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# Interval breast cancers — insights into a complex phenotype

**Yiwey Shieh**[1], **Elad Ziv**[1], **Karla Kerlikowske**[2,3]

[1]Division of General Internal Medicine, University of California, San Francisco, San Francisco, CA, USA

[2]Departments of Medicine and Epidemiology and Biostatistics, University of California, San Francisco, CA, USA

[3]General Internal Medicine Section, San Francisco Veterans Affairs Medical Center, San Francisco, CA, USA

## Abstract

Interval invasive breast cancers diagnosed after a normal mammogram but before the next screening examination have a different tumour biology than screen-detected breast cancers, and thus are not detected on mammography. Understanding the genetics and biology of interval invasive cancers could inform better approaches to detection.

Despite undergoing routine mammography screening, some women develop symptomatic invasive breast cancer following a normal screening mammogram, but before the next routine screen. These ‘interval cancers’ tend to present at an advanced stage and portend worse prognosis relative to screen-detected breast cancers[1]. Interval cancers comprise 20–30% of breast cancer diagnoses[1]. Thus, identifying women at high risk of an interval cancer is a major priority because these women might benefit from shorter screening intervals and/or supplemental screening with breast ultrasonography or MRI to enable early detection of these aggressive tumours[2, 3].

At least two factors contribute to the diagnosis of some breast cancers as interval cancers: tumour biology and masking. Interval cancers are enriched for biologically ‘aggressive’ tumours, as defined by clinicopathological[4] and geneexpression[5] characteristics, such that they are not present on a prior mammogram and grow quickly and present clinically before the next screen. Interval cancers also include tumours that were present and potentially detectable at the time of the previous mammogram, but were missed owing to dense breast tissue obscuring (masking) the tumour[1].

Genetic risk scores (GRSs), also called polygenic risk scores[6], representing the combined effects of multiple common genetic variants on susceptibility to breast cancer have been developed. GRSs can be used to predict overall breast cancer risk at least as accurately as is possible with traditional risk models based on clinical characteristics and family

Karla.Kerlikowske@ucsf.edu .

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history[6, 7]. However, GRSs tend to preferentially predict screen-detected cancers and are less effective in predicting interval cancer risk[8].

In a recent study, Grassmann and colleagues[9] conducted a case–case analysis involving 1,772 women with interval breast cancers and 13,074 with screen-detected breast cancers diagnosed in Sweden or the USA. They found that women with interval cancers were 43% more likely than those with screen-detected cancers to develop a non-breast cancer before, and 28% more likely to develop a non-breast cancer after, their breast cancer diagnosis ($P = 9.4 \times 10$ and $4.7 \times 10$ , respectively)[9]. To investigate whether shared genetic risk explained the link between interval breast cancers and non-breast cancers, the authors calculated the GRSs of these women for 13 cancer types — including breast cancer — and found that none of the GRSs was positively associated with interval breast cancer risk[9].

This analysis is one of the largest studies on genetics of interval cancer and one of the few studies examining the associations between interval breast cancers and non-breast cancers. Given their findings, Grassmann and colleagues suggest that rare, rather than common, genetic variants are likely to explain why some women with interval breast cancers also develop non-breast cancers. Although rare variants were not directly examined in this analysis, prior work by the same group revealed that women with interval breast cancers were more likely than those with screen-detected cancers to carry rare variants of genes associated with increased risk of breast cancer[8]. Through pleiotropic effects, these variants might also predispose women to develop non-breast cancers. The type of non-breast cancers associated with interval cancers in the current study were, however, somewhat unexpected. The genetic risk factors most commonly associated with breast cancer susceptibility include high-penetrance variants of *BRCA1* and *BRCA2* and moderate-penetrance variants in genes such as *PALB2*, *CHEK2* and *ATM*. Many of these variants also increase the risk of ovarian cancer[10], which was not significantly associated with interval breast cancer (OR 0.86, 95% CI 0.26–2.86 and OR 1.54, 95% CI 0.80–2.96 before and after breast cancer diagnosis, respectively)[9]. Similarly, several of these genes increase the risk of other cancers, such as melanoma[11] and pancreatic cancer[12], but neither of these cancers was significantly associated with interval breast cancer (OR 1.74, 95% CI 0.99–3.06 before and OR 1.10, 95% CI 0.67–1.81 after breast cancer diagnosis for melanoma, and OR 1.37, 95% CI 0.74–2.54 after breast cancer for pancreatic cancer)[9]. Interestingly, relative to screen-detected cancers, interval breast cancers were most strongly associated with an increased risk of lung cancer before (OR 2.57, 95% CI 1.09–6.06) and non-melanoma skin cancer before and after breast cancer diagnosis (OR 3.19, 95% CI 1.34–7.62 and OR 2.25, 95% CI 1.35–3.75, respectively)[9]. No known high or intermediate penetrance genes can explain this finding; however, most of the genetic risk of breast cancer remains unexplained, and undiscovered variants might account for these associations. Alternatively, non-genetic risk factors that overlap between breast cancer and other cancer types might explain these associations; both lung and non-melanoma skin cancers are strongly associated with environmental risk factors.

The work of Grassmann and colleagues provides insights into important avenues for future research. One insight relates to the importance of addressing the complexities of the interval cancer phenotype. Although these cancers are generally enriched for aggressive phenotypes

and hold a poor prognosis, some have a favourable biology and outcome[2]. To account for this heterogeneity, the authors excluded cancers that occurred in women with dense breasts in order to avoid confounding by indolent cancers missed or masked on a prior mammogram. The women with interval cancers included had a mean tumour size of 2 cm, ~80% had oestrogen receptor-positive disease and had, on average, one tumour-positive lymph node[9]. These distributions are in line with prior studies revealing that 70% of interval breast cancers are early stage (I or IIA)[2]. The associations with non-breast cancers might be stronger if tumour aggressiveness were more narrowly defined according to intrinsic subtype or prognostic gene signatures. Alternatively, one could use the concept of 'screening failure', defined as cancers presenting at an advanced stage (stage IIB or higher) regardless of the mode of detection[13], to enrich for aggressive cancers with a larger hereditary component in such analyses.

Although Grassmann and colleagues found no association between GRSs and interval breast cancers, it might be premature to completely disregard a role for common variants in the development of these cancers. Genome-wide association studies (GWAS) often include a large fraction of cancers with non-aggressive phenotypes, leading to the discovery of common variants that are best suited to the prediction of such cancers. The Breast Cancer Association Consortium is currently conducting GWAS aimed at identifying variants associated with intrinsic subtypes[14], and future efforts could leverage other measures of tumour aggressiveness to understand the connection between germline susceptibility factors and breast cancer intrinsic subtypes. Undiscovered variants, or a subset of previously discovered ones, might be preferentially associated with aggressive cancers. Selective inclusion of these variants could lead to the development of GRSs that are strongly associated with aggressive cancers.

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Enhancing our understanding of the genetics of aggressive cancers requires comprehensive tumour datasets combining rare and common genetic variants, deep tumour phenotyping (for example, by gene-expression profiling) and annotation of key clinical features such as mode of detection, breast density and obesity, which are factors associated with an increased risk of aggressive breast cancers. Supplemental imaging studies have shown screening ultrasonography and MRI can decrease interval breast cancer risk by as much as 50%, but to date these imaging studies have not resulted in a decrease in risk of advanced-stage cancer or lymph node-positive cancer[15]. Efforts to enrich our knowledge of the phenotypespecific risk of aggressive tumours and how these phenotypes are related to breast cancer detection and screening frequency could help to identify a group of women for whom tailored, risk-based screening may be considered.

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