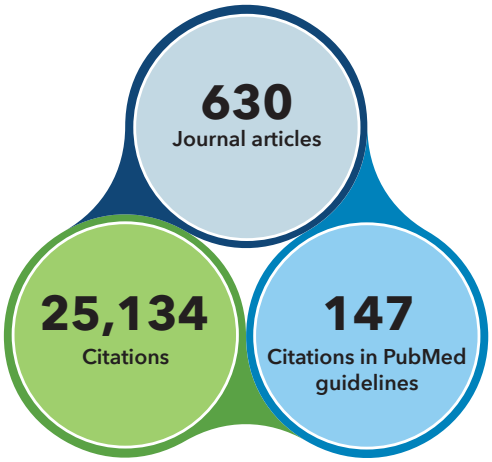
Kaiser Permanente Research Brief

Breast cancer

This brief summarizes the contributions of Kaiser Permanente Research since 2007 on the topic of breast cancer.

Breast cancer is a common disease. Approximately 1 in 8 American women and 1 in 1,000 American men will develop invasive breast disease during their lifetimes. Although the incidence of breast cancer has decreased since 2000, more than 340,000 new cases of breast cancer are expected to be diagnosed in 2022, including over 290,000 cases of invasive breast cancer and more than 51,000 cases of noninvasive "in situ" tumors. Improvements in detection and treatment have led to higher survival rates, but breast cancer is still expected to account for nearly 44,000 deaths in 2022 in the United States.[1] In situ tumors – that is, those still confined to the breast ducts or lobules – are associated with lower mortality risk than those that progress into other parts of the breast tissue, and some types of invasive breast cancer are more aggressive than others.

Kaiser Permanente publications related to breast cancer since 2007



Source: Kaiser Permanente Publications Library and Scite metrics, as of July 11, 2022.

Breast cancer is an active area of study for Kaiser Permanente Research. Scientists across the organization have used our rich, comprehensive, longitudinal data to advance knowledge in the areas of understanding risk, improving patient outcomes, and translating research findings into policy and practice. We have published 630 articles related to breast cancer since 2007.[2] Together, these articles have been cited over 25,000 times. These articles are the product of observational studies, randomized controlled trials, meta-analyses, and other studies led by Kaiser Permanente scientists. Our unique environment – a fully integrated care and coverage model in which our research scientists, clinicians, medical groups, and health plan leaders collaborate – lets us contribute important knowledge about breast cancer and many other research topics.

This brief summarizes a selection of the publications contained within the Kaiser Permanente Publications Library, which indexes journal articles and other publications authored by individuals affiliated with Kaiser Permanente. The work described in this brief originated from across Kaiser Permanente's 8 regions and was supported by a wide range of funding sources including internal research support as well as both governmental and nongovernmental extramural funding.

Understanding Risk

Who is at risk for developing breast cancer?

Most women diagnosed with breast cancer have no clear hereditary or genetic risk for the disease.[3-7] However, our scientists have helped to further the understanding of factors associated with elevated risk, including a personal history of benign breast disease,[5;8;9] histories of breast or ovarian cancer among first- or second-degree relatives,[5;6;9-11] and dense breasts,[4;5;7;12-16] as well as clinically significant genetic factors.[17-22]

Our researchers have studied links between breast cancer risk and race and ethnicity.[23] White women[24] and women of Ashkenazi Jewish ethnicity[17;25] are more likely to be diagnosed with breast cancer, while Black women are more likely to be diagnosed with aggressive subtypes of breast cancer.[26-29] Our research has also connected numerous reproductive factors with the risk for breast cancer. Women who experience menarche at earlier ages are at elevated risk,[30;31] as are women who enter menopause at later ages,[30;32] women who experience persistent hot flashes or night sweats during menopause,[33] and women with higher levels of circulating progesterone after menopause.[34] Higher risks have also been found in women who are at a later age when their first child is born.[9;35] Conversely, women who breastfeed[26] and have a greater number of children[35;36] are at lower risk.

In addition, Kaiser Permanente has conducted studies of numerous modifiable risk factors. Elevated breast cancer risk has been associated with smoking,[37;38] alcohol use,[37;39;40] and diets high in fat.[37;41;42] Obesity has also been associated with a greater risk of breast cancer,[14;37;43;44] and recent work has found that sustained weight loss may lower this risk.[45] In addition, use of menopausal hormone therapy has been associated with greater risk.[4;46-49] For example, in the Women's Health Initiative, a long-term national health study, the use of estrogen with progestin (relative to placebo) was associated with significantly greater risks of breast cancer and mortality.[47] Our scientists have also found that obesity,[50;51] body composition,[52] physical activity

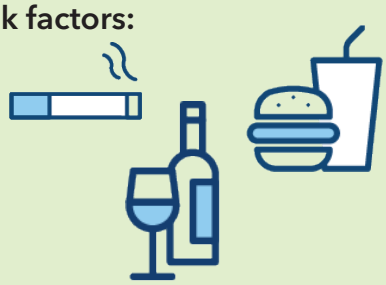
Numerous factors are associated with a higher risk of breast cancer, and not all of them can be altered through lifestyle choices.

Non-modifiable risk factors:

- History of breast cancer
- Breast cancer in a 1st-degree relative
- Breast cancer in a 2nd-degree relative before age 50
- Ovarian cancer in a 1st or 2nd-degree relative
- Dense breasts
- Older age
- White race
- Ashkenazi Jewish ethnicity
- Prior chest radiation therapy for lymphoma before age 25
- Menarche at younger age
- Menopause at later age

Modifiable risk factors:

- Smoking
- Alcohol use
- Obesity
- Diet
- First pregnancy at younger age
- Hormone therapy
- Not breastfeeding



patterns,[53] and dietary factors[54;55] are associated with the risk of dying from breast cancer.

What other health risks do people with breast cancer face?

In patients diagnosed with breast cancer, chemotherapies and other treatments can have significant side effects, including cardiovascular toxicity,[56-60] peripheral neuropathy,[61-64] joint pain,[65;66] and poor bone health.[67;68] For example, a population-based study using data from the Cancer Research Network found that, relative to women treated without chemotherapy, heart failure was 4 times more likely in women treated with trastuzumab and 7 times more likely in women treated with trastuzumab and anthracycline.[56] Even in women diagnosed with early-stage breast cancer, disease recurrence is a continued risk.[69-72] Older patients may also be more likely to experience cardiotoxicity or peripheral neuropathy from chemotherapy.[73;74] One study of breast cancer survivors found that those with fewer social supports received less intensive treatment[75] and experienced higher death rates.[76] Recent research also suggests that healthier diets may increase the odds of survival and lower the risk of disease recurrence in breast cancer patients.[77;78]

Improving Patient Outcomes

What strategies are effective in preventing breast cancer?

Kaiser Permanente researchers have evaluated numerous interventions for preventing breast cancer. In addition to its proactive programs to screen women at average risk for breast cancer, Kaiser Permanente has tailored efforts aimed at identifying women at high genetic risk,[79-82] and has studied the use of patient navigators and electronic alerts to physicians to increase the rate at which these patients are referred for genetic counseling.[79;83;84] In women at high risk for developing breast cancer, medications that block the effects of estrogen in breast cells, such as tamoxifen or raloxifene, are options.[85;86] However, concerns remain regarding the risks of cardiovascular disease or endometrial cancer in patients taking tamoxifen,[87] and while raloxifene appears to have fewer side effects, it may not be as effective in preventing breast cancer as tamoxifen.[87] In other women facing a high risk of breast cancer, prophylactic mastectomy may also be considered. However, poor psychosocial outcomes are not uncommon following this procedure.[88-90] A recent study also noted that for severely obese women, bariatric surgery was associated with a reduced risk of breast cancer.[91]

Kaiser Permanente programs increase rates of screening mammography

- **Reminder letters**[97]
- **Targeted screening**[7;94;95]
- **Community outreach**[101-103]
- **Phone reminders**[96]
- **No copays**[98]
- **Self-referral**[100]

How does early identification of breast cancer affect outcomes?

Years of research on screening have demonstrated that early detection of breast cancer is associated with lower mortality, superior treatment outcomes, and lower rates of disease recurrence.[72;92] Screening mammography is a well-established early detection strategy,[48] and our scientists have explored several approaches for improving screening rates and outcomes.[93] These have included a risk-based screening strategy for women age 40 to 49,[7] supplemental imaging for women with higher breast density,[94;95] mammography reminder programs including both written reminders and phone calls,[96;97] eliminating cost-sharing for mammograms,[98] using prior mammogram results to interpret new scans more accurately,[99] mammography self-referral,[100] and outreach efforts tailored to racial or ethnic minorities.[101-103] In addition, our researchers have been involved in the development of the Breast Cancer Re-

search Consortium Risk Calculator, an online tool that allows women to estimate their risk based on their clinical and demographic characteristics.[104-106] Other studies conducted by Kaiser Permanente scientists have identified opportunities for optimizing the use of various screening modalities,[107-111] including comparisons of digital breast tomosynthesis against digital mammography.[112-114] Conversely, other research has highlighted the challenges of maintaining access to mammography and timely workup of suspicious lesions during the COVID-19 pandemic.[115-120]

Breast cancer care pathway

Prevention and early detection

- Screening mammography
- Genetic testing/ counseling
- Prophylactic surgery or medication

Diagnosis

- Biopsy
- Disease staging and subtyping
- Treatment planning

Treatment

- Radiation
- Chemotherapy
- Surgery
- Adjuvant medications

Surveillance

- Routine mammography
- Other imaging may be recommended

Kaiser Permanente researchers have contributed to the development of risk prediction tools designed to identify patients who may derive greater benefits from ongoing surveillance,[121-125] and to the evaluation and validation of multigene tests that predict prognosis or response to therapy,[126-129] thus improving the matching of treatment dose with underlying risk. These multigene tests have allowed clinicians to identify patients who are more likely to experience overtreatment,[130] as well as those at greater risk of treatment failure.[131] Overdiagnosis is an acknowledged harm associated with breast cancer screening.[132;133] False positive screening results, and the identification of nonmalignant lesions via screening, can lead to psychological distress, financial burden, and even unnecessary treatment.[134-137]

What are the key factors in effective treatment of people with breast cancer?

At Kaiser Permanente, patients with breast cancer benefit from receiving care in an organization with ongoing research, and are frequently able to receive cutting-edge medicine through participation in clinical trials,[138-153] often through our involvement in the National Cancer Institute Community Oncology Research Program[154] and National Research Group[155-162] initiatives. In addition, as part of an integrated health care organization, Kaiser Permanente's researchers have a long-standing interest in improving care pathways for patients with breast cancer. Several studies have explored the impact of care team factors in the care of these patients, particularly the role of clinicians in helping patients navigate the health care system.[163-166] Of particular interest are factors that influence the time between an abnormal mammogram result and evaluation through biopsy.[167-170] Our scientists have also demonstrated the importance of maintaining care for other conditions,[171;172] as there is some evidence that patients with breast cancer are less likely to receive recommended primary care services following their diagnosis.[172]

Researchers at Kaiser Permanente have conducted several studies of the effectiveness of chemotherapy in patients with breast cancer.[142;143;155;173;174] We have studied factors associated with initiation of and adherence to adjuvant

endocrine therapies such as tamoxifen and aromatase inhibitors – these include the timeliness of treatment initiation,[175] social support[164;176] and other psychosocial factors,[177] age,[178-180] race,[180;181] receipt of other breast cancer treatment,[178] side effects,[182] tumor size,[179] and lymph node status.[183]

Our scientists have also studied numerous aspects of surgery for breast cancer.[184;185] Research conducted at Kaiser Permanente has linked improvements in care planning for disease survivors with superior treatment outcomes and longer survival.[186] Our researchers have also studied surgical approaches associated with improved cosmetic outcomes, including judicious use of breast-conserving surgery and appropriate avoidance of axillary lymph node dissection,[187-190] and the use of modern imaging technology to measure the removal of cancerous tissue.[191]

Even after successful treatment, breast cancer is best thought of as a chronic illness, in which the risks of recurrence, disease progression, and development of comorbid illnesses must be carefully monitored.[172;192;193] Our scientists have developed and validated an algorithm for identifying cases of breast cancer recurrence from health record and medical claims data.[194-196] Studies at Kaiser Permanente have also explored why some patients may struggle to follow recommendations for post-treatment surveillance,[172;192;193;197-201] including variations between facilities,[202] and are actively testing interventions that foster greater engagement with surveillance.

Translating Research Findings Into Policy and Practice

As part of a learning health care organization that uses research to inform and improve practice, Kaiser Permanente's research, clinical, and operational partners have tested a range of interventions to reduce the risk of breast cancer and improve outcomes for patients with this disease. Our work in risk prediction has enabled our clinicians to tailor more effective care pathways for individual patients with breast cancer. This has included the use of genetic profiling to optimize the use of chemotherapy,[80;126;130;203;204] personalized risk counseling for women with dense breasts[205] and those at high risk,[206] and

Our research has identified ways to improve the timing of the breast cancer care pathway

Compliance with surveillance care
More active PCP participation and survivorship programs
197

Timely radiotherapy
Patient and provider education, and navigation and notification programs
210

Initiation of adjuvant treatments
Patient education regarding efficacy and side effects
211;212

Timing of multiple chemotherapies
Sequential treatment may be superior to concurrent administration
172

the proper coordination of breast cancer surgery with the surgical removal of the ovaries and fallopian tubes.[207]

Our researchers also continue to explore ways to improve the timing of care pathway elements, including increasing appropriate use of surveillance mammography,[123;124;197;208;209] addressing delays in treatment,[210-212] and evaluating concurrent (versus sequential) use of multiple treatments.[173] Extensive interviews with Kaiser Permanente physicians have suggested new care pathways leading to enhanced care, including improving the quality of shared decision-making with patients,[213] increasing appropriate referrals for treatment of breast cancer-related lymphedema,[214] and using diagnostic and surveillance testing more effectively.[215;216] Our research on long-term surveillance practices has significantly improved the integration and coordination of care after our patients complete breast cancer treatment.[217-219] Studies of more advanced care practices include interventions aimed at maintaining patients' contact with their primary care

provider,[172] the use of wearable devices to encourage ongoing physical activity,[220-222] organized depression screening and treatment referral among patients with breast cancer,[223] and the use of specialized care teams (including nurse navigators)[83;224-226] to help patients effectively navigate through a system of multidisciplinary care.[172;192;197]

Kaiser Permanente hospitals in Northern California,[227] Hawaii,[228] Oregon[229], and Kaiser Permanente in the mid-Atlantic states[230] have received Commission on Cancer accreditation through the American College of Surgeons. In addition to providing organizational models and performance measurement tools that can lead to improved patient outcomes, accredited programs are also provided with extensive data on their patients, and may participate in special studies of important clinical questions facing patients with cancer.[231]

Collectively, research from Kaiser Permanente authors on the topic of breast cancer has been cited nearly 150 times within recent consensus statements and clinical practice guidelines published by a wide range of entities, including the American Cancer Society[232;233] and the American Society of Clinical Oncology.[234] Our researchers and clinician scientists have also directly contributed as authors of breast cancer-related guidelines and systematic reviews conducted for the U.S. Preventive Services Task Force[235] and the American College of Physicians.[236]

Kaiser Permanente has shown considerable leadership in the field of breast cancer research. Our scientists have led a number of prominent studies, including Northern California's Pathways Study, a study of lifestyle factors, quality of care, prognosis, and survival in women diagnosed with breast cancer;[237-242] the Breast Cancer Treatment Effectiveness in Older Women Study,[243] a randomized study of genetic counseling for women at high risk;[83] and a randomized trial assessing whether prescreening cessation of hormone replacement therapy increases mammogram accuracy.[244] Ongoing Breast Cancer Surveillance Consortium work of interest to the broader research community includes a study exploring ways of incorporating breast density information into decisions about screening and preoperative diagnosis,[245] efforts to compare breast density assessment between different types of digital screening,[246] research into applications of artificial intelligence technology toward improving the accuracy of screening mammography,[108;247-249] and efforts to develop performance benchmarks for diagnostic digital mammography[250] and screening MRI.[208] Kaiser Permanente oncologists in Northern and Southern California, Hawaii, Colorado, Washington, and the Northwest participate in the National Cancer Institute Community Oncology Research Program, which funds numerous trials of breast cancer treatment, prevention, imaging, and symptom control.[154] Scientists at Kaiser Permanente were also involved in an expert panel on early-onset breast cancer convened by the American College of Obstetricians and Gynecologists.[251] Our researchers are also involved in the development of novel breast cancer treatments, including next-generation genetic sequencing of tumor subtypes, and the evaluation of off-label treatments for advanced disease.[252;253]

Kaiser Permanente's 185 research scientists and 1,530 support staff members are based at 9 research centers. There are currently 2,355 studies underway, including clinical trials. Since 2007, our research scientists and clinicians have published more than 19,000 articles. Kaiser Permanente currently serves approximately 12.6 million members in 8 states and the District of Columbia.

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