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False-positive screening events and worry influence decisions about surgery among high-risk women

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Abstract

Objective—Studies of cancer screening have found that false positive screening events (FPSE) can affect worry about cancer risk and screening program use, we sought to further explore this.

Methods—In a study of 1,100 women at high risk for ovarian cancer who participated in a previously published randomized controlled trial (RCT), we sought to explore whether worry might also influence the use of risk-reducing surgical procedures by women. Participants included 234 women with BRCA1/2 mutations and 866 women with high-risk pedigrees. We followed the women for up to 6 years.

Results—Worry predicted risk reducing prophylactic bilateral salpingo-oophorectomy (pBSO) for both mutation carriers (HR = 1.74; p = 0.02), and women with high-risk pedigree (HR = 3.41; p <0.001). FPSE also predicted subsequent pBSO among women with a highrisk pedigree (HR 2.31; p < 0.01). While screening may reduce worry among those who never receive a positive result, FPSE increase worry at least temporarily. Worry about ovarian cancer risk predicted use of preventative pBSO among high-risk women including those with BRCA1/2 mutations enrolled in an ovarian cancer-screening program. FPSE also predicted risk-reducing ovarian surgery among high-risk women without a known mutation at the time of screening program enrollment.

Conclusions—Physicians who offer screening should know that false positive results may increase use of pBSO, how this should effect clinical practice is unclear.

Clinicaltrails.gov registration #

Keywords

Worry; ovarian cancer; high-risk; BRCA1; surgery

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Epithelial ovarian cancer (EOC), including serous ovarian, fallopian tube, and primary peritoneal carcinoma, is the most lethal gynecologic malignancy in the U.S. Only 0.8% of women in the general population, but 39% and 22% of BRCA1 and BRCA2 mutation carriers respectively, will be diagnosed with EOC by age 70 (Chen et al., 2006). Risk-reducing prophylactic bilateral salpingo-oophorectomy (pBSO) is recommended for women with documented deleterious mutations who have completed their families because it reduces their risk of ovarian cancer by about 80% (Bowen, Helmes, Powers, & Andersen, 2003; Clark & Domchek, 2011; Diefenbach, Miller, & Daly, 1999; Rebbeck, Kauff, & Domchek, 2009). Women who are at high risk for such a mutation based on family history, but do not pursue genetic testing, may also be candidates for pBSO, particularly if performed in the context of hysterectomy for a benign condition. For women at high familial risk and/or a known mutation who seek to avoid or delay surgical risk reduction, screening may be offered. Screening may include frequent CA125 testing and/or ultrasound. Because the efficacy of such screening remains uncertain (Menon et al., 2015), national guidelines ("Risk Assessment, Genetic Counseling, and Genetic Testing for BRCA-Related Cancer in Women," 2013; "Risk Assessment, Genetic Counseling, and Genetic Testing for BRCA-Related Cancer in Women," 2014) encourage high-risk women to seek pBSO when they have completed their families. Questions about high-risk screening programs include Does participation in screening reduce women's levels of worry about their risk, and thus worry-driven use of pBSO? Does worry increase use of surgery?

Screening programs inevitably include a percentage of events where the outcome of a screening visit is a positive test result that requires some form of follow-up. When a repetition of the biomarker after early recall or confirmatory screening visit fails to confirm suspicion for cancer, the majority of these test results are determined to be false-positive screening events (FPSE). These FPSE do not necessarily lead to ultrasound follow-up, biopsy, or referral for a surgical consult, nor do they necessarily signal any lasting change in the risk of developing cancer in the future but they may temporarily increase levels of worry (Portnoy, Loud, Han, Mai,& Greene, 2015). Worry and distress among women at high-risk for breast and ovarian cancer due to a strong family history or gene mutation has been the subject of considerable study. Some women are highly distressed about their high-risk status (M. R. Andersen, Bowen, Yasui, & McTiernan, 2002; M. R. Andersen et al., 2004; Audrain et al., 1997; Lerman & Schwartz, 1993), while others report very modest levels of worry similar to those of women of average risk (M. R. Andersen et al., 2004). Cancer screening participation and the associated FPSEs have the potential to influence levels of cancer worry (Aro, Pilvikki Absetz, van Elderen, van der Ploeg, & van der Kamp, 2000; Caryn Lerman, Bruce Trock, Barbara K. Rimer, et al., 1991) and these events and/or the associated worry can influence screening program participation (M. R. Andersen, Smith, Meischke, Bowen, & Urban, 2003; Diefenbach et al., 1999; Hay, McCaul, & Magnam, 2006; McCaul, Branstetter, Schroeder, & Glasgow, 1996). Studies of screening use and distress inform our understanding of the relationship of worry to self-protective behaviors. Although much is known about mild levels of worry and some self-protective behaviors, the degree to which more severe levels of worry influence use of behaviors such as risk reducing surgery is generally unknown. Ovarian cancer screening programs for high-risk women have been studied less frequently than breast cancer screening programs for average risk women and no

one has yet described use of surgery after ovarian cancer screening. Studies have sought to learn if distressed women who attend screening to seek reassurance report less distress after screening. It has been difficult to make the case that screening provides reassurance to high-risk women (M. Andersen et al., 2007; Brett, Bankhead, Henderson, Watson, & Austoker, 2005; Madalinska et al., 2005). In addition, questions arise about whether moderate and severe levels of worry, like those reported by some of the highest risk women, serve as a barrier rather than facilitator of self-protective activities including screening and surgery (M. R. Andersen et al., 2003). It is unknown how long worry levels are elevated after a FPSE and if FPSE or FPSE induced worry influences the process of informed decision-making about prophylactic surgery among high-risk women.

One study investigating FPSE in BRCA1/2 mutation carriers found that FPSE (e.g. breast MRI) increased levels of worry about breast cancer risk and that worry about cancer risk at screening program entry predicted use of risk-reducing surgery among mutation carriers (Portnoy et al., 2015). That study did not explore the effects of ovarian cancer screening FPSE, because of the rarity of ovarian FPSE in their program. We sought to expand on the Portnoy et al, study's findings with data from an ovarian cancer screening program that included a larger population of high-risk participants, including women who were either BRCA1/2 mutation carriers or who had a strong family history of disease but no mutation testing. This population was followed through several years of screening. This report describes a secondary analysis of data from a previously published randomized controlled trial (RCT) that examined the effectiveness of two different screening strategies for high-risk women (Karlan, 2014). Two screening protocols were compared, both using circulating CA125 and HE4 to select women for transvaginal sonography. Serum HE4 (Hellström et al., 2003; Hough et al., 2000; Schummer et al., 1999) is a biomarker that is more specific than CA125 in discriminating women with malignant tumors from those with benign tumors (Hellström et al., 2003; Moore et al., 2008) and was recently approved by the FDA for that use in combination with CA125 (Moore et al., 2011). The RCT examined the advantages associated with using HE4 as a first-line versus follow-up screening test. Protocol-indicated BSO was performed in six women, identifying two ovarian malignancies; however, most of the BSO surgeries (134 prophylactic BSO (pBSO) were performed on trial participants who did not receive a protocol-driven recommendation for surgical consult. These pBSO were performed to reduce ovarian cancer risk. Most were done at the time of hysterectomy for a benign condition, but some were performed as primary surgery. Included among the 134 pBSO are eight prophylactic bilateral salpingectomies with ovarian retention (pBSOR) performed for EOC risk-reduction. This report describes the effects of screening on cancer worry and the effect of worry and of FPSE as predictors of pBSO.

Methods:

Study populations.

Participants were recruited at four sites: Cedars-Sinai Medical Center, City of Hope, Swedish Cancer Institute/Fred Hutchinson Cancer Research Center, and Fox Chase Cancer Center. Participants were recruited between February 1, 2010 and October 31, 2013. The Fred Hutchinson Cancer Research Center served as the national Coordinating Center. All

participants completed written consent forms as part of an in-person consent process prior to study enrollment. Study activities were overseen by the IRBs of Cedars-Sinai Medical Center, City of Hope, Swedish Cancer Institute, Fox Chase Cancer Center, and that of the Fred Hutchinson Cancer Research Center.

Eligibility.

Eligible participants were high-risk women aged 25 to 80. Risk Group 1 included women 25–80 years old carrying a deleterious BRCA1 or BRCA2 germ line mutation. Risk Group 2 included women aged 35–80 who reported either a personal or family history of cancer suggesting inherited susceptibility for EOC. The group also included women who met NCCN V4.2013 Breast and Ovarian Cancer Genetic Assessment Guidelines for referral to a genetic counseling professional, and women with a deleterious mutation in HNPCC or P53 genes or a first-or second-degree relative positive for HNPCC. Women were ineligible for the study if they had a personal history of EOC, no ovaries, abdominal surgery within the last 3 months, a current pregnancy, a medical condition precluding phlebotomy, untreated malignancy (other than non-melanoma skin cancer), or receipt of adjuvant chemotherapy or radiation therapy for cancer (except tamoxifen or aromatase inhibitors +/− Lupron) within 3 months. At enrollment, eligible women signed a medical records release form, provided informed consent, and identified a care provider who agreed to receive screening results.

For these analyses, we focused on women's experiences of routine EOC screening in the absence of a diagnosis of cancer. At the time of the primary screening appointment immediately prior to the surgery, we censored data from the six women who had protocol-indicated BSO, and 23 women who had BSO due to suspicion of gynecologic cancer. Reasons for censoring included 1) surgery following a protocol-based recommendation for surgical consult due to suspected ovarian cancer, 2) ovaries removed at other cancer-related surgery not ovarian cancer, or 3) surgery performed due to symptoms suspected to be those of ovarian cancer. Censoring affected 23 primary screening visits and included 7 women diagnosed with cancer, not all of which were ovarian cancer. Although not all of the censored events resulted in a cancer diagnosis, they were removed from the group being investigated here in order to focus on the effects of biomarker-based FPSE. In the censored data, the presence of multiple symptoms, and screening or diagnostic results indicative of cancer made comparison of patient worry levels with those of women in routine screening experiencing biomarker-related screening events implausible. In addition, it should be noted that we did not censor the data associated with two pBSO surgeries performed in the absence of a protocol recommendation that occurred based on physician or patient requests for risk reduction, even though those surgeries later revealed occult early stage EOC. We chose not to censor these two surgeries because the clinical activities prior to these surgeries were identical to those of pBSO, where no occult early stage EOC was found. These surgeries occurred based on family history risk information or genetic testing risk information and, while they may have followed a FPSE event, that was NOT the most recent primary screen.

Intervention.

We evaluated two multimodal screening protocols as shown in Figure 1. They differed only in use of HE4 in the primary screen. In Arm 1, both CA125 and HE4 were measured at the primary screen; in Arm 2, only CA125 was measured at the primary screen. In both arms, a positive primary screen used a confirmatory blood test to select women for follow-up imaging. Both CA125 and HE4 were measured at confirmatory marker screens, and pelvic ultrasound was later performed if either CA125 or HE4 was positive. All women were screened semi-annually, with early recall, explained below, at 3 months. CA125 and HE4 were interpreted using the previously developed PEB longitudinal algorithm (Drescher et al., 2013). The PEB determines the expected value of a marker for each individual woman based on her menopause status and marker history. Thresholds for CA125 and HE4 positivity were set such that 10% of participants in each study arm were expected to be positive at each primary screen, and would be asked to return for a confirmatory screening visit or early recall. If either CA125 or HE4 was positive at a confirmatory screening visit, the woman was asked to return for ultrasound imaging. Screening tests were considered positive and a surgical consult was recommended if 2 of the 3 tests (CA125, HE4, ultrasound) were positive (using 95% PEB specificity thresholds for CA125 and HE4), or if confirmatory CA125 exceeded the PEB 99% specificity positivity threshold. Outcomes assessed as part of the RCT included surgical consults recommended, surgical procedures performed, and lesions identified. Further details on the trial are available in (Karlan et al., 2014).

Questionnaires.

Women completed questionnaires at the enrollment appointment that included their first primary screen and at each subsequent study screening appointment that included both primary and confirmatory screens. Questionnaires included items assessing worry about risk for cancer (C. Lerman et al., 1991) modified for this study. These items included one asking women about the frequency with which they have thoughts about getting ovarian cancer rated on a four-point scale from ”rarely or not at all” (1) to “almost all the time” (5). For impact of worry on mood and functioning, there were items on which women would rate the frequency with which thoughts about getting ovarian cancer affect their mood or ability to perform daily activities from “rarely or not at all’ (1) to “almost all the time” (5). Responses to these questions were used to categorize women’s reports of worry and distress about their risk of ovarian cancer consistent with several prior reports (M. Andersen et al., 2007; M. R. Andersen et al., 2004; M. R. Andersen, Peacock, et al., 2002). Women were considered not worried and put in the “none” category if they reported thinking about their risk “rarely or not at all”, and if worry about their risk affected their moods or daily activities “rarely or not at all”. Women were considered mildly worried if they reported thinking about their risk “sometimes” during the last month but did not report worries affecting their moods or daily activities. Women who reported thinking about their risk “often” or “almost all the time” or reported that their thoughts about their risk affected their mood “sometimes” were considered moderately worried. Those who reported that worry affected their mood “often” or “almost all the time” or reported that their thoughts about their risk affected their daily activities “sometimes,” “often,” or “almost all the time” were considered severely worried about their risk. Because any level of distress beyond mild is rare in a healthy average risk population. That rate have been reported to be less than 1% (M.R. Andersen et al., 2003).

Levels of worry that affect moods often or daily activities sometimes might deserve treatment and have been determined to have qualitatively different effects on mammography use than less severe levels of worry (M. R. Andersen et al., 2003). Thus, the categories were dichotomized to none or mild and moderate or severe for statistical analyses. This use of two instead of four categories also served to preserve power in survival analyses since the number of surgeries observed was low among women reporting severe worry. This characterization of worry is also consistent with some treatments of the screening consequences scale which is dichotomized for use as affected/unaffected in some studies (Bolejko, Hagell, Wann-Hansson, & Zackrisson, 2015).

Analysis plan.

For all analyses, women from both study arms were combined because these analyses did not focus on the effectiveness of the ovarian cancer screening protocols and no differences were found in worry or use of pBSO by study arm. There were no significant differences between the study arms in demographic or risk predictive variables. We summarized the baseline characteristics of participants by risk group and reported p-values for testing differences in the two risk groups using Fisher's exact test for categorical variables and a two-sample t-test for numeric variables. We constructed a riverplot to illustrate the movements of the study sample as a whole between low and high levels of worry, surgery, and lost to follow-up over the course of the screening program. We examined the effect of screening participation on ovarian cancer worry over time in the absence of FPSE. For the analyses of worry associated with screening participation, we combined women with BRCA1/2 mutations and women with a high-risk pedigree into a single population. At each primary screening visit, we calculated the percentage of women reporting moderate or severe ovarian cancer worry among those women who had not yet experienced a positive screening event and associated 95% confidence intervals. At each confirmatory screening visit, we calculated the percentage of women reporting an increase in ovarian cancer worry and associated 95% confidence intervals.

To test the effect of ovarian cancer worry and FPSE on the rate of pBSO, we fit separate Cox proportional hazards models for women with BRCA1/2 mutations and women with a high-risk pedigree. We did this because 1) pBSO is recommended more consistently for documented mutation carriers than for those with a strong family history but no known mutation, and 2) rates of known risk factors for ovarian cancer (family history of ovarian cancer, and age) were statistically significantly different between the two risk groups (Table 1). The Cox models were used to examine the effect of ovarian cancer worry on time to pBSO using proportional hazards models that compared time to pBSO among those in the two worry groups "none or mild" and "moderate or severe"). The worry variable is categorized as "moderate/severe" for a participant on study only for a period of time directly after she reported being moderately or severely worried and before any other report; at all other times the variable is categorized as "none/mild". We measured in years from enrollment. Thus, these models describe the amount of time for women in each worry category after enrollment before they chose surgery. Data were censored at the time of the primary screening appointment immediately prior to the surgery in women who underwent oophorectomy due to suspicion of ovarian cancer or cancer at another organ site (n=23), at

loss to follow up (n=54), at drop out (n=97) or end of study (n=796). We considered women as dropped out if they indicated directly that they no longer wanted to participate or considered passive refusal, i.e. non-compliant with the screening protocol. Loss to follow-up included women who died, moved away, became pregnant, received diagnosis or treatment for another cancer, or left the study due to other health related issues. We adjusted the models for age at baseline, family history of ovarian cancer, and study arm because the decision to have pBSO is highly dependent on age and women with a family history of ovarian cancer may be more worried about ovarian cancer risk (M. R. Andersen, Peacock, et al., 2002; Karlan et al., 2014). We tested directly the effect of family history on ovarian cancer worry using a Fisher's Exact test to compare ovarian cancer worry rates at baseline in women with and without a family history of ovarian cancer (one or more relatives diagnosed with ovarian cancer). We estimated the effect of FPSE on the rate of pBSO using Cox proportional hazards models including FPSE as a binary time-dependent predictor adjusted for age at baseline and study arm. The FPSE variable is negative for all time points where a woman has not had a positive screening event, becoming positive when a woman is asked for the first time to attend a confirmatory screen or return for early recall. To visualize the effect of ovarian cancer worry and FPSE on pBSO rates, we constructed Kaplan-Meier curves depicting the cumulative probability of pBSO. Because ovarian cancer worry and FPSE are time-dependent covariates, the Kaplan-Meier estimator evaluated the status of the women remaining at risk at each surgical event time. We performed statistical analyses using R (version 3.1.2: The R Foundation for Statistical Computing, Seattle WA.)

Results

Between February 1, 2010 and October 31, 2013, 1,100 women enrolled in the trial and were included in analyses. Participants, 234 women aged 25–80 with a documented BRCA1 or BRCA2 germ-line mutation (Risk Group 1) and 866 women aged 35–80 with a pedigree suggesting inherited cancer susceptibility (Risk Group 2), were screened semi-annually. There were no significant differences between the study arms in demographic or risk predictive variables. Participants were predominantly aged 45–65 (59%) and Caucasian (86%); about 21% were of Ashkenazi-Jewish descent. Approximately 31% had a personal history of breast cancer and 33% had a family history of EOC. Table 1 provides at enrollment information according to participant status as either Risk Group 1 or Risk Group 2. As expected, the two risk groups differed in the distribution of risk predictive variables. Positive predictive value of the two screening protocols, including protocol recommended surgeries and cancers, is reported in (Karlan et al., 2014).

Screening events and worry over time:

In an analysis of more than 4,700 primary screening visits, 258 women had a FPSE including early recall in 3 months (n = 53) or immediate recall for a confirmatory screening visit (n = 225; some women experienced more than on FPSE). Women generally participated in the screening program for more than 2 years. At study enrollment, approximately 29% of the women in the study reported moderate or severe worry about ovarian cancer risk, including 55.6% and 24.5% of those with and without a mutation respectively. In total, 137

women (12.5% of the sample) reported severe worry about their ovarian cancer risk at baseline.

Figure 2 illustrates changes in women's levels of worry about their ovarian cancer risk over time during their participation in the screening program. Women transitioning to surgery and to censoring (loss to follow-up, dropout or end of study) over time are also shown. Levels of worry recorded at confirmatory screens following a FPSE appear at the bottom of the figure. Overall, a majority of women report mild worry; rates of worry are higher among women sent for a confirmatory screen but these women often transition back to mild worry afterwards. Additional analyses, quantifying this, to follow. Those women who transition from screening to surgery do, however, appear to come equally from among those who reported mild and severe worry in spite of the relative infrequence of severely worried women in the population. Thus, demonstrating that higher levels of worry are a driver of the decision to pursue pBSO. Additional analyses, formally testing this hypothesis, to follow. Among those who transition to censoring the rate of drop out is modest (8.9%). Dropouts do not appear to come disproportionately from among the severely worried (25.7% of drop outs were moderately or severely worried at baseline compared to 31.3% of women who did not drop out).

Additional analyses exploring worry:

Collection of confirmatory visit data occurred prior to receiving associated confirmatory test results, a time when we expected elevated worry. Using data for 71 confirmatory tests at screen 1, 64 at screen 2, 50 at screen 3, 45 at screen 4, 40 at screen 5, 33 at screen 6, 37 at screen 7, and 36 at Screen 8 we found that at women at screens 1, 2, and 5 were significantly more worried at the time of their confirmatory screen than they were at the time of their preceding primary screen. At a confirmatory screening visit, almost 20% (screen 1) and 25% of women (screens 2, and 5) reported elevated levels of worry. Although wide confidence intervals precluded a finding that women's rates of transition to elevated levels of worry are normal suggesting reassurance at the time of their next primary screening visit, we found levels of elevated worry at the primary screening visits six month following a FPSE have generally fallen. At that point, the rate at which women are reporting a new transition to moderate or severe worry is not substantially elevated beyond that of women prior to other screening visits.

Considering the possibility of reassurance:

We examined the results of more than 4,700 screening visits; 1,100 from women at screening visit 1, 890 at visit 2, 742 at visit 3, 622 at visit 4, declining to 233 at visits 8–11. For each primary screening visit, we calculated the percentage of women reporting moderate or severe ovarian cancer worry among those women who participated and had not received a FPSE at any prior screening visit. More than 30% of women reported moderate or severe worry during the enrollment appointment. In the absence of a FPSE the percentage reporting those levels of worry fell to less than 20% by the time of the second and third screening appointment and to less than 15% by the fifth screening appointment (Chi-squared test for trend in proportions $x^2(1) = 131.91$, $p < 0.001$). The difference in the rates of moderate or severely worried women between the first screen and the second (30%-20%) does exceed the

confidence intervals for these estimates ($p < 0.05$). Reductions in the rate of moderately or severely worried women after the second screening visit are more modest and not statistically significant.

Predictors of pBSO:

We conducted analyses that examined use of pBSO separately for women with a BRCA1/2 mutation and for women with a high-risk pedigree. Overall, rates of surgery were lower in the high-risk women without a known mutation at time of enrollment (high-risk pedigree), than in mutation carriers. We observed three surgeries per 10 years of follow-up in mutation carriers compared to 0.3 surgeries per 10 years of follow-up in women with a high-risk pedigree ($p < 0.01$). Of note: Among women with BRCA1/2 mutations, women with a family history of one or more relatives diagnosed with ovarian cancer do not have a statistically significant higher rate of moderate/severe worry at study baseline. However, in women with a high-risk pedigree, family history of ovarian cancer is associated with a higher rate of moderate/severe worry at baseline (p-value<0.001, Fisher's Exact Test, Table 2).

Kaplan-Meier curves for women reporting either mild or no worry versus those reporting moderate or severe worry are in Figures 3 & 4. Higher levels of worry were strongly associated with time to pBSO both in women with BRCA1/2 mutations and those with a high-risk pedigree. As shown in Figure 3, the differences in rates of surgery diverge quickly among women with BRCA1/2 mutations. In a multivariate Cox proportional hazards analysis (Table 3), moderate or severe worry was a statistically significant predictor of pBSO in women with BRCA1/2 mutations, with an estimated hazard ratio (HR) of 1.74 (1.10, 2.73; $p = 0.017$). Older age at study entry also predicted surgery use. Ovarian cancer worry was also associated with rate of pBSO for women without known mutations at the time of study enrollment with estimated HR = 3.41 (1.89, 6.14; $p < 0.001$). Figure 3 also shows that in women with a high-risk pedigree, rates of surgery also diverge quickly. Age, family history of ovarian cancer and study arm all failed to predict pBSO in women with a high-risk pedigree (Table 4). Moderate or severe levels of ovarian cancer worry in women with a high-risk pedigree who reported "none" or "mild" worry at baseline is also strongly associated with rate of pBSO (data not shown) suggesting that worry acquired during screening is affecting behavior in women with a high-risk pedigree.

We also considered the hypothesis that women who receive FPSE are more likely to undergo pBSO than those who do not. Kaplan-Meier curves depicting cumulative pBSO rates in years from enrollment for women with and without an FPSE are presented in Figures 5 and 6. Examination of these curves shows rates of surgery differed among women with a high-risk pedigree. In a multivariate Cox proportional hazards analysis (Table 6), FPSE was a statistically significant predictor of pBSO, with an estimated HR of 2.31 (1.25, 4.63; $p < 0.01$). In women with known mutations, FPSE was not a statistically significant predictor of pBSO (Table 5). These results suggest that among high-risk women without known mutations at the time of their enrollment in a screening program, those who received at least one FPSE were more likely to pursue pBSO than those who did not.

Additional information about medical activities and surgeries received by women without a known genetic mutation at study entry:

Women pursuing pBSO while enrolled in the screening program differed substantially by risk group. Women with a known positive mutation at enrollment in the program received pBSO surgeries at an average age of 44.5 (sd = 8.8), while those with a high-risk pedigree received their surgeries at an average age of 57.0 (sd = 10.0). In addition, some women with a high-risk pedigree chose to pursue genetic testing while enrolled in the screening program with five of them pursuing pBSO after receiving a positive genetic result revealing a mutation, while 27 others pursued a pBSO in spite of a negative mutation finding. Seven of these surgeries in mutation negative women were performed opportunistically at the time of a surgery for another condition. Women who pursued surgery without knowledge of their mutations status (n = 19) were also likely (greater than 50%) to receive their pBSO opportunistically during an abdominal surgery being performed for some other reason.

Discussion

High-risk women participating in ovarian cancer screening may report moderate or severe worry about their cancer risk and experience worry that affects their moods and ability to engage in usual daily activities. Screening program participation may reduce their levels of worry over time if there are no FPSE, but FPSE during screening increase levels of worry in at least a transient fashion. More severely worried high-risk women with and without a known mutation are more likely to pursue risk-reducing pBSO than those who are less worried. The experience of FPSE also increased high-risk women's use of pBSO and, in this analysis, it occurred primarily among women without knowledge of their mutation status at enrollment. Some women in this group (n = 5) chose to have mutation testing and had pBSO surgery after receiving positive test results while others received their pBSO after a negative mutation test. Other predictors of use of pBSO among highrisk women included age with older high-risk women more likely to pursue pBSO regardless of mutation status. Mutation carriers were also found to seek pBSO an average of more than 10 years earlier than did those without a positive mutation result.

Overall, we found that moderate to severe levels of worry increase use of potentially difficult self-protective efforts including pBSO surgeries. FPSE were associated with and an increased use of surgery. However, it is unclear whether this is a direct effect of the FPSE or an indirect result of the FPSE leading to increased levels of worry. While pBSO surgeries in mutation carriers are encouraged, elevated levels of worry associated with frequent mood disturbance or interference in daily life activities are not.

Also of potential concern is the finding that FPSE appear to increase use of pBSO by women who have strong family histories but tested negative for a BRCA1/2 mutation. These women are not generally at higher risk for ovarian cancer because of their FPSE and these surgeries are not without risk. How concerned we should be about this result is unclear. Gene panel testing was not generally available at the time of this study and some of these women may have had mutations in recently identified moderate penetrate genes (e.g. BRIP1, PADS1d, RAD51c). In addition, most surgeries were in post-menopausal women who elected to

pursue pBSO surgery months or years after the FPSE during an already scheduled abdominal surgery for another medical condition. Therefore, these procedures, although predictable in part based on prior FPSE and inconsistent with guidelines, appear to be the result of careful consideration and not impulsive decisions based on high levels of fear.

For those interested in the issues associated with cancer worry among high-risk women, this paper expands on past findings. Most studies of the effects of FPSE have suggested that they can increase worry about risks for cancer, at least temporarily (Caryn Lerman, Suzanne M. Miller, et al., 1991; Caryn Lerman, Bruce Trock, Barbara Rimer, et al., 1991; Caryn Lerman, Bruce Trock, Barbara K. Rimer, et al., 1991) and increase use of self-protective behaviors including continued use of screening (Brewer, Salz, & Lillie, 2007; Caryn Lerman, Bruce Trock, Barbara K. Rimer, et al., 1991). This is the first study reporting that FPSE can increase use of more invasive risk-reducing activities, particularly surgery, and confirms the findings of Portnoy et al, who found that worry is associated with use of pBSO among mutation carriers (Portnoy et al., 2015).

Limitations of this study include the absence of an unscreened control group. Thus, we cannot compare the effects on cancer worry of screening program participation to no screening. In addition, participants in this research were high-risk women identified through careful review of family history information who may or may not have undergone mutation testing and who volunteered for a RCT of ovarian cancer screening for high-risk women. While selection procedures for this trial were similar to those that might occur as part of enrollment in other high-risk ovarian cancer screening programs, the selected women differ in some ways from a population sample of high-risk women including those with a BRCA mutation. Our participants included many women with a family history of ovarian cancer in addition to breast cancer. Although the presence of such a family history did not predict surgery use in either risk group, a family history of ovarian cancer is commonly considered a marker of higher risk for ovarian cancer among families at high-risk for breast and ovarian cancer. Family history of ovarian cancer was also found in other studies to predict elevated levels of concern about ovarian cancer risk in high-risk women as was found in our high-risk family history group women. Physicians offering high-risk screening should be aware of the potential of screening to both increase and reduce worry about cancer risks and the effects of FPSE and worry on use of pBSO use among high-risk women

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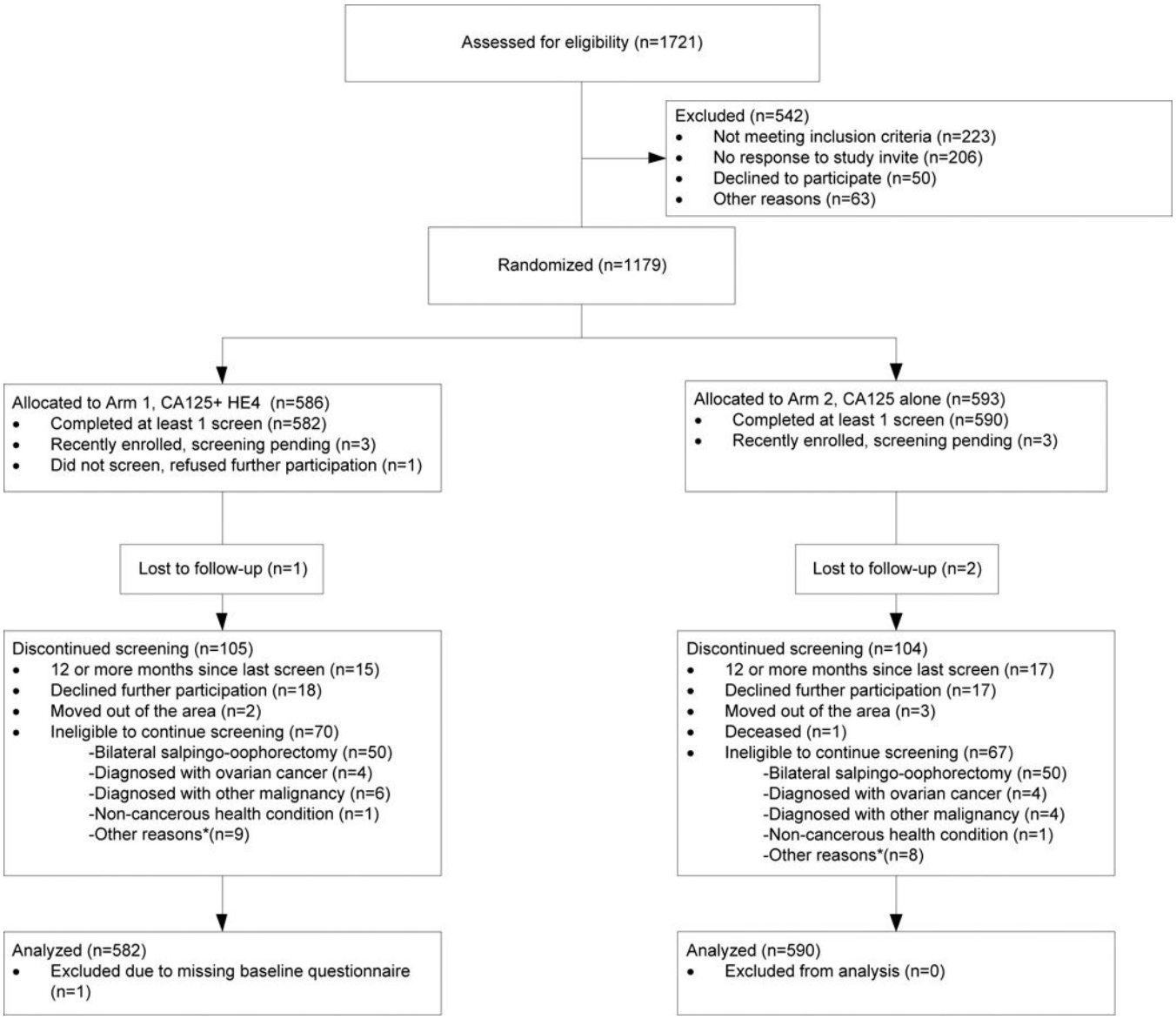


Figure 1. Participant Flow through the Protocol.

*includes women who are: currently pregnant or undergoing radiation or chemotherapy for cancer with the exception of tamoxifen or armatase inhibitors +/− Lupron.

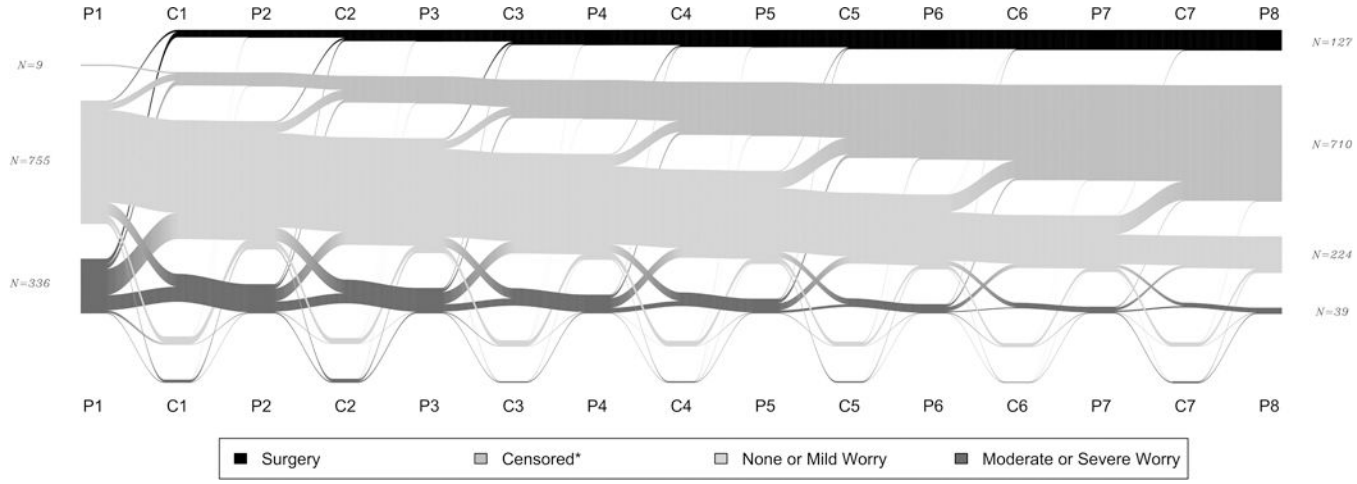
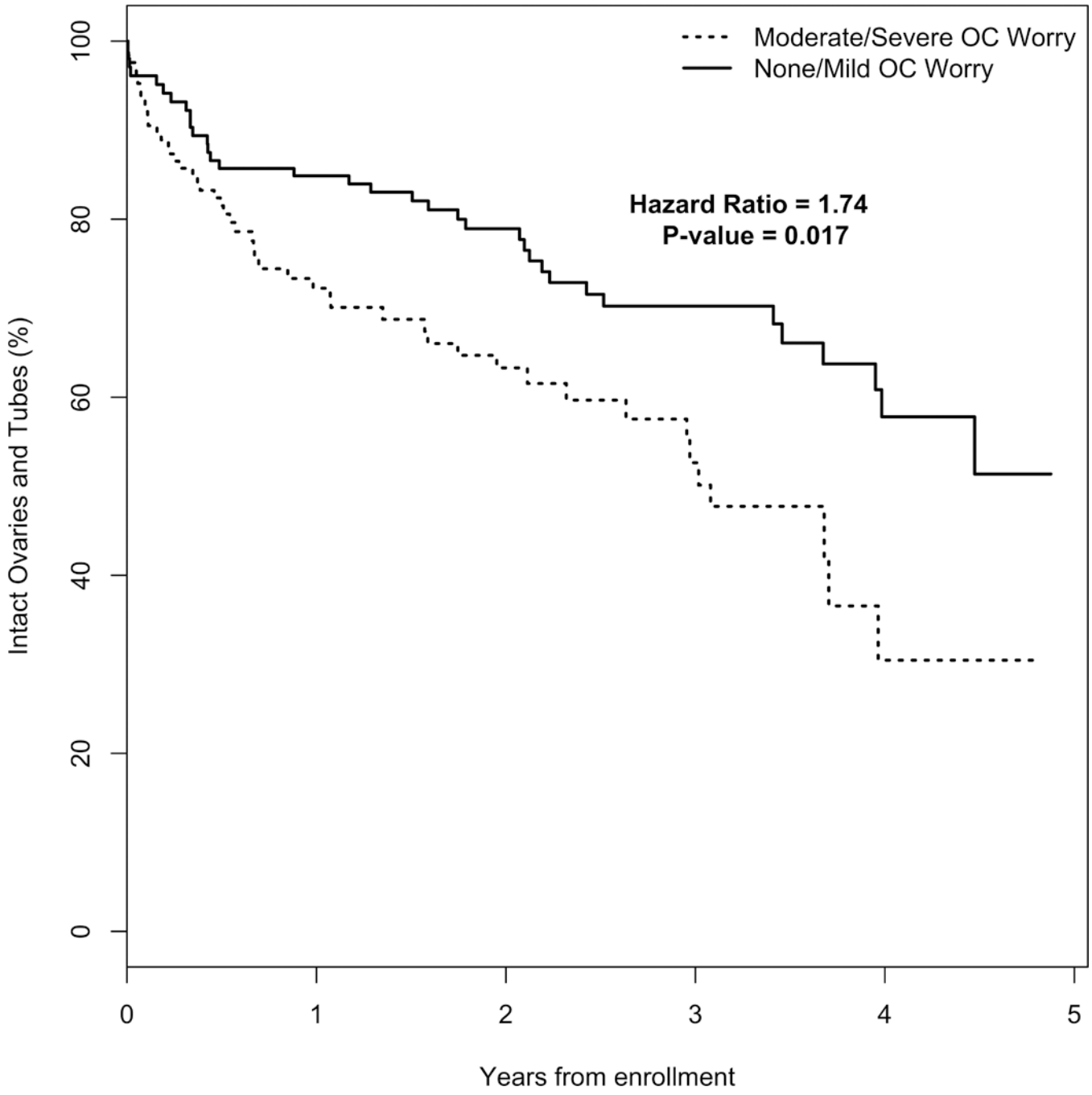


Figure 2: Riverplot of participant transitions in a screening

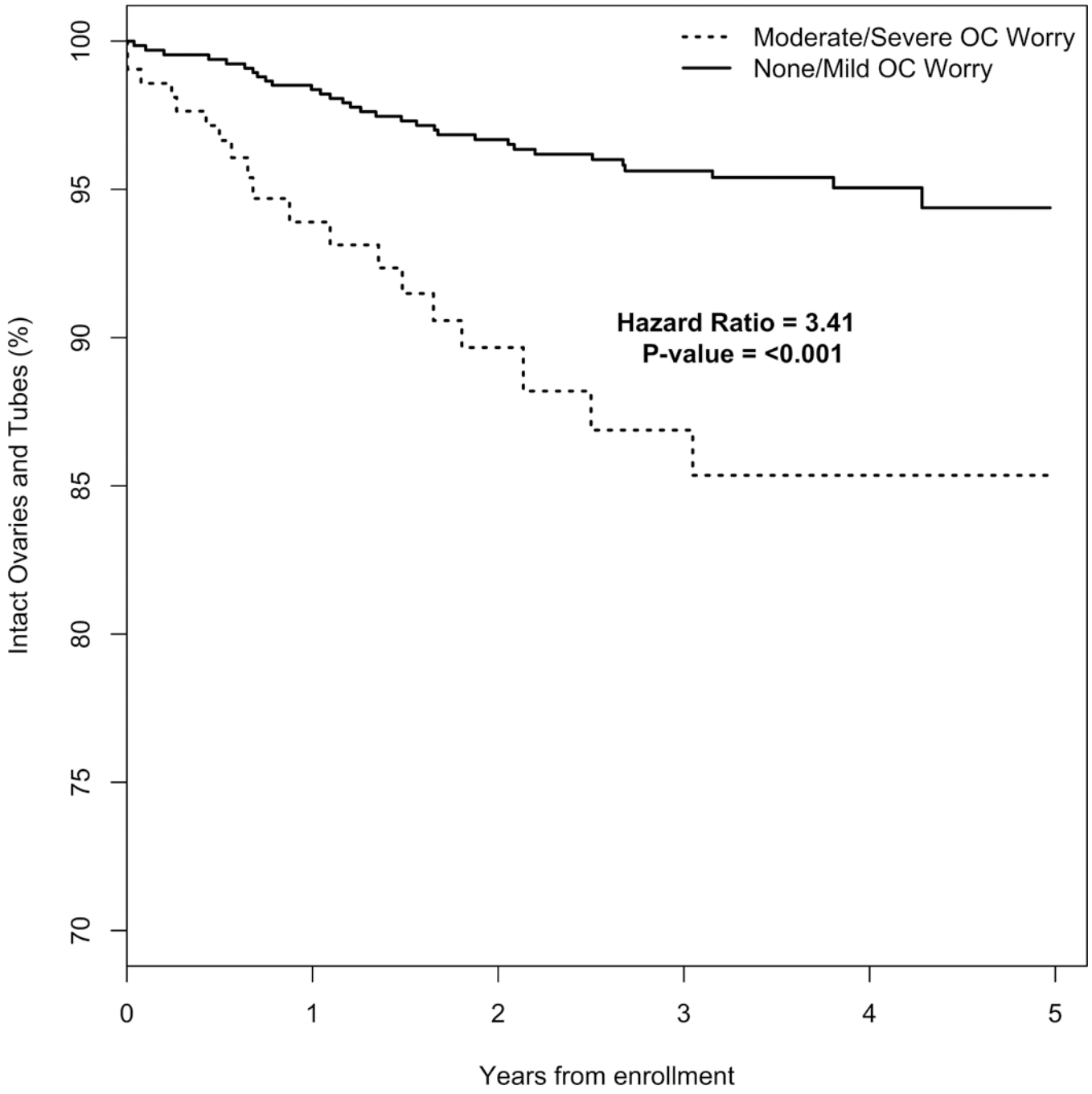
Women transitioning to surgery and to censoring at screen #8 (loss to follow-up (n = 54), dropout (n = 97), oophorectomy for other cause (n = 23), or end of study (n=976)) over time are also shown. Levels of worry recorded at confirmatory screens following a FPSE appear at the bottom of the figure.

P1-P8: Primary Screens 1-8

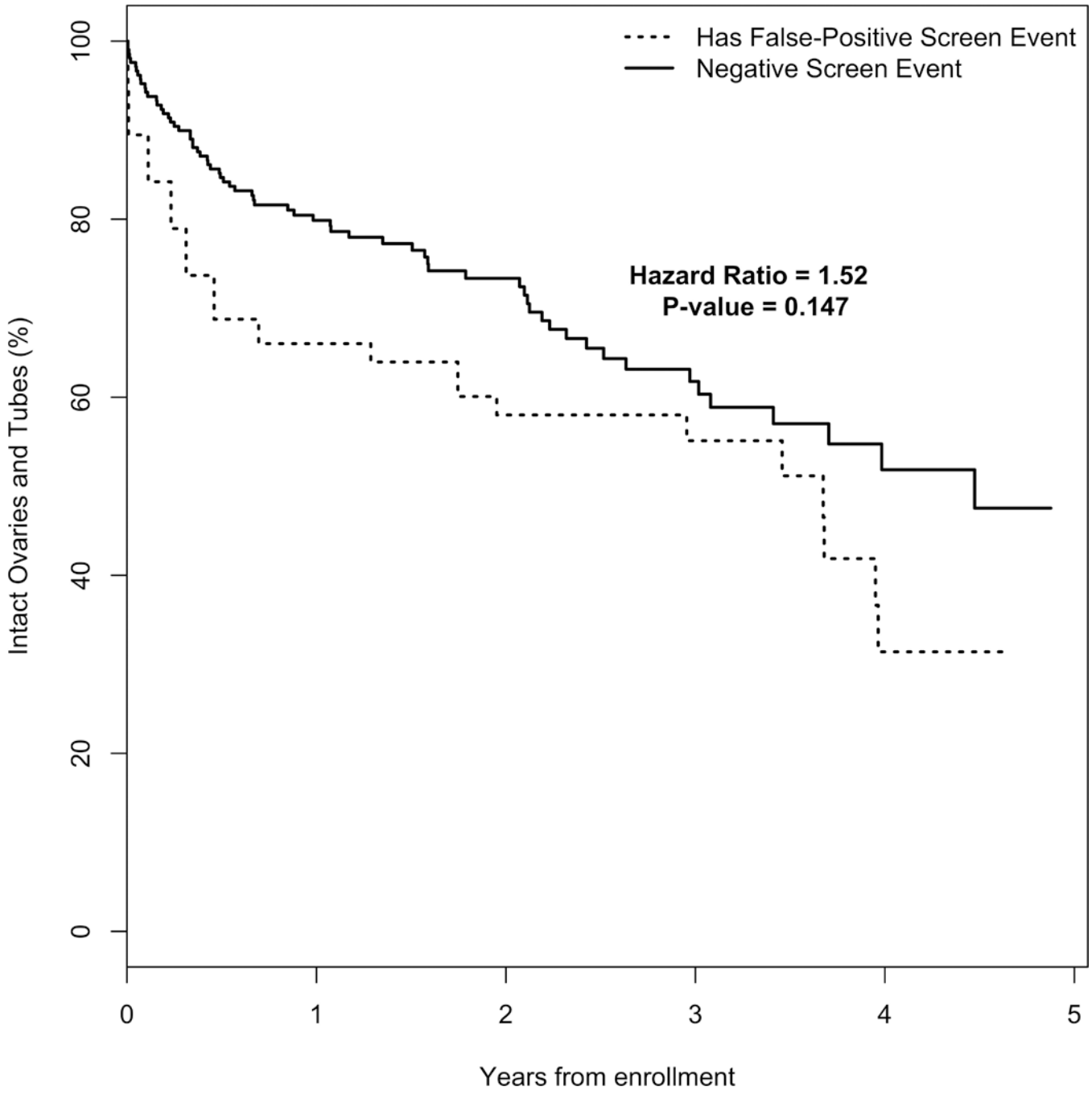
C1-C8: Confirmatory Screens 1-8



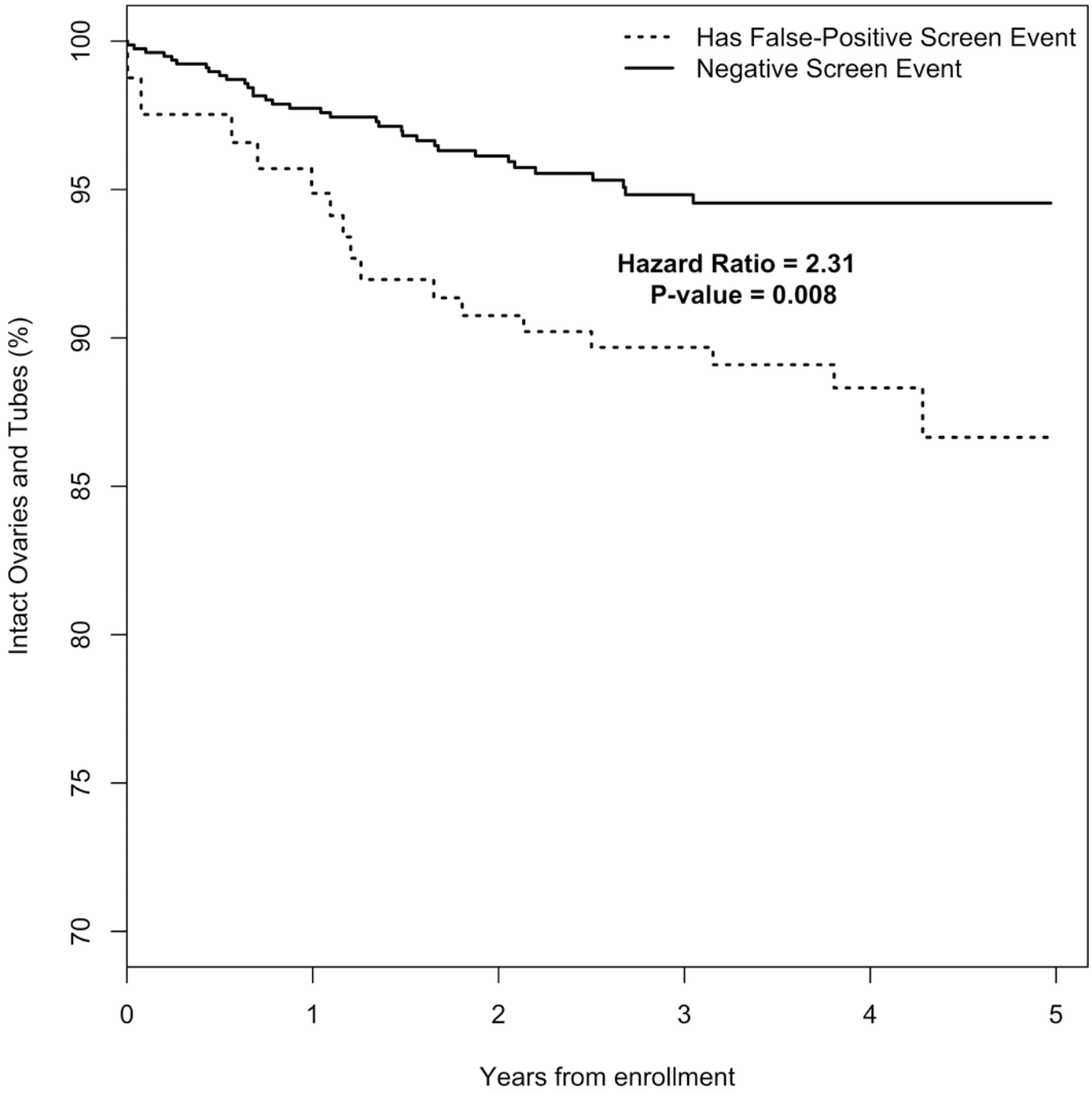
Figures 3:
Kaplan-Meier curves showing rates of pBSO in women with BRCA1/2 mutations (N=229) and those with significant pedigree (N=862), stratified by ovarian cancer worry



Figures 4:
Kaplan-Meier curves showing rates of pBSO in women with BRCA1/2 mutations (N=229) and those with significant pedigree (N=862), stratified by ovarian cancer worry



Figures 5:
Kaplan-Meier curves showing rates of pBSO in women with BRCA1/2 mutations (N=229) and those with significant pedigree (N=862), stratified by FPSE



Figures 6:
Kaplan-Meier curves showing rates of pBSO in women with BRCA1/2 mutations (N=229) and those with significant pedigree (N=862), stratified by FPSE

Table 1:

Summary of participant characteristics at baseline

Variable	Value	RG1: BRCA mutation carrier (N=234)	RG2: Significant pedigree (N=866)	P-value
Age at enrollment	Mean (SD)	39(9)	54(9)	<0.001
Age at enrollment (categorical)	25<=age<=44 45<=age<=54 55<=age<=64 65<=age<=85	187 (79.9%) 30 (12.8%) 11 (4.7%) 6 (2.6%)	119 (13.7%) 322 (37.2%) 286 (33.0%) 139 (16.1%)	<0.001
Self-reported race	White/Caucasian Non-white	188 (80.3%) 45 (19.2%)	755 (87.2%) 111 (12.8%)	0.0157
Ethnicity	Ashkenazi Jewish Hispanic	87 (37.2%) 22 (9.4%)	139 (16.1%) 33 (3.8%)	<0.001 0.001
Personal history of breast cancer	Yes	49 (20.9%)	289 (33.4%)	<0.001
Number of first-or second-degree relatives with ovarian cancer	0 1 2 3+	124 (52.9%) 81 (34.6%) 21 (9.0%) 8 (3.4%)	456 (52.5%) 336 (38.8%) 65 (7.5%) 9 (1.0%)	0.0438
Prior genetic test	Tested	234 (100%)	278 (32.1%)	<0.001
Genetic test results among participants with a prior genetic test	Negative Variant(s) of unknown significance Confirmed predisposition Inconclusive	0 (0%) 8 (3.4%) 234 (100%) 0 (0%)	226 (26.2%) 10 (3.6%) 20 (7.2%) 21(7.6%)	N/A
Ovarian cancer worry	Moderate/Severe	130 (55.6%)	212 (24.5%)	<0.001