline, with 693 prescriptions filled by 93 women, and imipramine, with 248 prescriptions filled by 37 women. Antidepressants classified as selective serotonin re-uptake inhibitors were used by very few women during the time period covered by this study. Although 80 prescriptions were filled for fluoxetine, this drug was only used by 9 women, or 1.1% of all controls. Sertraline was used by one control, while no controls had used paroxetine. Antidepressants classified as MAO

inhibitors were also rarely used. One woman had filled a total of 16 prescriptions for phenelzine, while no women in the control group had filled prescriptions for tranylcypromine.

Among benzodiazepines, diazepam was the most commonly used by controls in this study, with 932 prescriptions (41% of the total) filled by 143 women (Table 4). Alprazolam and flurazepam were the next most common, with 423 prescriptions (18.7% of the total) filled by 48 women for alprazolam and 404 prescriptions (17.9%) filled by 104 women for flurazepam.

Antipsychotic agents were used by very few women, with no more than eight women filling any prescriptions for an individual antipsychotic agent (Table 4). Because usage was so rare, no further analysis of antipsychotic use was performed.

Among the other agents acting on the central nervous system, the most commonly used were the sedative meprobamate (598 prescriptions filled by 110 controls) and meclizine, an antihistamine used in the treatment of vertigo (305 prescriptions filled by 130 controls; see Table 4). There were 21 controls with at least one prescription for phenobarbital, for a total of 170 prescriptions. Prescription amphetamines were rarely used, with 3 women in the control group filling a single prescription each.

Before examining the relationship between use of these medications and risk of epithelial ovarian cancer, we wanted to ensure that the prevalence of medication use was comparable across the two control groups before combining them. Since the two control groups differed with respect to age, we calculated age-adjusted distributions (adjusted for age at "diagnosis date") for the exposure variables of interest. We excluded women aged 35-49 from all of these calculations since there were only 3 existing controls in this age range. Table 5 shows these results for the variables measuring use of antidepressants and benzodiazepines. After age-adjustment, the distributions of these variables did not differ between the two control groups. For example, after age-adjustment, 74.8% of newly-identified controls had never

received a prescription for an antidepressant, compared to 73.9% of existing controls. Also, 17.1% of newly-identified controls had received at least two prescriptions for antidepressants within a 6-month period, compared to 15.8% of existing controls (after age-adjustment). Looking at women with the greatest use of these medications, 8.1% of newly-identified controls had received prescriptions for antidepressants totaling 500 or more pills, compared to 8.5% among the existing controls (after age-adjustment). The patterns of benzodiazepine use were similar between women in the two control groups as well.

Because newly-identified and existing controls were similar in their past usage of these medications, we combined the two groups when comparing them to women with epithelial ovarian cancer. Table 6 shows the results of this comparison for antidepressants. Cases were slightly less likely ever to have used these medications than were controls. Among cases, 79.9% had never filled a single prescription for an antidepressant, compared to 76.7% of controls. While 11.8% of cases had filled two prescriptions for a particular antidepressant within a 6-month period, 15.7% of controls had a history of such use. After adjustment for matching variables, the odds ratio for filling two prescriptions in a 6-month period was 0.71 (95% CI 0.47-1.05). We saw a similar pattern when we looked at continuous use of an antidepressant for at least 6 months, which we defined as an episode of use lasting at least 6 months and including at least two prescriptions where each prescription contained enough pills to last until the next prescription was filled, assuming daily use and 75% compliance. Among cases, 5.1% had used an antidepressant continuously for at least 6 months, compared to 7.5% of controls (OR 0.64, 95% CI 0.36-1.15, adjusted for age, calendar year, and length of GHC membership).

Relative to controls, cases also had a smaller total number of antidepressant prescriptions filled and pills dispensed (Table 6). However, among users of antidepressants,

there was no strong evidence of a trend toward decreased risk associated with increasing number of prescriptions filled or pills dispensed. With exposure variables grouped as shown in Table 6, the p-value for trend for number of prescriptions filled was 0.11 among ever-users, while for pills dispensed it was 0.20.

We examined a variety of logistic regression models to determine whether we needed to adjust for any covariates in modeling the relationship between antidepressant use and risk of epithelial ovarian cancer. Table 7 depicts the results produced by eight of these models. On the first page of Table 7, the first column ("Crude OR") presents odds ratios and 95% confidence intervals from an unconditional logistic regression model without adjustment for any covariates. The second column presents results from a conditional logistic regression model adjusting for matching variables (by matched set), which yielded results extremely similar to the first model. For example, the odds ratio for having two antidepressant prescriptions within a 6-month period changed from 0.72 to 0.71. In the third column, we present results from the same conditional logistic regression model after excluding women whose parity was unknown, as a baseline for comparison to the model in column 4, which adjusts for parity. Comparing columns 3 and 4 demonstrates that adjustment for parity did not alter our risk estimates substantially. On the second page of Table 7 (p. 70), we present the results from models that demonstrate the effects of adjustment for tubal ligation (p. 70, column 1 vs. column 2) or for history of oral contraceptive use, when known (p. 70, column 3 vs. column 4). These results indicate that adjustment for history of tubal ligation and oral contraceptive use did not substantially affect our risk estimates. We also performed analyses adjusting for hysterectomy status as well as for total number of prescriptions filled for other types of medications (as a continuous variable). Adjustment for these variables did not alter our risk estimates substantially (data not shown).

Cases were less likely ever to have used benzodiazepines than were controls, with 71.3% of cases never having filled a benzodiazepine prescription compared to 64.7% of controls (Table 8). Among cases, 13.7% had received two benzodiazepine prescriptions in a 6-month period, compared to 17.5% of controls (OR 0.70, with 95% CI 0.47-1.04, after adjustment for age, calendar year, and length of GHC membership). Only 1.0% of cases had a history of continuous use for at least 6 months, compared to 1.6% of controls (OR 0.53, 95% CI 0.15-1.87, after adjustment for age, calendar year, and length of GHC membership). Relative to controls, cases also had a smaller total number of prescriptions filled and pills dispensed. The adjusted odds ratio for having filled 5 or more benzodiazepine prescriptions was 0.68 (95% CI 0.42-1.09), and for receiving 500 or more pills it was 0.59 (95% CI 0.27-1.25). Among women who had ever used benzodiazepines, there was no clear trend toward decreasing risk associated with increasing number of prescriptions filled or pills dispensed. The p-value for trend for number of prescriptions was 0.87, while for number of pills it was 0.67.

Table 9 shows odds ratios and 95% confidence intervals from a variety of logistic regression models used to examine the association between benzodiazepine use and risk of epithelial ovarian cancer. . As in Table 7, which showed results of similar analyses for antidepressant use, column 1 of the first page (p. 73) shows crude results from an unconditional logistic regression model, while column 2 shows results of a conditional logistic regression model adjusting for matching variables (age, calendar year, and length of GHC membership). On page 73, columns 3 and 4 show the effects of adjusting for parity, while page 74 depicts the effects of adjusting for history of tubal ligation (column 1 vs. 2) or oral contraceptive use (column 3 vs. 4). These results demonstrate that adjusting for these covariates did not substantially alter our risk estimates. We also performed analyses adjusting for hysterectomy status as well as for total number of prescriptions filled for medications other than

benzodiazepines (as a continuous variable), which revealed that adjusting for this variable did not alter our risk estimates substantially (data not shown).

Overall, among our study subjects, women with epithelial ovarian cancer were slightly less likely than controls ever to have used either antidepressants or benzodiazepines. To investigate whether there might be some underlying bias in our data set, we repeated our analyses looking at two other commonly used drug classes, diuretics and beta-blockers, for which we had no reason to expect any association with ovarian cancer risk. First, we investigated whether it was appropriate to combine the two groups of controls for these analyses by examining the age-adjusted distributions of drug use variables in both groups. Based on these results, shown in Table 10, we decided that it was appropriate to combine the groups.

Table 11 presents the results of our analyses for diuretic use. Cases and controls were equally likely never to have filled a prescription (60.5% vs. 60.4%). There was no association between risk of ovarian cancer and having filled two prescriptions in a 6-month period (OR 0.99, 95% CI 0.74-1.33, adjusted for age, calendar year, and length of GHC membership) or between cancer risk and continuous use of diuretics for at least 6 months (adjusted OR 1.27, 95% CI 0.92-1.76). There was little evidence of a pattern of increasing risk with increasing number of prescriptions filled or pills dispensed. Based on a test for trend including only women who ever used diuretics, the p-values were 0.42 for number of prescriptions filled and 0.25 for number of pills dispensed (using the groupings shown in Table 11, which are based on tertiles of the control distribution for women who ever used diuretics).

Table 12 presents the results of similar analyses performed for beta-blockers. Cases were somewhat less likely ever to have used these medications: 83.1% were never-users, compared to 78.6% of controls. Among cases, 14.6% had received two prescriptions for beta-blockers within a 6-month period, compared to 18.6% of controls (OR 0.74, 95% CI 0.54-1.13,

adjusted for age, calendar year, and length of GHC membership). We saw similar results when we looked at continuous use for a 6-month period (adjusted OR 0.68, 95% CI 0.45-1.04), as well as for total number of prescriptions received and pills dispensed. There was little evidence to support a pattern of decreasing risk with increasing number of prescriptions filled or pills dispensed. Based on tests for trend including only women who had ever used beta-blockers, the p-values were 0.26 for number of prescriptions filled and 0.96 for number of pills dispensed (using the groupings shown in Table 12, which are based on tertiles of the distributions among controls who ever used beta-blockers).

We also performed analyses after grouping medications according to presumed mechanism of action. Table 13 shows the results for use of medications that act by inhibiting re-uptake of serotonin or of serotonin and norepinephrine. This group includes many of the antidepressants used by women in this study as well as lithium and buspirone. The results were similar to those presented in Table 6: a general pattern of somewhat less usage among cases compared to controls. For instance, 80.9% of cases had never received a prescription for a medication in this group, compared to 77.7% of controls. Among cases, 4.1% had ever used one of these medications continuously for 6 months or longer, compared to 6.8% of controls (adjusted OR 0.58, 95% CI 0.30-1.09). 3.2% of cases had received 500 or more pills for medications acting through these pathways, compared to 6.6% of controls (adjusted OR 0.45, 95% CI 0.22-0.93). However, based on the odds ratios, there did not appear to be a trend toward decreasing risk associated with increasing number of prescriptions filled or pills dispensed.

Cases and controls were quite similar in their usage of medications that act by modulating the re-uptake of dopamine or dopamine and norepinephrine, a grouping that included a number of antidepressants as well as prescription amphetamines. 2.9% of cases had

received two prescriptions for a medication in this group in a 6 month period, compared to 2.7% of controls (adjusted OR 0.96, 95% CI 0.44-2.13). Slightly more cases than controls had filled 5 or more prescriptions for medications in this group (2.2% vs. 1.3%) or had received 155 or more pills (2.5% vs. 1.6%; adjusted OR 1.28, 95% CI 0.52-3.13). Looking at the odds ratios, there did not appear to be a trend toward increasing risk with increasing number of prescriptions filled or pills dispensed.

Table 15 shows the results of similar analyses for medications acting through pathways involving the GABA receptor, the group which included benzodiazepines as well as barbiturates, anticonvulsants, meprobamate, and meclizine. Cases and controls were equally likely to have received two prescriptions in a six-month period (22.0% of cases vs. 22.8% of controls). However, cases were somewhat less likely to have taken any of these medications continuously for 6 months or longer (1.9% vs. 3.5%, adjusted OR 0.50, with 95% CI 0.20-1.23). Also, cases were less likely to have filled 5 or more prescriptions or received 500 or more pills for medications in this grouping. However, among women who had ever used GABA-ergic medications, there was little evidence of a trend of decreasing risk with increasing number of prescriptions filled or pills dispensed ($p=0.64$ for number of prescriptions filled and 0.46 for number of pills dispensed, based on tests for trend using the groupings shown in Table 15).

We repeated our analyses looking at antidepressant and benzodiazepine use among subgroups of women. When we limited the analyses to women with invasive disease and their matched controls, the results were quite similar to those seen for all women (Table 16). For instance, looking at the likelihood that a woman had filled two antidepressant prescriptions in a 6-month period, the odds ratio went from 0.71 to 0.67 when we limited the analysis to women with invasive disease. Looking at benzodiazepine use, the odds ratio for having filled two prescriptions in 6 months went from 0.70 to 0.66.

Table 17 shows the results of selected analyses after limiting the population to women with mucinous tumors and their matched controls (29 cases and 65 controls). For antidepressant use, cases with mucinous tumors had somewhat less usage compared to their matched controls. These results were generally similar to those observed when all cases were included in the analysis. Cases and controls were equally likely to have received two benzodiazepine prescriptions within 6 months (adjusted OR 1.03, 95% CI 0.19-5.53). More cases had received 1 benzodiazepine prescription (OR 1.36, 95% CI 0.37-4.96) or 2-4 prescriptions (OR 2.36, 95% CI 0.45-12.5) compared to controls. However, 0 cases and 3 controls had received 5 or more benzodiazepine prescriptions. Results observed for women with non-mucinous epithelial tumors (Table 18) were very similar to those observed for the entire group.

We examined use of these medications among women with local disease (SEER Stage 1), compared to their matched controls (Table 19). For antidepressants, cases were slightly more likely to be never-users, but cases and controls were equally likely to have filled at least two prescriptions in 6 months (13.0% vs. 12.9%). Cases were less likely to have used an antidepressant continuously for 6 months or longer (OR 0.66, 95% CI 0.26-1.68) or to have filled 1 or 2-4 prescriptions, but cases and controls were equally likely to have filled 5 or more prescriptions (OR 1.08, 95% CI 0.52-2.25). There was no pattern of either increasing or decreasing risk with increasing number of antidepressant prescriptions filled. Looking at benzodiazepine use, cases and controls were equally likely never to have received a prescription. Cases were slightly less likely to have received two benzodiazepine prescriptions in 6 months (OR 0.80, 95% CI 0.39-1.63), but there was no pattern of decreasing risk with increasing number of prescriptions filled.

Looking at women with distant disease (SEER Stage 3) and their matched controls (Table 20), cases were somewhat less likely to have used antidepressants compared to controls.

The results for these analyses were generally similar to those obtained when all subjects were included. Cases were less likely than controls to have received two prescriptions in a 6-month period (OR 0.64, 95% CI 0.37-1.09) or to have used an antidepressant continuously for 6 months or longer (OR 0.51, 95% CI 0.21-1.26). Cases were less likely to have received 5 or more prescriptions but more likely to have received a single prescription. In addition, cases were less likely to have used benzodiazepines compared to controls. Cases were considerably less likely than controls to have filled 5 or more benzodiazepine prescriptions (OR 0.50, 95% CI 0.26-0.98), but there was no clear pattern of decreasing risk with increasing number of prescriptions filled.

When we limited the analysis to women with age less than 50 (83 cases and 171 controls), we saw somewhat less usage of both antidepressants and benzodiazepines among cases compared to controls (Table 21). There was not a pattern of decreasing risk with increasing number of prescriptions filled for either type of medication. Among women with age 50 or greater (231 cases and 619 controls; Table 22), the results were quite similar to those obtained when all women were included in the analysis. Again, cases had somewhat less use of both types of medication.

The results for white women (Table 23) were generally similar to those obtained for all women, as were those obtained when the analysis was limited to parous women (Table 24).

DISCUSSION

This study has a number of limitations. One concern is the possibility for misclassification of exposure. We relied upon a computerized pharmacy database for all of our information about prescription drug use. This database records prescription fills but cannot provide information about whether women actually took any or all of the pills dispensed. We attempted to address this problem by creating exposure variables for having filled two or more prescriptions in a 6-month period and for continuous use for 6 months or longer. These variables are more likely to reflect actual usage of the medications of interest than would receipt of a single, isolated prescription.

Of greater concern is the fact that this database can only provide information about prescriptions filled at Group Health pharmacies. Research indicates that for most medications, GHC members are extremely likely to fill prescriptions within the Group Health system. One study conducted in 1986 found that participants had obtained, on average, between 0.18 and 0.24 prescriptions per year outside of GHC.[34] A survey of GHC enrollees treated for headache, back pain, or temporomandibular joint pain in 1989-1990 found that 100% of prescriptions for amitriptyline and doxepin were filled at GHC pharmacies, as were 98% of prescriptions for meprobamate and 93% for diazepam.[35] According to another survey, only 2.4% of subjects who were taking antidepressants in 1991-1992 had filled an antidepressant prescription outside of GHC within the past month.[35] However, antidepressants were not fully covered by Group Health's insurance plans until as late as 1990, and so prior to 1990 there could have been less incentive to pursue mental health treatment within GHC. If women received antidepressant prescriptions from physicians outside of the Group Health system, we will not have data on those exposures. Thus, a number of women who truly were exposed may be misclassified as

unexposed in our study. This issue should have little or no effect on our ascertainment of benzodiazepine usage, however.

The pharmacy database has been in existence since March 1977. We did not attempt to supplement it by obtaining information on medication usage from medical records for the years prior to 1977. Some of the drugs of interest were available as early as 1960 (for instance, the tricyclic antidepressants imipramine and amitriptyline), while others were not available until the 1980's (for example, the SSRI antidepressants). Furthermore, the pharmacy database can only provide information about medication use during the years that women were members of GHC. Thus, if women in our study received prescriptions for any of these medications prior to 1977 or prior to joining GHC, we would lack information about those exposures.

In addition, we lacked information about non-prescription use of these medications. For most of the drugs of interest, non-prescription use would be expected to be extremely rare. However, for one type of drug, amphetamines, there is a possibility that we could have missed a large proportion of use. Harlow et al. reported that 1.3% of their controls had ever used amphetamines but did not provide information about whether this usage was by prescription.[15] In contrast, only 0.4% of our controls (3 women) had received any prescriptions for amphetamines.

All of the factors discussed above could lead to misclassification of exposure status for women in this study. It seems likely that this misclassification would be non-differential, which would tend to bias risk estimates towards the null and reduce our power to detect differences between cases and controls. In addition, it seems unlikely that this misclassification could be substantial enough to reduce odds ratios of the magnitude reported in some prior studies, such as 1.8 or 2.1,[7] to the odds ratios of approximately 0.7 seen in this study.

There could be misclassification of a potential confounding factor, use of oral contraceptives. The high proportion of women with unknown values for oral contraceptive use (43.0% of cases and 50.3% of newly-identified controls) is one indicator of the difficulty we had in obtaining this information from medical records. One reason for this may be that many study subjects were post-menopausal, and any oral contraceptive usage is likely to have occurred 20 or more years prior to their reference date. We attempted to address this problem during the process of chart review through detailed rules, for instance by classifying women as never-users only if the chart explicitly stated that they had never used oral contraceptives. We did observe that cases were substantially less likely to have used oral contraceptives compared to newly-identified controls (25.5% vs. 34.1%). This is reassuring because it indicates that our assessment of this variable was good enough to provide results that are generally comparable to those found for oral contraceptive use in prior studies. In addition, in analyses limited to women for whom information on oral contraceptive use was available, adjustment for this variable did not alter our risk estimates appreciably.

We lacked information about another potential confounding factor, family history of ovarian cancer. If this variable were associated with use of antidepressants or benzodiazepines, then our risk estimates could be biased. However, the initial article that reported an association between use of these medications and increased risk of ovarian cancer did not adjust for this variable,[7] which suggests that the absence of information about family history does not fully explain our failure to observe an association between use of antidepressants or benzodiazepines and increased risk of epithelial ovarian cancer.

In this study, we did not observe an association between use of antidepressants or benzodiazepines and increaed risk of epithelial ovarian cancer. Cases were somewhat less likely to have used these medications compared to controls, but this association was within the

bounds of chance, and there was no clear pattern of decreased risk of ovarian cancer associated with increasing use of these medications as measured by the total number of prescriptions filled or pills dispensed.

For antidepressants, it is difficult to compare results across studies. While Harlow's initial study[7] examined relationships between antidepressants in general and risk of ovarian cancer, the second study[15] divided antidepressants into two groups based on putative mechanisms of action (serotoninergic vs. dopamine/norepinephrinergic) and added several other drugs acting on the central nervous system into these groupings, including amphetamines and the anti-anxiety drug buspirone. In addition, the particular drugs used by study subjects differed between the two studies. This is unavoidable because of the rapid changes in availability of various antidepressants, with new drugs becoming available and with changes in prescribing patterns over time.

Looking at antidepressant use overall, our results do not agree with those reported in Harlow's initial study. While we found less use of antidepressants among cases compared to controls (OR 0.71, 95% CI 0.47-1.05, for two prescriptions within 6 months), Harlow et al. reported increased use among cases, with an odds ratio of 2.1 (95% CI 0.9-4.8).[7] To facilitate comparison between our results and those of Harlow's second study, we also looked at drugs grouped by mechanism of action, basing our grouping scheme on that used by Harlow et al.[15] For drugs that act by inhibiting re-uptake of serotonin or serotonin and norepinephrine, our results are comparable to those of Harlow's second study and provide little evidence of an association with ovarian cancer risk. We found that a somewhat smaller proportion of cases than controls had taken drugs acting through these pathways (OR 0.71, 95% CI 0.47-1.08, for two prescriptions within 6 months). Harlow et al. reported similar usage between cases and controls, with an odds ratio of 0.9 (95% CI 0.5-1.8).[15]

However, for drugs that act by modulating re-uptake of dopamine and norepinephrine, our findings do not agree with those reported in the second study by Harlow et al.[15] We found about the same amount of usage in cases and controls, with 2.9% of cases and 2.7% of controls having filled two prescriptions for a medication in this group within 6 months (OR 0.96, 95% CI 0.44-2.13). Among cases, 1.0% (3 women) appeared to have used a medication in this group continuously for at least six months, compared to 0.4% of controls (3 women) (OR 1.79, 95% CI 0.36-8.97). We did not see a pattern of increasing risk with increasing usage of these medications: the odds ratio went from roughly 0.8 to 0.6 to 1.5 for women who had received 1, 2 to 4, or 5 or more prescriptions, respectively. In contrast, Harlow et al. found more usage of medications in the dopamine/norepinephrine group among women with ovarian cancer, with 4.8% of cases reporting use for 6 months or longer compared to 1.9% of controls (OR 2.4, 95% CI 1.1-5.2).[15]

One possible difference between our study and Harlow et al.'s second study is that they had information about non-prescription use of amphetamines, while we did not. Amphetamines were used by 2.8% of Harlow's cases and 1.3% of controls, which could account for part of the association observed by Harlow et al.[15] A major difference between our study and both studies conducted by Harlow et al. is that we obtained exposure information from a computerized pharmacy database, while they conducted in-person interviews.[7,15] On the one hand, it could be that nondifferential misclassification in our study created a bias toward the null; or on the other hand, recall and/or reporting bias in Harlow's studies could have created an apparent association when none truly exists. Comparison of our study with Harlow et al.'s second study[15] is also made difficult by the fact that so few women in our study had used medications in the dopamine/norepinephrine group, yielding risk estimates with wide confidence intervals.

For benzodiazepines, our findings are compatible with two of three previously published studies.[15,29] In our study, the odds ratio for receiving two benzodiazepine prescriptions in 6 months was 0.70, with 95% confidence limits from 0.47-1.04. Rosenberg et al. also found no association between sustained benzodiazepine use (defined as use at least 4 days per week for at least one month) and risk of ovarian cancer, with an odds ratio of 0.9 and 95% confidence limits 0.6-1.4.[29] In their 1998 study,[15] Harlow et al. observed somewhat more use of GABA-ergic medications (the category including benzodiazepines) among cases compared to controls, but this association was within the bounds of chance, with an odds ratio of 1.3 (95% CI 0.8-2.1). The findings from all three of these studies are compatible with the interpretation that there is no association between benzodiazepine use and risk of epithelial ovarian cancer. The only study with stronger findings is Harlow's initial one,[7] which reported benzodiazepine use among 8.9% cases compared to 5.3% of controls, with an odds ratio of 1.8 (95% CI 1.0-3.1). One possible explanation for the discrepancy is that in Harlow's initial study, women had used a limited range of benzodiazepines (only chlordiazepoxide, diazepam, and lorazepam), while in the other three studies subjects had used a much wider range of drugs belonging to this class. However, Rosenberg et al. did examine the association between diazepam use and risk of ovarian cancer and reported no association (OR 1.0, 95% CI 0.6-1.6).[29]

In summary, after reviewing our findings and those of prior studies, we conclude that there is not consistent evidence supporting an association between use of benzodiazepines, antidepressants, or selected other drugs acting on the central nervous system and increased risk of epithelial ovarian cancer. However, there is not sufficient evidence to rule out the possibility of increased risk following use of medications that act through pathways involving dopamine and/or norepinephrine. Further exploration of the association between medications acting

through pathways involving dopamine and/or norepinephrine and risk of ovarian cancer in other settings would be helpful, ideally with a large number of subjects and supplemental information about nonprescription amphetamine use.

Certain antidepressants that are widely used today have only been available for a limited time, and thus studies conducted to date provide little information about risks associated with their use. For instance, in our study, only one control had received any prescriptions for sertraline, a selective serotonin receptor that became available in 1991, while no controls had received prescriptions for paroxetine, available since 1992, or fluvoxamine, available since 1994. Potential risks associated with these drugs, if any exist, would become apparent only after they have been used by sufficient women for long enough duration. Thus, it would be useful to re-examine the association between ovarian cancer risk and antidepressant medications and tranquilizers in the future.

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Table 1: Selection and exclusion criteria for cases of epithelial ovarian cancer

Criteria	Number of Women
GHC members aged 35-79 diagnosed 3/81 through 6/97	400
With ≥ 4 years prior membership*	334
After exclusion of women with gaps in membership summing to ≥ half of time from date of enrollment to diagnosis	332
After exclusion of women with gaps of ≥ 2 years during time of pharmacy database (3/77-on)	323
After exclusion of 3 women who were not members of GHC's staff-model HMO (and therefore were unlikely to have used GHC pharmacies); and 6 women with miscellaneous other exclusions†	314

*Excludes one woman with inadequate information about dates of GHC enrollment.
†Miscellaneous exclusions include one woman with conflicting information regarding age at diagnosis (possibly off by 20 years) and three women with invalid information about home clinic (see Methods section). One woman was excluded due to ambiguities in her SEER record regarding tumor site. In addition, one eligible case was inadvertently excluded due to programming errors.

Table 2: Selected characteristics of newly-identified controls compared to existing controls

	Newly-identified controls (N=390)*			*Existing controls* (N=400)*		
	n	%	% excluding age 35-49†	n	%	Age-adjusted %‡
Age at diagnosis§						
35-39	33	8.5	—	0	0	—
40-49	135	34.6	—	3	0.8	—
50-59	76	19.5	—	71	17.8	—
60-69	102	26.2	—	149	37.3	—
70-79	44	11.3	—	177	44.3	—
Reference year¶						
1979-1981	65	16.7	—	0	0	—
1982-1985	143	36.7	—	0	0	—
1986-1988	43	11.0	—	147	36.8	—
1989-1991	42	10.8	—	128	32.0	—
1992-1994	49	12.6	—	125	31.3	—
1995	48	12.3	—	0	0	—
Length of GHC enrollment**						
2.5-4.9 years	46	11.8	7.2	35	8.8	10.3
5.0-9.9 years	103	26.4	29.3	85	21.3	22.4
10-14.9 years	103	26.4	25.7	90	22.5	22.7
15-19.9 years	59	15.1	14.4	84	21.0	21.1
20+ years	79	20.3	23.4	106	26.5	23.5
Length of GHC enrollment since inception of pharmacy database**						
2.5-4.9 years	112	28.7	30.2	35	8.8	10.3
5.0-9.9 years	167	42.8	47.7	107	26.8	28.2
10-14.9 years	74	19.0	11.3	202	50.5	48.9
15+ years	37	9.5	10.8	56	14.0	12.6
Marital status						
Single	22	5.6	2.3	16	4.0	4.0
Married	267	68.5	63.5	240	60.0	64.3
Divorced	31	8.0	8.6	34	8.5	8.9
Widowed	42	10.8	17.6	70	17.5	11.6
Separated	8	2.1	1.8	2	0.5	0.6
Unknown	20	5.1	6.3	38	9.5	10.6

Table 2, cont.: Selected characteristics of newly-identified controls compared to existing controls

	Newly-identified controls (N=390)*			*Existing controls* (N=400)*		
	n	%	% excluding age 35-49†	n	%	Age-adjusted %‡
Smoking status						
Current	78	20.0	21.6	67	16.8	17.8
Not current						
Never	42	10.8	8.1	112	28.0	27.4
Past	66	16.9	17.1	87	21.8	21.4
Not current NOS††	163	41.8	41.0	128	32.0	31.9
Unknown	41	10.5	12.2	6	1.5	1.5
Race						
White	292	74.9	74.3	287	71.8	69.5
Black	10	2.6	2.3	8	2.0	2.4
Asian/Pacific Islander	6	1.5	2.3	12	3.0	3.3
Other	10	2.6	1.4	3	0.8	1.4
Unknown	72	18.5	19.8	90	22.5	23.4
Parity						
0	54	13.9	9.9	36	9.0	8.3
1-2	182	46.7	39.2	137	34.3	33.7
3-4	110	28.2	33.8	150	37.5	39.2
5+	28	7.2	11.3	49	12.3	11.8
Unknown	16	4.1	5.9	28	7.0	6.9
Oral contraceptive use‡‡						
Never	67	17.2	24.8	268	67.0	56.2
Ever	156	40.0	23.4	86	21.5	30.3
Unknown	167	42.8	51.8	46	11.5	13.5
Tubal ligation§§						
Yes	68	17.4	—	not asked		
No	322	82.6	—	not asked		
Hysterectomy¶¶						
Yes	59	15.1	19.4	31	7.8	6.4
No	322	82.6	77.0	131	32.8	31.7
Unknown	9	2.3	3.6	238	59.5	61.8
Median number of prescriptions per year***	6.7			8.7		

Table 2, cont.: Selected characteristics of newly-identified controls compared to existing controls

	*Newly-identified controls** *(N=390)*	*Existing controls** *(N=400)*
Mean number of prescriptions per year [95% CI]***	10.4 [9.3, 11.5]	11.9 [10.8, 13.1]
Mean prescriptions per year, adjusted for age***	12.2 [10.9, 13.4]	10.2 [9.0, 11.4]
Mean prescriptions per year, adjusted for age and reference date***	12.8 [11.5, 14.0]	9.6 [8.4, 10.9]

*Newly-identified controls are those identified and chart-reviewed specifically for this study. Existing controls are those identified and chart-reviewed for a previous study of myocardial infarction and stroke.[31]

†Because there were so few women aged 35-49 at diagnosis among the existing controls, women in these age groups are omitted from all calculations of adjusted proportions. Percentages may not sum to 100% due to rounding.

‡Adjusted to the age distribution of newly-identified controls. Since there were so few women aged 35-49 at diagnosis among the existing controls, women in this age group were omitted from all calculations of adjusted proportions. Percentages may not sum to 100% due to rounding.

§or "pseudo-diagnosis date" for controls.

¶Information on prescription drug use and covariates was collected only up to this date. It was set 1.5 years prior to the date of diagnosis for cases. A comparable date was used for controls.

**Prior to reference date.

††NOS: not otherwise specified.

‡‡This variable was not collected in comparable ways for newly-identified and existing controls. For the purposes of this comparison, the oral contraceptive variable for newly-identified controls was created so as to be as similar as possible to existing controls. See Methods section.

§§Information on tubal ligation was not collected for existing controls.

¶¶Information on hysterectomy status was collected for existing controls only in certain years.

***Total number of prescriptions filled at GHC pharmacies prior to reference date (for any medication) divided by years of membership during the time that the pharmacy database was in existence. CI: confidence interval.

Table 3a: Selected characteristics of cases and all controls

	Cases (N=314)		*All controls (N=790)*	
	n	%	n	%
SEER stage at diagnosis*				
Local	100	31.9	NA	
Regional	22	7.0	NA	
Distant	182	58.0	NA	
Unknown	10	3.2	NA	
Age at diagnosis†				
35-39	17	5.4	33	4.2
40-49	66	21.0	138	17.5
50-59	65	20.7	147	18.6
60-69	97	30.9	251	31.8
70-79	69	22.0	221	28.0
Reference year‡				
1979-1981	32	10.2	65	8.2
1982-1985	71	22.6	143	18.1
1986-1988	63	20.1	190	24.1
1989-1991	57	18.2	170	21.5
1992-1994	63	20.1	174	22.0
1995	28	8.9	48	6.1
Length of GHC enrollment§				
2.5-4.9 years	36	11.5	81	10.3
5.0-9.9 years	75	23.9	188	23.8
10-14.9 years	76	24.2	193	24.4
15-19.9 years	55	17.5	143	18.1
20+ years	72	22.9	185	23.4
Length of GHC enrollment since inception of pharmacy database§				
2.5-4.9 years	68	21.7	147	18.6
5.0-9.9 years	110	35.0	274	34.7
10-14.9 years	98	31.2	276	34.9
15+ years	38	12.1	93	11.8
Marital status				
Single	17	5.4	38	4.8
Married	179	57.0	507	64.2
Divorced	45	14.3	65	8.2
Widowed	45	14.3	112	14.2
Separated	5	1.6	10	1.3
Unknown	23	7.3	58	7.3

Table 3a, cont.: Selected characteristics of cases and all controls

	Cases (N=314)		*All Controls (N=790)*	
	n	%	n	%
Race				
White	216	68.8	579	73.3
Black	4	1.3	18	2.3
Asian/Pacific Islander	7	2.2	18	2.3
Other	4	1.3	13	1.7
Unknown	83	26.4	162	20.5
Parity				
0	53	16.9	90	11.4
1-2	120	38.2	319	40.4
3-4	87	27.7	260	32.9
5+	29	9.2	77	9.8
Unknown	25	8.0	44	5.6
Median number of prescriptions filled per year[¶]	6.6		7.7	
Mean number of prescriptions filled per year [95% CI][¶]	10.3 [9.0, 11.5]		11.2 [10.4, 12.0]	
Mean prescriptions per year, adjusted for age [95% CI][¶]	10.6 [9.3, 11.8]		11.1 [10.3, 11.8]	

*SEER: Surveillance, Epidemiology and End Results.

[†]or "pseudo-diagnosis date" for controls.

[‡]Information on prescription drug use and covariates was collected only up to this date. It was set 1.5 years prior to the date of diagnosis for cases. A comparable date was used for controls.

[§]Prior to reference date.

[¶]Total number of prescriptions filled at GHC pharmacies prior to reference date (for any medication) divided by years of membership during the time that the pharmacy database was in existence. CI: confidence interval.

Table 3b: Selected characteristics of cases and newly-identified controls

	Cases (N=314)		*Newly-identified controls (N=390)*	
	n	%	n	%
Smoking status				
Current	47	15.0	78	20.0
Not current				
Never	36	11.5	42	10.8
Past	62	19.8	66	16.9
Not current NOS*	138	44.0	163	41.8
Unknown	31	9.9	41	10.5
Oral contraceptive use†				
Never	99	31.5	61	15.6
Ever	80	25.5	133	34.1
Unknown	135	43.0	196	50.3
Tubal ligation				
Yes	31	9.9	68	17.4
No	283	90.1	322	82.6
Hysterectomy				
Yes	49	15.6	59	15.1
No	247	78.7	322	82.6
Unknown	18	5.7	9	2.3

*NOS: not otherwise specified.

†Ever use is defined as use of at least two months' duration. The "unknown" group includes 19 cases and 29 controls with some mention of oral contraceptive use in the chart but duration of use unknown.

Table 4: Medications acting on the central nervous system that were used by controls

Generic name (brand name(s))	Number of prescriptions n	%*	Controls with at least one prescription (N=790) n	%†
Antidepressants				
Amitriptyline (Elavil, Endep)	693	32.7	93	11.8
Amoxapine (Asendin)	35	1.7	1	0.1
Bupropion (Wellbutrin)	0	0.0	0	0.0
Desipramine (Norpramin)	48	2.3	19	2.4
Doxepin (Adapin, Sinequan)	724	34.1	88	11.1
Fluoxetine (Prozac)	80	3.8	9	1.1
Imipramine (Tofranil)	248	11.7	37	4.7
Maprotiline (Ludiomil)	2	0.1	1	0.1
Nortriptyline (Pamelor)	60	2.8	16	2.0
Paroxetine (Paxil)	0	0.0	0	0.0
Perphenazine/amitriptyline (Etrafon, Triavil)‡	37	1.7	5	0.6
Phenelzine sulfate (Nardil)	16	0.8	1	0.1
Protriptyline (Vivactil)	23	1.1	8	1.0
Sertraline (Zoloft)	1	0.0	1	0.1
Tranylcypromine sulfate (Parnate)	0	0.0	0	0.0
Trazodone (Desyrel)	154	7.3	23	2.9
Total	*2121*	*100%*	—	—
Benzodiazepines				
Alprazolam (Xanax)	423	18.7	48	6.1
Chlordiazepoxide (Librium)	112	5.0	28	3.5
Clonazepam (Klonopin)	3	0.1	1	0.1
Clorazepate (Tranxene)	27	1.2	6	0.8
Diazepam (Valium)	932	41.2	143	18.1
Flurazepam (Dalmane)	404	17.9	104	13.2
Lorazepam (Ativan)	86	3.8	14	1.8
Midazolam (Versed)	3	0.1	2	0.3
Oxazepam (Serax)	30	1.3	12	1.5
Temazepam (Restoril)	20	0.9	11	1.4
Triazolam (Halcion)	220	9.7	49	6.2
Total	*2260*	*100%*	—	—

Table 4, cont.: Medications acting on the central nervous system that were used by controls

Generic name (brand name(s))	Number of prescriptions n	%*	Controls with at least one prescription (N=790) n	%†
Antipsychotic agents				
Chlorpromazine (Thorazine)	9	6.7	5	0.6
Fluphenazine (Permitil, Prolixin)	16	11.9	8	1.0
Haloperidol (Haldol)	3	2.2	2	0.3
Loxapine (Loxitane)	1	0.7	1	0.1
Molindone (Moban)	2	1.5	1	0.1
Perphenazine (Trilafon)	6	4.5	5	0.6
Perphenazine/amitriptyline (Etrafon, Triavil)‡	37	27.6	5	0.6
Thioridazine (Mellaril)	50	37.3	3	0.4
Thiothixene (Navane)	0	0.0	0	0.0
Trifluoperazine (Stelazine)	10	7.5	1	0.1
Total	*134*	*100%*	—	—
Other medications that act on the central nervous sytem§				
D-amphetamine (Eskatrol)	3	—	3	0.4
Carbamazepine (Tegretol, Carbatrol)	103	—	10	1.3
Lithium carbonate	52	—	5	0.6
Meclizine (Antivert, Bonine)	305	—	130	16.5
Meprobamate (Miltown, Equanil)	598	—	110	13.9
Pentobarbitol (Nembutal)	7	—	5	0.6
Phenobarbital	170	—	21	2.7
Phenytoin (Dilantin)	48	—	7	0.9
Secobarbitol	8	—	2	0.3

*Percentage of total prescriptions for drugs in this group. Except for minor discrepancies due to rounding, these percentages sum to 100% for a given group.

†Percentage of controls who filled at least one prescription for this drug.

‡Combination drug including an antidepressant (amitriptyline) and an antipsychotic agent (perphenazine). In this table, it is listed under both antidepressants and antipsychotics.

§Total number of prescriptions and % of total prescriptions not given for this group because these medications do not constitute a single class or share an indication for use.

Table 5: Prevalence of antidepressant and benzodiazepine use among newly-identified controls compared to existing controls*

	Antidepressant use						Benzodiazepine use					
	Newly-identified controls* (N=390)			Existing controls* (N=400)			Newly-identified controls* (N=390)			Existing controls* (N=400)		
	n	%	% excluding age 35-49†	n	%	Age-adjusted %‡	n	%	% excluding age 35-49†	n	%	Age-adjusted %‡
Prescription (Rx) pattern												
Never any Rx	304	78.0	74.8	302	75.5	73.9	261	66.9	64.4	250	62.5	61.8
Some Rx—never 2 in 6 months	24	6.2	8.1	36	9.0	10.3	70	18.0	17.1	71	17.8	18.3
Two Rx within 6 months	62	15.9	17.1	62	15.5	15.8	59	15.1	18.5	79	19.8	19.9
Continuity of use§												
Never used	304	78.0	74.8	302	75.5	73.9	261	66.9	64.4	250	62.5	61.8
Some use, never continuous for ≥ 6 months	61	15.6	17.6	64	16.0	17.4	122	31.3	32.4	144	36.0	36.6
Continuous use for ≥ 6 months	25	6.4	7.7	34	8.5	8.7	7	1.8	3.2	6	1.5	1.6
Number of prescriptions												
None	304	78.0	74.8	302	75.5	73.9	261	66.9	64.4	250	62.5	61.8
1	20	5.1	7.2	27	6.8	7.1	58	14.9	14.4	56	14.0	14.9
2-4	21	5.4	5.4	25	6.3	7.5	30	7.7	8.1	45	11.3	10.7
5+	45	11.5	12.6	46	11.5	11.6	41	10.5	13.1	49	12.3	12.6
Total number of pills dispensed												
0	304	78.0	74.8	302	75.5	73.9	261	66.9	64.4	250	62.5	61.8
1-100	31	8.0	9.9	37	9.3	10.5	89	22.8	22.5	102	25.5	25.8
101-200	9	2.3	2.3	15	3.8	3.8	14	3.6	4.5	15	3.8	3.9
201-499	19	4.9	5.0	13	3.3	3.4	11	2.8	3.2	13	3.3	3.2
500+	27	6.9	8.1	33	8.3	8.5	15	3.9	5.4	20	5.0	5.3

Table 5, cont.: Prevalence of antidepressant and benzodiazepine use among newly-identified controls compared to existing controls*

*Newly-identified controls are those identified and chart-reviewed specifically for this study. Existing controls are those identified and chart-reviewed for a previous study of myocardial infarction and stroke.[31]
†Because there were so few controls aged 35-49 among the existing controls, women in these age groups are omitted from all calculations of adjusted proportions. Percentages may not sum to 100% due to rounding.
‡Adjusted to the age distribution of newly-identified controls. Since there were so few women aged 35-49 among the existing controls, women in this age group were omitted from all calculations of adjusted proportions. Percentages may not sum to 100% due to rounding.
§Use was considered to be continuous when, within an episode of use lasting at least 6 months and including at least two prescriptions, each prescription contained enough pills to last until the next prescription was filled, assuming daily use and 75% compliance. See Methods section.

Table 6: Antidepressant use among women with epithelial ovarian cancer (cases) and controls

	Cases (N=314)		Controls (N=790)				
	n	%	n	%	Crude OR*	Adjusted OR*	95% CI*
Prescription (Rx) pattern							
Never any Rx	251	79.9	606	76.7	1.00 (Ref)	1.00 (Ref)	—
Some Rx—never 2 in 6 months	26	8.3	60	7.6	1.05	1.14	(0.69, 1.89)
Two Rx within 6 months	37	11.8	124	15.7	0.72	0.71	(0.47, 1.05)
Continuity of use†							
Never used	251	79.9	606	76.7	1.00 (Ref)	1.00 (Ref)	—
Some use, never continuous for ≥ 6 months	47	15.0	125	15.8	0.91	0.94	(0.64, 1.36)
Continuous use for ≥ 6 months	16	5.1	59	7.5	0.65	0.64	(0.36, 1.15)
Number of prescriptions							
None	251	79.9	606	76.7	1.00 (Ref)	1.00 (Ref)	—
1	22	7.0	47	5.9	1.13	1.23	(0.71, 2.11)
2-4	16	5.1	46	5.8	0.84	0.87	(0.48, 1.58)
5+	25	8.0	91	11.5	0.66	0.64	(0.40, 1.03)
Total number of pills dispensed							
0	251	79.9	606	76.7	1.00 (Ref)	1.00 (Ref)	—
1-100	28	8.9	68	8.6	0.99	1.06	(0.66, 1.70)
101-200	8	2.5	24	3.0	0.80	0.82	(0.36, 1.86)
201-499	12	3.8	32	4.1	0.91	0.89	(0.44, 1.77)
500+	15	4.8	60	7.6	0.60	0.59	(0.33, 1.07)

*OR: odds ratio; CI: confidence interval. Adjusted OR is calculated using conditional logistic regression (in Stata) with adjustment for age, calendar year, and length of GHC membership (by matched sets).

†Use was considered to be continuous when, within an episode of use lasting at least 6 months and including at least two prescriptions, each prescription contained enough pills to last until the next prescription was filled, assuming daily use and 75% compliance. See Methods section.

Table 7: Odds ratios (ORs) from different models involving antidepressant use

Exposure variable	Crude OR (95% CI)* N=1104	OR* adjusting for matching variables N=1104	Previous column, excluding women w/missing parity N=979	Previous column adjusted for parity N=979
Prescription (Rx) pattern				
Never any Rx	1.00 (Ref)	1.00 (Ref)	1.00 (Ref)	1.00 (Ref)
Some Rx—never 2 in 6 months	1.05 (0.65, 1.70)	1.14 (0.69, 1.89)	1.33 (0.78, 2.25)	1.31 (0.77, 2.23)
Two Rx within 6 months	0.72 (0.49, 1.07)	0.71 (0.47, 1.05)	0.72 (0.48, 1.08)	0.71 (0.47, 1.07)
Continuity of use†				
Never used	1.00 (Ref)	1.00 (Ref)	1.00 (Ref)	1.00 (Ref)
Some use, never continuous for ≥ 6 months	0.91 (0.63, 1.31)	0.94 (0.64, 1.36)	1.03 (0.70, 1.52)	1.01 (0.68, 1.50)
Continuous use for ≥ 6 months	0.65 (0.37, 1.16)	0.64 (0.36, 1.15)	0.63 (0.35, 1.14)	0.63 (0.35, 1.13)
Number of prescriptions				
None	1.00 (Ref)	1.00 (Ref)	1.00 (Ref)	1.00 (Ref)
1	1.13 (0.67, 1.91)	1.23 (0.71, 2.11)	1.42 (0.81, 2.52)	1.41 (0.79, 2.50)
2-4	0.84 (0.47, 1.51)	0.87 (0.48, 1.58)	1.00 (0.54, 1.86)	1.01 (0.55, 1.87)
5+	0.66 (0.42, 1.06)	0.64 (0.40, 1.03)	0.62 (0.38, 1.01)	0.61 (0.37, 1.00)
Total number of pills dispensed				
0	1.00 (Ref)	1.00 (Ref)	1.00 (Ref)	1.00 (Ref)
1-100	0.99 (0.63, 1.58)	1.06 (0.66, 1.70)	1.20 (0.73, 1.99)	1.20 (0.72, 1.98)
101-200	0.80 (0.36, 1.82)	0.82 (0.36, 1.86)	0.91 (0.40, 2.08)	0.92 (0.40, 2.09)
201-499	0.91 (0.46, 1.79)	0.89 (0.44, 1.77)	0.87 (0.43, 1.80)	0.84 (0.41, 1.74)
500+	0.60 (0.34, 1.08)	0.59 (0.33, 1.07)	0.59 (0.33, 1.08)	0.59 (0.32, 1.07)

Table 7, cont.: Odds ratios (ORs) from different models involving antidepressant use

Exposure variable	Adjusted for match & parity, excluding existing controls[‡] N=533	Previous column adjusted for history of tubal ligation N=533	Unmatched analysis, adjusted for age, excluding existing controls & women with missing OC information[§] N=373	Previous column adjusted for OC use (ever/never)[§] N=373
Prescription (Rx) pattern				
Never any Rx	1.00 (Ref)	1.00 (Ref)	1.00 (Ref)	1.00 (Ref)
Some Rx—never 2 in 6 months	1.25 (0.55, 2.85)	1.29 (0.56, 2.95)	1.24 (0.60, 2.55)	1.24 (0.60, 2.57)
Two Rx within 6 months	0.67 (0.39, 1.15)	0.68 (0.40, 1.18)	0.48 (0.26, 0.87)	0.49 (0.27, 0.90)
Continuity of use[†]				
Never used	1.00 (Ref)	1.00 (Ref)	1.00 (Ref)	1.00 (Ref)
Some use, never continuous for ≥ 6 months	0.95 (0.56, 1.63)	0.97 (0.56, 1.65)	0.83 (0.48, 1.43)	0.84 (0.49, 1.46)
Continuous use for ≥ 6 months	0.51 (0.22, 1.20)	0.53 (0.22, 1.25)	0.41 (0.17, 1.00)	0.42 (0.17, 1.05)
Number of prescriptions				
None	1.00 (Ref)	1.00 (Ref)	1.00 (Ref)	1.00 (Ref)
1	1.22 (0.51, 2.94)	1.26 (0.52, 3.04)	1.22 (0.56, 2.65)	1.20 (0.55, 2.61)
2-4	1.03 (0.44, 2.42)	1.01 (0.43, 2.38)	0.70 (0.29, 1.68)	0.73 (0.30, 1.77)
5+	0.58 (0.30, 1.09)	0.60 (0.31, 1.14)	0.44 (0.22, 0.90)	0.46 (0.22, 0.94)
Total number of pills dispensed				
0	1.00 (Ref)	1.00 (Ref)	1.00 (Ref)	1.00 (Ref)
1-100	0.97 (0.47, 2.02)	0.99 (0.48, 2.07)	0.98 (0.50, 1.94)	0.97 (0.49, 1.93)
101-200	1.22 (0.40, 3.77)	1.21 (0.39, 3.76)	0.53 (0.16, 1.79)	0.54 (0.16, 1.85)
201-499	0.80 (0.32, 1.96)	0.84 (0.34, 2.06)	0.67 (0.25, 1.79)	0.72 (0.27, 1.92)
500+	0.51 (0.22, 1.20)	0.52 (0.22, 1.22)	0.45 (0.18, 1.09)	0.47 (0.19, 1.14)

Table 7, cont.: Odds ratios (ORs) from different models involving antidepressant use

*OR: odds ratio; CI: confidence interval. Adjusted OR in second column was calculated using conditional logistic regression (in Stata) and adjusting for age, calendar year, and length of GHC membership (by matched sets).
†Use was considered to be continuous when, within an episode of use lasting at least 6 months and including at least two prescriptions, each prescription contained enough pills to last until the next prescription was filled, assuming daily use and 75% compliance. See Methods section.
‡Existing controls were excluded because information on tubal ligation was not collected for these women.
§OC: oral contraceptive. Existing controls were excluded because information on oral contraceptive use was not collected in a comparable way for these women (see Methods section). "Ever use" is defined as use of at least two months' duration.

Table 8: Benzodiazepine use among women with epithelial ovarian cancer (cases) and controls

	Cases (N=314)		Controls (N=790)				
	n	%	n	%	Crude OR*	Adjusted OR*	95% CI*
Prescription (Rx) pattern							
Never any Rx	224	71.3	511	64.7	1.00 (Ref)	1.00 (Ref)	—
Some Rx—never 2 in 6 months	47	15.0	141	17.9	0.76	0.76	(0.52, 1.11)
Two Rx within 6 months	43	13.7	138	17.5	0.71	0.70	(0.47, 1.04)
Continuity of use†							
Never used	224	71.3	511	64.7	1.00 (Ref)	1.00 (Ref)	—
Some use, never continuous for ≥ 6 months	87	27.7	266	33.7	0.75	0.74	(0.55, 1.00)
Continuous use for ≥ 6 months	3	1.0	13	1.6	0.53	0.53	(0.15, 1.87)
Number of prescriptions							
None	224	71.3	511	64.7	1.00 (Ref)	1.00 (Ref)	—
1	33	10.5	114	14.4	0.66	0.65	(0.42, 1.00)
2-4	30	9.6	75	9.5	0.91	0.91	(0.57, 1.45)
5+	27	8.6	90	11.4	0.68	0.68	(0.42, 1.09)
Total number of pills dispensed							
0	224	71.3	511	64.7	1.00 (Ref)	1.00 (Ref)	—
1-100	62	19.7	191	24.2	0.74	0.73	(0.52, 1.02)
101-200	11	3.5	29	3.7	0.87	0.88	(0.42, 1.83)
201-499	8	2.5	24	3.0	0.76	0.79	(0.35, 1.78)
500+	9	2.9	35	4.4	0.59	0.59	(0.27, 1.25)

*OR: odds ratio; CI: confidence interval. Adjusted OR is calculated using conditional logistic regression (in Stata) with adjustment for age, calendar year, and length of GHC membership (by matched sets).

†Use was considered to be continuous when, within an episode of use lasting at least 6 months and including at least two prescriptions, each prescription contained enough pills to last until the next prescription was filled, assuming daily use and 75% compliance. See Methods section.

Table 9: Odds ratios (ORs) from different models involving benzodiazepine use

Exposure variable	Crude OR (95% CI)* (N=1104)	OR* adjusting for matching variables (N=1104)	Previous column, excluding women w/missing parity (N=979)	Previous column adjusted for parity (N=979)
Prescription (Rx) pattern				
Never any Rx	1.00 (Ref)	1.00 (Ref)	1.00 (Ref)	1.00 (Ref)
Some Rx—never 2 in 6 months	0.76 (0.53, 1.10)	0.76 (0.52, 1.11)	0.84 (0.56, 1.24)	0.85 (0.57, 1.26)
Two Rx within 6 months	0.71 (0.49, 1.04)	0.70 (0.47, 1.04)	0.75 (0.50, 1.13)	0.77 (0.51, 1.16)
Continuity of use†				
Never used	1.00 (Ref)	1.00 (Ref)	1.00 (Ref)	1.00 (Ref)
Some use, never continuous for ≥ 6 months	0.75 (0.56, 1.00)	0.74 (0.55, 1.00)	0.79 (0.58, 1.08)	0.81 (0.59, 1.11)
Continuous use for ≥ 6 months	0.53 (0.15, 1.87)	0.53 (0.15, 1.87)	0.79 (0.21, 2.95)	0.81 (0.22, 3.04)
Number of prescriptions				
None	1.00 (Ref)	1.00 (Ref)	1.00 (Ref)	1.00 (Ref)
1	0.66 (0.43, 1.00)	0.65 (0.42, 1.00)	0.72 (0.46, 1.13)	0.74 (0.47, 1.15)
2-4	0.91 (0.58, 1.43)	0.91 (0.57, 1.45)	0.95 (0.59, 1.53)	0.95 (0.59, 1.55)
5+	0.68 (0.43, 1.08)	0.68 (0.42, 1.09)	0.75 (0.46, 1.22)	0.79 (0.48, 1.28)
Total number of pills dispensed				
0	1.00 (Ref)	1.00 (Ref)	1.00 (Ref)	1.00 (Ref)
1-100	0.74 (0.53, 1.03)	0.73 (0.52, 1.02)	0.79 (0.55, 1.12)	0.79 (0.56, 1.13)
101-200	0.87 (0.42, 1.76)	0.88 (0.42, 1.83)	0.95 (0.45, 2.00)	1.02 (0.48, 2.15)
201-499	0.76 (0.34, 1.72)	0.79 (0.35, 1.78)	0.84 (0.37, 1.93)	0.87 (0.38, 1.99)
500+	0.59 (0.28, 1.24)	0.59 (0.27, 1.25)	0.66 (0.30, 1.43)	0.71 (0.33, 1.53)

Table 9, cont.: Odds ratios (ORs) from different models involving benzodiazepine use

Exposure variable	Adjusted for match & parity, excluding existing controls[‡] N=533	Previous column adjusted for history of tubal ligation N=533	Unmatched analysis, adjusted for age, excluding existing controls & women with missing OC information[§] N=373	Previous column adjusted for OC use (ever/never)[§] N=373
Prescription (Rx) pattern				
Never any Rx	1.00 (Ref)	1.00 (Ref)	1.00 (Ref)	1.00 (Ref)
Some Rx—never 2 in 6 months	0.80 (0.47, 1.35)	0.83 (0.49, 1.39)	0.93 (0.54, 1.61)	0.97 (0.56, 1.67)
Two Rx within 6 months	0.82 (0.47, 1.43)	0.83 (0.47, 1.44)	0.93 (0.52, 1.65)	0.96 (0.54, 1.72)
Continuity of use[¶]				
Never used	1.00 (Ref)	1.00 (Ref)	1.00 (Ref)	1.00 (Ref)
Some use, never continuous for ≥ 6 months	0.78 (0.51, 1.19)	0.80 (0.52, 1.21)	0.94 (0.60, 1.47)	0.98 (0.62, 1.53)
Continuous use for ≥ 6 months	1.40 (0.31, 6.39)	1.44 (0.31, 6.59)	0.49 (0.04, 5.75)	0.52 (0.04, 6.24)
Number of prescriptions				
None	1.00 (Ref)	1.00 (Ref)	1.00 (Ref)	1.00 (Ref)
1	0.65 (0.36, 1.17)	0.66 (0.37, 1.20)	0.80 (0.44, 1.47)	0.82 (0.45, 1.51)
2-4	1.14 (0.59, 2.19)	1.15 (0.60, 2.21)	1.17 (0.56, 2.44)	1.21 (0.58, 2.52)
5+	0.79 (0.41, 1.53)	0.82 (0.42, 1.58)	0.93 (0.48, 1.82)	0.99 (0.50, 1.94)
Total number of pills dispensed				
0	1.00 (Ref)	1.00 (Ref)	1.00 (Ref)	1.00 (Ref)
1-100	0.81 (0.51, 1.29)	0.82 (0.52, 1.31)	0.93 (0.57, 1.54)	0.98 (0.59, 1.62)
101-200	0.55 (0.17, 1.81)	0.57 (0.17, 1.83)	0.84 (0.30, 2.36)	0.83 (0.29, 2.35)
201-499	0.74 (0.23, 2.40)	0.77 (0.24, 2.51)	1.77 (0.48, 6.46)	1.99 (0.54, 7.35)
500+	1.08 (0.42, 2.83)	1.14 (0.43, 2.98)	0.64 (0.22, 1.87)	0.64 (0.22, 1.88)

Table 9, cont.: Odds ratios (ORs) from different models involving benzodiazepine use

*OR: odds ratio; CI: confidence interval. Adjusted OR in second column was calculated using conditional logistic regression (in Stata) and adjusting for age, calendar year, and length of GHC membership (by matched sets).
†Use was considered to be continuous when, within an episode of use lasting at least 6 months and including at least two prescriptions, each prescription contained enough pills to last until the next prescription was filled, assuming daily use and 75% compliance. See Methods section.
‡Existing controls were excluded because information on tubal ligation was not collected for these women.
§OC: oral contraceptive. Existing controls were excluded because information on oral contraceptive use was not collected in a comparable way for these women (see Methods section). "Ever use" is defined as use of at least two months' duration.

Table 10: Prevalence of diuretic and beta-blocker use among newly-identified controls compared to existing controls*

	Diuretic use						Beta-blocker use					
	Newly-identified controls* (N=390)			Existing controls* (N=400)			Newly-identified controls* (N=390)			Existing controls* (N=400)		
	n	%	% excluding age 35-49†	n	%	Age-adjusted %‡	n	%	% excluding age 35-49†	n	%	Age-adjusted %‡
Prescription (Rx) pattern												
Never any Rx	255	65.4	55.0	222	55.5	58.4	323	82.8	76.6	298	74.5	75.6
Some Rx—never 2 in 6 months	31	7.9	8.1	26	6.5	6.2	9	2.3	2.7	13	3.3	3.4
Two Rx within 6 months	104	26.7	36.9	152	38.0	35.4	58	14.9	20.7	89	22.3	21.0
Continuity of use§												
Never used	255	65.4	55.0	222	55.5	58.4	323	82.8	76.6	298	74.5	75.6
Some use, never continuous for ≥ 6 months	68	17.4	17.1	57	14.3	16.2	18	4.6	5.9	34	8.5	8.4
Continuous use for ≥ 6 months	67	17.2	27.9	121	30.3	25.4	49	12.6	17.6	68	17.0	16.0
Number of prescriptions¶												
None	255	65.4	55.0	222	55.5	58.4	323	82.8	76.6	298	74.5	75.6
Tertile 1	52	13.3	14.0	51	12.8	12.6	22	5.6	8.1	34	8.5	8.9
Tertile 2	52	13.3	18.0	47	11.8	12.7	28	7.2	9.9	27	6.8	6.4
Tertile 3	31	7.9	13.1	80	20.0	16.3	17	4.4	5.4	41	10.3	9.1
Total number of pills dispensed¶												
None	255	65.4	55.0	222	55.5	58.4	323	82.8	76.6	298	74.5	75.6
Tertile 1	54	13.8	13.5	49	12.3	12.3	21	5.4	7.7	35	8.8	8.6
Tertile 2	52	13.3	19.4	54	13.5	14.4	27	6.9	9.9	29	7.3	7.2
Tertile 3	29	7.4	12.2	75	18.8	14.9	19	4.9	5.9	38	9.5	8.5

Table 10, cont.: Prevalence of diuretic and beta-blocker use among newly-identified controls compared to existing controls*

*Newly identified controls are those identified and chart-reviewed specifically for this study. Existing controls are those identified and chart-reviewed for a previous study of myocardial infarction and stroke.[31]
†Because there were so few controls aged 35-49 among the existing controls, women in these age groups are omitted from all calculations of adjusted proportions. Percentages may not sum to 100% due to rounding.
‡Adjusted to the age distribution of newly-identified controls. Since there were so few women aged 35-49 among the existing controls, women in this age group were omitted from all calculations of adjusted proportions. Percentages may not sum to 100% due to rounding.
§Use was considered to be continuous when, within an episode of use lasting at least 6 months and including at least two prescriptions, each prescription contained enough pills to last until the next prescription was filled, assuming daily use and 75% compliance. See Methods section.
¶Cutpoints are based on tertiles of the distribution among controls who filled at least one prescription for the type of medication being considered.

Table 11: Diuretic use among women with epithelial ovarian cancer (cases) and controls

	Cases (N=314)		Controls (N=790)				
	n	%	n	%	Crude OR*	Adjusted OR*	95% CI*
Prescription (Rx) pattern							
Never any Rx	190	60.5	477	60.4	1.00 (Ref)	1.00 (Ref)	—
Some Rx—never 2 in 6 months	29	9.2	57	7.2	1.28	1.31	(0.81, 2.13)
Two Rx within 6 months	95	30.3	256	32.4	0.93	0.99	(0.74, 1.33)
Continuity of use†							
Never used	190	60.5	477	60.4	1.00 (Ref)	1.00 (Ref)	—
Some use, never continuous for ≥ 6 months	38	12.1	125	15.8	0.76	0.78	(0.52, 1.16)
Continuous use for ≥ 6 months	86	27.4	188	23.8	1.15	1.27	(0.92, 1.76)
Number of prescriptions‡							
None	190	60.5	477	60.4	1.00 (Ref)	1.00 (Ref)	—
1-5	39	12.4	103	13.0	0.95	0.99	(0.65, 1.49)
6-23	38	12.1	99	12.5	0.96	0.95	(0.63, 1.42)
24+	47	15.0	111	14.1	1.06	1.26	(0.83, 1.92)
Total number of pills dispensed‡							
None	190	60.5	477	60.4	1.00 (Ref)	1.00 (Ref)	—
1-269	35	11.1	103	13.0	0.85	0.88	(0.58, 1.34)
270-2157	46	14.6	106	13.4	1.09	1.08	(0.74, 1.59)
2158+	43	13.7	104	13.2	1.04	1.22	(0.79, 1.89)

*OR: odds ratio; CI: confidence interval. Adjusted OR is calculated using conditional logistic regression (in Stata) with adjustment for age, calendar year, and length of GHC membership (by matched sets).

†Use was considered to be continuous when, within an episode of use lasting at least 6 months and including at least two prescriptions, each prescription contained enough pills to last until the next prescription was filled, assuming daily use and 75% compliance. See Methods section.

‡Cutpoints are based on tertiles of the distribution among controls who filled at least one diuretic prescription.

Table 12: Beta-blocker use among women with epithelial ovarian cancer (cases) and controls

	Cases (N=314)		Controls (N=790)				
	n	%	n	%	Crude OR*	Adjusted OR*	95% CI*
Prescription (Rx) pattern							
Never any Rx	261	83.1	621	78.6	1.00 (Ref)	1.00 (Ref)	—
Some Rx—never 2 in 6 months	7	2.2	22	2.8	0.76	0.78	(0.33, 1.84)
Two Rx within 6 months	46	14.6	147	18.6	0.74	0.78	(0.54, 1.13)
Continuity of use†							
Never used	261	83.1	621	78.6	1.00 (Ref)	1.00 (Ref)	—
Some use, never continuous for ≥ 6 months	21	6.7	52	6.6	0.96	1.00	(0.58, 1.70)
Continuous use for ≥ 6 months	32	10.2	117	14.8	0.65	0.68	(0.45, 1.04)
Number of prescriptions‡							
None	261	83.1	621	78.6	1.00 (Ref)	1.00 (Ref)	—
1-7	22	7.0	56	7.1	0.93	0.96	(0.57, 1.62)
8-21	16	5.1	55	7.0	0.69	0.68	(0.38, 1.21)
22+	15	4.8	58	7.3	0.62	0.70	(0.38, 1.28)
Total number of pills dispensed‡							
0	261	83.1	621	78.6	1.00 (Ref)	1.00 (Ref)	—
1-453	20	6.4	56	7.1	0.85	0.88	(0.51, 1.50)
454-2099	13	4.1	56	7.1	0.55	0.55	(0.30, 1.03)
2100+	20	6.4	57	7.2	0.83	0.93	(0.53, 1.62)

*OR: odds ratio; CI: confidence interval. Adjusted OR is calculated using conditional logistic regression (in Stata) with adjustment for age, calendar year, and length of GHC membership (by matched sets).

†Use was considered to be continuous when, within an episode of use lasting at least 6 months and including at least two prescriptions, each prescription contained enough pills to last until the next prescription was filled, assuming daily use and 75% compliance. See Methods section.

‡Cutpoints are based on tertiles of the distribution among controls who filled at least one beta-blocker prescription.

Table 13: Use of medications that inhibit re-uptake of serotonin or serotonin and norepinephrine*

	Cases (N=314)		Controls (N=790)				
	n	%	n	%	Crude OR†	Adjusted OR†	95% CI†
Prescription (Rx) pattern							
Never any Rx	254	80.9	614	77.7	1.00 (Ref)	1.00 (Ref)	—
Some Rx—never 2 in 6 mos	26	8.3	62	7.8	1.01	1.11	(0.68, 1.83)
Two Rx within 6 months	34	10.8	114	14.4	0.72	0.71	(0.47, 1.08)
Continuity of use‡							
Never used	254	80.9	614	77.7	1.00 (Ref)	1.00 (Ref)	—
Some use, never continuous for ≥ 6 months	47	15.0	122	15.4	0.93	0.96	(0.66, 1.40)
Continuous use for ≥ 6 months	13	4.1	54	6.8	0.58	0.58	(0.30, 1.09)
Number of prescriptions§							
None	254	80.9	614	77.7	1.00 (Ref)	1.00 (Ref)	—
1-2	29	9.2	74	9.4	0.95	1.02	(0.64, 1.63)
3-7	18	5.7	44	5.6	0.99	0.98	(0.54, 1.77)
8+	13	4.1	58	7.3	0.54	0.54	(0.29, 1.00)
Total number of pills dispensed							
0	254	80.9	614	77.7	1.00 (Ref)	1.00 (Ref)	—
1-100	30	9.6	74	9.4	0.98	1.05	(0.66, 1.67)
101-200	6	1.9	25	3.2	0.58	0.57	(0.23, 1.40)
201-499	14	4.5	25	3.2	1.35	1.30	(0.66, 2.53)
500+	10	3.2	52	6.6	0.46	0.45	(0.22, 0.93)

*Drugs classified as acting through serotoninergic pathways included the following: trazodone, fluoxetine, sertraline, paroxetine, doxepin, amitriptyline, imipramine, buspirone, phenelzine, tranylcypromine, and lithium.

†OR: odds ratio; CI: confidence interval. Adjusted OR is calculated using conditional logistic regression (in Stata) with adjustment for age, calendar year, and length of GHC membership (by matched sets).

Table 13, cont.: Use of medications that inhibit re-uptake of serotonin or serotonin and norepinephrine*

‡Use was considered to be continuous when, within an episode of use lasting at least 6 months and including at least two prescriptions, each prescription contained enough pills to last until the next prescription was filled, assuming daily use and 75% compliance. See Methods section.
§Cutpoints based on tertiles of the distribution among controls who had ever used these medications.

Table 14: Use of medications that modulate the re-uptake of dopamine and norepinephrine*

	Cases (N=314)		Controls (N=790)				
	n	%	n	%	Crude OR†	Adjusted OR†	95% CI†
Prescription (Rx) pattern							
Never any Rx	298	94.9	750	94.9	1.00 (Ref)	1.00 (Ref)	—
Some Rx—never 2 in 6 months	7	2.2	19	2.4	0.93	0.81	(0.33, 2.02)
Two Rx within 6 months	9	2.9	21	2.7	1.08	0.96	(0.44, 2.13)
Continuity of use‡							
Never used	298	94.9	750	94.9	1.00 (Ref)	1.00 (Ref)	—
Some use, never continuous for ≥ 6 months	13	4.1	37	4.7	0.88	0.80	(0.42, 1.55)
Continuous use for ≥ 6 months	3	1.0	3	0.4	2.52	1.79	(0.36, 8.97)
Number of prescriptions							
None	298	94.9	750	94.9	1.00 (Ref)	1.00 (Ref)	—
1	6	1.9	17	2.2	0.89	0.77	(0.29, 2.01)
2-4	3	1.0	13	1.6	0.58	0.56	(0.16, 2.00)
5+	7	2.2	10	1.3	1.76	1.48	(0.55, 3.94)
Total number of pills dispensed§							
0	298	94.9	750	94.9	1.00 (Ref)	—	—
1-50	5	1.6	14	1.8	0.90	0.78	(0.28, 2.18)
51-154	3	1.0	13	1.6	0.58	0.57	(0.16, 2.04)
155+	8	2.5	13	1.6	1.55	1.28	(0.52, 3.13)

*Drugs classified as acting through dopaminergic or mixed dopamine/norepinephrine pathways included the following: amphetamines, bupropion, desipramine, nortriptyline, protriptyline, maprotiline, and amoxapine.

†OR: odds ratio; CI: confidence interval. Adjusted OR is calculated using conditional logistic regression (in Stata) with adjustment for age, calendar year, and length of GHC membership (by matched sets).

‡Use was considered to be continuous when, within an episode of use lasting at least 6 months and including at least two prescriptions, each prescription contained enough pills to last until the next prescription was filled, assuming daily use and 75% compliance. See Methods section.

Table 14, cont.: Use of medications that modulate the re-uptake of dopamine and norepinephrine*

§Cutpoints based on tertiles of the distribution among controls who ever used these medications.

Table 15: Use of medications acting through GABA-ergic pathways*

	Cases (N=314)		Controls (N=790)				
	n	%	n	%	Crude OR†	Adjusted OR†	95% CI†
Prescription (Rx) pattern							
Never any Rx	179	57.0	411	52.0	1.00 (Ref)	1.00 (Ref)	—
Some Rx—never 2 in 6 months	66	21.0	199	25.2	0.76	0.77	(0.55, 1.08)
Two Rx within 6 months	69	22.0	180	22.8	0.88	0.91	(0.64, 1.28)
Continuity of use‡							
Never used	179	57.0	411	52.0	1.00 (Ref)	1.00 (Ref)	—
Some use, never continuous for ≥ 6 months	129	41.1	351	44.4	0.84	0.86	(0.65, 1.14)
Continuous use for ≥ 6 months	6	1.9	28	3.5	0.49	0.50	(0.20, 1.23)
Number of prescriptions							
None	179	57.0	411	52.0	1.00 (Ref)	1.00 (Ref)	—
1	46	14.6	132	16.7	0.80	0.81	(0.54, 1.20)
2-4	47	15.0	110	13.9	0.98	1.00	(0.67, 1.50)
5+	42	13.4	137	17.3	0.70	0.72	(0.48, 1.09)
Total number of pills dispensed							
0	179	57.0	411	52.0	1.00 (Ref)	1.00 (Ref)	—
1-100	86	27.4	231	29.2	0.85	0.86	(0.63, 1.18)
101-200	19	6.1	51	6.5	0.86	0.86	(0.49, 1.53)
201-499	13	4.1	40	5.1	0.75	0.83	(0.42, 1.63)
500+	17	5.4	57	7.2	0.68	0.70	(0.40, 1.24)

*GABA: gamma-aminobutyric acid. Drugs classified as acting through GABA-ergic pathways included the following: benzodiazepines, barbiturates (phenobarbitol, pentobarbitol, secobarbitol), meprobamate, meclizine, carbamazepine, and phenytoin.

†OR: odds ratio; CI: confidence interval. Adjusted OR is calculated using conditional logistic regression (in Stata) with adjustment for age, calendar year, and length of GHC membership (by matched sets).

Table 15, cont.: Use of medications acting through GABA-ergic pathways*

‡Use was considered to be continuous when, within an episode of use lasting at least 6 months and including at least two prescriptions, each prescription contained enough pills to last until the next prescription was filled, assuming daily use and 75% compliance. See Methods section.

Table 16: Use of antidepressants and benzodiazepines among women with invasive disease, compared to controls

	Cases (N=260) n	%	Controls (N=669) n	%	Crude OR*	Adjusted OR (95% CI)*
Antidepressants						
Prescription (Rx) pattern						
Never any such Rx	204	78.5	506	75.6	1.00 (Ref)	1.00 (Ref)
Some Rx—never 2 in 6 months	24	9.2	49	7.3	1.21	1.34 (0.78, 2.28)
Two Rx within 6 months	32	12.3	114	17.0	0.70	0.67 (0.44, 1.03)
Continuity of use†						
Never used	204	78.5	506	75.6	1.00 (Ref)	1.00 (Ref)
Some use, never continuous for ≥ 6 months	43	16.5	111	16.6	0.96	0.98 (0.66, 1.45)
Continuous use for ≥ 6 months	13	5.0	52	7.8	0.62	0.60 (0.31, 1.14)
Number of prescriptions						
None	204	78.5	506	75.6	1.00 (Ref)	1.00 (Ref)
1	20	7.7	37	5.5	1.34	1.48 (0.82, 2.65)
2-4	16	6.2	43	6.4	0.92	0.93 (0.51, 1.71)
5+	20	7.7	83	12.4	0.60	0.57 (0.34, 0.96)
Benzodiazepines						
Prescription (Rx) pattern						
Never any Rx	188	72.3	429	64.1	1.00 (Ref)	1.00 (Ref)
Some Rx—never 2 in 6 months	37	14.2	121	18.1	0.70	0.70 (0.46, 1.07)
Two Rx within 6 months	35	13.5	119	17.8	0.67	0.66 (0.42, 1.02)
Number of prescriptions						
None	188	72.3	429	64.1	1.00 (Ref)	1.00 (Ref)
1	26	10.0	98	14.6	0.61	0.61 (0.38, 0.98)
2-4	26	10.0	64	9.6	0.93	0.93 (0.56, 1.54)
5+	20	7.7	78	11.7	0.59	0.57 (0.33, 0.98)

*OR: odds ratio; CI: confidence interval. Adjusted OR is calculated using conditional logistic regression (in Stata) with adjustment for age, calendar year, and length of GHC membership (by matched set).
†Use was considered to be continuous when, within an episode of use lasting at least 6 months and including at least two prescriptions, each prescription contained enough pills to last until the next prescription was filled, assuming daily use and 75% compliance. See Methods section.

Table 17: Use of antidepressants and benzodiazepines among women with mucinous tumors, compared to controls

	Cases (N=29) n	%	Controls (N=65) n	%	Crude OR*	Adjusted OR (95% CI)*
Antidepressants						
Prescription (Rx) pattern						
Never any Rx	26	89.7	58	89.2	1.00 (Ref)	1.00 (Ref)
Some Rx—never 2 in 6 months	1	3.4	2	3.1	1.12	1.14 (0.10, 12.7)
Two Rx within 6 months	2	6.9	5	7.7	0.89	0.80 (0.16, 4.12)
Continuity of use†						
Never used	26	89.7	58	89.2	1.00 (Ref)	1.00 (Ref)
Some use, never continuous for ≥ 6 months	2	6.9	3	4.6	1.49	1.44 (0.24, 8.67)
Continuous use for ≥ 6 months	1	3.4	4	6.2	0.56	0.50 (0.06, 4.47)
Number of prescriptions						
None	26	89.7	58	89.2	1.00 (Ref)	1.00 (Ref)
1	1	3.4	2	3.1	1.12	1.14 (0.10, 12.7)
2-4	0	0.0	0	0.0	—	—
5+	2	6.9	5	7.7	0.89	0.80 (0.16, 4.12)
Benzodiazepines						
Prescription (Rx) pattern						
Never any Rx	21	72.4	50	76.9	1.00 (Ref)	1.00 (Ref)
Some Rx—never 2 in 6 months	6	20.7	10	15.4	1.43	1.47 (0.44, 4.91)
Two Rx within 6 months	2	6.9	5	7.7	0.95	1.03 (0.19, 5.53)
Number of prescriptions						
None	21	72.4	50	76.9	1.00 (Ref)	1.00 (Ref)
1	5	17.2	9	13.8	1.32	1.36 (0.37, 4.96)
2-4	3	10.3	3	4.6	2.38	2.36 (0.45, 12.5)
5+	0	0.0	3	4.6	0.00	—

*OR: odds ratio; CI: confidence interval. Adjusted OR is calculated using conditional logistic regression (in Stata) with adjustment for age, calendar year, and length of GHC membership (by matched set).
†Use was considered to be continuous when, within an episode of use lasting at least 6 months and including at least two prescriptions, each prescription contained enough pills to last until the next prescription was filled, assuming daily use and 75% compliance. See Methods section.

Table 18: Use of antidepressants and benzodiazepines among women with non-mucinous epithelial tumors, compared to controls

	Cases (N=285) n	%	Controls (N=725) n	%	Crude OR*	Adjusted OR (95% CI)*
Antidepressants						
Prescription (Rx) pattern						
Never any Rx	225	78.9	548	75.6	1.00 (Ref)	1.00 (Ref)
Some Rx—never 2 in 6 mos	25	8.8	58	8.0	1.05	1.14 (0.68, 1.91)
Two Rx within 6 months	35	12.3	119	16.4	0.72	0.70 (0.46, 1.06)
Continuity of use†						
Never used	225	78.9	548	75.6	1.00 (Ref)	1.00 (Ref)
Some use, never continuous for ≥ 6 months	45	15.8	122	16.8	0.90	0.92 (0.63, 1.35)
Continuous use for ≥ 6 months	15	5.3	55	7.6	0.66	0.65 (0.36, 1.20)
Number of prescriptions						
None	225	78.9	548	75.6	1.00 (Ref)	1.00 (Ref)
1	21	7.4	45	6.2	1.14	1.23 (0.71, 2.14)
2-4	16	5.6	46	6.3	0.85	0.87 (0.48, 1.58)
5+	23	8.1	86	11.9	0.65	0.63 (0.38, 1.03)
Benzodiazepines						
Prescription (Rx) pattern						
Never any Rx	203	71.2	461	63.6	1.00 (Ref)	1.00 (Ref)
Some Rx—never 2 in 6 mos	41	14.4	131	18.1	0.71	0.71 (0.47, 1.06)
Two Rx within 6 months	41	14.4	133	18.3	0.70	0.68 (0.45, 1.03)
Number of prescriptions						
None	203	71.2	461	63.6	1.00 (Ref)	1.00 (Ref)
1	28	9.8	105	14.5	0.61	0.60 (0.38, 0.95)
2-4	27	9.5	72	9.9	0.85	0.85 (0.52, 1.39)
5+	27	9.5	87	12.0	0.70	0.70 (0.43, 1.13)

*OR: odds ratio; CI: confidence interval. Adjusted OR is calculated using conditional logistic regression (in Stata) with adjustment for age, calendar year, and length of GHC membership (by matched set).
†Use was considered to be continuous when, within an episode of use lasting at least 6 months and including at least two prescriptions, each prescription contained enough pills to last until the next prescription was filled, assuming daily use and 75% compliance. See Methods section.

Table 19: Use of antidepressants and benzodiazepines among women with local disease (SEER Stage 1), compared to controls

	Cases (N=100) n	%	Controls (N=233) n	%	Crude OR*	Adjusted OR (95% CI)*
Antidepressants						
Prescription (Rx) pattern						
Never any Rx	82	82.0	181	77.7	1.00 (Ref)	1.00 (Ref)
Some Rx—never 2 in 6 months	5	5.0	22	9.4	0.50	0.53 (0.19, 1.49)
Two Rx within 6 months	13	13.0	30	12.9	0.96	0.91 (0.45, 1.86)
Continuity of use†						
Never used	82	82.0	181	77.7	1.00 (Ref)	1.00 (Ref)
Some use, never continuous for ≥ 6 months	12	12.0	33	14.2	0.80	0.83 (0.40, 1.75)
Continuous use for ≥ 6 months	6	6.0	19	8.2	0.70	0.66 (0.26, 1.68)
Number of prescriptions						
None	82	82.0	181	77.7	1.00 (Ref)	1.00 (Ref)
1	3	3.0	16	6.9	0.41	0.44 (0.12, 1.56)
2-4	2	2.0	11	4.7	0.40	0.42 (0.09, 2.01)
5+	13	13.0	25	10.7	1.15	1.08 (0.52, 2.25)
Benzodiazepines						
Prescription (Rx) pattern						
Never any Rx	67	67.0	156	67.0	1.00 (Ref)	1.00 (Ref)
Some Rx—never 2 in 6 months	20	20.0	40	17.2	1.16	1.14 (0.61, 2.14)
Two Rx within 6 months	13	13.0	37	15.9	0.82	0.80 (0.39, 1.63)
Number of prescriptions						
None	67	67.0	156	67.0	1.00 (Ref)	1.00 (Ref)
1	12	12.0	33	14.2	0.85	0.82 (0.38, 1.73)
2-4	12	12.0	22	9.4	1.27	1.18 (0.54, 2.57)
5+	9	9.0	22	9.4	0.95	1.00 (0.43, 2.34)

*OR: odds ratio; CI: confidence interval. Adjusted OR is calculated using conditional logistic regression (in Stata) with adjustment for age, calendar year, and length of GHC membership (by matched set).
†Use was considered to be continuous when, within an episode of use lasting at least 6 months and including at least two prescriptions, each prescription contained enough pills to last until the next prescription was filled, assuming daily use and 75% compliance. See Methods section.

Table 20: Use of antidepressants and benzodiazepines among women with distant disease (SEER Stage 3), compared to controls

	Cases (N=182) n	%	Controls (N=478) n	%	Crude OR*	Adjusted OR (95% CI)*
Antidepressants						
Prescription (Rx) pattern						
Never any Rx	147	80.8	369	77.2	1.00 (Ref)	1.00 (Ref)
Some Rx—never 2 in 6 months	15	8.2	33	6.9	1.14	1.25 (0.64, 2.43)
Two Rx within 6 months	20	11.0	76	15.9	0.66	0.64 (0.37, 1.09)
Continuity of use†						
Never used	147	80.8	369	77.2	1.00 (Ref)	1.00 (Ref)
Some use, never continuous for ≥ 6 months	28	15.4	77	16.1	0.91	0.92 (0.57, 1.49)
Continuous use for ≥ 6 months	7	3.8	32	6.7	0.55	0.51 (0.21, 1.26)
Number of prescriptions						
None	147	80.8	369	77.2	1.00 (Ref)	1.00 (Ref)
1	14	7.7	27	5.6	1.30	1.43 (0.70, 2.92)
2-4	11	6.0	29	6.1	0.95	0.99 (0.48, 2.04)
5+	10	5.5	53	11.1	0.47	0.43 (0.21, 0.91)
Benzodiazepines						
Prescription (Rx) pattern						
Never any Rx	132	72.5	310	64.9	1.00 (Ref)	1.00 (Ref)
Some Rx—never 2 in 6 months	26	14.3	87	18.2	0.70	0.69 (0.42, 1.14)
Two Rx within 6 months	24	13.2	81	16.9	0.70	0.66 (0.39, 1.13)
Number of prescriptions						
None	132	72.5	310	64.9	1.00 (Ref)	1.00 (Ref)
1	20	11.0	73	15.3	0.64	0.63 (0.37, 1.10)
2-4	17	9.3	39	8.2	1.02	1.08 (0.57, 2.05)
5+	13	7.1	56	11.7	0.55	0.50 (0.26, 0.98)

*OR: odds ratio; CI: confidence interval. Adjusted OR is calculated using conditional logistic regression (in Stata) with adjustment for age, calendar year, and length of GHC membership (by matched set).
†Use was considered to be continuous when, within an episode of use lasting at least 6 months and including at least two prescriptions, each prescription contained enough pills to last until the next prescription was filled, assuming daily use and 75% compliance. See Methods section.

Table 21: Use of antidepressants and benzodiazepines among cases aged less than 50 at diagnosis, compared to controls

	Cases (N=83) n	%	Controls (N=171) n	%	Crude OR*	Adjusted OR (95% CI)*
Antidepressants						
Prescription (Rx) pattern						
Never any Rx	71	85.5	139	81.3	1.00 (Ref)	1.00 (Ref)
Some Rx—never 2 in 6 mos	3	3.6	7	4.1	0.84	0.92 (0.22, 3.83)
Two Rx within 6 months	9	10.8	25	14.6	0.70	0.67 (0.29, 1.55)
Continuity of use†						
Never used	71	85.5	139	81.3	1.00 (Ref)	1.00 (Ref)
Some use, never continuous for ≥ 6 months	7	8.4	23	13.5	0.60	0.57 (0.22, 1.44)
Continuous use for ≥ 6 months	5	6.0	9	5.3	1.09	1.09 (0.36, 3.27)
Number of prescriptions						
None	71	85.5	139	81.3	1.00 (Ref)	1.00 (Ref)
1	3	3.6	5	2.9	1.17	1.21 (0.28, 5.13)
2-4	0	0	9	5.3	0.00	0.00
5+	9	10.8	18	10.5	0.98	0.97 (0.40, 2.35)
Benzodiazepines						
Prescription (Rx) pattern						
Never any Rx	65	78.3	119	69.6	1.00 (Ref)	1.00 (Ref)
Some Rx—never 2 in 6 mos	10	12.0	34	19.9	0.54	0.45 (0.19, 1.06)
Two Rx within 6 months	8	9.6	18	10.5	0.81	0.82 (0.32, 2.14)
Number of prescriptions						
None	65	78.3	119	69.6	1.00 (Ref)	1.00 (Ref)
1	7	8.4	27	15.8	0.47	0.40 (0.15, 1.03)
2-4	5	6.0	13	7.6	0.70	0.63 (0.21, 1.92)
5+	6	7.2	12	7.0	0.92	0.98 (0.33, 2.93)

*OR: odds ratio; CI: confidence interval. Adjusted OR is calculated using conditional logistic regression (in Stata) with adjustment for age, calendar year, and length of GHC membership (by matched set).
†Use was considered to be continuous when, within an episode of use lasting at least 6 months and including at least two prescriptions, each prescription contained enough pills to last until the next prescription was filled, assuming daily use and 75% compliance. See Methods section.

Table 22: Use of antidepressants and benzodiazepines among cases aged 50 or older at diagnosis, compared to controls

	Cases (N=231) n	%	Controls (N=619) n	%	Crude OR*	Adjusted OR (95% CI)*
Antidepressants						
Prescription (Rx) pattern						
Never any Rx	180	77.9	467	75.4	1.00 (Ref)	1.00 (Ref)
Some Rx—never 2 in 6 mos	23	10.0	53	8.6	1.13	1.18 (0.69, 2.02)
Two Rx within 6 months	28	12.1	99	16.0	0.73	0.72 (0.46, 1.13)
Continuity of use†						
Never used	180	77.9	467	75.4	1.00 (Ref)	1.00 (Ref)
Some use, never continuous for ≥ 6 months	40	17.3	102	16.5	1.02	1.04 (0.69, 1.57)
Continuous use for ≥ 6 months	11	4.8	50	8.1	0.57	0.54 (0.27, 1.08)
Number of prescriptions						
None	180	77.9	467	75.4	1.00 (Ref)	1.00 (Ref)
1	19	8.2	42	6.8	1.17	1.23 (0.68, 2.20)
2-4	16	6.9	37	6.0	1.12	1.17 (0.63, 2.19)
5+	16	6.9	73	11.8	0.57	0.54 (0.30, 0.97)
Benzodiazepines						
Prescription (Rx) pattern						
Never any Rx	159	68.8	392	63.3	1.00 (Ref)	1.00 (Ref)
Some Rx—never 2 in 6 mos	37	16.0	107	17.3	0.85	0.87 (0.57, 1.33)
Two Rx within 6 months	35	15.2	120	19.4	0.72	0.68 (0.44, 1.06)
Number of prescriptions						
None	159	68.8	392	63.3	1.00 (Ref)	1.00 (Ref)
1	26	11.3	87	14.1	0.74	0.76 (0.47, 1.22)
2-4	25	10.8	62	10.0	0.99	0.99 (0.59, 1.67)
5+	21	9.1	78	12.6	0.66	0.63 (0.37, 1.07)

*OR: odds ratio; CI: confidence interval. Adjusted OR is calculated using conditional logistic regression (in Stata) with adjustment for age, calendar year, and length of GHC membership (by matched set).
†Use was considered to be continuous when, within an episode of use lasting at least 6 months and including at least two prescriptions, each prescription contained enough pills to last until the next prescription was filled, assuming daily use and 75% compliance. See Methods section.

Table 23: Use of antidepressants and benzodiazepines among white cases and controls

	Cases (N=216) n	%	Controls (N=579) n	%	Crude OR*	Adjusted OR (95% CI)*
Antidepressants						
Prescription (Rx) pattern						
Never any Rx	163	75.5	430	74.3	1.00 (Ref)	1.00 (Ref)
Some Rx—never 2 in 6 mos	20	9.3	42	7.3	1.26	1.27 (0.72, 2.24)
Two Rx within 6 months	33	15.3	107	18.5	0.81	0.81 (0.53, 1.25)
Continuity of use†						
Never used	163	75.5	430	74.3	1.00 (Ref)	1.00 (Ref)
Some use, never continuous for ≥ 6 months	38	17.6	99	17.1	1.01	1.02 (0.67, 1.54)
Continuous use for ≥ 6 months	15	6.9	50	8.6	0.79	0.79 (0.43, 1.45)
Number of prescriptions						
None	163	75.5	430	74.3	1.00 (Ref)	1.00 (Ref)
1	16	7.4	34	5.9	1.24	1.25 (0.67, 2.34)
2-4	15	6.9	37	6.4	1.07	1.08 (0.58, 2.03)
5+	22	10.2	78	13.5	0.74	0.74 (0.45, 1.23)
Benzodiazepines						
Prescription (Rx) pattern						
Never any Rx	146	67.6	350	60.4	1.00 (Ref)	1.00 (Ref)
Some Rx—never 2 in 6 mos	35	16.2	115	19.9	0.73	0.73 (0.48, 1.12)
Two Rx within 6 months	35	16.2	114	19.7	0.74	0.74 (0.48, 1.13)
Continuity of use†						
Never used	146	67.6	350	60.4	1.00 (Ref)	1.00 (Ref)
Some use, never continuous for ≥ 6 months	68	31.5	218	37.7	0.75	0.75 (0.54, 1.05)
Continuous use for ≥ 6 months	2	0.9	11	1.9	0.44	0.44 (0.10, 2.00)
Number of prescriptions						
None	146	67.6	350	60.4	1.00 (Ref)	1.00 (Ref)
1	24	11.1	94	16.2	0.61	0.61 (0.38, 1.00)
2-4	25	11.6	59	10.2	1.02	1.02 (0.62, 1.70)
5+	21	9.7	76	13.1	0.66	0.67 (0.40, 1.12)

*OR: odds ratio; CI: confidence interval. Adjusted OR is calculated using unconditional logistic regression (in Stata) with adjustment for age.

†Use was considered to be continuous when, within an episode of use lasting at least 6 months and including at least two prescriptions, each prescription contained enough pills to last until the next prescription was filled, assuming daily use and 75% compliance. See Methods section.

Table 24: Use of antidepressants and benzodiazepines among parous cases and controls

	Cases (N=238) n	%	Controls (N=656) n	%	Crude OR*	Adjusted OR (95% CI)*
Antidepressants						
Prescription (Rx) pattern						
Never any Rx	186	78.2	508	77.4	1.00 (Ref)	1.00 (Ref)
Some Rx—never 2 in 6 mos	22	9.2	47	7.2	1.28	1.30 (0.76, 2.22)
Two Rx within 6 months	30	12.6	101	15.4	0.81	0.82 (0.52, 1.27)
Continuity of use†						
Never used	186	78.2	508	77.4	1.00 (Ref)	1.00 (Ref)
Some use, never continuous for ≥ 6 months	38	16.0	101	15.4	1.03	1.04 (0.69, 1.57)
Continuous use for ≥ 6 months	14	5.9	47	7.2	0.81	0.82 (0.44, 1.52)
Number of prescriptions						
None	186	78.2	508	77.4	1.00 (Ref)	1.00 (Ref)
1	18	7.6	38	5.8	1.29	1.31 (0.73, 2.36)
2-4	16	6.7	38	5.8	1.15	1.17 (0.64, 2.16)
5+	18	7.6	72	11.0	0.68	0.68 (0.40, 1.18)
Benzodiazepines						
Prescription (Rx) pattern						
Never any Rx	165	69.3	418	63.7	1.00 (Ref)	1.00 (Ref)
Some Rx—never 2 in 6 mos	38	16.0	125	19.1	0.77	0.77 (0.52, 1.16)
Two Rx within 6 months	35	14.7	113	17.2	0.78	0.80 (0.52, 1.22)
Number of prescriptions						
None	165	69.3	418	63.7	1.00 (Ref)	1.00 (Ref)
1	26	10.9	99	15.1	0.67	0.67 (0.42, 1.06)
2-4	25	10.5	63	9.6	1.01	1.02 (0.62, 1.69)
5+	22	9.2	76	11.6	0.73	0.75 (0.45, 1.24)

*OR: odds ratio; CI: confidence interval. Adjusted OR is calculated using unconditional logistic regression (in Stata) with adjustment for age.

†Use was considered to be continuous when, within an episode of use lasting at least 6 months and including at least two prescriptions, each prescription contained enough pills to last until the next prescription was filled, assuming daily use and 75% compliance. See Methods section.

CURRICULUM VITAE: SASCHA DUBLIN

EDUCATION

M.D./Ph.D (in Epidemiology), University of Washington, Seattle, WA, degrees in progress
A.B. Renaissance Studies, *magna cum laude* and with Honors, Brown University, Providence, RI, 1992

HONORS AND AWARDS

1999 Abraham Lilienfeld Prize, Society for Epidemiologic Research
1999 Outstanding Student Award, Epidemiology Dept., Univ. of Washington, Seattle, WA
1998 Achievement Rewards for College Scientists fellowship
1997 Magnuson Scholar, University of Washington, Seattle, WA
1997 Mensa Education and Research Foundation Scholarship
1997 Association of Women in Science Citation of Merit
1997 Klea Bertakis Award for Outstanding Oral Presentation, Western Student Medical Research Forum, Carmel, CA
1997 Mensa of Western Washington Scholarship
1994 Carroll L. Birch Award, American Medical Women's Association, for best original research paper submitted by a medical student
1992 Thomas & Lydia Carpenter Premium, Brown University, Providence, RI
1991 Phi Beta Kappa
1990 Kenneth Grief Prize for essay on Shakespeare, Brown University, Providence, RI

RESEARCH EXPERIENCE

Research Associate, Fred Hutchinson Cancer Research Ctr., Seattle, WA 1996-1999

- Analyzed data on the association of hormone replacement therapy with endometrial cancer.
- Designed & conducted case-control study of ovarian cancer and prescription drug use.
- Developed study protocols & manual, including medical record abstraction form and detailed instructions. Trained and supervised two chart abstractors in use of abstraction form.
- Performed data management & analysis using software including Microsoft Access, SAS, and Stata.

Consultant, QUEST Study, Fred Hutchinson Cancer Research Ctr., Seattle, WA 1998

- Trained health counselors about epidemiologic issues related to screening tests and ovarian cancer.
- Assisted with development of curriculum to educate study participants about ovarian cancer risk and epidemiology and screening issues.

Dept. of Biological Structure, University of Washington, Seattle, WA 6/94-8/94

- Examined effect of peptides on production and secretion of collagen by endothelial cells.
- Performed cell culture, SDS-PAGE electrophoresis, Western blotting, Northern blotting, and ELISA.

Dept. of Medical Genetics, University of Washington, Seattle, WA **7/93-9/93**
- Developed rapid PCR method to detect a mutation in the gene for neurofibromatosis type 1.

Student Trainee, National Cancer Institute, Bethesda, MD **summers 1991-1993**
- Analyzed data on the association of perinatal transmission of HIV with maternal serological reactivity.
- Analyzed predictors of high-risk sexual behavior among couples discordant for HIV infection.
- Developed questionnaire about attitudes and beliefs associated with high-risk behaviors.

Laboratory Technician, Dept. of Pathology, U.C.S.F., San Francisco, CA **6/92-5/93**
- Investigated the effect of mutations in HIV-*rev* protein on mRNA processing and trafficking.
- Developed plasmids for use in experiments to determine the role of Epstein-Barr Virus proteins in protecting cells from apoptosis.
- Used techniques including cell culture, transfection, transformation, plasmid maxi- and mini-preps, DNA sequencing, thin-layer chromatography, restriction enzyme digests, and agarose gel electrophoresis.

AIDS Control Program, Rhode Island Dept. of Health, Providence, RI **6/90-12/90**
- Researched and wrote report for Rhode Island legislature summarizing current literature regarding the efficacy of needle-exchange programs.
- Investigated impact of AIDS on mortality rates among men and women age 15-44.

TEACHING EXPERIENCE

<u>University of Washington School of Medicine, Seattle, WA</u>

1998 & 1999	**Small group leader, Epidemiology**	**10 students; ~6 contact hrs**
	Led small group discussions for first-year medical students.	
1998	**Tutor, Epidemiology**	**3-50 students; ~12-15 contact hrs**
	Led weekly small group reviews for first-year medical students; developed handouts and exercises that allowed students to apply principles of epidemiology and biostatistics and to practice interpreting results of clinical studies. Led review sessions for USMLE Boards parts I and II for UW medical students.	
1996-1998	**T.A., Medicine, Health & Society**	**150 students; 30 contact hrs.; 3 yrs**
	Participated in development of curriculum and syllabus for introductory course in health policy & economics for second-year medical students; organized and led small group discussion sessions.	
1994	**T.A., Anatomy & Embryology**	**100 students; ~70 contact hours**

<u>Kaplan Educational Centers, New York, NY and Seattle, WA</u>

1996-1999	**Seattle head MCAT instructor, supervising 4-6 other instructors**	
1994-1999	**MCAT instructor; typical class: 20 students, 16 wks, 45 contact hrs.**	
1996	**National organic chemistry coordinator for MCAT program**	
	Revised course materials, developed workshops, videotaped lessons.	

GRANTS AND CONTRACTS

Johnson & Johnson/Woodrow Wilson Foundation Dissertation Grant in Women's Health, 1997. Direct grant of $2000 (unrestricted use).

Ovarian Cancer and Prescription Drug Use. University of Washington Royalty Research Fund. Project director (dissertation project; P.I was Dr. Noel Weiss). August 1997-July 1998. Direct costs: $16,266.

INVITED WORKSHOPS

New Investigators' Workshop, American Society for Preventive Oncology, New Orleans, LA, March 1997.
Student Workshop, Society for Epidemiologic Research, Edmonton, Canada, June 1997.

PUBLICATIONS

1. Dublin S, Rosenberg P, Goedert JJ. Patterns and predictors of high-risk sexual behavior in female partners of HIV-infected men with hemophilia. *AIDS* 1992; 6:475-82.

2. Dublin S, Blattner WA, White GC, Goedert JJ. Procreation and HIV (letter). *Lancet* 1993; 342:1241-2.

3. Goedert JJ, Dublin S. Perinatal transmission of HIV type 1: associations with maternal anti-HIV serological reactivity. *AIDS Research and Human Retroviruses* 1994; 10:1125-33.

4. Dublin S, Riccardi V, Stephens K. Methods for rapid detection of a recurrent nonsense mutation and documentation of phenotypic features in neurofibromatosis type 1 patients. *Human Mutation* 1995; 5:81-5.

5. Weiss NS, Dublin S. Accounting for time-dependent covariates whose levels are influenced by exposure status. *Epidemiology* 1998; 9:436-440.

6. English D, Dublin S. Review of *Workbook of Epidemiology* (book review). *Statistics in Medicine* 1998; 17:2155-6.

PRESENTATIONS, POSTERS AND ABSTRACTS

Weiss NS, Dublin S. Accounting for Time-Dependent Covariates whose Levels are Influenced by Exposure Status. 30th Annual Meeting of the Society for Epidemiologic Research, Edmonton, Canada, June 12-14, 1997.

Dublin S, Kaplan R, Lydon-Rochelle M, Watts DH, Critchlow CR. Outcomes Associated with Non-Indicated Induction of Labor in Washington State, 1989-1993. National Student Research Forum, Galveston, TX, April 16-18, 1997.

Dublin S, Kaplan R, Lydon-Rochelle M, Watts DH, Critchlow CR. Outcomes Associated with Non-Indicated Induction of Labor in Washington State, 1989-1993. Western Student Medical Research Forum/American Federation for Clinical Research, Carmel, CA, February 1997. Abstract published in Journal of Investigative Medicine 1997; Supplement 1.

Dublin S, Kaplan R, Lydon-Rochelle M. Outcomes associated with Non-Indicated Induction of Labor in Washington State: 1989-1993 (poster). Third Annual Washington State Joint Conference on Health, Sept. 30-Oct. 2, 1996, Tacoma, WA.

Dublin S, Royal S, Goedert JJ. Why Not Safe Sex? Sexual Behavior and Decision-Making in Women at Risk for HIV Infection. National Congress of Family Practice Residents/National Congress of Student Members, American Academy of Family Practice, Kansas City, MO, July 1995.

Dublin S, Royal S, Goedert JJ. Sexual Behavior and Decision-Making in Human Immunodeficiency Virus-Discordant Couples. Journal of Investigative Medicine 1995; 43:Supplement 1, Abstract 122A. Paper presented at Western Student Medical Research Forum/American Federation for Clinical Research, Carmel, CA, February 1995.

Procreational Sex and Other Behavioral Studies. Multicenter Hemophilia Cohort Study Annual Collaborators Meeting, Washington, DC, 1993.

Preliminary Results of Female Partner Supplementary Data. Multicenter Hemophilia Cohort Study Annual Collaborators Meeting, Washington, DC, 1992.

Patterns and Predictors of High-Risk Sexual Behavior. Multicenter Hemophilia Cohort Study Annual Collaborators Meeting, Washington, DC, 1991.

PROFESSIONAL ACTIVITIES AND MEMBERSHIPS

Peer reviewer for submitted articles, *Epidemiology* and *Obstetrics & Gynecology*
Curriculum Committee, University of Washington School of Medicine, 1993-present
Medical Students for Choice, University of Washington, Seattle, WA
American Medical Women's Association

MENTORING AND COMMUNITY INVOLVEMENT

Mentor, Making Connections (six-month mentoring program for high school girls), 1999
Presenter, Expanding Your Horizons, one-day workshop for middle school girls exploring science and math, 1998 and 1999
Mentoring program, Alpha Epsilon Delta (pre-medical society), University of Washington
Secretary & board member, Savoy Swing Club, Seattle, WA, 1999
Instructor, Basic Mountaineering, Boeing Alpine Club, 1997-1999