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Scottish Referral Guidelines for Suspected Cancer Update – Evidence review for suspected breast cancer

The purpose of this document is to synthesise and critique evidence and insight related to referral guidelines for suspected breast cancer. Key themes have been determined from the literature. For each key theme e.g., individual symptoms, the papers are summarised separately with some high-level synthesis to provide steer on how this may impact referral guidelines. At the end of the document, a table comparing NICE NG12 and Scottish referral guidelines for suspected cancer (SRG) can be found for reference.

This document includes evidence on the following topics:

- Individual symptoms.
- Symptom combinations.
- Primary care investigations relevant to breast cancer.
- Safety netting those with signs and symptoms of breast cancer.
- Risk stratification.
- Other topics where the evidence base is emerging.

Any papers that are repeated in further sections within the review are **coloured in light grey.** Note that evidence on breast cancer in men and women will be included in this evidence review.

Background

Breast cancer is the most common cancer in women in Scotland, with around 4,900 new cases each year.[1] Most cancers are diagnosed early (at stage 1 or 2); On average each year, between 2018 and 2019, 39.6% of cases were diagnosed at stage 1, 46.1% were diagnosed at stage 2, 6.6% were diagnosed at stage 3, 5.0% were diagnosed at stage 4,and 2.7% were diagnosed at an unknown stage.[2] Women diagnosed at an earlier stage will have better treatment options and an improved chance of survival, as seen in most UK nations; survival

[1] Cancer Research UK. 2017-2019, ICD10 C50, average annual number of new breast cancer cases in females in Scotland. Similar data can be found here: https://www.cancerresearchuk.org/health-professional/cancer-statistics/statistics-by-cancer-type/breast-cancer/incidence-invasive#heading-Zero

[2] Public Health Scotland, Detect Cancer Early Staging Data. Summarised by Cancer Research UK, Early Diagnosis Data Hub. https://crukcancerintelligence.shinyapps.io/EarlyDiagnosis/

data by stage is not available for Scotland.[2] Stage distribution differs by deprivation quintile, with the women living in more deprived areas being more likely to experience an advanced stage breast cancer diagnosis[3].

Breast cancer is characterised by a narrow symptom signature, meaning that most people present with only a few specific symptoms such as breast lump, and typically have relatively short diagnostic intervals. There are several risk factors for breast cancer, including having family history of breast cancer or an associated genetic mutation, but most risk factors are primarily related to a women's reproductive history, such as early menarche, oral contraceptive use or hormone replacement therapy, older age at first giving birth, not giving birth, not breastfeeding, or older age at menopause.[4] Help-seeking behaviours and awareness of symptoms varies by demographic. There is evidence suggesting that first-generation Black African and Black Caribbean women in the UK who were diagnosed with symptomatic breast cancer had lower symptom awareness and faced barriers which resulted in delayed help-seeking.[5] Health care professionals should consider these factors when making decisions about management.

Search Strategy

Search terms: A combination of: "breast cancer", symptom, symptomatic, "positive predictive value", "breast lump", lump, nipple, "nipple abnorm*", "nipple discharge", pain, presentation, "symptom profile", prevalence, risk, recognition, referral, stage, "breast exam*", "clinical exam*", mammogram, mammography, "diagnostic accuracy", repeat, "repeat exam*", "high risk", "high-risk", incidence, comorbidities, demographic

Date: 2015-present. Section summaries may include papers from pre-2015 that are relevant for explaining the differences in the SRG and NICE NG12 guidelines. These have been gathered from NICE NG12 Evidence Review[6] document.

[3] Public Health Scotland, Detect Cancer Early Staging Data
[4] Cancer Research UK, Breast cancer risk. https://www.cancerresearchuk.org/health-professional/cancer-statistics/statistics-by-cancer-type/breast-cancer/risk-factors Accessed February 2024
[5] Jones CE, Maben J, Lucas G, Davies EA, Jack RH, Ream E. Barriers to early diagnosis of symptomatic breast cancer: a qualitative study of Black African, Black Caribbean and White British women living in the UK. BMJ Open. 2015;5(3):e006944. Published 2015 Mar 13. doi:10.1136/bmjopen-2014-006944
[6] National Institute for Health and Care Excellence (NICE). Suspected cancer: Recognition and referral NICE guideline appendix F: Evidence review. 2015. Available from: https://www.nice.org.uk/guidance/ng12/evidence/appendix-f-pdf-74333343

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Peer-reviewed literature

Topic: Individual symptoms			
Summary: • The evidence base supports the inclusion of all the existing suspected breast cancer symptoms currently in the Scottish Referral Guidance (SRG) for Suspected Cancer. Evidence suggests against including breast pain as a symptom in the SRG. Note that there was more evidence on prevalence of symptoms at presentation in the breast cancer population rather than specific positive predictive values of symptoms (this is likely due to the fact that the search was restricted to 2015 and later). • **Breast lump** is the most common symptom of breast cancer and has a relatively high predictive value for breast cancer. In majority of breast cancer patients, this occurred as the **only symptom**. For this reason, breast cancer is known as a cancer which has a **narrow symptom signature.** • Other symptoms that occurred in people diagnosed with breast cancer included: **Nipple abnormalities (including discharge, retraction, distortion, or nipple changes), skin changes, axillary lump, breast pain, and back pain** • Studies report **no significant association between breast pain and breast cancer**, concluding that although referring patients to a breast diagnostic clinic for breast pain is common, it likely drains workforce, capacity, and resources, and overburdens clinics. • The overall quality of evidence for evaluation of breast cancer symptoms is high. Most studies used large national primary care cohorts, had rigorous methodology for analysis, and reported any limitations freely. Most research is primarily in an England context. The SRG includes breast pain persisting over 3 months in post-menopausal women as criteria for routine referral which is not included in NICE. Current evidence does not support including breast pain as a symptom. Additionally, the SRG include skin changes such as skin tethering, fixation, ulceration, or peau d'orange as criteria for urgent referral which NICE does not include. The evidence around specific positive predictive values for skin changes in breast cancer are lacking which is likely why it is not included in NICE NG12 guidance. But there is evidence that skin changes are prevalent in people diagnosed with breast cancer. Most recent studies quote a small frequency (between 2-5%) of people with breast cancer reporting skin changes as a symptom. Paper 8 below provides more specific evidence on the positive predictive value for skin changes in men.			

Paper number	**Evidence Paper**	**Summary**	**Notes**

1	Koo MM, Swann R, Mcphail S, Abel GA, Elliss-Brookes L, Rubin GP et al. Presenting symptoms of cancer and stage at diagnosis: evidence from a cross-sectional, population-based study. 2019. doi:10.1016/S1470-2045(19)30595-9.	This paper examined associations between common presenting symptoms of cancer and stage at diagnosis. There has been debate around whether symptoms present at an early enough stage for there to be possibility for meaningful clinical intervention. This study indicated that of the 20 symptoms evaluated, **breast lump** was the most common (1260 patients), and that it presents in majority of people at an early stage where there are better treatment options and better prognoses. Only 5% of patients who presented with a breast lump had a stage 4 diagnosis. 85% of patients who presented with breast lump had that as their only symptom (of the 20 symptoms evaluated) and 3% of these patients had a stage 4 diagnosis.	• Cross-sectional population-based study • Sample size: 7,997, aged 25 or older • National Cancer Diagnosis Audit (NCDA) and National Cancer Registration and Analysis Service (NCRAS) data (2014), England only • Limitation: recording of symptoms and extraction of information from primary care records might be incomplete or biased; • Did not report positive predictive values (PPV)
2	Zakkak N, Barclay ME, Swann R, McPhail S, Rubin G, Abel GA et al. The presenting symptom signatures of incident cancer: evidence from the English 2018 National I Cancer Diagnosis Audit. *OPEN Epidemiology British Journal of Cancer* 2024; 130: 297–307.	This paper examined (1) the frequency of presenting symptoms by cancer site and (2) the frequency of cancer site by presenting symptom. Breast cancer was found to be a cancer which was dominated by a frequent single presenting symptom (75% with breast lump/mass). Among breast cancer patients, **breast lump/mass** was the most common symptom. 91.8% of breast cancer patients presented with at least one symptom. Of the breast cancer cohort:	• Sample size: 55,122 patients; 6,166 breast cancer patients • Aged 25 or older • NCDA 2018 data, England only • Limitations: case-only analysis so cannot make inferences about PPV and surveys for GPs regarding the presenting symptoms were filled out retrospectively and

		• 86.9% patients presented with breast symptoms including **axillary lumpiness, breast lumpiness, breast pain, nipple changes, and nipple discharge** • 3.52% with **non-specific symptoms** • 1.52% with **respiratory symptoms** • 1.22% with **musculoskeletal symptoms** • 8.19% had nothing recorded. *Note: it is unclear whether these symptoms occurred individually or in combination with others.*	therefore, could be prone to bias.
3	Koo MM, Von Wagner C, Abel GA, Mcphail S, Rubin GP, Lyratzopoulos G. Typical and atypical presenting symptoms of breast cancer and their associations with diagnostic intervals: Evidence from a national audit of cancer diagnosis. 2017. doi:10.1016/j.canep.2017.04.010.	This study aimed to describe the range of presenting symptoms of breast cancer and the association between different symptomatic presentations with the length of diagnostic intervals. Frequency of symptoms among breast cancer patients (*note there are more symptoms, but all the rest had a <1% frequency)*: • **breast lump** (83%) • **nipple abnormalities** (6.8%) • **breast pain** (6.4%) • **breast skin abnormalities** (2%) • **axillary lump** (1.2%) • **breast ulceration** (1.1%) • **back pain** (1%)	• NCDA 2009-2010 data, England only • N=2316 • Limitations: Potential bias in patients accurately recalling symptoms and doctors accurately recording them; non-specific symptoms may be under captured because patients analysed retrospectively; unable to examine diagnostic intervals by level of deprivation or other patient-level characteristics
4	Koo MM, Hamilton W, Walter FM, Rubin GP, Lyratzopoulos G. Symptom Signatures and	This systematic review summarised available evidence on the association between symptomatic presentations and diagnostic intervals.	• Systematic review

	Diagnostic Timeliness in Cancer Patients: A Review of Current Evidence. *Neoplasia* 2018; 20: 165–174.	Breast cancer was found to have a **narrow symptom signature**, with most women initially presenting with **breast lump** which has a relatively high predictive value for breast cancer. The paper summarised the following 3 studies in a table to show the population-based estimates of the frequency of presenting symptoms among breast cancer patients: Walker et al., 2014; Redaniel et al., 2015; Koo et al., 2017. Among the most common in all 3 studies was **breast lump** (44.1%, 93.5%, 83% respectively), **breast pain** (2.4%, 4.6%, 6.4% respectively), **and nipple abnormalities** as defined in the Koo 2017 paper (6.8%).	• Included UK studies using CPRD data as well as NCDA England data • Some overlap between cohorts – Walker et al. 2014 used CPRD data from 2000-2009, including women 40+. Redaniel et al., 2015 also used CPRD data from 1998-2009 and included a wider population of women 15+. Koo et al., 2017 used NCDA data from 2009-2010.
5	Redaniel MT, Martin RM, Ridd MJ, Wade J, Jeffreys M. Diagnostic Intervals and Its Association with Breast, Prostate, Lung and Colorectal Cancer Survival in England: Historical Cohort Study Using the Clinical Practice Research Datalink. 2015. doi:10.1371/journal.pone.0126608.	This study assessed associations of diagnostic intervals with survival and stratified these by NICE-qualifying alert and non-alert symptom presentations for breast, lung, prostate, and colorectal cancer. They looked at the year prior to a person's diagnosis to gather the symptoms that they presented to primary care with. • 94.3% of breast cancer patients presented with **alert symptoms** in the year prior to diagnosis. • Women with breast cancer had the shortest diagnostic interval compared to the other cancers (median 14 days). • Amongst breast cancer patients, 92.5% presented with a **breast lump** (i.e., alert symptom). • The five-year relative survival was highest for breast cancer, at 80.5% overall.	• Retrospective cohort study • Clinical Practice Research Datalink data. England only • N=8,639 female breast cancer patients • Included people diagnosed between 1998 and 2009, aged 15 or older. • Limitations: Did not have information for all factors that could affect survival (i.e., stage); excluded patients diagnosed through emergency or screening

		There was no evidence of an association between diagnostic interval and mortality for breast cancer. When stratifying by NICE-qualifying alert and non-alert symptoms, five-year relative survival was slightly higher in women who first presented with non-alert symptoms compared to those who presented with alert symptoms (85.8% vs. 80.1%). The researchers did not look at stage or diagnostic interval for alert vs. non-alert symptoms which could have helped explain this survival difference, but we do note that Paper 1, Koo et al. 2019 suggests that breast lump (an alert symptom) is associated with earlier stage at diagnosis.	routes which could impact diagnostic interval and mortality; symptoms recorded by GP are prone to bias.
6	Dave R V, Bromley H, Taxiarchi VP, Camacho E, Chatterjee S, Barnes N et al. No association between breast pain and breast cancer: a prospective cohort study of 10 830 symptomatic women presenting to a breast cancer diagnostic clinic. *Br J Gen Pract* 2022; 72: e234–e243.	This study aimed to investigate breast cancer incidence in women presenting with breast pain compared to other breast symptoms such as lump and establish cost-effectiveness of referring women with only breast pain to secondary care. They categorised patients based on 4 distinct **groups of symptoms**: • **breast lump** (**lump in breast or axilla**, with or without **associated pain** or **nipple symptoms**) – 61.9% of cohort. • **nipple symptoms** (including **discharge**, **distortion**, or **skin changes**, with or without **associated pain** but **no lump**) – 4.4% of cohort. • **breast pain** (unilateral or bilateral, with no other breast symptoms) – 18.2% of cohort. • other symptoms – 15.4% of cohort.	• Prospective cohort study • England secondary breast diagnostic clinic • Studied patients between April 2019 and March 2020 • N=10,830; 3804 had symptoms which included breast pain, and 1972 (18%) had breast pain alone • Limitations: lack of family history data collected; spectrum bias is a possibility due to the study group being the referred population; cyclical and non-cyclical breast pain are not distinctly categorised in the study

		They found that in the absence of other breast symptoms, **there is no association between only breast pain and breast cancer**. Women referred with breast pain alone were 20 times less likely to have breast cancer compared to those in the breast lump symptom group, after adjustment for age (OR 0.05, 95% CI = 0.02 to 0.09; P<0.001). The incidence of breast cancer in women in the study referred with breast pain alone was lower than the rate of cancer found in asymptomatic breast screening (0.4% vs. 0.8%). Referring women with breast pain alone was associated with increased costs and is not an effective use of healthcare resources.	
7	Cook N, Batt J, Fowler C. Symptomatic Breast Cancers and Why Breast Pain May not Always Need Clinical Review. *Eur J Breast Health* 2020; 16: 267–269.	This study evaluated the link between breast pain and new cancer diagnosis at a single breast clinic in England. Symptomatic patients were categorised by their symptom: (1) new **ipsilateral breast lump**, (2) **nipple changes** such as **discharge** or **dysmorphia**, and (3) **breast pain** (defined as **isolated, unilateral, persistent, non-cyclical pain in the absence of abnormal clinical examination**). Of the 334 symptomatic referrals: • breast lump was the most common reason for referral (88%) • 8% patients were referred for nipple changes such as distortion or discharge • 4% were referred for breast pain with a normal breast examination.	• Retrospective cohort study • England-based centre • 2017-2018 • Small number - 334 referrals to single symptomatic breast clinic

		Among the 12 of patients referred with breast pain, 4 patients were diagnosed with ipsilateral cancer. Additionally, 8 of the 12 patients referred with breast pain only were found to have contralateral disease (cancer in the breast which was not paining). Upon examination, 3 of the patients with contralateral disease were found to have breast lumps on the affected breast. It was concluded **that breast pain should not be a referral reason for breast cancer**, as incidence of cancer in this group is low (1%) and it significantly drains workforce, resources, and contributes to over burdening breast clinics with inappropriate referrals.	
8	Shin K, Whitman GJ. Clinical Indications for Mammography in Men and Correlation With Breast Cancer. *Curr Probl Diagn Radiol*. 2021;50(6):792-798. doi:10.1067/j.cpradiol.2020.11.001	This study investigated the presenting clinical symptoms in **male patients** and correlated them with the diagnosis of breast cancer. The following symptoms and their sensitivity, specificity, NPV and PPV, respectively, were reported: • **Palpable abnormality** (the most common symptom) had a sensitivity of 76%, a specificity of 36%, a NPV of 90% and a PPV of 16%. • **Nipple changes** with a sensitivity of 15%, a specificity of 100%, a NPV of 85% and a PPV of 100%. • **Skin changes**: sensitivity of 17%, specificity of 98%, NPV of 87%, and PPV of 43%. • **Breast enlargement, focal pain, nonfocal pain, and breast swelling** all had sensitivities and PPVs of 0. The authors conclude that any nipple and skin changes are important to note on physical examination of the male	• Retrospective cohort study of a single site in the USA • Male patients only • January 2004 – December 2014 • N=291 (all symptomatic) • Limitations: USA-based (there may be differences between help-seeking and recognition and referral between USA and UK); small sample size; most male patients do not have imaging or clinical follow ups so it is unclear whether some of these patients were diagnosed at a later time.

		breast, but breast pain, swelling, or enlargement should not cause alarm to clinicians as they are often associated with benign conditions.	

Topic: Symptom combinations

Summary:

- Studies that *clearly* analyse combinations of symptoms for breast cancer and their associated predictive values are lacking. This is likely because breast lump has been reported to be the most prevalent, and in many cases, only symptom of breast cancer. Therefore, symptom combinations are few and far between, usually consisting of nipple abnormalities, skin changes, axillary lumps, or other symptoms with small frequencies (back pain, breast pain, non-specific symptoms, etc.). The evidence supports the current symptoms included in the referral guidance.

Paper Number	Evidence Paper	Summary	Notes
1	Koo MM, Swann R, Mcphail S, Abel GA, Elliss-Brookes L, Rubin GP et al. Presenting symptoms of cancer and stage at diagnosis: evidence from a cross-sectional, population-based study. 2019. doi:10.1016/S1470-2045(19)30595-9.	This paper examined associations between common presenting symptoms of cancer and stage at diagnosis. There has been debate around whether symptoms present at an early enough stage for there to be possibility for meaningful clinical intervention. This study indicated that of the 20 symptoms evaluated, **breast lump** was the most common (1260 patients). Of this population, 186 people reported **other symptoms alongside breast lump.** Majority of these people were diagnosed with early stage disease; only 22 of were diagnosed with stage 4 disease. This suggests that symptoms that present alongside breast lump do often present at an early enough stage for meaningful clinical intervention.	• Cross-sectional population-based study • Sample size: 7,997 • NCDA 2014 data and NCRAS to obtain stage information • England only data • Limitation: recording of symptoms and extraction of information from primary care records might be incomplete or biased

3	Koo MM, Von Wagner C, Abel GA, Mcphail S, Rubin GP, Lyratzopoulos G. Typical and atypical presenting symptoms of breast cancer and their associations with diagnostic intervals: Evidence from a national audit of cancer diagnosis. 2017. doi:10.1016/j.canep.2017.04.010.	This study aimed to describe the range of presenting symptoms of breast cancer and the association between different symptomatic presentations with the length of diagnostic intervals. 99% of women belonged to **4 symptom groups: "lump only" (76%), "non-lump only" (11%), "both lump and non-lump" (6%) and "non-breast symptoms" (5%).** About 1 in 6 women presented without a breast lump and experienced a wide spectrum of symptoms before seeking help. Those who presented with "lump only" had the shortest primary care interval (median = 2 days) while those with "non-breast symptoms" had the longest primary care interval (median = 105 days). Women in the "both lump and non-lump" group had longer patient intervals compared to the "breast lump only" group. The authors suggested that this could be due to women normalising a lump in the breast in the presence of other non-lump breast symptoms. There was no difference in frequency of symptom groups or time between symptom onset and presentation by age or ethnicity.	• NCDA 2009-2010 data • England only • N=2316 Limitations: Potential bias in patients accurately recalling symptoms and doctors accurately recording them; non-specific symptoms may be under captured because patients analysed retrospectively; unable to examine diagnostic intervals by level of deprivation or other patient-level characteristics

Topic: Investigation findings
Summary:

- Research evidence on the accuracy of clinical examinations or other primary care investigations for breast cancer and it's use in referral are lacking, however it is generally understood that most investigations for breast cancer happen in secondary care after referral (i.e., mammogram, ultrasound, MRI).
- Dave et al., 2022 reported that a normal clinical evaluation in women with breast pain alone had a positive predictive value of 99% in predicting a normal mammogram, which supports the notion that breast pain alone should not be considered as a reason to refer patients to a breast cancer pathway.

Paper Number	Evidence Paper	Summary	Notes
6	Dave R V, Bromley H, Taxiarchi VP, Camacho E, Chatterjee S, Barnes N et al. No association between breast pain and breast cancer: a prospective cohort study of 10 830 symptomatic women presenting to a breast cancer diagnostic clinic. *Br J Gen Pract* 2022; 72: e234–e243.	This study aimed to investigate breast cancer incidence in women presenting with breast pain compared to other breast symptoms such as lump and establish cost-effectiveness of referring women with only breast pain to secondary care. They categorised patients based on 4 distinct **groups of symptoms**: • **breast lump** (**lump in breast or axilla**, with or without **associated pain** or **nipple symptoms**) • **nipple symptoms** (including **discharge**, **distortion**, or **skin changes**, with or without **associated pain** but **no lump**) • **breast pain** (unilateral or bilateral, with no other breast symptoms) • other symptoms Results showed that women referred with breast pain alone were unlikely to have clinically abnormal findings on breast examination.	• Prospective cohort study • England secondary breast diagnostic clinic • Studied patients between April 2019 and March 2020 • N=10,830; 3804 had symptoms which included breast pain, and 1972 (18%) had breast pain alone • Limitations: lack of family history data collected; spectrum bias is a possibility due to the study group being the referred population; cyclical and non-cyclical breast pain are not distinctly categorised in the study

		• Of the 1112 women with breast pain alone who underwent **mammography,** it was normal/benign in 98%. • For patients with breast pain alone, a **normal breast examination** had a positive predictive value of 99% (accuracy of 99%) in predicting a normal mammogram. Mammography has high negative predictive value in women with breast pain, but positive predictive value for breast cancer is low, 8–14%, meaning that investigations in this cohort of women can result in significant false positive findings or incidental findings (seen in 5% of patients with breast pain alone).	

Topic: Safety netting

Summary:

- Risk of screen-detected or interval breast cancer is twice as high in women with prior false-positive mammography screening test results and four times as high in women with two prior false-positive mammography screening test results. As such, it may be important for GPs to remain cautious toward patients who were recently screened for breast cancer and called back after their mammogram for further testing as they may be at a higher risk.

Paper Number	Evidence Paper	Summary	Notes
9	Román M, Hofvind S, von Euler-Chelpin M, Castells X. Long-term risk of screen-detected and interval breast cancer after false-positive results at mammography screening: joint analysis of three national cohorts. *Br J Cancer.*	This study evaluated the association between a first and second false-positive screening result (mammography) and the long-term risk of interval breast cancer and screen-detected cancer among three national European cohorts (Denmark, Norway and Spain). The researchers defined "false-positive" as any time a woman was asked to come back for further assessment without confirmation of a cancer	• Joint cohort analysis • Individual level data from mammography programs in Copenhagen, Norway, and Spain • N=1,149,467

	2019;120(2):269-275. doi:10.1038/s41416-018-0358-5	diagnosis, regardless of the procedures performed (i.e., additional imaging and/or invasive procedures with benign outcomes). Results showed that: • Women with prior false-positive results had double the risk of screen-detected and interval breast cancer compared to those with negative tests. • Women with two prior false-positive results experienced quadruple the risk. • The increased risk remained increased 12 years after experiencing the false-positive result.	• Limitations: screening programmes differ from Scotland slightly (the countries analysed in the study screen every 2 years, whereas Scotland does it every 3 years); there was variation found across countries analysed in the study (to be expected – researchers noted that this could be due to variation in clinical practice or population characteristics, but sensitivity analysis showed little impact on results); did not consider whether people had biopsy; breast density information lacking;

	Topic: Risk stratification (e.g. by demographics)
	<u>Summary:</u> • There is evidence to show that the following groups of people are at an increased risk of breast cancer: women who use oral contraceptives, women who had a young age of menarche, women who did not give birth, women who had their first child after 30 years old, women who did not breast-feed, women who are postmenopausal, women who use tobacco, and women with a family history of breast cancer. There is also some evidence to suggest that women from more deprived areas have a

higher incidence of advanced stage disease. GPs may benefit from being aware of these risk factors to better assess a patient's risk prior to referring.

- There is conflicting evidence on the impact of comorbidities on risk of breast cancer.
- Transgender individuals have a higher risk of breast cancer compared to cisgender men, but a lower risk compared to cisgender women.
- Evidence suggests that Black and Asian women diagnosed with breast cancer were more likely to experience more than one symptom, and there was weaker evidence suggesting Black women were more likely to experience breast pain than White women.

Note on age-thresholds

The SRG and NICE NG12 guidance both specify age thresholds for certain symptoms (i.e., 30 or over in SRG and NICE NG12, 35 or over in SRG, 50 or over in NICE NG12). However, there is a lack of robust, recent evidence to justify the age thresholds currently specified in the SRG or NICE guidance. **Costa L, Kumar R, Villarreal-Garza C, et al. Diagnostic delays in breast cancer among young women: An emphasis on healthcare providers. *Breast*. Published online December 13, 2023. doi:10.1016/j.breast.2023:** This study suggests that young women (< 40 years old) often experienced delayed breast cancer diagnoses, likely due to (1) the stereotype that breast cancer is associated with older age groups and (2) symptoms are often dismissed as benign issues which lead to lack of proper investigation. Particularly young mothers can have breast lumps misattributed as galactoceles (milk-filled cysts) in the absence of clear guidance for healthcare providers regarding those presenting with symptoms at younger ages.

The rationale for the age thresholds used in the NICE suspected breast cancer referral guidance is explained in the November 2014 full guideline draft for consultation.[7] It was noted that the most reliable evidence on breast lump at the time of review was from Walker et al. (2014) which included women aged 40 and over[8]. Results indicated that that the PPV for breast lump was >3% for women aged 40-49 and increased as women got older. The guideline development group did not think it likely that the PPV would

[7] National Collaborating Centre for Cancer. Suspected cancer: recognition and management of suspected cancer in children, young people and adults – Clinical Guideline. November 2014. Available from: https://www.nice.org.uk/guidance/ng12/update/NG12/documents/suspected-cancer-update-draft-guideline2

[8] Walker S, Hyde C, Hamilton W. Risk of breast cancer in symptomatic women in primary care: a case-control study using electronic records. Br J Gen Pract. 2014;64(629):e788-e793. doi:10.3399/bjgp14X682873

	decrease significantly below age 40 but also noted that breast cancer is extremely rare in people younger than 30 years old, hence the age threshold >/=30 in the guidance. It was noted that although rare, breast cancer can still occur in those <30 so they kept the recommendation for routine referral in this group. For nipple retraction and nipple discharge, the PPV reported in Walker et al. (2014) was only greater than the 3% threshold in those aged 60 and over and 70 and older, respectively, although the study does not distinguish between unilateral and bilateral symptoms. Due to this, the guidelines development group thought that the PPV would likely be higher if only unilateral was included, hence they decided to reduce the age to those 50 or over experiencing nipple symptoms such as discharge, retraction, or other changes of concern. Additional older evidence regarding age and breast cancer is summarised below: • **Eberl MM, Phillips RL Jr, Lamberts H, Okkes I, Mahoney MC. Characterizing breast symptoms in family practice. *Ann Fam Med*. 2008;6(6):528-533. doi:10.1370/afm.905** found that 78% of breast malignancies were in women aged 45 or older. A very small rate of breast cancer was found in those younger than 25. The study also noted that the highest rate of breast-related complaints occurred in a younger cohort aged 25-44 years old. Breast lump or mass had a high positive likelihood ratio for breast cancer generally so the researchers suggest clinical work up of such symptoms, regardless of age. • **Newton P, Hannay DR, Laver R. The presentation and management of female breast symptoms in general practice in Sheffield. *Fam Pract*. 1999;16(4):360-365. doi:10.1093/fampra/16.4.360** found that younger women aged 16-39 presenting with breast symptoms in general practice were more likely to experience multiple consultations before receiving a referral. In general, about one-third of women aged 16-39 years received a referral at all compared to one-half of women aged 65+, despite presenting with symptoms.

Paper number	Evidence Paper	Summary	Notes
10	Barclay ME, Abel GA, Greenberg DC, Rous B, Lyratzopoulos G. Socio-demographic variation in stage at diagnosis of breast, bladder, colon, endometrial, lung, melanoma, prostate, rectal, renal and ovarian cancer in England and its population impact. *Br J*	This study examined the association between stage at diagnosis for common cancers in England and socio-demographic variation. The following associations were found:	• Cross sectional study • Data from the English cancer registry in 2015 • N=202,001 • Limitations: stage data missing for some patients; health-care related factors were not considered;

	Cancer. 2021;124(7):1320-1329. doi:10.1038/s41416-021-01279-z	• **Age** had a u-shape association for advanced stage breast cancer with risk increasing at younger and older ages (<40 and >65). • Patients from more **deprived** areas were at a higher risk of advanced stage of diagnosis for breast cancer (and this remained after adjusting for screening detection). An estimated 2.1% increase in stage 1 and 2 breast cancers may occur if socio-demographic inequalities in stage at diagnosis were eliminated (note: this was the smallest increase among cancers studied in the paper).	
11	Barańska A, Błaszczuk A, Kanadys W, Malm M, Drop K, Polz-Dacewicz M. Oral Contraceptive Use and Breast Cancer Risk Assessment: A Systematic Review and Meta-Analysis of Case-Control Studies, 2009-2020. *Cancers (Basel)* 2021; 13. doi:10.3390/cancers13225654.	This paper explored the association between oral contraceptive pills use and breast cancer risk. Results showed that: • The use of **oral contraceptives** was associated with an increased risk of breast cancer (OR=1.15, p=0.0358). • An **age of menarche younger than 13 years old** was associated with higher breast cancer risk (OR = 1.18, p = 0.0016). • Women who **did not give birth** had a higher risk of breast cancer compared to women who did give birth (OR=1.22, p=0.0146). • Women who had their **first child after the age of 30** had a higher risk of breast cancer (OR=3.08, p=0.0322). • **Non-breastfeeding** was associated with a higher risk of breast cancer compared to women that breast fed (OR=1.36, p=0.0010)	• Systematic review and meta-analysis • 42 studies included; 110,580 women • Limitations: High heterogeneity; English only studies; case-control only studies; self-reported data; lack of uniform definition of "ever" use of oral contraceptives; genetic factors not explored; different varieties of oral contraceptives not explored.

		• Increased risk of breast cancer among **postmenopausal women** compared to premenopausal women (OR=1.36, p=0.0007) • **Tobacco use** increased breast cancer risk (OR=1.52, p=0.0000). • **Family history of breast cancer** in the first or second relatives was associated with higher risk of breast cancer (OR=1.72, p=0.0001).	
12	Brewer HR, Jones ME, Schoemaker MJ, Ashworth A, Swerdlow AJ. Family history and risk of breast cancer: an analysis accounting for family structure. *Breast Cancer Res Treat* 2017; 165: 193–200	This study analysed breast cancer **incidence risks** in relation to a **family history** score (first primary breast cancers in relatives divided by the number of expected breast cancers which was calculated through person-years in the family cohort and age-specific incidence by calendar year). Results showed that **risk of breast cancer increased significantly as the family history score increased**. Participants in the highest family history score category had a relative risk of 3.50 ($p < 0.0001$) compared with those with no affected relatives. **Family size and age at diagnosis also impacts risk:** • Women with at least one first-degree female relative with breast cancer had higher risk than those without a family history (HR = 1.77, $p < 0.0001$). • Women with two or more relatives diagnosed with breast cancer had more than double the risk (HR = 2.52, $p < 0.0001$).	• Analysis of data from the Generations prospective cohort study in the UK • Data from June 2003-2012 • N=103,738; 1,733 diagnosed with breast cancer • Limitations: family history was collected through questionnaires and not confirmed;

		• Women with family members who were diagnosed before age 45 also had higher risk compared to those who had family members diagnosed after age 45.	
13	Boakye D, Günther K, Niedermaier T, Haug U, Ahrens W, Nagrani R. Associations between comorbidities and advanced stage diagnosis of lung, breast, colorectal, and prostate cancer: A systematic review and meta-analysis. *Cancer Epidemiol* 2021; 75: 102054.	This review analysed the association between comorbidities and incidence of advanced stage disease for prostate, breast, lung, and colorectal cancer. Results of the meta-analysis showed a **non-significant association between Charleston Comorbidity Index (CCI) score and advanced stage disease for breast cancer** (OR=1.19, CI: 0.96-1.48), however studies in the narrative synthesis had more **conflicting results**. One study reported no association between CCI and advanced stage breast cancer, whereas others suggested that comorbidities which are life threatening (renal disease, liver disease, heart failure) are associated with advanced stage breast cancer but non-life threatening conditions such as arthritis show no association. One study also showed an association between major depression and advanced stage breast cancer but not schizophrenia and phobia.	• Systematic review and meta-analysis • 37 studies included; 18/37 examined breast cancer • Studies included up to 3rd June 2021
14	Corso G, Gandini S, D'Ecclesiis O, et al. Risk and incidence of breast cancer in transgender individuals: a systematic review and meta-analysis. *Eur J Cancer Prev.* 2023;32(3):207-214.	This review evaluated the impact of breast cancer in transgender individuals (male-to-female and female-to-male). Findings showed that female-to-male and male-to-female transgender individuals had a higher incidence risk for breast	• Systematic review and meta-analysis • 6 cohort studies included; 35 case reports included

	doi:10.1097/CEJ.0000000000000784	cancer compared to cisgender men (standardised incidence ratio (SIR) = 63.4 and 22.5, respectively), but a lower risk than cisgender women (SIR=0.42 and 0.30, respectively).	
15	Martins T, Ukoumunne OC, Lyratzopoulos G, Hamilton W, Abel G. Are There Ethnic Differences in Recorded Features among Patients Subsequently Diagnosed with Cancer? An English Longitudinal Data-Linked Study. Cancers (Basel). 2023;15(12):3100. Published 2023 Jun 7. doi:10.3390/cancers15123100	This study investigated possible ethnic differences in the number and type of cancer features (as defined by NICE NG12) recorded in primary care before a cancer diagnosis. Results showed: • The odds of having multiple features were higher among Asian patients with breast cancer (Adjusted Odds Ratio (AOR) = 1.56, 95% CI: 1.04–2.33) and Black patients with breast cancer (AOR = 2.94, 95% CI: 1.94–4.46) than White patients with breast cancer. • There was weak evidence that Black patients were more likely than White patients to have breast pain (AOR = 1.42, 95% CI: 0.98–2.07). • Overall, non-White patients were less likely to have alarm features recorded in primary care.	• Clinical Practice Research Datalink (CPRD-Aurum) • England only • Included cancers diagnosed between 1 January 2006 and 31 December 2016 in those 40 or older • N= 130,944 (92.3% White, 1.95% Black, 1.61% Asian, 1.88% Mixed, 2.27% Other) • Limitations: Sample size in ethnic minority groups is smaller compared to White ethnic group.

Emerging Topics

Risk stratification/prediction tools: There is emerging research on the utility of risk stratification or prediction tools in breast cancer, however most of the evidence is in regard to asymptomatic screening populations. Ramzi et al. (2021)[9] explored the accuracy of the urgent suspected breast cancer referral pathway (two-week-wait pathway) and compared it to an age-only model and a multivariable prediction model which combined different clinical features and demographics/history. Findings showed that both models outperformed the urgent suspected breast cancer referral pathway in discriminating between breast cancer versus no breast cancer. The worse

[9] Ramzi S, Cant PJ. Comparison of the urgent referral for suspected breast cancer process with patient age and a predictive multivariable model. BJS Open. 2021;5(2):zraa023. doi:10.1093/bjsopen/zraa023

performance of the two-week-wait pathway was suggested by the authors to be due to each symptom criteria having predictive risks that could be quite different from each other (i.e., breast lumps' PPV is higher compared to nipple discharge). They also suggest that age may not be weighted properly in the two-week-wait pathway and that the two-week-wait pathway does not consider negative predictors of breast cancer such as gravidity which were influential in their study. They acknowledge as well that referral can be dependent on GP resources, access to investigations, patient demand, and pressures from governance bodies which could impact the accuracy of the pathway.

Breast pain management pathways:

- The Association of Breast Surgery (ABS) in England released **a position statement on breast pain**[10] in May 2022. They note that referrals to breast cancer diagnostic clinics have grown by almost 100% but diagnoses have only risen by 14%. It was estimated that approximately 41% of patients referred to a breast cancer diagnostic clinic reported breast pain alone. Despite guidance suggesting to not refer women with breast pain, this statement suggests that **some women still perceive breast pain to be linked with breast cancer** and that **some GPs are concerned about the risk if they do not refer.** The increase in referrals has made it challenging to meet two week wait targets. In the position statement, ABS notes that they are working with NHS England on the Faster Diagnosis Breast Pathway with the hope that a new pathway would allow stratification of new patient breast referrals, potentially to local solutions such as breast pain clinics. ABS is currently collating examples of the various pathways being used across the UK.
- Some cancer alliances in England have started **triaging referrals** such that a patient with only breast pain may have a **telephone consultation** with a nurse or other clinician to determine whether scans are necessary given the nature of the symptoms. This has helped alleviate the burden on one-stop breast cancer diagnostic clinics.
    - Ellis et al. (2023)[11] evaluated an advanced-nurse practitioner led telephone breast pain service and found that four of every five women with breast pain were able to avoid attending the one-stop clinic, creating more capacity for women with "red flag" symptoms. 49% of women in the study with breast pain were referred onward for mammography, but these appointments were not held within the one-stop clinic and rate of cancer detection was still low (0.6%), indicating that telephone triage may be a useful way for managing patients with breast pain.

[10] Association of Breast Surgery. Position Statement on Breast Pain. May 2022. Available from: https://associationofbreastsurgery.org.uk/media/419972/breast-pain-statement-final.pdf
[11] Ellis KS, Robinson CE, Foster R, Fatayer H, Gandhi A. Efficient management of new patient referrals to a breast service: the safe introduction of an advanced nurse practitioner-led telephone breast pain service. Ann R Coll Surg Engl. Published online August 29, 2023. doi:10.1308/rcsann.2023.0056

- Rao et al. (2021)[12] also studied **web-based or app-based self-referral** using a validated questionnaire/application and found it to be a useful tool to improve workload in primary and secondary care, especially as breast pain was found to be the biggest cause of inappropriate referral.

- In England some local pathways have been developed for **breast pain-specific clinics** to help reduce burden on the one-stop-shop breast cancer diagnosis clinics.
  - One such pathway was evaluated by Jahan et al. (2022)[13] in Mid-Nottinghamshire and showed that among those referred, there were no cancer diagnoses, and only 5 patients required any imaging, suggesting patients with breast pain can be successfully managed in primary care or within the community.
  - A similar pathway, called a **"blue flag clinic",** was implemented in the Royal Cornwall NHS Trust. Hubbard et al. (2023)[14] conducted its evaluation which showed that it effectively allowed primary care professionals to triage referrals for patients that exhibited a breast symptom that was not initially suspected of cancer. In this clinic, imaging is performed on a separate day, after clinical evaluation, freeing up capacity for patients requiring more urgent investigation/assessment.

Current NICE NG12 and SRG for suspected breast cancer

NICE NG12	SRG

[12] Rao A, Razzaq H, Panamarenko B, Bottle A, Majeed A, Gray E. Online application for self-referral of the patients with breast symptoms. Ann Med Surg (Lond). 2021;66:102372. Published 2021 May 8. doi:10.1016/j.amsu.2021.102372

[13] Jahan M, Bartholomeuz T, Milburn N, Rogers V, Sibbering M, Robertson J. Transforming the 2-week wait (2WW) pathway: management of breast pain in primary care. BMJ Open Qual. 2022;11(1):e001634. doi:10.1136/bmjoq-2021-001634

[14] Hubbard T, Liu X, Sulieman M, et al. Evaluating a novel patient pathway to manage symptomatic breast referrals (the blue flag clinic): a longitudinal observational study. Ann R Coll Surg Engl. Published online July 25, 2023. doi:10.1308/rcsann.2023.0028

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Refer people using a **suspected cancer pathway referral** for breast cancer if they are:
• aged 30 and over and have an unexplained breast lump with or without pain **or**
• aged 50 and over with any of the following symptoms in one nipple only:
  ○ discharge
  ○ retraction
  ○ other changes of concern. [2015]
 	
Consider a **suspected cancer pathway referral** for breast cancer in people:
• with skin changes that suggest breast cancer **or**
• aged 30 and over with an unexplained lump in the axilla. [2015]
 	
Consider non-urgent referral in people aged under 30 with an unexplained breast lump with or without pain. See also recommendations 1.16.2 and 1.16.3 for information about seeking specialist advice. [2015]
	Urgent suspicion of breast cancer referral for:
	• **Lump:**
	  ○ Any new discrete lump in patients 30 years and over
	  ○ New asymmetrical nodularity that persists at review after two to three weeks (in patients over 35 years)
	  ○ Unilateral isolated axillary lymph node in women persisting at review after two to three weeks
	  ○ Recurrent lump at the site of a previously aspirated cyst
	• **Nipple symptoms**:
	  ○ Visibly bloodstained discharge
	  ○ New unilateral nipple retraction
	  ○ Nipple eczema if unresponsive to moderately potent topical steroids after a minimum of two weeks
	• **Skin changes:**
	  ○ Skin tethering
	  ○ Fixation
	  ○ Ulceration
	  ○ Peau d'orange
	• **Abscess/infection**:
	  ○ Mastitis or breast inflammation which does not settle or recurs after one course of antibiotics
	
	Routine referral for:
	• **Lump:**
	  ○ Any new discrete lump in patients under 30 years with no other suspicious features
	  ○ New asymmetrical nodularity that persists at review after two to three weeks (in patients under 35 years)

	• **Nipple symptoms:**
	  ○ Persistent unilateral spontaneous discharge sufficient to stain outer clothes
	• **Breast pain:**
	  ○ Unilateral pain persisting over three months in post-menopausal women
	  ○ Intractable pain that interferes with the person's lifestyle or sleep
	• **Gynaecomastia:**
	  ○ Exceptional aesthetics referral to plastic surgery pathway if appropriate (i.e. NOT to the breast service)
	• **Breast implants**
	  ○ If appropriate, refer to the service that first inserted the implant (usually plastic surgery)