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An Empirical Analysis of Precision Previvorship: Are Familial and High-Risk Cancer Preventive Programs Evidence Based?

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INTRODUCTION

Over the last decade, some academic medical centers have launched new cancer screening or preventive programs, often appealing to individuals with family history or known elevated genetic risk. Preventive and screening services are offered for a breadth of tumor types, including pancreatic, hematologic, breast, and lung cancers. Standard services available are cancer prevention counseling, prophylactic surgery, personalized genomic risk profiling, removal of precancerous growths, ongoing surveillance, access to clinical trials, and exercise and nutrition plans.

These academic programs tend to utilize multidisciplinary and personalized approaches to prevention and care. Just as precision oncology promises to pair drugs with specific tumor mutations, *precision previvorship* pairs the identification of novel genomic biomarkers with personalized counseling to prevent or reduce the risk of developing cancer.[1] Previvors are considered individuals who are proactive in reducing or eliminating the risk of developing genetic cancer.[2] By being proactive, many of these programs advertise a goal of "preventing cancer," which may be misleading if these claims are not evidence based.

The primary goal of screening and testing is to inform care decisions, or in preventive medicine, promote health and precautionary measures. However, these evaluations are not benign. The value of these tests depends on their accuracy, costs, and risks, as well as the benefits and potential harms of preventive efforts.[3,4] There is widespread interest in eliminating the chances a patient develops cancer, especially one to which they have may have a predisposition. But an increased opportunity to receive essential screening or genetic counseling is not proof of benefit. Empirical verification is warranted for these programs and the interventions they utilize.

We sought to examine the frequency of these programs and the evidence base for genetic risk profiling, nutrition, exercise, and screening for common tumor types. Specifically, what is the cited evidence for these services? How many studies measure patient-centered outcomes (eg, survival, quality-of-life)? Of studies that measure patient-centered outcomes, how many report all-cause mortality or quality-of-life endpoints? What is the research quality of these endpoints? We set out to address these questions by performing a systematic review of high-risk cancer preventive programs.

METHODS

Program Identification

We identified academic cancer preventive programs using a Google search. Search terms used were "cancer" and "prevention center" or "high-risk prevention center". Preventive programs were searched for each sex-specific tumor type from the American Cancer Society's leading sites of new cancer cases and deaths for 2021.[5] Male cancer-specific searches included: prostate, lung and bronchus, colon and rectum, urinary bladder, melanoma, kidney and renal, non-Hodgkin lymphoma, oral cavity and pharynx, leukemia, and pancreas cancer. Female cancer-specific searches

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Authorship: VP conceptualized study design; KP reviewed and abstracted data; AH reviewed and confirmed abstracted data; KP wrote the first draft of the manuscript; and all authors reviewed and revised subsequent and finalized draft of the manuscript.

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included all of the above (excluding urinary bladder and prostate) plus breast, uterine corpus, and thyroid cancer. The first 100 non-private results were analyzed for 1) academic affiliation, 2) act (ie, management, prevention), 3) threat (ie, familial, high-risk), and 4) cancer type. Eight tumor types were identified from the program identification search. In addition, we supplemented our findings from links within the academic program website that offered services for other tumor-type prevention.

Literature Search

Our literature search was conducted systematically using PubMed from March 21, 2021, to April 8, 2021. We sought to examine 4 different interventions across 8 different tumor types. PubMed search terms consisted of "genetic screening or counseling" or "screening" or "nutrition" or "exercise" and "*cancer type*" and "prevention". Parameters were kept uniform by utilizing the following search input, "*intervention* for *cancer* prevention" (eg, "screening for breast cancer prevention"). The first 50 results, filtered by clinical trials, observational studies, and randomized controlled trials (RCTs), were used for data abstraction. This process was repeated for the 4 interventions we sought to examine across 8 different tumor types. Many of the searches did not have at least 50 results, contributing to fewer studies than expected. We did not restrict subgroup analyses or the setting of the medical interventions. Studies that lacked specific variable criteria or did not define their observational modeling a priori were excluded due to potential issues of multiplicity.[6]

Data Abstraction

We independently extracted data for the academic cancer preventive programs on screening use, genomic risk profiling, risk-assessment planning, access to curative clinical trials, access to preventive clinical trials, and nutrition, lifestyle, or exercise counseling. It was also determined whether the academic program presented data from the literature to support their programs. Additionally, we recorded their *U.S. News & World Report's* rankings for "best hospitals for cancer."[7]

We gathered information by conducting a literature review to assess the evidence base of the interventions. Data were extracted based on cancer type, intervention, participant age, study design, and the range of time (ie, dates) the data were used for observational studies. The principal outcomes examined in the experimental and control arms included incidence reduction, cancer mortality, overall mortality, quality of life, and program adherence/participation. Relative risk (eg, risk ratio, hazard ratio, or odds ratio) was recorded for cancer-specific mortality, all-cause mortality, and observed incidence. For studies that used rank-order grouping (eg, quartile reporting), unadjusted risk ratios were calculated using the highest-quality quartile (eg, micronutrient intake) compared with the reference or lowest category. For studies that reported data on multiple tumor types, we recorded information for each cancer type separately. If a clinical trial did not have any data posted, reviewers referenced the trial identification number to ensure the trial was still ongoing. Reviews, commentaries, and meta-analyses that showed up in the results were excluded from the analysis.

Statistical Analysis

We reported results in frequencies and percentages. All analyses were performed in Microsoft Excel, version 16.43 (Microsoft Corporation, Redmond, Wash). We did not need the consent of the institutional review board because we used freely accessible data that did not include personally identifiable information.

RESULTS

Sixty-nine familial or high-risk preventive cancer programs were identified. Of those, 65 (94%) were affiliated with an academic institution located in the United States. The average *US News & World Report* ranking for best cancer hospitals was 23 (1-52) for the institutions identified.[7] We looked at what services these programs provided and found that 62 (95%) offered early cancer screening (eg, magnetic resonance imaging, colonoscopy), 50 (77%) offered genetic testing and counseling, 44 (68%) developed tailored risk-assessment scores, and 15 (23%) and 28 (43%) created personalized nutrition and exercise/lifestyle programs, respectively. In addition to personalized prevention, 20 (31%) of these programs offered access to preventive cancer trials, which explore novel methods for early detection and risk mitigation, while 8 (12%) provided access to clinical trials if patients developed cancer in the future.

We found 4 (6%) of the 65 programs cited literature or studies (eg, National Lung Screening Trial) to support their program. Only centers for prostate, pancreatic, lung, melanoma, gynecologic, colorectal, leukemia, and breast cancers were identified. Even though the American Cancer Society's leading sites of new cancer cases and deaths for 2021 contain more tumor types, the systematic analysis of the evidence base only included these tumor types.[5]

Of the 1174 studies found regarding these interventions, 158 studies were omitted as they were not primary studies (eg, reviews, meta-analyses, and commentaries), leaving 1016 that met our predefined inclusion criteria. The most common study designs were: observational studies (n = 524; 52%), RCTs (n = 263; 26%), non-randomized clinical trials (n = 88; 9%), protocol or feasibility trails (n = 79; 8%), post hoc analyses (n = 33; 3%), laboratory experiments (n = 22; 2%), and qualitative research (n = 7; <1%). A total of 191 (19%) studies measured the impact of cancer screening, 184 (18%) measured the effects of exercise, 157 (15%) measured the effects of nutrition, and 130 (13%) measured genomic screening and risk profiling. The remaining interventions (n = 354, 34%) were excluded, unless they reported on patient-centered outcomes (PCOs), in which case their data are included in Table 1. Prevention

Table 1 Number and Percentage of Studies Reporting on the Evidence of Cancer Prevention Services, Based on Patient-Centered Outcomes, Study Design, and Effectiveness Across all Preventive Interventions

	RCT n (%)	Non-RCT n (%)	All Studies n (%)
Incidence (n = 86)			
Reduced	7 (8)	22 (26)	29 (34)
No effect	11 (13)	26(30)	37 (43)
Increased	6 (7)	11 (13)	17 (20)
Mixed results	1 (1)	2 (2)	3 (3)
Cancer mortality (n = 40)			
Reduced	11 (28)	14 (35)	25 (63)
No effect	5 (12)	10 (25)	15 (37)
All-cause mortality (n = 34)			
Reduced	N/A (0)	3 (9)	3 (9)
No effect	19 (56)	12 (35)	31 (91)
Quality of life (n = 9)			
Improved	2 (22)	N/A (0)	2 (22)
Mixed	N/A (0)	1 (11)	1 (11)
No effect	5 (56)	1 (11)	6 (67)

RCT = randomized controlled trial.

was assessed based on tumor type: breast (n = 186; 18%), prostate (n = 174; 17%), colorectal (n = 145; 14%), lung (n = 100; 10%), pancreatic (n = 96, 9%), leukemia (n = 66, 7%), melanoma (n = 56, 6%), obstetrics/gynecology (n = 45, 4%), and other diseases (n = 148, 15%) that were not applicable to our analysis. The obstetrics/gynecology category included cervical, ovarian, and uterine cancer.

Just 142 (14%) of the 1016 studies looked at PCOs, for example, survival or quality of life, while 534 (53%) analyzed disease-oriented endpoints. We found 340 (33%) studies that reported on patients who had already developed cancer, which was out of the preventive scope of our analysis. The Figure illustrates a detailed breakdown of the endpoints from the 142 studies that evaluated PCOs. Of the 86 studies that reported on the rate of new cancer cases (ie, incidence), 20 (34%) showed a decrease in incidence, 37 (43%) showed no difference, 17 (20%) showed increased rates of cancer, and 3 (3%) had mixed results depending on sub-group.

The number and percentage of trials that reported PCOs, not limited by intervention type, are presented in Table 1. In general, we found that a notable percentage of trials (43%) found no reduction in incidence. And, while most studies found a reduction in cancer-specific mortality (63%), most studies did not find a reduction in overall mortality (91%). Further, we did not find any RCTs that showed a reduction in all-cause mortality, whereas 19 showed no impact.

We also reported these data, along with their median relative risk ratios, stratified by study design (eg, RCT vs non-RCT) and intervention type (eg, screening, exercise), in Table 2. Notably, we found only 1 RCT that assessed a PCO for exercise and none for genomic screening and risk profiling. In the studies we evaluated, we found no

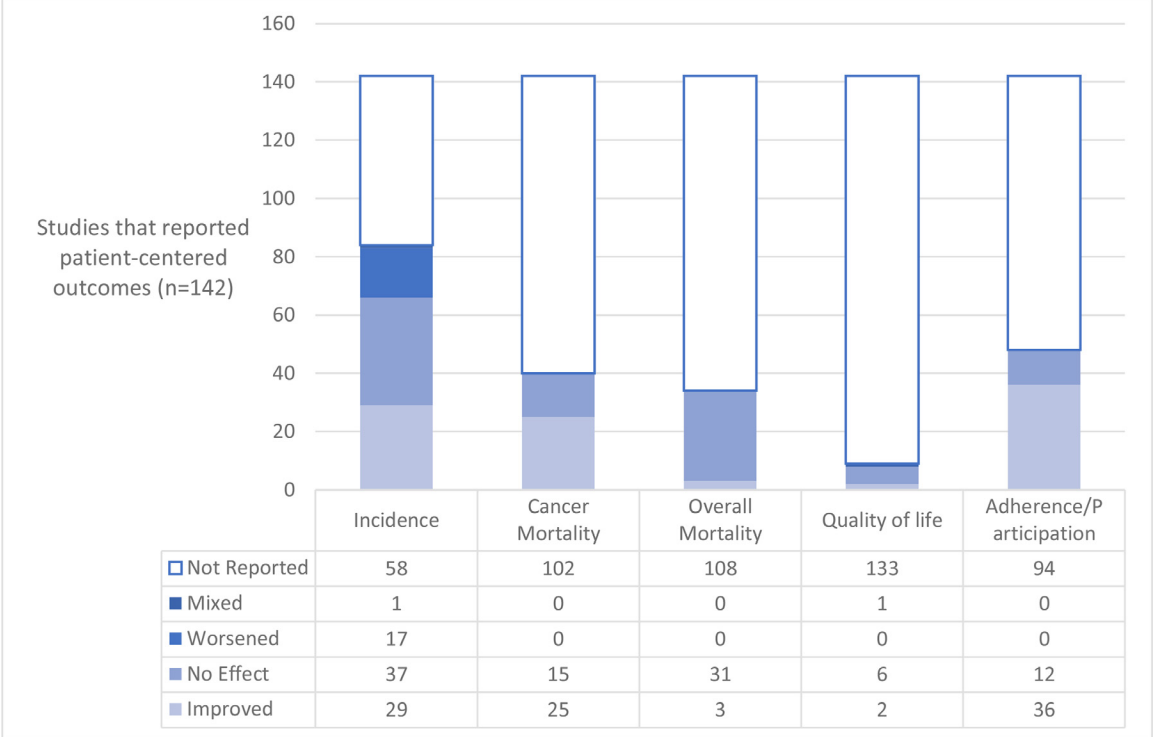

Figure Results of studies that reported patient-centered outcomes.

Table 2 Relative Risk Ratios of Studies Reporting on the Evidence of Cancer Prevention Services, Based on Intervention Type, Study Design, and Effectiveness

	RCT Median RR Range (n)	Non-RCT Median RR Range (n)
Screening		
Reduced incidence	N/A (0)	0.64, 0.04 (2)
No effect on incidence	1.01, 0.75 (4)	1.09, 0.08 (4)
Increased incidence	1.67, 1.42 (4)	1.27, 0.72 (9)
Reduced cancer mortality	0.72, 0.51 (8)	0.77, 0.34 (9)
No effect on cancer mortality	0.92 (1)	1.03, 0.37 (7)
Reduced all-cause mortality	N/A (0)	0.35 (1)
No effect on all-cause mortality	0.99, 0.21 (6)	0.99, 0.04 (7)
Genomics		
Reduced incidence	N/A (0)	0.62 (1)
No effect on incidence	N/A (0)	3.94, 5.68 (2)
Reduced cancer mortality	N/A (0)	0.65 (1)
No effect on cancer mortality	N/A (0)	2.49 (1)
Reduced all-cause mortality	N/A (0)	0.35 (1)
No effect on all-cause mortality	N/A (0)	N/A (0)
Nutrition		
Reduced incidence	0.48, 1.12 (4)	0.82, 0.39 (10)
No effect on incidence	1.09, 2.0 (7)	0.95, 0.23 (10)
Increased incidence	1.17 (1)	N/A (0)
Reduced cancer mortality	0.49, 0.03 (2)	0.75, 0.25 (4)
No effect on cancer mortality	0.75-0.00 (3)	N/A (0)
Reduced all-cause mortality	N/A (0)	0.73 (1)
No effect on all-cause mortality	0.83, 0.13 (11)	0.95, 0.06 (3)
Exercise		
Reduced incidence	N/A (0)	0.74, 0.38 (9)
No effect on incidence	N/A (0)	0.99, 0.21 (9)
Increased incidence	1.76 (1)	1.16, 0.22 (2)
Reduced cancer mortality	N/A (0)	0.78 (1)
No effect on cancer mortality	N/A (0)	N/A (0)
Reduced all-cause mortality	N/A (0)	N/A (0)
No effect on all-cause mortality	N/A (0)	0.92 (1)

RCT = randomized controlled trial; RR = risk ratio.

randomized studies for any of the intervention types that reduced overall mortality, and only 3 interventions with 1 non-randomized study each that reported a lower overall mortality.

DISCUSSION

Many people are rightfully concerned about their chances of developing cancer if they have relatives that have been diagnosed with or died from the disease. Some people may seek out preventive or screening services to lower their risk of developing cancer or detect it early. Our analysis indicates they have many options to participate in specialized cancer prevention clinics. Here, we identified 65 high-risk preventive cancer programs affiliated with an academic institution, most of which provided services that lacked high-quality evidence.

Because only 4 of the academic prevention programs cited evidence to support the services they provided, and none of the programs performed their own trials to test the effectiveness of their services, we conducted our own literature review. A majority (53%) of the studies measured surrogate markers of the etiology or pathophysiology of disease (ie, disease-oriented). Only 14% of studies measured patient-centered outcomes—endpoints that inherently matter to patients—such as morbidity, quality of life, and mortality.[8] This could be due to capturing a small scope of the literature, but it could also reflect the increasing trend in oncology research to use surrogate endpoints.[9] Previous research, both in oncology and other disciplines, has demonstrated the shortcomings of using such endpoints to represent benefits to patients in the real world.[10,11]

Non-RCT exercise and nutrition research were the primary drivers for the observed lowered incidence and cancer mortality in 29 (34%) of the studies. Accounting for the said interventions, screening also led to a decrease in cancer mortality for 25 (63%) of the studies. Table 2 shows that while some studies show benefit, many have no impact, particularly when higher-quality study design and more rigorous endpoints are considered. For instance, 19 RCTs looked at all-cause mortality, but none of them found any improvement in overall survival, and only 2 of 7 showed an improvement in quality of life. We must ask ourselves whether these services are merely medicalizing healthy people without providing health gains.[12,13]

If these services are largely not evidence based, are they akin to executive physicals? Korenstein et al[14] investigated the level of evidence supporting executive physicals provided by top-ranked hospitals, finding that many of the services offered lacked adequate evidence per US Preventive Services Task Force recommendations.[15] Another issue related to our results is that because these academic medical centers are esteemed, the services they provide can be implicitly deemed valuable, resulting in wasteful spending and low-value care.[14] Moreover, these programs may solicit people with the financial resources to travel and pay for the assessments and tests.

An issue of semantics also emerges when discussing how these academic programs are marketed to the general public. *Prevention*, to the layman, likely means to stop something from happening in the first place.[16] However, detecting disease early on or delaying its development is typically

considered screening.[17-19] We found that the intervention most commonly promoted by these academic centers was screening. The average person may thus be confused by the marketing and messaging of these programs.

Limitations

This study has 4 main limitations. First, we captured only a small scope of the literature (n = 1174). A more representative sample of the literature may have been captured if more studies were analyzed or if different search engines or parameters were used. However, we are unsure if that would alter our findings.

Second, we did not conduct independent searches for the effectiveness of chemo- or drug prevention in our research. Studies have been conducted to measure the effects of certain drugs and cancer prevention, such as tamoxifen for breast cancer and finasteride for prostate cancer.[20,21] However, we did not include these interventions because most academic programs did not market chemo- or drug prevention.

Third, we excluded secondary studies, such as meta-analyses. While these might have been noteworthy to consider, many included a mixture of randomized and observational data, and as such we felt categorization would be unnecessarily confusing. We encourage others to expand our efforts.

Lastly, we identified 26 clinical trials that were still ongoing during this analysis. It's possible that the findings of these studies will have a significant effect on the literature in terms of cancer prevention. Future researchers are encouraged to compare the findings of our study with the outcomes of these trials to discover potential differences.

CONCLUSION

We found 69 high-risk cancer prevention or screening programs, and 65 were associated with academic institutions, the majority of which offered clinical services with low-quality evidence. Our findings raise concerns that the services provided by these academic medical centers are based on weak evidence. The preventive message that these programs advertise may lead to excessive spending, low-value care, and mixed messaging to the public.

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