

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 breast cancer during their lifetimes. Although the incidence of breast cancer has decreased since 2000, more than 330,000 new cases of breast cancer are expected to be diagnosed in 2019, including over 270,000 cases of invasive breast cancer and nearly 63,000 cases of non-invasive “in situ” tumors. Improvements in detection and treatment have led to higher survival rates, but breast cancer still accounts for about 41,000 deaths every year in the United States.¹ In situ tumors – that is, those still confined to the breast ducts or lobules – are less dangerous than those that progress into other parts of the breast tissue, and some types of invasive breast cancer are more aggressive than others.

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 nearly 560 articles related to breast cancer since 2007. Together, these articles have been cited almost 19,000 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 topics of research.

Kaiser Permanente Publications Related to Breast Cancer Since 2007



Source: Kaiser Permanente Publications Library and PlumX metrics, as of July 24, 2019.

- a Number of citing journal articles, according to Scopus.
- b Number of references in PubMed guidelines.
- c Citations in DynaMed Plus, a point-of-care clinical reference tool.

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.²⁻⁶ However, our scientists have helped to further the understanding of factors associated with elevated risk, including a personal history of benign breast disease,^{4,7,8} histories of breast or ovarian cancer among first- or second-degree relatives,^{4,5,8-10} and dense breasts,^{3,4,6,11} as well as clinically significant genetic factors.^{12,13}

Our researchers have studied links between breast cancer risk and race and ethnicity.¹⁴ Caucasian women¹⁵ and those of Ashkenazi Jewish heritage^{12,16} are more likely to be diagnosed with breast cancer, while African-American women are more likely to be diagnosed with aggressive subtypes of breast cancer.¹⁷⁻¹⁹ 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,^{20,21} as well as those who enter menopause at later ages.^{20,22} Higher risks have also been found in women whose first child is born at a later age.^{8,23} Conversely, women who breastfeed¹⁷ and have a greater number of children^{23,24} are at lower risk.

In addition, Kaiser Permanente researchers have studied numerous modifiable risk factors. Elevated breast cancer risk has been associated with smoking,^{25,26} alcohol use,^{25,27,28} obesity,^{25,29,30} and diets high in fat.^{25,31,32} In addition, use of menopausal hormone therapy has been associated with greater risk.^{3,33-36} 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.³⁴

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 cardiotoxicity,³⁷⁻⁴⁰ peripheral neuropathy,⁴¹⁻⁴³ joint pain,^{44,45} and poor bone health.^{46,47} 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 those treated

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 1st or 2nd-Degree Relative Before Age 50
- Ovarian Cancer in a 1st or 2nd-Degree Relative
- Dense Breasts
- Older Age
- Caucasian 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



with trastuzumab and 7 times more likely in those treated with trastuzumab and anthracycline.³⁷ Even in those diagnosed with early-stage breast cancer, disease recurrence is a continued risk, even in older women,⁴⁸⁻⁵¹ who may be more likely to experience cardiotoxicity or peripheral neuropathy from chemotherapy.^{52,53} A recent study of breast cancer survivors found that those with fewer social supports received less intensive treatment⁵⁴ and experienced higher death rates.⁵⁵

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,⁵⁶⁻⁵⁸ 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.^{56,59,60} 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.^{61,62} However, concerns remain regarding the risks of cardiovascular disease or endometrial cancer in patients taking tamoxifen,⁶³ and while raloxifene appears to have fewer side effects, it may not be as effective in preventing breast cancer as tamoxifen.⁶³ 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.⁶⁴⁻⁶⁶ A recent study also noted that for severely obese women, bariatric surgery was associated with a reduced risk of breast cancer.⁶⁷

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.^{51,68} Screening mammography is a well-established early detection strategy,³⁵ and our scientists have explored several approaches for improving screening rates and outcomes. These have included a risk-based strategy for screening women ages 40-49 years,⁶ supplemental imaging for women with higher breast density,⁶⁹ mammography reminder programs including both written reminders and phone calls,^{70,71} eliminating cost-sharing for mammograms,⁷² using prior mammogram results to interpret new scans more accurately,⁷³ mammography self-referral,⁷⁴ and outreach efforts tailored to racial or ethnic minorities.⁷⁵⁻⁷⁷ In addition, our researchers have been involved in the development of the Breast Cancer Research Consortium's

Kaiser Permanente Programs Increase Rates of Screening Mammography



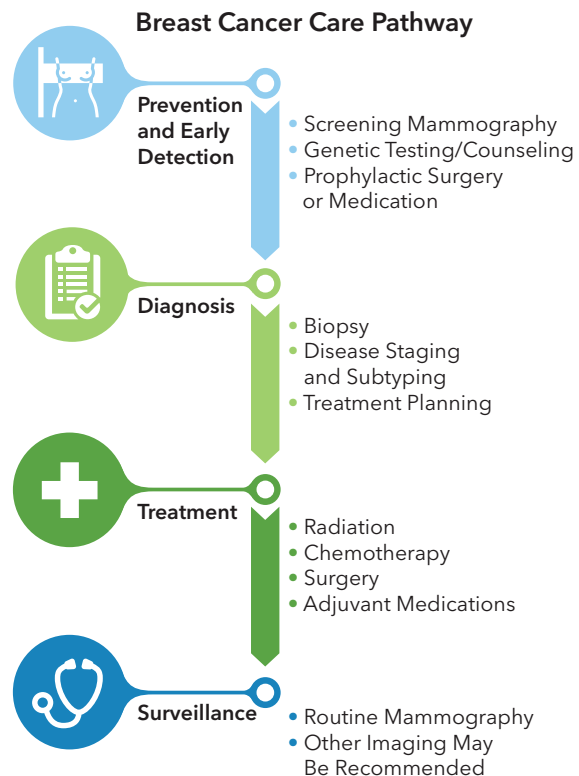
Risk Calculator, an online tool that allows women to estimate their risk based on their clinical and demographic characteristics.⁷⁸⁻⁸⁰ Other studies conducted by Kaiser Permanente scientists have identified opportunities for optimizing the use of screening MRI.^{81,82}

Kaiser Permanente researchers have contributed to the development of risk prediction tools designed to identify patients who may derive greater benefits from ongoing surveillance,⁸³⁻⁸⁶ and to the validation of multi-gene tests that predict prognosis or response to therapy,⁸⁷⁻⁸⁹ thus improving the matching of treatment dose with underlying risk. These multi-gene tests have allowed clinicians to identify patients who are more likely to experience overtreatment,⁹⁰ as well as those at greater risk of treatment failure.⁹¹ Overdiagnosis is an acknowledged harm associated with breast cancer screening. False positive screening results, and the identification of non-malignant lesions via screening, can lead to psychological distress, financial burden, and even unnecessary treatment.⁹²⁻⁹⁴

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 a system with ongoing research, and are frequently able to receive cutting-edge medicine through participation in clinical trials,⁹⁵⁻¹⁰³ often through our involvement in the National Cancer Institute’s Community Oncology Research Program¹⁰⁴ and National Research Group¹⁰⁵⁻¹⁰⁸ 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 to navigate the health care system.¹⁰⁹⁻¹¹² Of particular interest are factors that influence the time between an abnormal mammogram result and evaluation through biopsy.¹¹³⁻¹¹⁶ Our scientists have also demonstrated the importance of maintaining care for other conditions,^{117,118} as there is some evidence that patients with breast cancer are less likely to receive recommended primary-care services following their diagnosis.¹¹⁸

Researchers at Kaiser Permanente have conducted several studies of the effectiveness of chemotherapy in patients with breast cancer.^{99,100,105,119,120} We have studied factors associated with initiation of and adherence to adjuvant endocrine therapies such as tamoxifen and aromatase inhibitors – these include social support¹¹⁰ and other psychosocial factors,¹²¹ age,¹²²⁻¹²⁴ race,¹²⁴ receipt of other breast cancer treatment,¹²² side effects,¹²⁵ tumor size¹²³ and lymph node status.¹²⁶



Our scientists have also studied numerous aspects of surgery for breast cancer.^{127,128} Research conducted at Kaiser Permanente has linked improvements in care planning for disease survivors with superior treatment outcomes and longer survival.¹²⁹ 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.¹³⁰⁻¹³³

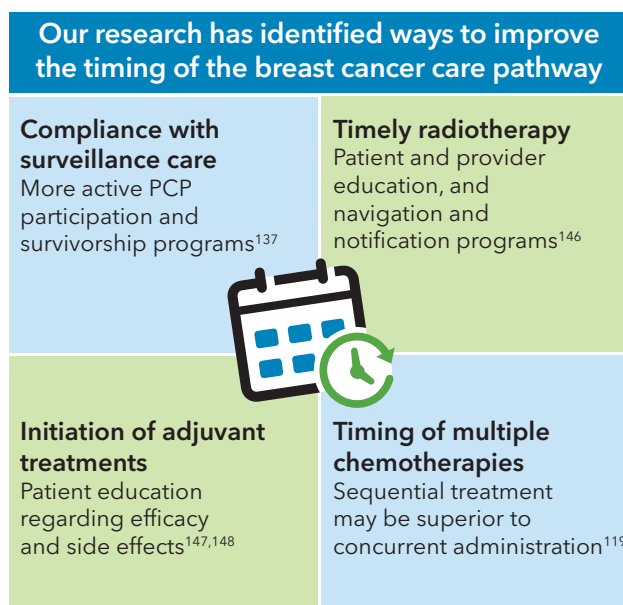
Even after successful treatment, breast cancer is best thought of as a chronic illness, in which the risks of recurrence, disease progression, and development of comorbid illnesses must be carefully monitored.^{118,134,135} Our scientists have developed and validated an algorithm for identifying cases of breast cancer recurrence from health record and medical claims data.¹³⁶ Studies at Kaiser Permanente have also explored why some patients may struggle to follow recommendations for post-treatment surveillance,^{118,134,135,137-141} and are actively testing interventions that foster greater engagement with surveillance.

Translating Research Findings into Policy and Practice

How has Kaiser Permanente research on breast cancer contributed to changes in 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,^{57,87,90,142,143} personalized risk counseling for women with dense breasts,¹⁴⁴ and the proper coordination of breast cancer surgery with the surgical removal of the ovaries and fallopian tubes.¹⁴⁵

Our researchers also continue to explore ways to improve the timing of care pathway elements, including increasing appropriate use of surveillance mammography,^{85,86,137} addressing delays in treatment,¹⁴⁶⁻¹⁴⁸ and evaluating concurrent (versus sequential) use of multiple treatments.¹¹⁹ 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,¹⁴⁹ increasing appropriate referrals for treatment of breast cancer-related lymphedema,¹⁵⁰ and using diagnostic and surveillance testing more effectively.^{151,152} Our research on long-term surveillance practices has significantly improved the integration and coordination of care after our patients complete breast cancer treatment.^{153,154} Studies



of more advanced care practices include interventions aimed at maintaining patients' contact with their primary-care provider,¹¹⁸ the use of wearable devices to encourage ongoing physical activity,¹⁵⁵⁻¹⁵⁷ and the use of specialized care teams (including nurse navigators)^{59,158-160} to help patients effectively navigate through a system of multidisciplinary care.^{118,134,137}

Kaiser Permanente hospitals in Northern California,¹⁶¹ Hawaii,¹⁶² the Mid-Atlantic States,¹⁶³ and Oregon¹⁶⁴ 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.¹⁶⁵

Collectively, research from Kaiser Permanente authors on the topic of breast cancer has been cited over 130 times within recent consensus statements and clinical practice guidelines published by a wide range of entities, including the American Cancer Society^{166,167} and the American Society of Clinical Oncology.¹⁶⁸ 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 Force¹⁶⁹ and the American College of Physicians.¹⁷⁰

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;¹⁷¹⁻¹⁷³ the Breast Cancer Treatment Effectiveness in Older Women Study;¹⁷⁴ a randomized study of genetic counseling for women at high risk;⁵⁹ and a randomized trial assessing whether pre-screening cessation of hormone replacement therapy increases mammogram accuracy.¹⁷⁵ 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 around screening and pre-operative diagnosis,¹⁷⁶ research into applications of artificial intelligence technology toward improving the accuracy of screening mammography,^{177,178} and efforts to develop performance benchmarks for diagnostic digital mammography¹⁷⁹ and screening MRI.¹⁸⁰ Kaiser Permanente oncologists in Northern and Southern California, Hawaii, Colorado, Georgia, Washington, and the Northwest participate in the National Cancer Institute's Community Oncology Research Program, which funds numerous trials of breast cancer treatment, prevention, imaging, and symptom control.¹⁰⁴ 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.^{181,182}

Kaiser Permanente's nearly 170 research scientists and more than 1,600 support staff are based at 8 regional research centers and one national center. There are currently more than 2,400 studies underway, including clinical trials. Since 2007, our research scientists and clinicians have published more than 12,000 articles. Kaiser Permanente currently serves more than 12.3 million members in 8 states and the District of Columbia.

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