Research Square

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Multi-cancer screening patterns and gaps among pathogenic variant carriers and non- carriers in a diverse high-risk registry

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Abstract

Background

Genetic cancer risk clinics offer risk assessment and management strategies for high-risk populations. Evidence suggests missed opportunities for comprehensive genetic testing and multi-cancer screening. This study aims to examine comprehensive cancer screening uptake in relation to carrier status of pathogenic variant or likely pathogenic variant (PV/LPV) in cancer predisposition genes among high-risk individuals.

Methods

Between July and September 2023, we conducted a survey study among participants enrolled in the University of Chicago Cancer Prone Study, a registry of diverse high-risk families who were counseled and received testing results from a cancer geneticist. Carrier status of PV/LPV in cancer predisposition genes, penetrance level of genes, and screening for breast, ovarian, cervical, colorectal, prostate, and lung cancers were assessed.

Results

Of 912 participants (mean age 58.2 years [SD, 13.5]), 80.4% were female; 39.4% are PV/LPV carriers and of whom, 78.1% carry a high-penetrant gene. Cancer screening uptake varied by cancer type and penetrance level of genes. In the cancer-specific adjusted models, carriers had higher odds of having screened for breast cancer (MRI: adjusted odds ratio [AOR], 30.86; 95% CI, 10.14–93.84), ovarian cancer (CA-125 blood test: AOR, 5.84; 95% CI, 2.48–13.75), and colon cancer (colonoscopy: AOR, 6.90; 95% CI, 2.89–16.49) than non-carriers. The odds of having screened for cervical cancer (HPV testing: AOR, 1.33; 95% CI, 0.87–2.05), prostate cancer (PSA test: AOR, 0.95; 95% CI, 0.33–2.69), and lung cancer (low-dose CT: AOR, 1.13; 95% CI, 0.66–1.93) between carriers and non-carriers were not statistically significant.

Conclusion

This study highlights varying uptake of cancer screening and the need to evaluate significant gaps in prevention and practice that impact genetic testing and multi-cancer screening among high-risk individuals. It’s critical that cancer risk clinics work with patients and advocates who are community facing and enhance their partnerships with local organizations to help increase awareness of genetic testing and cancer screening for high-risk individuals in the community.

Introduction

In the United States (U.S.), it is estimated that more than 2 million adults were diagnosed with cancer in 2025.[1] Specifically, prostate, lung, and colorectal cancers accounted for 49% of the new cancer cases among men, whereas breast, lung, and colorectal malignancies accounted for 51% of cancer incidence among women in 2025.[1] Screening guidelines and practices vary across populations, including persons at average risk and high risk, such as those with genetic, personal and/or family history of cancer, lifestyle behavioral factors, and environmental precursors. Prior studies have explored factors associated with cancer genetic testing and disclosure and uptake of cancer screening and risk-reduction interventions among individuals at a high risk for cancer.[2,3] Age, race, ethnicity, socioeconomic status, and pathogenic variant or likely pathogenic variant (PV/LPV) in cancer predisposition genes have been linked to prevention-seeking behaviors, including genetic testing and cancer screening.[2–4]

According to a recent report from the American Cancer Society, the prevalence of screening for breast, cervical, colorectal, lung, and prostate cancers at the population level remain suboptimal and vary widely by sex, by race/ethnicity, and/or by state in the US.[5] Genetic cancer risk clinics provide risk assessment, preventive services, genetic counseling, and risk management and interventions for people with a high cancer risk. These programs are both interdisciplinary and multidisciplinary in nature. However, current evidence demonstrates a missed opportunity to comprehensively raise awareness and knowledge of genetic testing and cancer risk as well as screening for, detecting and preventing many major types of cancers.[6,7] To address the paucity of data on genetic risk and multi-cancer screening in the literature, the current study aims to examine the uptake of screening for breast, cervical, ovarian, colorectal, prostate, and lung cancers, and the relations to carrier status of PV/LPV in cancer predisposition genes among high-risk individuals in a diverse registry cohort.

Materials and methods

Study design and population

This study used a cross-sectional design, with genetic testing data verified through patients' electronic health records. Between July and September 2023, we surveyed high-risk individuals enrolled in the University of Chicago Cancer Prone Study (UCCPS). UCCPS is a hospital-based registry initiated in 1992 that had enrolled more than 5,00 high-risk participants as of September 2024. A total of 2,404 email invitations and 611 mail invitations were sent to participants with available contact information documented in the study database or clinical records. However, 325 patients could not be reached due to undeliverable mailing addresses. Upon survey closure, we received a total of 912 returned questionnaires from respondents. The University of Chicago Institutional Review Board reviewed and approved the conduct of both UCCPS and this study. All participants provided written informed consent to the UCCPS registry and follow-up surveys. This study followed the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) reporting guidelines.[8]

Independent variable and covariates

Carrier status of PV/LPV was the main independent variable, which was assessed by asking individuals whether they had been told by a genetic counselor or health provider that they had a gene variant(s) or change(s) that increase their risk of cancer. Further, carriers were asked about the specific PV/LPV in cancer predisposition genes they carry, and were classified the cancer predisposition genes into either high or moderate level of penetrant genes according to known clinical actionability and cancer-specific risk (**Supplementary Table 1**). Demographic and socioeconomic covariates included age at time of survey, sex assigned at birth (female or male), race and ethnicity (non-Hispanic Asian, non-Hispanic Black, Hispanic, or non-Hispanic White), marital status (married, single, divorced or separated, or widowed), level of educational attainment (high school or less, post-high school or some college, Associate's degree, Bachelor's degree, or graduate or professional degree), health insurance coverage (Medicaid, Medicare, private, other, or uninsured), annual household income (<$50,000, $50,000-$74,999, $75,000-$99,999, $100,000-$149,999, $15,000-$199,999, or ≥$200,000), and smoking status (past, current, or never).

Outcomes and measures

Our survey assessed screening for breast, cervical, ovarian, colorectal, prostate, and lung cancers. Participants were asked 1) whether they had been screened for any of the cancers above; 2) the type of screening exam(s) they received which was specific to each cancer type; 3) their most recent screening exam or test; 4) their age at first screening exam; and 5) whether a health provider had recommended annual screening or testing. For breast cancer screening, methods included mammogram, magnetic resonance imaging (MRI), ultrasound, and clinical breast exam. Cervical cancer screening approaches included Pap smear and human papillomavirus (HPV) testing. For ovarian cancer, transvaginal ultrasound and the cancer antigen-125 (CA-125) blood test were assessed. Regarding colorectal cancer, we included colonoscopy, sigmoidoscopy, computed tomography (CT) colonography or virtual colonoscopy, fecal occult blood test or fecal immunochemical (FIT) test, and Cologuard stool DNA test. For prostate cancer, the testing of interest was prostate-specific antigen (PSA). For lung cancer, exposure to smoking as a risk factor was probed, along with the use of a low-dose CT scan.

Statistical analysis

Summary statistics were calculated and used to describe the study sample, overall and by carrier status. We performed bivariate analyses using *t*-test, Wilcoxon rank-sum test, Chi-squared test, ANOVA, or Fisher's exact test where appropriate. To examine the associations between carrier status of PV/LPV in cancer predisposition genes and cancer screening uptake, separate multivariable logistic regression models were fit for various types of cancer screening. Each model was both cancer- and test-specific, with the consideration of participants who carry a PV/LPV in cancer predisposition genes. Additionally, regression analyses of breast and ovarian cancer screening were limited to those who did not undergo a

mastectomy and/or an oophorectomy. When modeling for prostate cancer screening, the sample was restricted to individuals who were male sex in participant records. For cervical and ovarian cancer screening, the regression models included only participants who identified as female sex. A stepwise regression model-building approach was deployed. Specifically, Model 1 included only age, given that it's a key risk factor for cancers; and Model 2 additionally adjusted for race and ethnicity, marital status, level of educational attainment, health insurance coverage, and annual household income. For colorectal and lung cancers, we also included sex variables in Model 2. For low-dose CT scan, we fit a third model further controlling for smoking status because of the well-known risk factor for lung cancer. Adjusted odds ratios (AOR) and 95% confidence intervals (95% CI) were generated and reported. A *P* value of < 0.05 was considered statistically significant. All hypothesis tests were two-sided, and all analyses were performed using Stata version 18.0 (StataCorp LLC, College Station, TX).

Results

Cohort characteristics

Of the 912 study participants included (**Table 1**), the mean age was 58.2 years (SD, 13.5) overall; 39.4% (n = 333) reported carrying a PV/LPV in cancer predisposition genes; 80.4% were female; 3.2% identified as non-Hispanic Asian, 10.3% as non-Hispanic Black, 3.9% as Hispanic, and 82.7% as non-Hispanic White. 44.3% of the participants reported obtaining a graduate or professional degree; 30.7% reported having an annual household income of ≥$200,000. 63.3% and 31.4% were privately insured and on Medicare/Medicaid, respectively. Among carriers, 39.0% have a *BRCA1* (n = 70 [21.0%]) or *BRCA2* (n = 60 [18.0%]) gene mutation, followed by 7.2% (n = 24) *CHEK2*, 5.4% (n = 18) *APC*, 5.4% (n = 18) *ATM*, 4.5% (n = 15) *MSH2*, 3.9% (n = 13) *PALB2*, 3.6% (n = 12) *MLH1*, 3.6% (n = 12) *MSH6*, 2.7% (n = 9) *CDH1*, and 1.2% (n = 4) *TP53* (**Supplementary Table 2**).

Compared to non-carriers, PV/LPV carriers were younger (mean age, 55.4 years [SD, 14.0] vs. 60.0 years [SD, 13.0]; *P* <0.001) and privately insured (69.2% vs. 60.2%; *P* = 0.001) (**Table 1**); and were more likely to have received recommendation for annual screening breast MRI from a provider (36.4% vs. 15.3%; *P* <0.001), have undergone a mastectomy for prophylactic (26.6% vs. 0.0%; *P* <0.001) or therapeutic indications (30.3% vs. 9.5%; *P* <0.001). Similarly, salpingo-oophorectomies were more prevalent in PV/LPV carriers than in non-carriers (57.7% vs. 24.7%; *P* <0.001), were mostly bilateral (93.6% vs. 85.4%, *P* = 0.04), and for prophylactic reasons (89.7% vs. 81.5%; *P* <0.001) (**Supplementary Table 3**).

Uptake and patterns of cancer screening

Breast cancer

A significantly higher percentage of PV/LPV carriers underwent a breast MRI than that of non-carriers (87.2% vs. 24.1%; *P* <0.001); the distribution of having a mammogram was similar between carriers and non-carriers (84.6% vs. 86.7%; *P* = 0.72) (**Figure 1**). 51.1% had an ultrasound, with no difference observed between carriers and non-carriers (**Supplementary Table 4**). The majority (82.2%) had a mammogram

less than 1 year ago, and 41.8% had an MRI in the last 6 months. PV/LPV carriers reported breast cancer screening (both mammogram and MRI) at a younger age than non-carriers (**Table 2**). In the adjusted models (Model 2), PV/LPV carriers had significantly greater odds of having undergone a breast MRI than non-carriers (AOR, 30.86; 95% CI, 10.14-93.84; *P* <0.001). The odds of having a mammogram were also higher in carriers than non-carriers, though this difference was not statistically significant (AOR, 2.92; 95% CI, 0.83-10.24; *P* = 0.09) (**Table 3**).

Cervical cancer

The percentage of having received a Pap smear was similar between PV/LPV carriers and non-carriers (86.8% vs. 88.8%; *P* = 0.47); whereas carriers reported a significantly higher proportion of HPV testing than non-carriers (29.0% vs. 21.1%; *P* = 0.04) (**Figure 1**). Overall, 31.9% received a Pap smear a year ago, and 30.3% had an HPV test within the last year. There was no difference in the age of first cervical cancer screening between carriers and non-carriers (mean age, 24.2 years [SD, 7.6] vs. 24.7 years [SD, 9.1]; *P* = 0.60) (**Table 2**). On multivariable analyses (Model 2), the odds of having received a Pap smear (AOR, 0.72; 95% CI, 0.40-1.29; *P* = 0.27) or HPV testing (AOR, 1.33; 95% CI, 0.87-2.5; *P* = 0.19) were not statistically significantly different between PV/LPV carriers and non-carriers (**Table 3**).

Ovarian cancer

Compared to PV/LPV non-carriers, carriers reported significantly higher proportions of both having a transvaginal ultrasound (46.5% vs. 26.7%; *P* = 0.007) and receiving a CA-125 blood test (39.5% vs. 12.2%; *P* <0.001) (**Figure 1**). Within the last year, 30.0% and 45.8% reported having a transvaginal ultrasound and a CA-125 blood test, respectively. Furthe, PV/LPV carriers were more likely to have done so than non-carriers (ultrasound; 68.4% vs. 20.9%; CA-125 blood test; 88.2% vs. 22.5%; both *P* = 0.001) (**Table 2**). In adjusted models (Model 2), carriers had greater odds of having received a CA-125 blood test than non-carriers (AOR, 5.84; 95% CI, 2.48-13.75; *P* <0.001). The odds of having an ultrasound were also greater in PV/LPV carriers than non-carriers; however, this difference became statistically non-significant when further controlling for socioeconomic indicators (AOR, 1.97; 95% CI, 0.92-4.20; *P* = 0.08) (**Table 3**).

Colorectal cancer

Overall, the most common type of colorectal cancer screening was colonoscopy (79.0%) (**Supplementary Table 4**), followed by sigmoidoscopy (7.0%), Cologuard stool DNA test (6.7%), and FIT test (5.9%). Significantly higher percentages of PV/LPV carriers had received a colonoscopy (90.2% vs. 77.2%; *P* = 0.003) (**Figure 1**) or a sigmoidoscopy (12.7% vs. 6.1%; *P* = 0.01) in the past (**Supplementary Table 4**) compared to that of non-carriers. Furthermore, 31.5% of the individuals reported that their most recent colonoscopy was within 1 year ago. PV/LPV carriers underwent colorectal cancer screening at a younger age than non-carriers (mean age, 38.0 year [SD, 11.3] vs. 46.0 years [9.8]; *P* <0.001) (**Table 2**). On multivariable analyses (Model 2), the odds of having received a colonoscopy were significantly greater in PV/LPV carriers than non-carriers (AOR, 6.90; 95% CI, 2.89-16.49; *P* <0.001) (**Table 3**).

Prostate cancer

Most (81.7%) male individuals had received a PSA test for the purpose of prostate cancer screening (**Supplementary Table 4**). The distribution of PSA testing was similar between PV/LPV carriers and non-carriers (81.8% vs. 81.7%; *P* = 0.99) (**Figure 1**). Additionally, 77.6% had undergone PSA testing for prostate cancer within the last year, with no statistically significant difference between carriers and non-carriers (80.7% vs. 76.5%; *P* = 0.49) (**Table 2**). This difference remained statistically non-significant even in the adjusted models (Model 2), as carriers and non-carriers had similar odds of having received a PSA test (AOR, 0.95; 95% CI, 0.33-2.69; *P* = 0.93) (**Table 3**).

Lung cancer

Only 11.9% of the study cohort underwent a low-dose CT scan for lung cancer overall (**Supplementary Table 4**). The percentage of low-dose CT scan was very similar by carrier status of PV/LPV in cancer predisposition genes (carriers [11.5%] vs. non-carriers [11.6%]; *P* = 0.99) (**Figure 1**). Among those who had a scan, 48.9% reported their most recent one was within the last year. No difference in receiving a scan between carriers and non-carriers was observed (51.5% vs. 60.0%; *P* = 0.84) (**Table 2**). On multivariable regression (Model 2), PV/LPV carriers had greater odds of having undergone a low-dose CT scan than non-carriers; however, this difference remained statistically non-significant (AOR, 1.13; 95% CI, 0.66-1.93; *P* = 0.65) (**Table 3**).

Discussion

Our study demonstrates varying uptake of cancer screening among high-risk individuals in the UCCPS diverse registry. Compared to non-carriers, carriers of PV/LPV in cancer predisposition genes had a significantly higher likelihood of having received an MRI for breast cancer, having received a CA-125 blood test for ovarian cancer, and having undergone a colonoscopy for colorectal cancer. Although this study suggests individualized, risk-appropriate screening, there remain gaps in the comprehensive uptake of cancer screening, specifically for cervical, prostate, and lung cancers among the PV/LPV carriers. This finding highlights the importance of coordinated clinical programs in identifying and addressing barriers to improve these observed gaps in genetic testing and multi-cancer screening among high-risk individuals.

Cancer screening among PV/LPVs carriers was higher for cancers with a clearly defined hereditary cause and with a highly penetrant gene cause, including breast MRI, CA-125 blood test, and colonoscopy. The vast majority of the participants had a mammogram within the past year, with a similar rate between PV/LPV carriers and non-carriers. Carriers were more likely to have undergone a breast MRI than non-carriers. The results tend to follow the general mammogram screening guidelines for average-risk populations and recommendations for supplemental MRI in high-risk populations according to the U.S. Preventive Services Task Force (USPSTF) and the American College of Radiology.[9–11] For ovarian cancer screening, the odds of having undergone a CA-125 blood test was higher in carriers than non-

carriers. There is currently not a reliable screening test for ovarian cancer, and therefore, it's not recommended for asymptomatic women by the USPSTF.[12] However, for women with known high risk, health care providers may recommend a combination of pelvic examination, transvaginal ultrasounds, and/or a CA-125 test for monitoring in this high-risk population.[13] Given that not all populations have equal cancer risk, patients and providers should discuss and make shared decision making regarding individualized, risk-based screening approaches based on their identified PV/LPV in cancer predisposition genes.

Among female high-risk individuals in this cohort, more than 80% had a Pap smear and approximately one in 4 received an HPV test in the past. This study also reported that less than one-third of the women screened for cervical cancer within the last year, and the rates did not differ, regardless of PV/LPV carrier status. For colorectal cancer, three in 4 individuals reported having undergone a colonoscopy, and carriers were more than 6 times as likely as non-carriers to have done so. These results are encouraging, however, the differences in these cancer screening uptakes between PV/LPV carriers and non-carriers were no longer significant after adjusting for age and other socioeconomic indicators. Collectively, these findings suggest that high-risk individuals particularly those carrying a PV/LPV in cancer predisposition genes might not be well aware of their risk for cancer and not be able to receive adequate cancer-specific screening. Reinforcing the role of clinical program coordination is vital in identifying and mitigating potential barriers to genetic testing and cancer screening, which can help improve rates of screening uptake and risk-reduction prevention among high-risk communities.

Additionally, we also found a markedly more than 80% having received a PSA screening test for prostate cancer. This result may reflect an increased awareness of risk and individualized decision making to screen for prostate cancer among male individuals at high risk. But it is possible that some individuals may have recalled the test for different purposes other than prostate cancer. Although the USPSTF currently does not recommend the PSA test for routine prostate cancer screening, it suggests personalized screening approaches for men at high risk.[14] In contrast, the uptake of lung cancer screening was low and was similar between PV/LPV carriers and non-carriers, as only one in 9 high-risk individuals reported having received a low-dose CT scan overall. This result from our high-risk cohort is comparable to the rate (between 12% and 18%) of low-dose CT scan in the general U.S. population[5,15,16] Our finding may suggest a lower or not well-understood genetic risk for lung cancer. Uncertainty of PV/LPVs screening guidelines and risk management also deters engagement in cancer risk assessment programs.[17,18] For example, a nationwide analysis of lung cancer screening patterns among smokers has shown an overall rate of only 1.9%.[19] Literature on multi-cancer screening and early detection in hereditary cancer management programs is scarce. Our study findings present an opportunity for these programs to offer context-appropriate information, screening, and prevention for a wide range of malignancies, beyond the specific cancers conferred by the existing familial genes.

The current study is not without limitations. First, self-reported survey data are prone to recall error and social desirability bias. However, this bias is expected to be very minimal. Our research staff had limited-

to-no direct interaction with participants at the time of the survey, and thus, their responses were unlikely to have been influenced. It is important to point out that self-reported data on PV/LPV in cancer predisposition genes were verified independently by our clinical investigators to ensure its accuracy according to individuals' records documented in the registry database or patients' clinical charts. Moreover, there are other unmeasured characteristics, such as perceived cancer risk, degree of exposure to cancer risk, cultural beliefs, and health-seeking behavior, that may offer a better explanation for the findings observed in this study. Therefore, future investigations should consider the impact of these factors on cancer screening and how they intersect with genetic testing and counseling among individuals at high risk. Lastly, given the single clinical setting at an urban cancer center, the UCCPS cohort may not be representative of all high-risk individuals in the U.S., limiting the generalizability of the study findings.

Conclusion

In this registry of diverse high-risk individuals, carrier status of PV/LPV in cancer predisposition genes was associated with screening for breast, ovarian, and colorectal cancers. Our findings highlight an increased awareness and uptake of cancer screening, although the uptake remains suboptimal for cervical, prostate, and lung cancers. This study also suggests the need to evaluate how preventive services and clinical practices impact genetic testing and multi-cancer screening in high-risk populations, particularly those who carry a PV/LPV in cancer-specific predisposition genes. Importantly, it is critical that cancer risk clinics work with patients and advocates who are community facing while enhancing their partnerships with local organizations to help increase uptake of genetic testing and multi-cancer screening for high-risk individuals in the community.

Declarations

Conference presentation

The study results were presented at the 2024 American Society of Clinical Oncology (ASCO) Annual Meeting in Chicago, IL; May 31-June 4, 2024.

Ethics and consent to participate declarations

The University of Chicago Institutional Review Board reviewed and approved the conduct of both UCCPS and this study. All participants provided written informed consent to the UCCPS registry and follow-up surveys. This study followed the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) reporting guidelines.

Competing interest

Dr. Olufunmilayo I. Olopade has declared financial relationships with CancerIQ and TempusAI; research funding from Color Genomics and Roche/Genentech. All other authors declare no competing interests.

Electronic supplementary material

Supplementary Material Online

Competing Interests

Dr. Olufunmilayo I. Olopade has declared financial relationships with CancerIQ and TempusAI; research funding from Color Genomics and Roche/Genentech. All other authors declare no competing interests.

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Author Contribution

Conceptualization: J.Q.F., A.V.C.M., F.Z., E.K., C.D., O.I.O., D.Z.; Methodology: J.Q.F., A.V.C.M., F.Z., O.I.O., D.Z.; Investigation: J.Q.F., A.V.C.M., F.Z., E.K., I.R., O.I.O., D.Z.; Data Curation: J.Q.F, F.Z., D.Z.; Formal Analysis: J.Q.F., A.V.C.M., D.Z.; Visualization: J.Q.F., A.V.C.M.; Validation: D.Z.; Funding Acquisition: J.Q.F., A.V.C.M., O.I.O., D.Z.; Resources: F.Z., E.K., C.D., I.R.; Supervision: O.I.O., D.Z.; Writing–original draft: J.Q.F., A.V.C.M.; Writing–review and editing: J.Q.F., A.V.C.M., F.Z., E.K., C.D., I.R., O.I.O., D.Z.

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Data Availability

Individual-level patient data were analyzed in this study, which cannot be shared publicly due to patient confidentiality and privacy concerns. However, the data can be requested upon reasonable request, pending the approval of the University of Chicago Institutional Review Board and the corresponding authors.

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Tables

Table 1 to 3 are available in the Supplementary Files section.

Figures

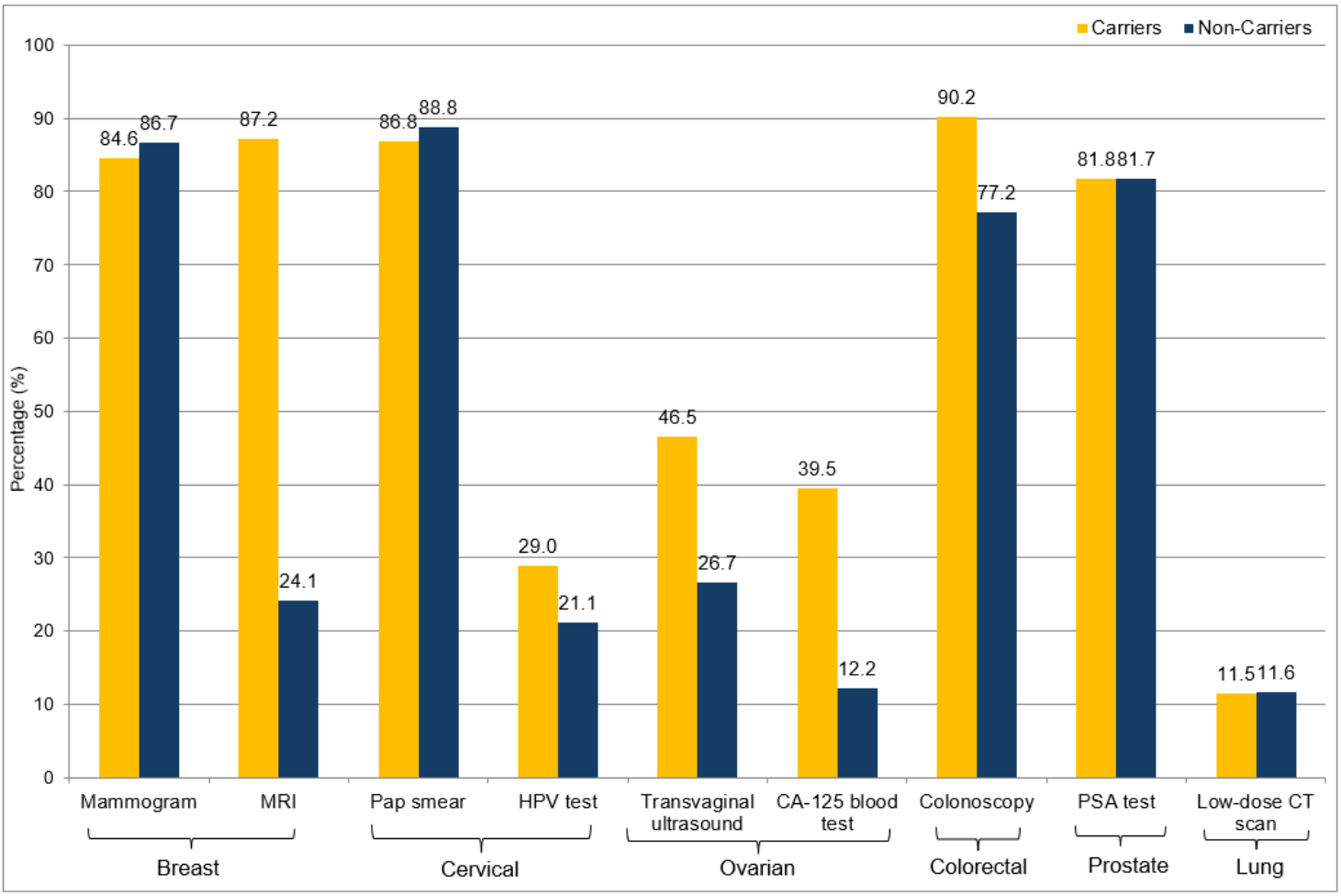


Figure 1

Prevalence of cancer screening uptake in high-risk individuals by carrier status of PV/LPV in cancer predisposition genes

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- TablesMulticancerscreeningpatterns.docx
- Suppl.MaterialsMulticancerscreeningpatterns.docx