Calcium Channel Blockers and Breast Cancer
Is the Block Worth the Risk?

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Learning Objectives:

1. Discuss epidemiology and pathophysiology of breast cancer
2. Identify known risk factors for breast cancer
3. Describe carcinogenic mechanisms of calcium channel blockers
4. Critique primary literature correlating calcium channel blockers and breast cancer risk
5. Recognize types of calcium channels blockers that may be associated with breast cancer
I. Epidemiology and Economic Cost
   A. Estimated that 67 million Americans have high blood pressure
      1. Impacts one in every three American Adults
      2. In 2009, more than 348,000 deaths attributed to hypertension
      3. Accounts for $47.5 billion annually in direct medical expenses
   B. Approximately 13.7 million Americans are living with cancer
      1. Five-year relative survival rate for all cancers has increased in recent years
         a. 2002-2008: 68%
         b. 1975-1977: 49%
      2. Overall costs of cancer in 2008 were $201.5 billion
         a. Direct medical costs: $77.4 billion
         b. Indirect mortality costs: $124 billion
   C. Hypertension is the most common comorbidity encountered in cancer patients
      1. Thirty seven percent of cancer patients have high blood pressure
      2. Prevalence before chemotherapy is similar to the general population

II. History of Hypertension and Cancer
   A. Hypothesis was generated over 30 years ago
   B. Dyer and colleagues
      1. First prospective study to report an association between hypertension and cancer
      2. Evaluated systolic and diastolic blood pressure and subsequent 14-year mortality in 1,233 white males
      3. Multivariate analysis revealed strong correlation with elevated blood pressure and cancer mortality
   C. Recognizing comorbidities in cancer patients can be challenging
      1. Multiple risk factors are often present
      2. No way to directly tie cause and effect relationship to use of antihypertensive alone

Figure 1. Risk factors for cancer
Calcium Channel Blockers and Cancer

I. Calcium and Cancer
   A. In multicellular organisms, homeostasis is maintained through a balance of cell proliferation and programmed cell death or apoptosis
   B. Apoptosis is regulated by a growing list of genes with the potential to cause cancer or oncogenes (i.e. Bcl-2)
   C. Calcium plays an important role in apoptosis
      1. Extracellular agonists, calcium ionophores, or the endoplasmic reticular Ca\(^{2+}\) ATPase antagonists are capable of triggering calcium release
      2. A sustained rise in cytosolic ionized calcium initiates apoptosis
      3. Calcium is also involved in activation of the endonuclease enzyme which leads to DNA fragmentation

![Figure 2. Calcium initiated apoptosis](image)

II. Epidemiology/Economic cost
   A. Prevalence of antihypertensive use 77.3\% from 2009-2010
   B. Calcium channel blockers (CCBs) are the ninth most widely prescribed class of medicines in the United States
   C. CCBs mainly used to treat hypertension, angina, arrhythmias

<table>
<thead>
<tr>
<th></th>
<th>β-blockers</th>
<th>ACE Inhibitors</th>
<th>Diuretics</th>
<th>CCBs</th>
<th>ARBs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Value</td>
<td>191.5</td>
<td>168.7</td>
<td>131.0</td>
<td>97.9</td>
<td>83.7</td>
</tr>
</tbody>
</table>

ACE= Angiotensin converting enzyme, ARBS= angiotensin receptor blockers
III. Mechanism of Action of CCBs\textsuperscript{10,11}
   A. L-type calcium channels are responsible for contraction of smooth muscle and hormone secretion in endocrine cells
   B. Binds to the \( \alpha_1 \) subunit of the L-type \( Ca^{2+} \) and reduce \( Ca^{2+} \) flux through the channel
      1. Smooth-muscle dilation
      2. Negative inotropic effect on myocardial cells
   C. Types of CCBs
      1. Dihydropyridines (DHP)
         a. Minimum effect on cardiac conduction or heart rate
         b. Potent arteriolar vasodilators
      2. Non-dihydropyridines (non-DHP)
         a. Slow atrioventricular node conduction and decrease sinoatrial node automaticity
         b. Decrease heart rate

\begin{figure}[h]
\centering
\includegraphics[width=0.5\textwidth]{ccb_mechanism}
\caption{CCB mechanism}
\end{figure}

IV. Complex role of CCBs in cancer\textsuperscript{5}
   A. Apoptosis inhibition
      1. Calcium antagonists may function as cancer promoters
      2. Therapeutic concentrations of verapamil were shown to increase the growth of human breast and colon cancer cell lines in vitro
   B. Apoptosis promotion
      1. CCBs have been associated with inhibition of cell growth through promoting apoptosis
      2. Toxic dosages of CCBs
         a. Damage the cell membrane
         b. Increase intracellular calcium levels

\begin{table}[h]
\centering
\begin{tabular}{|l|l|}
\hline
\textbf{Breast Cancer} & \\
\hline
I. & Epidemiology\textsuperscript{2,12} \\
A. & Most common malignancy in women in the United States \\
    & 1. Currently over two million women are living with breast cancer in the United States \\
B. & Lifetime risk of developing breast cancer: 1 in 8 women (12.3\%) \\
    & 1. Overall five-year relative survival: 89.2\% \\
\hline
\end{tabular}
\end{table}

Figure 3. Filled prescriptions of antihypertensives in 2010 by millions
II. Pathophysiology\textsuperscript{13,14}
   
   A. Molecular alterations at the cellular level results in breast epithelial cells with immortal features and uncontrolled growth
   
   B. Several pathologic types of breast cancer:
      
      1. Lobular carcinoma in situ (LCIS)
         
         a. Not a premalignant lesion
         b. Risk factor for breast cancer
      2. Ductal carcinoma in situ (DCIS)
         
         a. Premalignant lesion
         b. Often curable with resection alone
      3. Invasive ductal carcinoma (IDC)
         
         a. Most common type of breast cancer
         b. Poor prognosis
      4. Invasive lobular carcinoma (ILC)
         
         a. Second most common type of breast cancer
         b. More likely to metastasize to serosal surfaces
      5. Others: tubular, mucinous, papillary and medullary
         
         a. Better prognosis compared to IDC

III. Risk Factors\textsuperscript{13}
   
   A. Age
      
      1. Incidence increases with age
         
         a. More than half that risk occurs after the age of 60
         b. More than 60% of breast cancer patients have only age and female gender as risk factors
   
   B. Family history
      
      1. First degree relative with breast cancer increases risk by up to three fold
      2. Having any second-degree relative
         
         a. Depends on other family history patterns
         b. Risk is generally lower than that of first-degree relatives
   
   C. Genetic mutations
      
      1. BRCA1 and BRCA2
         
         a. Tumor suppressor genes
         b. Carriers have increased incidence of breast and ovarian cancers
         c. Relatively rare in general population
         d. Ashkenazi Jewish women are an at risk population
2. p53
   a. Tumor suppressor gene
   b. Approximately 30% of breast cancers have mutation

D. Endogenous estrogen exposure
   1. Early menarche (≤12 years of age)
   2. Late menopause (≥ 55 years of age)
   3. Nulliparity and a late age at first birth (≥ 30 years of age)
   4. Bilateral oophorectomy prior to age 40 reduces risk

E. Exogenous estrogen exposure
   1. Hormone replacement therapy (HRT) and oral contraceptives (OC) - controversial
   2. Relative risk associated with OC

Table 1. Oral contraceptives and risk

<table>
<thead>
<tr>
<th>Use</th>
<th>Relative Risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>Current use</td>
<td>1.5</td>
</tr>
<tr>
<td>Past use</td>
<td>1.0</td>
</tr>
<tr>
<td>Never use</td>
<td>1.0</td>
</tr>
</tbody>
</table>

F. Benign breast disease
   1. Classified as proliferative vs. nonproliferative
      a. Proliferative disease without atypia leads to small increase in risk

G. Radiation exposure
   1. Radiotherapy for lymphoma or other cancer
   2. Environmental/occupational exposure (i.e. atomic bomb)

H. Obesity
   1. Complex association between body mass index (BMI), obesity, and breast cancer incidence
   2. Higher BMI associated with increased risk in postmenopausal women (opposite effect in premenopausal women)

I. Physical activity
   1. Increased physical activity lowers risk
   2. Stronger association for postmenopausal vs. premenopausal

J. Alcohol
   1. Risk increases with consumption
   2. Causal relationship has not been proven

K. Receptor status
   1. Estrogen/progesterone (ER/PR)
   2. Human Epidermal Growth Receptor-2 (HER2)
      a. Overexpressed in 20-25% of cases
      b. Amplification associated with poor prognosis
Table 2. Magnitude of Risk of Known Breast Cancer Risk Factors

<table>
<thead>
<tr>
<th>Relative Risk &lt; 2</th>
<th>Relative Risk 2-4</th>
<th>Relative Risk &gt;4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Early menarche</td>
<td>One first-degree relative with breast cancer</td>
<td>Mutation BRCA1 OR BRCA2</td>
</tr>
<tr>
<td>Late menopause</td>
<td>Age &gt; 35 first birth</td>
<td>LCIS</td>
</tr>
<tr>
<td>Nulliparity</td>
<td>Proliferative breast disease</td>
<td>Atypical hyperplasia</td>
</tr>
<tr>
<td>Estrogen plus progesterone HRT</td>
<td>Mammographic breast density</td>
<td>Radiation exposure before age 40</td>
</tr>
<tr>
<td>Alcohol use</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Postmenopausal obesity</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

IV. Risk Assessment Models

A. Gail model
   1. Estimates the chance a woman with given age and risk factors will develop breast cancer over a specified interval
   2. Useful for Caucasian women with a limited family history
   3. Most often used to determine eligibility for chemoprevention with tamoxifen, raloxifene, or clinical trial

B. Claus model
   1. Estimates risk based on age, family history, and age of onset in affected relatives
   2. Does not take into account race, personal medical history, or reproductive history
   3. Slightly better predictor than Gail for patients with significant family history

V. Screening

A. Breast self-examination
   1. Not generally recommended
   2. Little data supporting reduction in mortality when used alone

B. Clinical breast exam
   1. Not uniformly recommended
   2. American Cancer Society (ACS) recommends at least every three years for women aged 20-39 years and annually for women ≥ 40 years

C. Mammography
   1. Annual screening reduces mortality from breast cancer in women ≥ 50 years
   2. Women ages 40-49 years is still controversial but should take into account an individualized assessment of risk for breast cancer to help guide decisions

D. Breast MRI
   1. ACS breast MRI appropriate as adjunct to mammography
   2. Recommended for women with the following:
      a. BRCA mutation carrier
      b. Or first degree relative of carrier, untested
      c. Lifetime risk of ≥ 20%

VI. Clinical Presentation

A. Patients are usually asymptomatic
B. May be found incidentally on routine screening mammography
Table 3. Signs and symptoms

<table>
<thead>
<tr>
<th>Local</th>
<th>Systemic Metastases</th>
</tr>
</thead>
<tbody>
<tr>
<td>Painless, palpable lump</td>
<td>Bone pain</td>
</tr>
<tr>
<td>Nipple discharge, retraction, or dimpling</td>
<td>Difficulty breathing</td>
</tr>
<tr>
<td>Skin edema</td>
<td>Abdominal pain or enlargement</td>
</tr>
<tr>
<td>Redness or warmth</td>
<td>Jaundice</td>
</tr>
<tr>
<td>Palpable local-regional lymph nodes</td>
<td>Mental status changes</td>
</tr>
</tbody>
</table>

VII. Diagnosis¹³⁻¹⁴
   A. History and physical exam
   B. Imaging
      1. Ultrasound
      2. Diagnostic mammogram
   C. Biopsy of palpable mass

VIII. Risk reduction strategies¹³
   A. Intensive surveillance
      1. Monthly breast self-examination
      2. Annual screening mammography
      3. Clinical breast exam once or twice yearly
   B. Chemoprevention
      1. Selective estrogen receptor modulators (SERMs)
         a. Tamoxifen and raloxifene
         b. Both SERMS have been shown to reduce the incidence of ER-positive breast cancer
      C. Prophylactic surgery
         1. Bilateral mastectomy
            a. Decreases risk by ≤ 90%
         2. Bilateral salpingo-oophorectomy
            a. Decreases estrogen exposure
            b. Decreases risk by about 50%

Literature Review

I. Background Literature⁵⁻⁶
   A. Hypothesis of CCBs causing breast cancer initiated in 1996
   B. Pahor and colleagues
      1. Prospective cohort study of 5052 participants ≥ 71 years
      2. Reported an 72% increase risk of all cancers among CCBs users in an elderly cohort
      3. Increasing dose of CCBs associated with increased risk of cancer
      4. Found a non-significant 65% increase risk of breast cancer
      5. No association with cancer was found with other antihypertensives
   C. Several studies evaluated types of CCB and duration of use in relation to cancer risk
      1. Verapamil and nifedipine found to be associated with cancer risk in some studies
      2. No association with diltiazem and cancer risk
3. High doses of CCBs associated with increased risk of cancer

Table 4. Use of individual CCBs and risk of cancer

<table>
<thead>
<tr>
<th>Study</th>
<th>Verapamil RR</th>
<th>Verapamil 95% CI</th>
<th>Nifedipine RR</th>
<th>Nifedipine 95% CI</th>
<th>Diltiazem RR</th>
<th>Diltiazem 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>EPESE</td>
<td>2.46</td>
<td>1.17-5.17</td>
<td>2.34</td>
<td>1.09-5.03</td>
<td>1.40</td>
<td>0.59-3.28</td>
</tr>
<tr>
<td>SPRINT</td>
<td>ND</td>
<td>ND</td>
<td>1.06</td>
<td>0.52-2.18</td>
<td>1.22</td>
<td>0.70-2.12</td>
</tr>
<tr>
<td>Olsen et al.</td>
<td>1.09</td>
<td>0.92-1.27</td>
<td>ND</td>
<td>ND</td>
<td>1.04</td>
<td>0.85-1.25</td>
</tr>
<tr>
<td>Hardell et al.</td>
<td>2.2</td>
<td>2.4-4.80</td>
<td>ND</td>
<td>ND</td>
<td>ND</td>
<td>ND</td>
</tr>
<tr>
<td>Jick et al.</td>
<td>1.83</td>
<td>0.94-3.56</td>
<td>1.32</td>
<td>0.99-1.76</td>
<td>1.33</td>
<td>0.74-2.39</td>
</tr>
</tbody>
</table>

EPESE = Established Populations for Epidemiologic Studies of the Elderly; ND = No Data; RR = Relative Risk; SPRINT = Secondary Prevention Reinfarction Israeli Nifedipine Trial

Table 5. CCBs dosage and risk of cancer

<table>
<thead>
<tr>
<th>Study</th>
<th>Low Dosage RR</th>
<th>Low Dosage 95% CI</th>
<th>Median or Modal Dosage RR</th>
<th>Median or Modal 95% CI</th>
<th>High Dosage RR</th>
<th>High Dosage 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>EPESE</td>
<td>1.19</td>
<td>0.56-2.52</td>
<td>1.58</td>
<td>0.84-2.98</td>
<td>2.09</td>
<td>1.10-3.98</td>
</tr>
<tr>
<td>CHS</td>
<td>2.29</td>
<td>0.56-9.39</td>
<td>1.53</td>
<td>0.70-3.37</td>
<td>4.42</td>
<td>1.37-14.27</td>
</tr>
<tr>
<td>Jick et al.</td>
<td>1.21</td>
<td>0.86-1.71</td>
<td>1.17</td>
<td>0.85-1.61</td>
<td>1.71</td>
<td>1.06-2.78</td>
</tr>
</tbody>
</table>

CHS = Cardiovascular Health Study; CI = confidence interval; EPESE = Established Populations for Epidemiologic Studies of the Elderly; RR = Relative Risk

D. Clinical questions

1. Are different types and doses of CCBs associated with breast cancer risk?
2. Does duration of use of CCBs increase risk?
3. Should CCBs be avoided in patients with increased risk of breast cancer?
### Objective
To evaluate associations between CCBs and breast cancer risk in postmenopausal women.

### Study Design
- Observational cohort study, subgroup analysis of the Cardiovascular Health Study
- Standard questionnaires were administered at four study sites annually from 1989-1990 and 1993-1994

### Patients
**Inclusion:**
- Age ≥ 65 years
- Noninstitutionalized

**Exclusion:**
- Wheel-chair bound
- Under hospice care
- Receiving radiation or chemotherapy

### Statistics
Cox proportional hazard analyses examined time to first hospitalization for incident invasive breast carcinoma

### Results
**Baseline characteristics:**
- N = 3,198 postmenopausal women, 759 cases exposed to CCBs
  - Average age = 72 years
  - Seventy-five cases of incident invasive breast carcinoma diagnosed during follow-up

<table>
<thead>
<tr>
<th>Class of Antihypertensive with Incident Breast Carcinoma</th>
<th>Antihypertensive use</th>
<th>No. Breast cancer</th>
<th>HR*</th>
<th>95% CI</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>No CCB use</td>
<td>2439</td>
<td>55</td>
<td>1.00</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Any CCB use</td>
<td>759</td>
<td>20</td>
<td>2.57</td>
<td>1.47-4.49</td>
<td>0.0009</td>
</tr>
<tr>
<td>No beta blocker use</td>
<td>2685</td>
<td>60</td>
<td>1.00</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Any beta blocker use</td>
<td>513</td>
<td>15</td>
<td>1.14</td>
<td>0.58-2.25</td>
<td>0.71</td>
</tr>
<tr>
<td>No ACE inhibitor use</td>
<td>2769</td>
<td>67</td>
<td>1.00</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Any ACE inhibitor use</td>
<td>429</td>
<td>8</td>
<td>0.93</td>
<td>0.37-2.34</td>
<td>0.88</td>
</tr>
<tr>
<td>No diuretic use</td>
<td>1931</td>
<td>47</td>
<td>1.00</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Any diuretic use</td>
<td>1267</td>
<td>28</td>
<td>1.38</td>
<td>0.83-2.29</td>
<td>0.22</td>
</tr>
<tr>
<td>No vasodilator use</td>
<td>2835</td>
<td>69</td>
<td>1.00</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Any vasodilator use</td>
<td>363</td>
<td>6</td>
<td>0.30</td>
<td>0.07-1.21</td>
<td>0.09</td>
</tr>
</tbody>
</table>

*Adjusted for age, race, parity, age at menopause, and self-reported diabetes

- Increased risk with high dose CCBs (HR: 4.42; 95% CI, 1.37-14.27)
- Risk further increased with concurrent immediate release CCB use and estrogen replacement therapy (HR: 8.48; 95% CI, 2.99-24.08, p < 0.001)

### Authors’ Conclusion
- Use of CCBs is related to increased risk of breast carcinoma
- Further investigation warranted

### Critique
- Confounding variables including family history or unreported comorbidities were not assessed
- Previous CCB use and length of duration prior to the study was not determined
- Selection and recall bias
- Follow-up time insufficient

### Take home
- CCBs associated with increased risk of breast carcinoma in postmenopausal women
  - Higher doses of CCBs associated with increased risk of breast cancer
  - Concurrent immediate release CCBs + estrogen increases risk
Table 7.

<table>
<thead>
<tr>
<th>Regimen</th>
<th>Cases (n=975)</th>
<th>Controls (n=1007)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No.</td>
<td>%</td>
</tr>
<tr>
<td>Never use</td>
<td>446</td>
<td>45.7</td>
</tr>
<tr>
<td>Any CCB ever use</td>
<td>149</td>
<td>15.3</td>
</tr>
<tr>
<td>6 mos to 5 yr</td>
<td>69</td>
<td>7.1</td>
</tr>
<tr>
<td>5-15 yr</td>
<td>60</td>
<td>6.2</td>
</tr>
<tr>
<td>15yr</td>
<td>11</td>
<td>1.1</td>
</tr>
<tr>
<td>Former use</td>
<td>19</td>
<td>1.9</td>
</tr>
<tr>
<td>Current use</td>
<td>133</td>
<td>13.6</td>
</tr>
</tbody>
</table>

Authors’ Conclusion
- Immediate-release CCBs may be associated with increased breast cancer risk
- Inappropriate to alter current clinical recommendations for treatment based on results

Critique
- Observational study
- Recall and selection bias
- Study may not be applicable to younger or older women

Take home
- Longer duration of CCB use not associated with increased breast cancer risk
- No difference in non-dihydropyridines and dihydropyridines and breast cancer risk
- Immediate release CCBs may be associated with increased risk
**Study Design**
- Population-based case-control study
  - Case patients identified through population tumor based registry
  - Controls identified through randomized dialing of land-line telephones
- Case patients and controls interviewed in person
  - Detailed history obtained
  - Hypertension and heart disease
  - Use of ACEIs, ARBs, β-blockers, CCBs, diuretics, and combination antihypertensives

**Patients**
- **Inclusion:** All women aged 55-74 years diagnosed having a primary invasive breast cancer (IDC or ILC) between January 2000- December 2008
- **Exclusion:** Prior history of other cancers

**Statistics**
- Logistic regression to calculate odds ratios (ORs) and their associated 95% CIs to compare IDC and ILC cases with controls

**Results**

### Baseline characteristics
- N=2,881; 891 Control, 905 IDC, 1,085 ILC
- Similar baseline characteristics
- ILC case patients less likely to be African American and obese

**Antihypertensive use and risk:** Overall current, former, and short-term use of antihypertensives were not associated with risk of either IDC and ILC

<table>
<thead>
<tr>
<th>Duration</th>
<th>Control No. (%)</th>
<th>Cases (%)</th>
<th>OR (95% CI)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 5 years</td>
<td>35 (6.3)</td>
<td>36 (6.1)</td>
<td>0.9 (0.6-1.5)</td>
<td>NS</td>
</tr>
<tr>
<td>5 - 9.9 years</td>
<td>23 (4.1)</td>
<td>26 (4.4)</td>
<td>1.2 (0.7-2.2)</td>
<td>NS</td>
</tr>
<tr>
<td>≥ 10 years</td>
<td>12 (2.2)</td>
<td>27 (4.5)</td>
<td>2.4 (1.2-4.9)</td>
<td>.04</td>
</tr>
</tbody>
</table>

*All models are adjusted for age, reference year, county, race/ethnicity, and recency of alcohol use*

<table>
<thead>
<tr>
<th>Duration</th>
<th>Control No. (%)</th>
<th>Cases (%)</th>
<th>OR (95% CI)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 5 years</td>
<td>35 (6.3)</td>
<td>34 (5.0)</td>
<td>0.8 (0.5-1.3)</td>
<td>NS</td>
</tr>
<tr>
<td>5 - 9.9 years</td>
<td>23 (4.1)</td>
<td>32 (4.7)</td>
<td>1.3 (0.8-2.4)</td>
<td>NS</td>
</tr>
<tr>
<td>≥ 10 years</td>
<td>12 (2.2)</td>
<td>31 (4.6)</td>
<td>2.6 (1.3-5.3)</td>
<td>.01</td>
</tr>
</tbody>
</table>

*All models are adjusted for age, reference year, county, race/ethnicity, and recency of alcohol use*

- Ten years or longer of current calcium channel blocker use did not vary when results were further stratified by estrogen receptor status (ER)
- Calcium channel blocker formulation and risk
  - Risk may be higher with short-acting formulation
  - Current use of non-dihydropyridines for any duration was associated with a nonsignificant increase in risk of IDC and ILC
  - Current use of dihydropyridines ≥ 10 years associated with significant risk of ILC only
    - IDC: OR, 3.0 (95% CI, 1.0-8.9)
    - ILC: OR, 3.4 (95% CI 1.1-9.9)

**Authors’ Conclusion**
- Long-term use of calcium channel blockers may be associated with an increased risk of breast cancer
- Further efforts to confirm this association are needed

**Critique**
- Observational study
- Potential for recall and selection bias

**Take home**
- Longer duration of CCBs associated with increased risk of IDC and ILC

<table>
<thead>
<tr>
<th>Objective</th>
<th>Determine if long term use of ACE inhibitors, CCBs, or β-blockers may be associated with breast cancer risk</th>
</tr>
</thead>
</table>
| Study Design | • Case control analysis  
• Information acquired from United Kingdom General Practice Research Database (GPRD)  
• Breast cancer cases were reviewed and medication exposure information collected |
| Patients | Inclusion:  
• Women ≥ 50 years of age who had a first time diagnosis of incident breast cancer between January 1, 1992 and September 30, 1997  
• Prescription drug history in the GPRD ≥ 3 years  
Exclusion: Diagnosis of malignancy prior to the breast cancer diagnosis |
| Statistics | Conditional logistic regression models analyzed the risk of developing breast cancer in relation to previous use of antihypertensives |
| Results | Relative Risk Estimates of Developing BRCA for Users and Nonusers of CCBs for ≥ 5 Yrs |

<table>
<thead>
<tr>
<th>Drug and Duration (yrs)</th>
<th>Cases</th>
<th>Controls</th>
<th>OR (95%CI)*</th>
</tr>
</thead>
<tbody>
<tr>
<td>None</td>
<td>2567</td>
<td>9745</td>
<td>1.0 (reference)</td>
</tr>
<tr>
<td>ACE inhibitors</td>
<td>112</td>
<td>403</td>
<td>1.0 (0.9-1.2)</td>
</tr>
<tr>
<td>1-2</td>
<td>47</td>
<td>188</td>
<td>0.9 (0.7-1.3)</td>
</tr>
<tr>
<td>3-4</td>
<td>16</td>
<td>56</td>
<td>1.1 (0.6-1.9)</td>
</tr>
<tr>
<td>≥ 5</td>
<td>28</td>
<td>108</td>
<td>1.0 (0.7-1.5)</td>
</tr>
<tr>
<td>CCBs</td>
<td>190</td>
<td>735</td>
<td>1.0 (0.8-1.1)</td>
</tr>
<tr>
<td>1-2</td>
<td>79</td>
<td>293</td>
<td>1.0 (0.8-1.3)</td>
</tr>
<tr>
<td>3-4</td>
<td>19</td>
<td>75</td>
<td>1.0 (0.7-1.5)</td>
</tr>
<tr>
<td>≥ 5</td>
<td>53</td>
<td>226</td>
<td>0.9 (0.7-1.2)</td>
</tr>
<tr>
<td>β-blockers</td>
<td>498</td>
<td>1888</td>
<td>1.0 (0.9-1.1)</td>
</tr>
<tr>
<td>1-2</td>
<td>135</td>
<td>527</td>
<td>1.0 (0.8-1.2)</td>
</tr>
<tr>
<td>3-4</td>
<td>73</td>
<td>277</td>
<td>1.0 (0.8-1.3)</td>
</tr>
<tr>
<td>≥ 5</td>
<td>167</td>
<td>633</td>
<td>1.0 (0.8-1.2)</td>
</tr>
</tbody>
</table>

*Adjusted for smoking status and body mass index

<table>
<thead>
<tr>
<th>Drug</th>
<th>No. Case Subjects</th>
<th>No. Control Subjects</th>
<th>OR (95% CI)*</th>
</tr>
</thead>
<tbody>
<tr>
<td>None</td>
<td>2567</td>
<td>9745</td>
<td>1.0 (reference)</td>
</tr>
<tr>
<td>Nifedipine</td>
<td>41</td>
<td>159</td>
<td>1.0 (0.7-1.4)</td>
</tr>
<tr>
<td>Other DHPs</td>
<td>0</td>
<td>0</td>
<td>-</td>
</tr>
<tr>
<td>Diltiazem</td>
<td>2</td>
<td>10</td>
<td>0.8 (0.2-3.6)</td>
</tr>
<tr>
<td>Verapamil</td>
<td>7</td>
<td>26</td>
<td>1.0 (0.4-2.4)</td>
</tr>
<tr>
<td>Mixed CCB use</td>
<td>3</td>
<td>31</td>
<td>0.4 (0.1-1.2)</td>
</tr>
</tbody>
</table>

*Adjusted for smoking status and body mass index

Formulation and Hormone Replacement Therapy:  
• No differences found for nifedipine fast acting vs. slow release and breast cancer risk  
• Concurrent use of CCBs and estrogen replacement therapy for ≥ 3 years was not associated with increased risk of breast cancer (OR 0.8; 95% CI, 0.3-2.0)

Authors' Conclusion | Longer term use of ACE inhibitors or CCBs does not affect the risk of developing breast cancer

Critique | Longer term follow-up needed  
• Cofounding variables such as ethnic origin, family history, socioeconomic status, and physical activity were not assessed

Take home | Type of CCB and duration of use was not associated with breast cancer risk  
• Concurrent use of CCB and estrogen replacement did not increase risk of breast cancer
To investigate the relation of CCBs and cancer

**Objective**

- Case-control study
- Information acquired from the United Kingdom GPRD
  - Hypertensive patients who were current users of one of the following only: ACE inhibitors, CCBs, β-blockers and first time diagnosis of cancer recorded in 1995.
- Questionnaire sent to attending general practitioners for all cancer patients to obtain information on diagnosis, date, any history of cancer

**Patients**

Inclusion: Patient must have taken only one of the study drugs during the year before the index date
Exclusion: History of cancer before 1995 and first time diagnosis of cancer was not confirmed

**Statistics**

Conditional logistic regression was used to control for confounding variables

### Baseline characteristics:

- N = 446 cases of cancer and 1,750 controls
- Mean age = 71 years
- Case and control groups were similar in terms of smoking status, duration of hypertension, and antihypertensive use

### Adjusted Relative Risk Estimates for All Cancers with Use of Antihypertensives

<table>
<thead>
<tr>
<th>Drug</th>
<th>No. of Cases</th>
<th>RR (95% CI)*</th>
</tr>
</thead>
<tbody>
<tr>
<td>B-blockers</td>
<td>183</td>
<td>1.0</td>
</tr>
<tr>
<td>CCBs</td>
<td>178</td>
<td>1.17 (0.98-1.63)</td>
</tr>
<tr>
<td>ACE inhibitors</td>
<td>85</td>
<td>0.79 (0.58-1.06)</td>
</tr>
</tbody>
</table>

*Adjusted for smoking, body mass index, duration of hypertension, change of medication and use of diuretics

### Adjusted Relative Risk Estimates for Specific CCBs

<table>
<thead>
<tr>
<th>CCB</th>
<th>No. of Cases</th>
<th>RR (95% CI)*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nifedipine</td>
<td>112</td>
<td>1.32 (0.99-1.76)</td>
</tr>
<tr>
<td>Amlodipine</td>
<td>26</td>
<td>0.85 (0.52-1.37)</td>
</tr>
<tr>
<td>Verapamil</td>
<td>14</td>
<td>1.83 (0.94-3.56)</td>
</tr>
<tr>
<td>Diltiazem</td>
<td>18</td>
<td>1.33 (0.74-2.39)</td>
</tr>
</tbody>
</table>

*β-blockers as reference group

### Adjusted Relative Risk Estimates for Specific Cancer Types

<table>
<thead>
<tr>
<th>Site</th>
<th>No. of Cases</th>
<th>RR (95% CI)*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Breast</td>
<td>80</td>
<td>1.32 (0.72-2.41)</td>
</tr>
<tr>
<td>Prostate</td>
<td>62</td>
<td>1.27 (0.63-2.56)</td>
</tr>
<tr>
<td>Bowel</td>
<td>59</td>
<td>1.41 (0.65-3.06)</td>
</tr>
<tr>
<td>Esophagus/stomach</td>
<td>42</td>
<td>0.98 (0.41-2.38)</td>
</tr>
<tr>
<td>Kidney/bladder</td>
<td>42</td>
<td>1.27 (0.54-2.96)</td>
</tr>
<tr>
<td>Lung</td>
<td>33</td>
<td>2.22 (0.76-6.55)</td>
</tr>
<tr>
<td>Uterus/ovary</td>
<td>22</td>
<td>1.23 (0.32-4.71)</td>
</tr>
<tr>
<td>Other</td>
<td>92</td>
<td>1.22 (0.70-2.13)</td>
</tr>
</tbody>
</table>

*β-blockers as reference group

### Adjusted Relative Risk Estimates for All Cancers by Duration and Dose of CCBs

<table>
<thead>
<tr>
<th>Duration of CCB, yrs</th>
<th>No. of Cases</th>
<th>RR (95% CI)*</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 1.0</td>
<td>19</td>
<td>1.46 (0.80-2.63)</td>
</tr>
<tr>
<td>1.0-3.9</td>
<td>79</td>
<td>1.26 (0.90-1.76)</td>
</tr>
<tr>
<td>≥ 4</td>
<td>80</td>
<td>1.23 (0.90-1.68)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Dose of CCB</th>
<th>No. of Cases</th>
<th>RR (95% CI)*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low</td>
<td>66</td>
<td>1.21 (0.86-1.71)</td>
</tr>
<tr>
<td>Modal**</td>
<td>73</td>
<td>1.17 (0.85-1.61)</td>
</tr>
<tr>
<td>High</td>
<td>30</td>
<td>1.71 (1.06-2.78)</td>
</tr>
</tbody>
</table>

*β-blockers as reference group  **Modal: most frequently prescribed dose
<table>
<thead>
<tr>
<th>Authors’ Conclusion</th>
<th>Small positive association between CCBs and risk of cancer is unlikely causal since there is no increase risk with increasing duration of CCB</th>
</tr>
</thead>
<tbody>
<tr>
<td>Critique</td>
<td>• Dose and duration of antihypertensives for at least 4 years prior to diagnosis was obtained</td>
</tr>
<tr>
<td></td>
<td>• However, cannot rule out an effect of longer term CCB use and risk of cancer</td>
</tr>
<tr>
<td>Take home</td>
<td>• CCBs were not significantly associated with increased risk of breast cancer or any type of cancer</td>
</tr>
<tr>
<td></td>
<td>• High dose CCB significantly increased risk of all cancers</td>
</tr>
</tbody>
</table>
I. Carcinogenicity of CCBs
   A. A sustained rise in cytosolic calcium initiates programmed cell death
   B. CCBs may be cancer promoters through inhibition of apoptosis, allowing damaged cells with malignant potential to continue to divide

II. Summary

<table>
<thead>
<tr>
<th>Type</th>
<th>No difference seen in DHP vs. Non-DHP</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Small risk seen with immediate release CCBs</td>
</tr>
</tbody>
</table>

| Dose       | High dose associated with increased risk |

<table>
<thead>
<tr>
<th>Duration</th>
<th>No difference seen in most studies</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Longer use (≥ 10 years) may be associated with increased risk in women 55-74 but not with elderly population</td>
</tr>
</tbody>
</table>

| CCB + HRT  | Conflicting results |

III. Recommendation
   A. Focus on known risk factors for breast cancer and prevention
   B. Continue CCB use in non-cancer patients with appropriate indications
   C. Avoid baseline high doses of CCBs especially in patients at highest risk
      1. Daily dosage may be the most relevant factor
      2. Risk most significant at high dosages
   D. Weigh risks and benefits of estrogen replacement therapy in women despite CCB use
   E. Duration of CCBs is controversial
      1. Data beyond 10 years of CCB and breast cancer risk is limited
      2. Data limited to observational studies which cannot prove causality, therefore not practice changing
   F. Future research directions
      1. Large, multicentered prospective cohort studies are needed
      2. Studies should further exam:
         a. Long term use of CCBs (≥ 10 years) and breast cancer risk
b. Dose of CCB and breast cancer risk

c. Concurrent CCB and HRT use and breast cancer risk

d. CCB and breast cancer risk in diverse populations

e. CCB use and breast cancer in patients with family history and genetic predisposition

3. Upcoming study\textsuperscript{25}

a. IMI PROTECT (Pharmacoepidemiological Research on Outcomes of Therapeutics by a European Consortium)

i. Retrospective observational study evaluating the possible role of CCB and the risk of cancer using two sources of data (GPRD and the Danish national databases)

ii. Evaluate patients 18 to 79 years of age from January 1, 1996 to December 31, 2009

iii. Study aims to investigate the potential association between the use of CCBs and risk of all forms of breast cancer in women
References

Table 1. Screening Recommendations for Breast Cancer12-14

<table>
<thead>
<tr>
<th>Average Risk</th>
<th>ACS</th>
<th>NCCN</th>
<th>USPSTF</th>
</tr>
</thead>
<tbody>
<tr>
<td>BSE</td>
<td>Age ≥ 20; discuss of risks and benefits; periodic exam acceptable</td>
<td>Age ≥ 20; breast awareness</td>
<td>Not recommended</td>
</tr>
<tr>
<td>CBE</td>
<td>Age 20-39; every 3 years</td>
<td>Age ≥ 20-39; every 1-3 years</td>
<td>Insufficient evidence</td>
</tr>
<tr>
<td></td>
<td>Age ≥ 40; annually</td>
<td>Age ≥ 40; annually</td>
<td></td>
</tr>
<tr>
<td>Mammogram</td>
<td>Age ≥ 40; annually</td>
<td>Age ≥ 40; annually</td>
<td>Age 50-74; biennial Age 40-50; decision to start biennial is individualized</td>
</tr>
<tr>
<td>High Risk</td>
<td>BSE</td>
<td>NA</td>
<td>All ages; breast awareness</td>
</tr>
<tr>
<td></td>
<td>CBE</td>
<td>NA</td>
<td>All ages; every 6-12 months</td>
</tr>
<tr>
<td></td>
<td>Mammogram</td>
<td>Annually w/ MRI</td>
<td>Prior radiation therapy or strong family history or genetic predisposition, age ≥ 25; annually + CBE</td>
</tr>
<tr>
<td></td>
<td>Breast MRI</td>
<td>Annually w/ MRI</td>
<td>Recommended annually w/ mammogram + CBE for patients with prior RT (age ≥25) Consider annually w/ mammogram + CBE for patients with lifetime risk &gt; 20%</td>
</tr>
</tbody>
</table>

Abbreviations: ACS = American Cancer Society; BSE = breast self-exam; CBE = clinical breast exam; MRI = magnetic resonance imaging; NA = Not applicable; NCCN = National Comprehensive Cancer Network; USPSTF = United States Preventative Services Task Force

a. High risk is defined by ACS as women with 1) a known BRCA1/2 gene mutation; 2) untested women with first-degree relative with a known BRCA1/2 gene mutation; 3) lifetime risk of breast cancer of ≥20% using a risk assessment tool; 4) radiation therapy to the chest between the ages of 10-30 years; 5) Li-Fraumeni syndrome, Cowden syndrome, Bannayan-Riley-Ruvalcaba syndrome or first-degree relatives with one of these syndromes

b. High risk is defined by NCCN as women with 1) prior thoracic radiation therapy; 2) 5-year risk of ≥1.7% of invasive breast cancer in women ≥ 35 years old (Gail Model); 3) lifetime risk of ≥20% as defined as model that are largely based on family history; 4) pedigree suggestive of genetic predisposition; 5) LCIS/atypical hyperplasia; 6) prior history of breast cancer

Table 2. Outcome of Tamoxifen Chemoprevention Studies*

<table>
<thead>
<tr>
<th>Study</th>
<th>Median Follow-up (mo)</th>
<th>Total Cancers</th>
<th>Placebo</th>
<th>Tamoxifen</th>
<th>RR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Royal Marsden</td>
<td>70</td>
<td>70</td>
<td>5.0</td>
<td>4.7</td>
<td>0.94 (0.59-1.43)</td>
</tr>
<tr>
<td>NSABP P1</td>
<td>54.6</td>
<td>368</td>
<td>6.8</td>
<td>3.4</td>
<td>0.51 (0.39-0.66)</td>
</tr>
<tr>
<td>Italian</td>
<td>81.2</td>
<td>79</td>
<td>2.3</td>
<td>2.1</td>
<td>0.87 (0.62-1.14)</td>
</tr>
<tr>
<td>IBIS</td>
<td>50</td>
<td>170</td>
<td>6.7</td>
<td>4.6</td>
<td>0.68 (0.50-0.92)</td>
</tr>
</tbody>
</table>

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