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COMMENT

Use of calcium channel blockers does not increase breast cancer risk: findings from a nationwide population-based cohort study in Taiwan

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Calcium channel blockers (CCBs) have been shown to inhibit cell apoptosis in mice, potentially leading to cancer development. Consequently, there has been concern regarding the possible association between CCB use and cancer development, leading to a long-standing debate [1]. While some reports suggest that CCBs are not linked to cancer [2, 3], studies have indicated that CCB use may actually improve survival in cancer patients [4]. On the other hand, meta-analyses of retrospective studies have reported an association between CCB use and prostate cancer [5]. However, it is important to note that many of these studies relied on case-control designs or self-reported information on medications, which could introduce selection bias or misclassification bias. Furthermore, some studies included individuals who did not use hypertension medications as a comparison group, which may be confounded by indication bias. Breast cancer is the most common cancer and the fourth leading cause of death among women, making it of significant societal interest to investigate the potential relationship between CCB use and the risk of breast cancer.

Lin et al. conducted a nationwide population-based cohort study in Taiwan to investigate the relationship between CCB use and breast cancer risk [6]. One strength of this study is that it compared the incidence of breast cancer in women aged 55 years or older who initiated treatment with CCBs or angiotensin-converting enzyme inhibitors (ACEIs)/angiotensin II receptor blockers (ARBs) using data from the 2002–2015 Health and Welfare Database, which includes approximately 23 million individuals in Taiwan. Both ACEIs/ARBs and CCBs are recommended as first-line agents in the Taiwanese hypertension management guidelines [7]. In this retrospective cohort study, the risk of breast cancer in the Asian population was similar for users of CCBs and ACEIs/ARBs (adjusted hazard ratio and 95% CI = 1.03 [0.80–1.34]). The authors examined dihydropyridine and non-dihydropyridine CCBs separately, but results were consistent with the main analysis, with both classes of CCBs not associated with a higher risk of breast cancer. In addition, the risk of breast cancer was significantly lower in patients treated with CCBs than in patients treated with ACEI/ARB when treatment duration was 5 years or longer (adjusted hazard ratio and 95% CI = 0.57 [0.33–0.98]).

The study utilized the Nationwide Health Insurance database to comprehensively gather data on hypertensive patients. Two analyses, namely the as-started analysis and on-treatment analysis, were employed to validate the results, yielding similar findings in both analyses. The study observed that the use of CCBs was not associated with an increased risk of breast cancer when compared to the control group of patients using ACEIs/ARBs for hypertension. Patients who initiated antihypertensive treatment with diuretics or beta blockers were not included in the study, as their disease severity and demographic characteristics may differ from those of CCBs and ACEIs/ARBs patients. The selection of CCBs and ACEI/ARBs as study agents was based on their similar therapeutic role in hypertension monotherapy. Given that hypertension treatment is typically lifelong, it is crucial to assess whether such treatment carries an elevated risk of breast cancer. This study holds clinical significance as it refutes the possibility that antihypertensive

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drugs contribute to the development of certain malignancies.

Breast cancer risk is influenced by multiple factors, and estrogen levels play a crucial role. Estrogen can stimulate breast tissue and contribute to the development and growth of breast cancer. Consequently, a reduction in estrogen production after menopause is associated with a decreased risk of breast cancer. However, the risk of breast cancer does not completely vanish after menopause. In fact, there remains a constant risk of breast cancer incidence following menopause, potentially influenced by other risk factors such as family history, genetic factors, and obesity. Some women may undergo hormone replacement therapy (HRT) after menopause, which involves the administration of estrogen and progesterone to alleviate postmenopausal symptoms. However, it is important to note that HRT may slightly increase the risk of breast cancer. The current study suggests that the use of CCBs in patients undergoing HRT is not associated with a significant change in breast cancer risk compared to the use of ACEIs/ARBs.

However, there are some concerns regarding this study. Firstly, the effects of ACEIs and ARBs on tumor progression may differ, but in this study, they were analyzed together. Secondly, the sample size of patients receiving long-term monotherapy with CCBs or ACEIs/ARBs (more than 5 years) was limited, with only 3540 patients remaining on treatment for over 5 years. In comparison to ACEIs/ARBs with a treatment duration of 5 years or more, CCBs showed a potentially protective effect; however, this result was only marginally significant. Patients on CCB monotherapy for 5 years or more may be healthier and have fewer comorbidities due to the cardiorenal protective effects and the wide range of indications for ACEIs/ARBs. Therefore, no definitive conclusions can be drawn from the present findings regarding the long-term effects of CCB use, and further studies are necessary. It should also be noted that this study was conducted in Taiwan, and the results may vary among different racial populations.

Various validations of the association between antihypertensive drugs and cancer have been conducted, including basic research, epidemiological studies, and randomized controlled trials. While basic studies have provided detailed insights into the mechanisms linking antihypertensive agents and cancer, they have limitations in terms of replicating human disease. Furthermore, retrospective epidemiological studies cannot entirely eliminate biases such as selection bias, information bias, and confounding bias. The causal relationship between antihypertensive drugs and cancer incidence, as well as the potential beneficial effects of specific antihypertensive drugs in cancer treatment, have remained unclear. However, the results of the present study suggest that the risk of breast cancer is similar between users of CCBs and ACEIs/ARBs in the Asian population. Therefore, when managing hypertension in postmenopausal women, physicians may consider the recommendations provided in hypertension management guidelines to guide their choice of medications.

Intracellular calcium ions are important second messengers and play a critical role in malignant transformation and cancer progression, and potential applications of calcium channel modulators in cancer therapy have been reported [8]. Currently, there is a growing interest in exploring the potential applications of CCBs in combination with existing treatments, such as chemotherapy or immunotherapy. The modulation of Ca^{2+} signaling represents a promising strategy that can enhance the effectiveness of immunotherapy and chemotherapy. Synergistic administration of CCBs with chemotherapeutic agents has demonstrated the ability to induce cell apoptosis and autophagy in various cancer cell types, including gastric cancer, neuroblastoma, and multidrug-resistant leukemia cells. Additionally, blocking Ca2+ signaling in vascular endothelial cells may improve the delivery of chemotherapeutic drugs to tumor sites, thereby enhancing their therapeutic efficacy. Immunotherapy primarily targets programmed death 1 (PD-1) and its ligand (PD-L1) as key components. Interestingly, studies have shown that certain CCBs, such as nifedipine and amlodipine, can augment the effects of immunotherapy by reducing the expression of PD-L1. By mimicking the action of PD-1/PD-L1 inhibitors within tumors, CCBs have demonstrated potential in combination with anti-PD-1 therapy for breast cancer, colorectal cancer, and colon cancer. In summary, the exploration of CCBs in conjunction with existing cancer treatments offers promising avenues for improving therapeutic outcomes. Consideration of the appropriate antihypertensive medications for hypertensive patients may have a positive impact on their cancer treatment.

The Japanese Society of Hypertension believes that a strategic and focused effort to provide evidence on hypertension and cancer is important. Therefore, we have proposed a new scientific area called “Onco-Hypertension” in the journal Hypertension in 2021 [9]. Specifically, we advocate identifying potential mechanisms linking hypertension and cancer and cancer-related factors that increase blood pressure in cancer patients. There are common risk factors and interrelationships between hypertension and cancer, and hypertension and cancer, alone or in combination, can lead to cardiovascular disease and consequently to poor quality of life and prognosis [10]. Future comprehensive studies are needed on the association between hypertension and cancer, cancer-related factors that increase blood pressure, and drugs and cancer risk. We believe it is essential for the implementation of this field to promote multidisciplinary cooperation should be common driving

forces for the synergistic evolution of oncology and hypertension management.

Compliance with ethical standards

Conflict of interest The author declares no competing interests.

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