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The effect of bisphosphonates on the risk of endometrial and ovarian malignancies☆

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HIGHLIGHTS

- Use of bisphosphonates for more than one year prior to diagnosis was associated with reduced ovarian and endometrial cancer risk.
- A 60% reduction in risk was found in users of either bisphosphonates.

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ABSTRACT

Objective. The use of bisphosphonates has been associated with reduced risk and improved survival of breast and colorectal malignancies. This study was aimed at studying the effects of bisphosphonates on gynecological cancers.

Methods. The Cancer in the Ovary and Uterus Study (CITOUS) is a case–control study of newly diagnosed cases of gynecological malignancies and age/clinic/ethnic-group matched population controls. The use of bisphosphonates prior to, and following, diagnosis was assessed in 424 cases of ovarian and endometrial cancers and 341 controls, all postmenopausal at recruitment, enrolled in Clalit Health Services (CHS), using pharmacy records.

Results. The use of bisphosphonates for more than 1 year prior to diagnosis was associated with a significantly reduced risk of ovarian cancer (OR = 0.49, 95% CI: 0.26–0.93) and endometrial cancer (OR = 0.39, 95% CI: 0.24–0.63). The association with endometrial cancer (OR = 0.48, 0.27–0.84) remained statistically significant after adjustment for a variety of putative effect modifiers (RR = 0.48, 0.26–0.89). The association with ovarian cancer remained significant when adjusted to statin use (0.46, 0.23–0.90) but not for other modifiers (0.58, 0.29–1.18). A strong negative association was found in an adjusted model for the use of either bisphosphonates or statins for more than 1 year (0.40, 0.23–0.68).

Conclusion. The use of bisphosphonates, with or without statins, for more than 1 year before diagnosis was associated with reduced risk of endometrial and ovarian cancers.

Introduction

Bisphosphonates are now well established agents for the prevention and treatment of postmenopausal osteoporosis and corticosteroid-induced bone loss, as well as for management of bone metastases secondary to breast cancer, prostate cancer and multiple myeloma [1]. Recent studies suggest that, alongside its known anti-osteoclastic activity this class of drugs could also exhibit direct anti-tumor effect.

Several reports have suggested that this class of drugs might also be associated with reduced risk of cancer in various organs such as the colon and rectum, breast, and other organs [2–11]. Bisphosphonates inhibit protein prenylation through inhibition of the mevalonate pathway. Specifically they inhibit Farnesyl Pyrophosphate Synthase (FPPS), which is downstream of HMGCoA reductase inhibited by statins, in the mevalonate pathway, leading to decreased post-translational prenylation of small membrane-bound GTP-binding proteins such as RAS, members of the RAB family and the RHO family, and to promotion of tumor cell proliferation. Inhibition of cell proliferation and angiogenesis, cell-cycle arrest, induction of cancer cells apoptosis, and activation of immune cells are some of the suggested anticancer mechanisms of bisphosphonates [12]. Studies of malignant ovarian cell lines and in vivo animal models have shown anti-proliferative and pro-apoptotic activity induced by bisphosphonates [13–18] but data on an association between bisphosphonate use and the risk of gynecological cancers in post-menopausal

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women are lacking. This study was aimed at evaluating the association between the use of bisphosphonates and reduced incidence and mortality of gynecological cancers.

Patients and methods

Participants

The Haifa Cancer in the Ovary and Uterus Study (CITOUS) is a case–control study of incident gynecological cancer diagnosed at Carmel Medical Center in Haifa and individually matched population controls. Recruitment to this on-going study started on February 1, 2003. Controls were identified from the same source population using a population register. Analysis was restricted to Clalit Health Services (CHS) members for whom reliable pharmacy databases were available for exact measurement of bisphosphonate prescriptions. CHS is the largest health care provider in Israel and covered, during the study years, approximately 70% of the older population (persons at least 60 years of age). Health care coverage in Israel is mandatory and is provided by four groups akin to not-for-profit health maintenance organizations. Thus, all study participants (patients and controls) had similar basic health insurance plan and similar access to health services. Controls were individually matched to cases by year of birth, residence (as defined by primary clinic location), and ethnic group (Jewish vs. Arabs). If the randomly chosen control refused, another potential control was randomly chosen according to the same matching criteria. Potential cases and controls were excluded if they had a history of prior cancer in a gynecological organ. Participants provided written informed consent at the time of enrollment and were personally interviewed to obtain information about their personal and family history of cancer, reproductive history, medical history, medication use and a variety of health habits. A validated food-frequency questionnaire adapted to the Israeli diet [19] was used to study the association of various dietary components with the risk of a gynecological cancer. The institutional review board at the Carmel Medical Center, Haifa, approved all procedures.

Exposure data

The use of bisphosphonates was determined on the basis of CHS pharmacy records that were available for all study participants included in this analysis. Detailed prescription information enabled us to evaluate dose–response relationship between duration of bisphosphonate use and the risk of endometrial cancer or ovarian cancer. The pharmacy records of CHS are a reliable source of data as due to the very low copayment for drugs in Israel, it is unlikely that prescription medications, such as bisphosphonates, were purchased in private, non-CHS, pharmacies and therefore not accounted for in the CHS pharmacy records. All prescriptions of oral bisphosphonates were accounted for including alendronic acid (9425 prescriptions, 1565 daily, 7860 weekly) and risedronic acid (1923 prescriptions, 1062 weekly, 861 monthly).

Relevant exposure variables known to be associated with the risk of cancer in the endometrium or the ovary were tested as possible confounders or effect modifiers. These include: family history defined as the report of endometrial cancer or colorectal cancer (to cover for a possible Lynch syndrome) or ovarian cancer or breast cancer (to cover for breast–ovarian cancer syndrome) in at least one first-degree relative; self-reported participation in sports activity as a dichotomous variable; Jewish ethnic group, determined by self-described ethnic group and by country of birth of parents and grandparents, and analyzed as Ashkenazi or Eastern European Jews compared to all other Jewish groups and all Jews compared to Arabs or to non-Jews/non-Arabs; vegetable consumption, categorized into two groups based on the median number of servings consumed per day in the control group (<5, 5+ servings per day); similarly, fruit consumption, was categorized into two groups (<3, 3+ servings per day); BMI (calculated from self-reported height and weight) categorized into normal and overweight vs. obese (BMI ≥30). The use of any post-menopausal hormones was included as self-reported, dichotomous variable.

Statistical analysis

Statistical analyses were performed using SPSS (v18.0), with reported two-sided P values. A contingency table was used to assess associations between bisphosphonate use and the risk of ovarian and endometrial cancers. Unconditional logistic regression was employed to assess the association between bisphosphonate use and the risk of gynecological cancers, adjusting for other known risk factors. Matched analysis was not possible because only postmenopausal women were included.

Results

Findings reported here are based on data from two groups: 149 cases of ovarian cancer and 117 controls; and 308 cases of endometrial cancer and 224 controls, recruited between 2003 and 2010, for which all data sources (questionnaires, pharmacy data) were available at the time of analysis. The overall study response rate was 70.0% of all eligible cases; among those who were located and approached, 80% agreed to participate. The median time between diagnosis and interview was 4.3 months and median time between case interview and its matched control interview was 5.8 months.

Major differences in risk factor prevalence were noted between ovarian and endometrial cancer cases. The use of bisphosphonates for more than 1 year before diagnosis (in the cases) or before date of interview (of the controls) was significantly higher among the controls (12.8% vs. 23.1%, $P = 0.026$ among the ovarian cancer cases and controls; 9.7% vs. 21.9%, $P < 0.001$ among the endometrial cancer cases and controls). Only age ($P = 0.023$) and the use of statins ($P = 0.001$) and bisphosphonates were associated with the risk of ovarian cancer (Table 1) while BMI >30 ($P < 0.001$), number of pregnancies ($P < 0.001$), the use of post menopausal hormone replacement therapy ($P = 0.003$), consumption of vegetables ($P = 0.04$) and sports activity ($P = 0.02$), as well as the use of bisphosphonates ($P = 0.001$) were associated with the risk of endometrial cancer (Table 2).

Among women who used bisphosphonates at least 1 year prior to diagnosis of the gynecological cancer there was a significant reduction in the risk of both ovarian cancer (RR = 0.49, 0.26–0.93) and endometrial cancer (RR = 0.39, 0.24–0.63) in a univariate analysis. Results did not substantially change with increasing duration of bisphosphonates use (Table 3).

The association between bisphosphonates use for more than 1 year and endometrial cancer risk did not change significantly in an unconditional logistic regression model that included age, ethnicity, first degree family history of endometrial cancer or colorectal cancer, BMI, sports participation, number of pregnancies, age at first pregnancy, duration of breast feeding, fruit and vegetable consumption, and post-menopausal hormones; RR = 0.48 (95% CI: 0.27–0.84) (Table 4). A similar model fitted to estimate the association of statins with ovarian cancer risk yielded an odds ratio that was not statistically significant RR = 0.58 (95% CI: 0.29–1.18). However, when bisphosphonates us was adjusted to statin use, or when a combined use of bisphosphonates and statins was entered into a multivariate model, their use was found significantly associated with reduced risk of ovarian cancer (0.46, 0.23–0.90 and 0.40, 0.23–0.68 respectively). Removal of ovarian cancer cases which were BRCA mutation carriers did not meaningfully change the results.

Discussion

Our data show a significant negative association between the use of bisphosphonates, alone or in combination with statins, for more than 1 year and ovarian and endometrial cancer risk.