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Clinical Outcomes of Breast Cancer in Women at High Genetic Risk under Structured Surveillance: Evidence from a Person-Centered Screening Program

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ABSTRACT

Data are scarce on breast cancers (BC) identified in females with elevated genetic susceptibility, and comparisons are lacking between periods before and after they entered a sustained risk-governance scheme based on genetic risk stratification. We investigated clinical endpoints within the cohort enrolled in the Phare Grand Ouest (PGO) project. The PGO project enrolls BRCA1 and BRCA2 pathogenic variant (PV) carriers, as well as high-risk females without a BRCA PV, from eight clinical cancer genetics services. The analytical dataset consisted of all women with either newly arising (incident) or pre-existing (prevalent) BC, matched 1:1 on age at first tumor detection. Associations between tumor dimensions and disease stage, and the following explanatory factors were examined using multivariable generalized linear and logistic regression models: chronological age, tumor molecular subtype, PV carrier status, incident/prevalent BC category, and measures of healthcare accessibility. Within the paired cohort, women with incident BC joined the program at a significantly younger chronological age, yet age at initial tumor discovery was similar. They bore smaller tumors, and the likelihood of being diagnosed with advanced-stage illness was roughly 30% lower relative to women in the prevalent BC group (OR = 0.29, $P < 0.01$). Early age and a triple-negative profile were both independently tied to larger tumor dimensions. Healthcare accessibility measures exerted no discernible impact. The coordinated, person-centered framework for governing high genetic risk embedded in the PGO was plausibly associated with earlier BC detection, both in PV carriers and in high-risk non-carriers. These results reinforce the incremental worth of person-focused surveillance pathways that fuse genetic risk appraisal with extended clinical monitoring, while simultaneously opening avenues for deeper exploration in this domain.

Keywords: BRCA1, BRCA2, Breast cancer, Clinical outcomes, Early detection, Genetic testing

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Introduction

Women who carry pathogenic variants (PV) in BRCA1 and BRCA2 confront a substantially higher probability of developing breast cancer (BC) than the background population. By age 80, cumulative BC risk reaches an estimated 72% (95% CI: 65%-79%) among BRCA1 carriers and 69% (95% CI: 61%-77%) among BRCA2 germline carriers [1-3]. Whether an individual learns of her germline PV is usually shaped by her family cancer history. This issue becomes especially pressing in presentations that appear sporadic, where early-onset BC itself serves as the first signal of a heritable predisposition, arising without any documented family background of breast or ovarian tumors and before the guideline-directed age for population-wide BC screening. By contrast, when BC-relevant family history data are available, clinical cancer genetics teams can furnish a formal risk estimate by applying the Breast and Ovarian Cancer Analysis of Disease Incidence and Carrier Estimation Algorithm (BOADICEA) [4, 5].

For a woman confirmed to harbor a germline PV, international recommendations advocate intensified surveillance pairing MRI with mammography to secure detection at the earliest feasible phase [6-9]. In France, bilateral prophylactic mastectomy constitutes the sole approach for reducing risk [10]. Yet committing to such a procedure requires age-attuned peer support and psychological guidance, so that any clinical recommendation remains aligned with the affected person's values and preferences [11, 12].

National French guidelines advise PV carriers to follow an intensified screening rhythm: an annual MRI plus mammogram, supplemented by clinical breast examinations every six months from age 30 to 65 years, then solely annual mammography after age 65 years [10, 13]. Even with these standards in place, a woman's awareness of bearing a markedly elevated genetic BC risk may not reliably translate into thorough adherence or demonstrably better clinical endpoints at the time of primary BC diagnosis, a gap documented even within healthcare systems conceived to provide uniform access [14, 15]. Multiple barriers prevent screening from being equally effective across the high-risk BC population [16]. These include imbalanced geographic access to services, limited MRI slot availability, insufficiently personalized protocols, and organizational fragmentation. The raison d'être of coordinated surveillance programs, therefore, is to boost adherence to screening recommendations by directly confronting organizational and access-related impediments [5, 17]. Although the benefits of population-based BC screening are robustly documented [18], there is a shortage of direct empirical evidence that screening confers comparable benefits in PV carriers. Modeling work indicates that management strategies designed for high-risk groups can be both efficacious and cost-effective [19], but such models typically assume perfect adherence [5, 20]. A real-world analysis conducted by Saule *et al*. [21] aimed to compare BC outcomes diagnosed before and after genetic risk estimation. Even so, published data remain very limited for comparing BC diagnosed before and after entry into an organized, longitudinal risk-management infrastructure rooted in genetic risk appraisal.

The present study examines the extent to which a person-centered screening infrastructure shapes clinical outcomes among women enrolled in a management program serving a high-risk genetic population.

Materials and Methods

Study population

Conceived as a coordination and risk-governance hub, the Phare Grand Ouest program (PGO) serves individuals carrying a high genetic susceptibility to a spectrum of malignancies, including BC. The program's reach extends across four western French regions, with a coordinating mandate that spans eight cancer genetics units. Eligible participants encompass germline BRCA1 and BRCA2 PV carriers (BRCA1+, BRCA2+), together with women who test negative for BRCA PV yet whose BOADICEA-derived lifetime BC probability exceeds 20% (designated High risk without BRCA) [5]. The study sample consists of all women enrolled in PGO, classified according to whether their BC was diagnosed before or after entering the risk-management framework. Women categorized as having prevalent BC received their tumor diagnosis before joining PGO. At the time of that primary diagnosis, they were not necessarily undergoing intensified surveillance, since genetic counseling was frequently initiated only after the cancer was discovered. A separate subset of women, however, had already been identified as PV carriers before their diagnosis, and their referring general practitioner or gynecologist may have launched intensified screening procedures for them. What was missing for virtually all of them was systematic, longitudinal coordination of surveillance adherence. Women categorized as having incident BC, conversely, were free of cancer when they entered the program. When their primary tumor was subsequently detected, they were not only aware of their PV carrier status but were also being actively tracked and managed within the PGO coordination framework.

Ethical agreement

This research endeavor does not qualify as a study involving human participants, in keeping with the Reference Methodology (MR-004) established by the French National Data Protection Authority (CNIL). The MR-004 framework applies to "research that does not involve human subjects, studies, or evaluations." The dataset pertains to adult women aged 18 years and above who provided written informed consent to undergo monitoring within the cancer surveillance infrastructure and did not object to their records being reused for research purposes. On 28 April 2022, formal clearance for reusing the fully anonymized dataset for research purposes and subsequent journal submission was obtained from both the Data Protection Officer (DPO) and the CREDO (Comité Recherche et Exploitation des DOnnées) at the host data center (Eugene Marquis Cancer Center) (N°T-411).

Genetic testing

Once written informed consent had been secured, genetic testing was undertaken through the cancer genetics units. Isolation of genomic DNA from peripheral blood samples was followed by germline screening for pathogenic variants in BRCA1 and BRCA2, performed within certified testing platforms of the GGC-UNICANCER network. Every step of these processes adheres to the frameworks set forth by the INCa (French National Institute for Cancer) and UNICANCER. At the time of analysis, both gene sequencing and assessments for major rearrangements were conducted according to the standard methodologies then in routine use.

PGO: a person-centered risk management and coordination program

Within the French system, cancer genetics clinics generally supply counseling and diagnostic testing, yet they seldom incorporate systematic, longitudinal risk governance once a pathogenic variant is substantiated. The PGO coordination program was expressly created to rectify the mismatch between a momentary diagnostic event and protracted screening. Patient navigation fabricates a functional thread of care that ties together medical imaging facilities, GPs, gynecologists, and other clinical sectors. Whether at intake or during subsequent follow-up encounters, coordinators compile data covering comorbidities, prior malignancies, barriers to healthcare access, and individual constraints. These inputs are then harnessed to recalibrate person-centered, risk-tailored screening roadmaps. Institutional factors, notably a regimented recall infrastructure, have emerged as a decisive element underpinning adherence to the PGO framework [5]. Women are encouraged to maintain regular dialogue with coordinators and to transmit their imaging documentation, thereby fostering an interactive feedback cycle that nurtures self-determination and helps overcome psychological impediments [12, 22]. The literature addressing person-centered care for those who carry a BRCA pathogenic variant underscores “the need for emotional support, empathy, and respect” [23]. In line with this, screening coordination within PGO eschews a paternalistic oversight model in favor of an adaptive paradigm. It embeds personal realities — such as screening choices or rejections, the reachability of medical infrastructure, and domestic duties — inside a holistic decisional calculus. Should medical or life situations become transiently incompatible with BC screening (for instance, pregnancy, lactation, or therapy directed at another tumor type), coordinators can advise postponement until circumstances again permit screening. The ensuing screening milestones are thus rescheduled. After each screening cycle concludes, coordinators consolidate the MRI and mammography results, prepare technical reports in accessible language, and outline future steps. Far from banking on the expectation that women will passively follow clinical advice by making appointments with their GP, the screening coordination unit adopts a forward-leaning approach. This methodology is intended to equip women with agency and to advance their independence in governing their personal health and wellness.

Matching

We began by designating every woman tracked within the PGO initiative who subsequently experienced an incident BC. For each such case, a 1:1 age-matched pair was selected from the prevalent BC pool to identify women with a primary diagnosis. The pathogenic variant class was likewise used as a matching variable. When an exact match for variant type could not be realized owing to constraints in sample numbers, priority was assigned to alignment on age.

Outcomes and explanatory variables

Population characteristic data were drawn from the PGO registry. The principal study endpoints comprised clinicopathological attributes of BC, compiled from medical records. Staging followed the ESMO consensus guidelines for BC [24]. Death from any cause constituted the secondary endpoint. The registry was updated to embed the latest mortality intelligence by linking records to MatchID, a freely queryable tool for identifying deceased persons built on INSEE (the French national statistics and economic studies institute) death archives. We also make note of potential case overdiagnosis [25, 26].

Among explanatory covariates, two area-level variables were incorporated into regression models to account for geographic asymmetries in medical resources — for instance, GP availability and the presence of imaging technology in sparsely populated zones. These were the Local Potential Accessibility (LPA) score, which captures spatial ease of reaching private-practice GPs standardized by municipal age distribution [27], and MRI density, operationalized as the volume of MRI examinations per 200,000 residents within the county of domicile [28].

Statistical analysis

Summary statistics were applied to characterize the study sample, expressing continuous variables as median and interquartile range (IQR) and categorical variables as absolute counts and percentages. Contrasts in clinical and histopathological profiles between the incident and prevalent BC strata were probed using Kruskal-Wallis and Fisher's exact tests. A two-tailed p-value falling below 0.05 was taken to denote statistical significance. Graphical plots visualized age at primary diagnosis and tumor dimensions stratified by prevalent versus incident BC classification. A survival investigation was undertaken, using the Kaplan–Meier estimator for all-cause mortality within the prevalent BC set and across BRCA1/2 pathogenic variant subgroups, with divergences assessed using the log-rank test.

For multivariable modeling, a generalized linear model (GLM) with a logarithmic link and gamma error distribution was fitted, with tumor size as the dependent variable. The model incorporated the following predictors: age at primary diagnosis (continuous), TNBC designation (Yes/No), pathogenic variant carrier status, prevalent/incident BC grouping, LPA score (continuous), and MRI unit density. The identical predictor set was carried over into a logistic regression formulation in which cancer stage acted as the binary response. In line with the most current scholarship, stages 0 and I were collapsed into the earlier BC (0) category, whereas stages II, III, and IV were grouped as advanced disease (1) [21, 24]. All statistical processing was performed with the STATA® 19 software suite.

Results and Discussion

From January 2011 through June 2022, the PGO program incorporated 1,233 women. **Figure 1** illustrates that among these, 526 (43%) carried a diagnosis of prevalent BC upon entry, 65 (5%) received an 'incident' BC diagnosis during the surveillance period, and 642 (52%) stayed cancer-free. Those diagnosed with incident BC tended to be younger at the point of enrollment (median age 42.2, IQR = 37.6—51.6) relative to women bearing prevalent BC (median age at enrollment 49.9, IQR: 42.3-57.8). Examining the matched subset (n = 129), women with incident BC were significantly younger (P < 0.01) than those with prevalent BC (median age at enrollment: 55.9, IQR: 47.5–62.7); indeed, 38% had not yet reached age 40 **(Table 1).** Age at the time of primary detection did not differ meaningfully between the two arms (median age at enrollment: 45.4, IQR: 39.3–56.8; 47.1, IQR: 40.6–56.0; P = 0.50), and diagnoses occurring before age 50 years accounted for 63% of both groups. The time elapsed between first diagnosis and PGO enrollment proved shorter for the incident BC arm (median: 3.3 years, IQR: 1.4–6.6) than for the prevalent BC arm (median: 6.0 years, IQR: 3.3 – 10.7) **(Table 1).** Pathogenic BRCA1/2 variants were identified in 71% of the full cohort, with BRCA1 PV showing a slight excess among incident BC cases; however, within the matched dataset, the mutational profile did not distinguish incident and prevalent cases (P = 0.97) **(Table 2).**

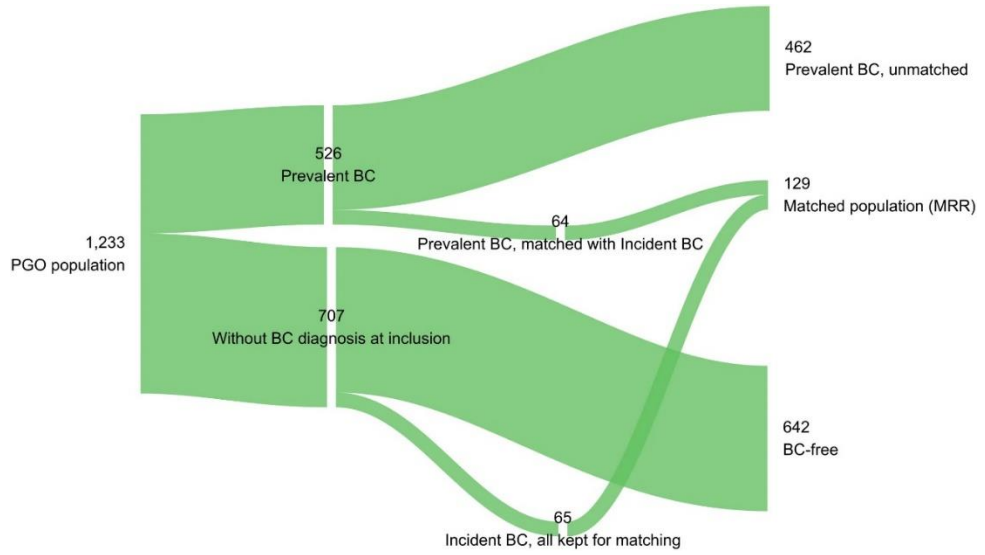

Figure 1. Sanky flow diagram of the study population (BC, breast cancer; MRR, medical record review).

Table 1. Patient characteristics of the matched cohort.

Clinical and demographic characteristics of prevalent and incident breast cancer cases					
Variable	**P-value**	**Incidental breast cancer**		**Prevalent breast cancer**	
		N	(%)	N	(%)
Total		65	(100)	64	(100)
Age at inclusion (years)					
Age group	**P-value**	**Incident BC**		**Prevalent BC**	
< 40 years		25	(38)	6	(9)
40–49 years		21	(32)	14	(22)
≥ 50 years		19	(29)	44	(69)
Median (IQR)	< 0.01	42.2 (37.6–51.6)		55.9 (47.5–62.7)	
Pathogenic variant status					
Genetic category	**P-value**	**Incident BC**		**Prevalent BC**	
BRCA1 positive	0.97	33	(51)	31	(48)
BRCA2 positive		26	(40)	26	(41)
High-risk without a BRCA pathogenic variant		6	(9)	7	(11)
Age at primary breast cancer diagnosis					
Age group	**P-value**	**Incident BC**		**Prevalent BC**	
< 40 years		16	(25)	18	(28)
40–49 years		25	(38)	22	(34)
≥ 50 years		24	(37)	24	(38)
Early-onset breast cancer (<50 years)		41	(63)	40	(63)
Late-onset breast cancer		24	(37)	24	(38)
Median (IQR)	0.50	47.1 (40.6–56.0)		45.4 (39.3–56.8)	
Time between primary diagnosis and inclusion					
Time interval	**P-value**	**Incident BC**		**Prevalent BC**	
< 5 years		42	(65)	27	(42)
5–10 years		22	(34)	20	(31)
> 10 years		1	(2)	17	(27)
Median (IQR)		3.3 (1.4–6.6)		6 (3.3–10.7)	
Vital status (all-cause mortality)					
Outcome	**P-value**	**Incident BC**		**Prevalent BC**	
Death (Yes)		1	(2)	7	(11)
Death (No)		64	(98)	57	(89)

H. risk w/o BRCA PV, High risk without BRCA PV.

Histological features were broadly alike across the incident and prevalent BC arms. Unilateral, invasive ductal carcinomas constituted the bulk of the tumor burden. High-grade invasive lesions were numerically dominant on histoprognostic grading (58–67%). Ductal carcinoma in situ occurred at a somewhat higher frequency in the incident arm than in the prevalent arm (15% versus 8%), though this difference did not reach statistical significance **(Table 2).** T1a-b primary tumors, denoting smaller lesion sizes, were considerably more commonplace among women with incident BC than among those with prevalent BC (58% and 10%, respectively). Node-negative status (N0) was documented at a significantly higher rate in the incident arm relative to the prevalent arm ($P < 0.001$). Early-stage BC comprised upward of three-quarters of incident diagnoses but fell short of half among prevalent diagnoses ($P < 0.001$) **(Table 3).** This stark contrast, visualized in **Figure 2**, stems from a consistently narrower distribution of tumor sizes across the age continuum in the incident arm compared with the prevalent arm. Tumor phenotype profiles did not materially differ between arms ($P = 0.42$). Triple-negative disease was pervasive in both the prevalent and incident subgroups (55% and 42%, respectively). Conversely, HR+/HER2- tumors presented more often within the incident arm (51% versus 36%), while HER2+ cases remained uncommon in both **(Table 3)**. **Figure 3** charts overall survival according to BRCA PV carrier status within the prevalent BC subset ($n = 526$). A trend toward diminished survival was observed among BRCA2 PV

carriers compared with BRCA1 carriers and high-risk women lacking a BRCA PV, although this did not reach statistical significance **(Figure 3).**

Table 2. Clinical characteristics of the matched cohort.

Clinicopathological characteristics of prevalent and incident breast cancer cases					
Variable	**P-value**	**Incident BC**		**Prevalent BC**	
		N	(%)	N	(%)
Total		65		64	
Pathogenic variant status					
Category	**P-value**	**Incident BC**		**Prevalent BC**	
BRCA1 positive	0.97	33	(51)	31	(48)
BRCA2 positive		26	(40)	26	(41)
High-risk without a BRCA pathogenic variant		6	(9)	7	(11)
Tumor laterality					
Side of the tumor	**P-value**	**Incident BC**		**Prevalent BC**	
Right-sided	0.99	28	(43)	29	(45)
Left-sided		35	(54)	34	(53)
Bilateral		2	(3)	1	(2)
Missing data		0		0	
Invasive tumor grading					
Grade	**P-value**	**Incident BC**		**Prevalent BC**	
Low grade	0.71	7	(13)	4	(7)
Intermediate grade		15	(28)	14	(26)
High grade		31	(58)	36	(67)
Missing data		12		10	
Presence of an in situ tumor					
Status	**P-value**	**Incident BC**		**Prevalent BC**	
Present	0.27	10	(15)	5	(8)
Absent		55	(85)	59	(92)
Grade of in situ tumor					
Grade	**P-value**	**Incident BC**		**Prevalent BC**	
Total cases		10	(100)	5	(100)
Low grade	0.99	0	(0)	0	(0)
Intermediate grade		4	(40)	2	(40)
High grade		6	(60)	3	(60)
Histological subtype					
Histology	**P-value**	**Incident BC**		**Prevalent BC**	
Ductal carcinoma	0.73	57	(88)	56	(89)
Lobular carcinoma		3	(5)	1	(2)
Other types		5	(8)	6	(10)

H. risk w/o BRCA PV, High risk without BRCA PV.

Table 3. Clinical characteristics of the matched cohort.

Variable	**P-value**	**Incident BC**		**Prevalent BC**	
		N	(%)	N	(%)
Primary tumor (T stage)					
T stage	**P-value**	**Incident BC**		**Prevalent BC**	
Tis		10	(15)	5	(8)
T1mi		4	(6)	0	(0)
T1a		23	(35)	2	(3)
T1b		15	(23)	4	(7)
T1c		1	(2)	28	(47)

T2		12	(18)	20	(33)
T3–T4		0	(0)	1	(2)
Missing data		0		4	
Tumor size (mm)					
Measure	**P-value**	**Incident BC**		**Prevalent BC**	
Median (IQR)	< 0.001	10 (7–17)		16 (15–30)	
Missing data		0		4	
Regional lymph node status (N stage)					
N stage	**P-value**	**Incident BC**		**Prevalent BC**	
N0	< 0.001	58	(89)	41	(67)
N1		7	(11)	20	(33)
Missing data		0		3	
Distant metastasis (M stage)					
M stage	**P-value**	**Incident BC**		**Prevalent BC**	
M0	< 0.001	65	(100)	60	(98)
M1		0	(0)	1	(2)
Missing data		0		3	
Overall cancer stage					
Stage	**P-value**	**Incident BC**		**Prevalent BC**	
0	< 0.001	10	(15)	5	(8)
I		40	(62)	24	(40)
II		15	(23)	29	(48)
III		0	(0)	1	(2)
IV		0	(0)	1	(2)
Missing data		0		4	
Tumor phenotype					
Subtype	**P-value**	**Incident BC**		**Prevalent BC**	
HER2 positive	0.42	4	(7)	5	(9)
HR-/HER2- (TNBC)		23	(42)	31	(55)
HR+/HER2-		28	(51)	20	(36)
Missing data		10		8	
Ki-67 (20% cutoff)					
Ki-67 status	**P-value**	**Incident BC**		**Prevalent BC**	
Negative	< 0.001	6	(22)	2	(17)
Positive		21	(78)	10	(83)
Missing data		38		52	

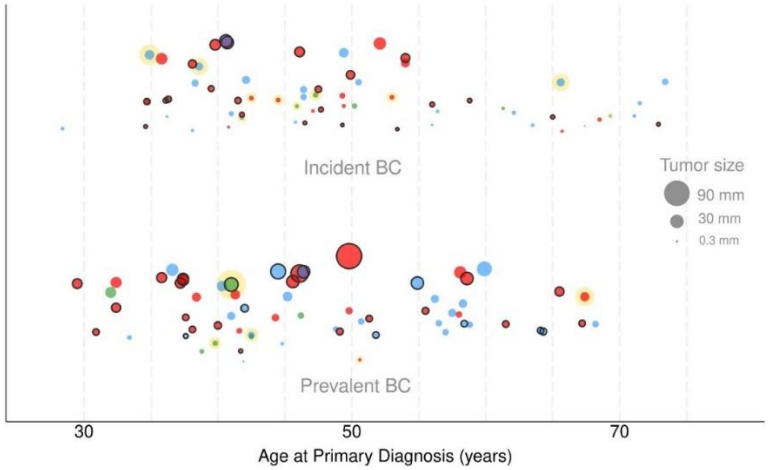

Figure 2. Frequency distribution of the tumor location among colorectal cancer patients in Qatar during 2023 (n = 169).

Figure 2. Tumor size and age at primary diagnosis, by prevalent/incident BC status. (BC, breast cancer; tumor size is represented by different-sized circles, applying a weighted scale; red – BRCA1+, blue – BRCA2+, green – high-risk without BRCA PV; black outline – triple-negative BC, without outline – HR+ or HER2+ BC; yellow halo – in situ BC, without halo – invasive BC).

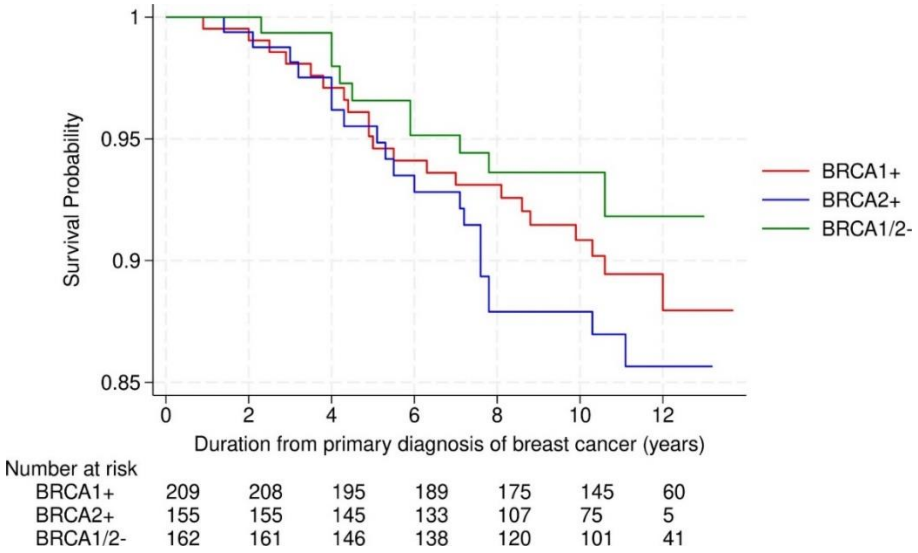

Figure 3. Kaplan–Meier survival curves for all-cause mortality in the prevalent BC sub-population (n = 526). H. risk w/o BRCA PV, High risk without BRCA PV.

Table 4 summarizes the multivariable modeling of contributors to tumor dimensions and disease stage. After controlling for the remaining covariates, an inverse relationship emerged between age at primary detection and tumor dimensions (P = 0.02), suggesting that younger age at diagnosis was associated with larger tumor bulk. A TNBC phenotype was also independently associated with larger tumor size (P = 0.04), whereas belonging to the incident BC group was associated with substantially smaller tumor measurements in the GLM framework. The relative odds of harboring advanced-stage malignancy stood at 0.29 in the incident arm relative to the prevalent arm (OR = 0.29, 95% CI: 0.12-0.66, P < 0.01). Women carrying a BRCA1 PV had approximately 15-fold higher odds of receiving an advanced-stage BC classification than high-risk women lacking a BRCA1 PV (OR = 14.92, 95% CI: 1.60 to 138.90, P = 0.02). Neither BRCA2 PV carriage nor age at diagnosis yielded statistically significant associations in these adjusted models. In parallel, GP accessibility and MRI unit density showed no meaningful influence. Two participants in the incident group who were older than 65 years at diagnosis presented with carcinoma in situ, which could conceivably be flagged as instances of overdiagnosis **(Figure 2).**

Table 4. Multivariable analysis.

Covariate	Cancer stage (Logistic regression)				Tumor size (Generalized linear model)			
	Coefficient (95% CI)	p-value	z	SE	Coefficient (95% CI)	p-value	z	SE
Age at primary diagnosis (continuous)								
Variable	**Cancer stage model**				**Tumor size model**			
Age (continuous)	0.97 (0.93 to 1.01)	0.13	-1.53	0.02	-0.01 (-0.02 to -0.02)	0.02	-2.34	0.01
Triple-negative breast cancer (TNBC)								
Category	**Cancer stage model**				**Tumor size model**			
Yes	1.58 (0.65 to 3.82)	0.31	1.02	0.71	0.24 (0.01 to 0.47)	0.04	1.00	0.12
No (reference)	–	–	–	–	–	–	–	–
Mutation status								

Category	Cancer stage model				Tumor size model			
BRCA1 positive	14.93 (1.61 to 138.90)	0.02	2.38	16.99	0.26 (-0.12 to 0.63)	0.18	1.35	0.19
BRCA2 positive	8.24 (0.89 to 75.93)	0.06	1.86	9.34	0.27 (-0.10 to 0.64)	0.15	1.43	0.19
High-risk without BRCA pathogenic variant (reference)	–	–	–	–	–	–	–	–
Breast cancer status (prevalent vs incident)								
Category	**Cancer stage model**				**Tumor size model**			
Incidental breast cancer	0.29 (0.13 to 0.66)	< 0.01	-2.94	0.12	-0.48 (-0.69 to -0.27)	< 0.001	-4.51	0.11
Prevalent breast cancer (reference)	–	–	–	–	–	–	–	–
Local potential accessibility (continuous)								
Variable	**Cancer stage model**				**Tumor size model**			
Accessibility index	1.10 (0.73 to 1.69)	0.66	0.44	0.24	0.09 (-0.02 to 0.20)	0.13	1.53	0.06
MRI availability (per 200,000 inhabitants)								
Variable	**Cancer stage model**				**Tumor size model**			
MRI units	1.05 (0.59 to 1.87)	0.87	0.17	0.31	0.03 (-0.11 to 0.17)	0.68	0.42	0.07
Intercept								
Model	**Cancer stage model**				**Tumor size model**			
Intercept	0.26 (0.01 to 6.95)		-0.80	0.44	2.94 (2.26 to 3.61)	< 0.001	8.49	0.35

H. risk w/o BRCA PV, High risk without BRCA PV.

The central objective of this work was to generate real-world data speaking to whether BC uncovered while a patient is under the supervision of a coordinated risk-governance initiative materially diverges from BC identified in the absence of such structured oversight. Our evidentiary base was drawn from women carrying a confirmed elevated BC predisposition, ascertained via oncogenetic evaluation and germline analysis. We documented appreciably more favorable tumor dimensions and disease stage at the point of first detection among malignancies captured during active program-based monitoring. These results collectively signal that this breed of risk-management platform, built on genetic diagnostics, has a strong chance of being clinically impactful in enabling earlier capture of BC cases driven by heritable mutations.

To contend with the reality that prevalent BC cases were struck by cancer at an earlier chronological point than incident BC cases, age at primary diagnosis was used as the basis for matching before any chart abstraction. Across the matched set, women in the incident BC arm were younger at program entry than their prevalent BC counterparts, a finding that aligns with the slightly elevated share of BRCA1 PV carriers and the younger tumor-onset characteristic of this genotype. Incident tumors were more apt to be categorized as stage 0-I and manifested more compact sizes, contrasting sharply with prevalent tumors, which tended to occupy more advanced stages. This differential proved statistically robust and held steady whether examined through unadjusted or adjusted analytic lenses. Even after disentangling the role of clinical variables known to shape tumor stage — such as age at first diagnosis, triple-negative designation, and PV carrier type — involvement in the risk-governance program appeared to foster earlier malignancy ascertainment independently. Notably, the area-based characteristics capable of influencing the promptness of BC detection, entered into models as statistical controls, namely measures of healthcare accessibility, showed no statistically significant correlation with tumor dimensions or stage at presentation. On the clinical features front, the overwhelming majority of BCs across both arms were unilateral

invasive ductal carcinomas, HER2+ tumors represented a small minority, and no statistically reliable distinctions separated incident from prevalent cases. The comparatively modest cell sizes within certain analytical strata may partly underlie this absence of detectable divergence. We had hypothesized that BRCA1 carriers would exhibit a more aggressive BC disease trajectory, given the known overrepresentation of triple-negative tumors in this group [29]. The data did not confirm this expectation. Despite the constraints imposed by a limited number of observations, ductal carcinoma in situ — an entity viewed as a very early BC form — was picked up at double the frequency in the incident arm relative to the prevalent arm [25]. The findings also illuminate a telling dynamic in the prevalent BC subgroup, which, as already observed, comprised women who received their diagnosis at a considerably younger age than the incident subgroup. This phenomenon very plausibly captures the scenario in which early-onset BC, arising in the absence of any suggestive familial background, acts as the de facto sentinel event revealing an occult hereditary predisposition.

Earlier scholarship has approached the characterization of BC in BRCA1/2 carriers through two dominant comparative frameworks: imaging-detected lesions versus interval cancers, and tumors diagnosed before versus following genetic testing [13, 21]. These earlier contributions yielded congruent evidence that earlier-stage detection tracks with more contained disease, paralleling our observation that incident tumors were more often classified as stage 0-I and were smaller in diameter. This pattern diverges from that seen in the matched prevalent BC group, which was defined by comparatively advanced-stage disease. The current study adds fresh perspectives to the accumulated body of work in this arena. To begin with, the analytical emphasis fell squarely on the specific contribution of a structured risk-governance apparatus. Earlier designs separated study arms based on whether subjects received genetic testing paired with intensive screening or no such testing [21, 30]. This analysis pivots to a subsequent phase, contrasting outcomes with and without ongoing follow-up, anchored in a risk-management framework that delivers a person-centered, continuous-care trajectory. The encouraging clinical endpoints observed within the PGO framework most plausibly reflect its person-focused coordination blueprint. Beyond this, our investigation furnishes pragmatic, real-world corroboration for patterns previously documented in the general screening-eligible population, where fidelity to nationwide screening recommendations has been correlated with BC detected at more favorable clinical stages [18]. This body of empirical observations thus holds particular value in enriching the modeling-driven cost-effectiveness literature [19]. Within the incident BC arm, two women exceeding 65 years of age who were found to harbor carcinoma in situ could constitute overdiagnosed cases [25, 26]. The definitive yardstick for quantifying overdiagnosis remains the conduct of a randomized controlled trial juxtaposing cumulative incidence figures in screened against unscreened arms; this represents an avenue compelling enough for future work. However, overdiagnosis entails incremental economic expense and detracts from quality of life; earlier cost-effectiveness evaluations of intensified screening protocols omitted consideration of this facet [16, 19, 25, 26, 30]. Upcoming economic appraisals specific to the PGO model could incorporate these inputs to arrive at a more complete assessment of the program's overall merit.

This analysis is subject to several limitations. The study draws heavily on group sample sizes that mirror the reality that, unlike the population-wide BC screening apparatus, France currently lacks a single, nationally unified scheme addressing high genetic BC risk. At present, 17 separate programs at either the regional or inter-regional level serve this very-high-risk segment. Heterogeneity within the high-risk non-carrier subgroup represents another concern, given that BC risk was calculated using the BOADICEA algorithm, which remains unrefined by the inclusion of environmental exposures or polygenic risk scores (PRS). It is worth noting, however, that an investigation by Bhatt *et al*. [4] probing whether PRS and other risk determinants influence BC progression reported negligible differences in sojourn time between low- and high-risk strata defined by PRS. Because of specific features of both the population under surveillance and the program's architecture, we advocate that subsequent evaluations of program impact adopt a more multidimensional approach. One concrete avenue would be to mount qualitative research exploring women's lived experiences and perceptions. The PGO initiative was deliberately conceptualized as a person-centered risk-governance instrument intended to operate within the cancer genetics units responsible for conveying genetic findings to patients. To fully appraise the phases that follow from awareness of genetic status — encompassing patients' values and choices linked to autonomy, patterns of screening uptake, and the sustained support required along an extended care trajectory — access to both qualitative descriptors and quantitative metrics would be immensely advantageous. Finally, we operationalized patients' socioeconomic circumstances and related contextual features through geographically aggregated variables. A preferable methodological approach would be to adopt an address-level deprivation index to mitigate ecological bias [31, 32].

Beyond health outcomes alone, a substantial strength of this work lies in its augmentation of the thin empirical record on screening-associated effects among women who carry BC-linked BRCA1 and BRCA2 PV. Hard data for this precise demographic are in short supply. The present analysis brings to the literature a contemporaneous update and a detailed assessment of one of the regional high-risk genetic screening programs operating in France. The patterns distilled here have the potential to deepen the collective understanding of the clinical and genetic phenotypes that accompany BC, as revealed through structured, person-centered risk screening. Such a deepened understanding could, in turn, smooth the path toward optimized long-term monitoring strategies for women bearing a high genetic BC susceptibility. Moreover, the results cast a spotlight on the practical benefit of mining programmatic data gathered in routine practice to sharpen screening recommendations and to more faithfully estimate the tangible returns of high-risk surveillance when it is implemented under real-world conditions [5, 20]. Bringing the threads together, this dissection of the PGO cohort highlights the clinical and genetic signatures of BC arising against a structured surveillance backdrop, compared with those diagnosed before intake into the program. The inquiry provides novel insights into breast cancers detected through person-centered risk-governance platforms and lends weight to calls for further prospective evaluation of their capacity to deliver sustained effectiveness in the preventive management of high genetic BC risk.

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