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MESTRADO INTEGRADO EM MEDICINA

EVALUATION OF THE KNOWLEDGE AND USE OF PROSTATE CANCER RISK CALCULATORS BY GENERAL PRACTITIONERS

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INSTITUTO DE CIÊNCIAS BIOMÉDICAS ABEL SALAZAR
UNIVERSIDADE DO PORTO

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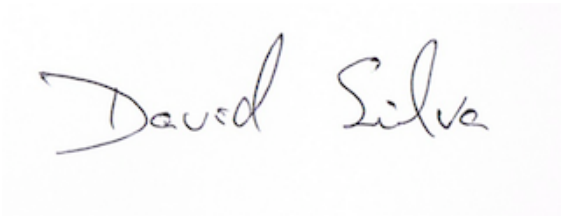
Junho de 2019



Junho de 2019

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Gostaria ainda de agradecer a todos os médicos que se disponibilizaram a responder ao inquérito, permitindo concluir o trabalho de investigação que me propus a fazer.

RESUMO

Introdução e Objetivos

O uso de calculadoras de risco para cancro da próstata é recomendado para identificar homens em risco de ter este cancro. O nosso objetivo é perceber se médicos de Medicina Geral e Familiar conhecem estas calculadoras e se as usam na sua prática clínica, e também medir a mudança na sua decisão após saberem o risco para cancro da próstata.

Métodos

Questionários foram enviados para médicos de Medicina Geral e Familiar em Portugal, onde foi questionado quais calculadoras de risco conheciam e quais usavam. De seguida foram apresentados seis casos clínicos sem o risco calculado e foi perguntado quais refeririam para especialidade hospitalar. Depois de dada a resposta, os riscos calculados foram apresentados e foi feita a mesma questão. Foi usado o teste de McNemar para determinar se havia alteração na decisão após saberem o risco para cancro da próstata.

Resultados

92% dos participantes não usam calculadoras de risco para cancro da próstata na sua prática clínica. Comparando as respostas com e sem o risco calculado, verificou-se uma mudança estatisticamente significativa em todos os casos. Em 66.6% dos casos a mudança foi de referenciar para não referenciar para especialidade hospitalar.

Conclusão

Com este questionário percebemos que, apesar do seu uso ser recomendado por várias *guidelines* de urologia e ter sido mostrado que reduzem o número de biópsias desnecessárias, a maioria dos médicos de Medicina Geral e Familiar não usam nem conhecem calculadoras de risco para cancro da próstata. Isto pode dever-se ao facto de as 'Normas de Orientação Clínica', usadas pelos médicos desta especialidade em Portugal, não referirem a recomendação do uso de calculadoras de risco.

Palavras-chave: cancro da próstata, calculadoras de risco, PSA, médicos de Medicina Geral e Familiar, sobrediagnóstico, hipertratamento

ABSTRACT

Introduction and Objectives

The use of multivariable risk calculators predicting prostate cancer is recommended to identify men at risk for prostate cancer. We aimed to understand if general practitioners know about any risk calculators for prostate cancer and if they use them in their daily practice, and also to measure a change in attitude after knowing the risk for prostate cancer.

Methods

Surveys were sent to General Practitioners in Portugal asking which risk calculators they are familiar with and use. This was followed by six clinical scenarios presented without the calculated risk for prostate cancer, where practitioners had to answer which cases they would refer to urology. After answering, the calculated risks were presented and the same question was asked. McNemar's test was used to determine whether there was a change in the decision after knowing the risk for prostate cancer.

Results

92% of participants do not use risk calculators for prostate cancer in their daily practice. Comparing the answers with and without showing the PCa and csPCa risk, there was a statistically significant change in attitude in all cases. In 66.6% of cases, the change was from referral to non-referral.

Conclusion

In this survey, we found that the majority of general practitioners do not use risk calculators for prostate cancer, nor did they know of the 7 risk calculators listed, even though they are recommended in various urology guidelines and have been found to reduce the number of unnecessary biopsies. This could be because the 'Norms of Clinical Orientation', used by general practitioners in Portugal, don't refer to the use of risk calculators.

Keywords: prostate cancer, risk calculators, PSA, general practitioners, overdiagnosis, overtreatment

ABBREVIATIONS

ACeS: Agrupamento de Centros de Saúde
csPCa: Clinically significant Prostate Cancer
EAU: European Association of Urology
ERSPC: European Randomised Study of Screening for Prostate Cancer
ESTRO**:** European Society for Radiotherapy & Oncology
ESUR: European Society of Urogenital Radiology
GP: General Practitioner
PCa: Prostate Cancer
PLCO: Prostate, Lung, Colorectal and Ovarian
PSA: Prostatic Specific Antigen
RPCRC**:** Rotterdam Prostate Cancer Risk Calculator
SIOG: International Society of Geriatric Oncology

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INTRODUCTION

Prostate Cancer

Prostate Cancer (PCa) is the most prevalent cancer in men globally. It was the second most frequently diagnosed cancer in 2018, with around 1.3 million new cases, and is the fifth leading cause of death in men worldwide. In Europe, it is the most frequently diagnosed cancer, and the third most common cause of death among men.[1]

Screening for prostate cancer

The large number of men affected by prostate cancer worldwide led to the conduction of several studies that tried to establish the effect of Prostatic Specific Antigen (PSA)-based screening on prostate cancer mortality.

However, prostate cancer screening is still one of the most controversial topics in urological literature.[2] Although the introduction of PSA screening in the early 90s has significantly increased the number of prostate cancers diagnosed,[3] there's controversy to whether there's a benefit of this screening.[4]

The results of two large prospective randomized controlled trials of prostate cancer screening with PSA reported different conclusions: the U.S.-based Prostate, Lung, Colorectal and Ovarian (PLCO) Cancer Screening demonstrated no benefit to screening[5], while the European Randomised Study of Screening for Prostate Cancer (ERSPC) showed a 21% reduction in prostate cancer deaths applying PSA based screening[6].

The prostate cancer mortality reduction is an obvious benefit of screening; however, there are negative consequences associated with PSA testing and prostate biopsy, and possible harms related to the treatment of prostate cancer[7,8,9]. Studies showed that men with false-positive PSA results reported a greater worry about prostate cancer and underwent more tests and urology visits compared to those who had true-negative tests.[10,11]

The most common risks related to prostate biopsy are bleeding and infection. Although major complications that require hospitalization are rare, minor complications such as hematuria (66%) and genitourinary tract infection (6.1%) are more frequent.[12]

Prostate cancer screening with PSA can also lead to overdiagnosis and overtreatment.[13] Overdiagnosis is the detection of prostate cancer that would have never become symptomatic or clinically apparent in the absence of screening.[14] It is estimated that overdiagnosis ranges from 23% to 42% due to screening.[15] After a follow-up of 13 years, the ERSPC investigators noted that to prevent one death from prostate cancer, 781 men needed to be screened and 27 patients needed to be treated.[6]

Overtreatment occurs when these overdiagnosed cases are treated,[15] and are related to the adverse effects of the treatment. Urinary incontinence and sexual dysfunction are the two most common adverse effects of the most common treatment options, surgery (i.e., radical prostatectomy) and radiation therapy.[16]

To overcome these problems, the guidelines of the European Association of Urology (EAU), European Society for Radiotherapy & Oncology (ESTRO), European Society of Urogenital Radiology (ESUR) and International Society of Geriatric Oncology (SIOG) recommend an individualised risk-adapted strategy for early detection to a well-informed man with a good performance status and a life expectancy of at least ten to fifteen years. These guidelines also state that informed men who request an early diagnosis should be given a PSA test, undergo a digital rectal examination and his potential risk of cancer should be assessed using risk calculators, reducing the number of unnecessary biopsies.[2,13] There are several prostate cancer risk calculators and, according to these same guidelines, none of the risk calculators has clearly shown superiority and it's a matter of personal choice as to which one to use.[13] However, a recent study compared several different risk calculators predicting biopsy outcome and showed the Rotterdam Prostate Cancer Risk Calculator (RPCRC) is superior in identifying those men at risk for clinically significant prostate cancer (CsPCa) (i.e. Gleason$\geq$3+4)[17].

As General Practitioners (GPs) are, usually, the first point of contact for patients, and are responsible for making the decision of whether or not to refer the patients

to a urologist, it is important that they know that there are risk calculators which can assist them in making this decision and how to use them.

The aim of this study is to understand if general practitioners know about any risk calculators for prostate cancer and if they use them in their daily practice, and also to measure a change in attitude after knowing the risk for prostate cancer.

METHODS

Sample

After the approval from the Executive Council of a regional network of GP surgeries (ACeS Grande Porto II - Gondomar), surveys were sent out centrally to the coordinator of each GP surgery who, in turn, sent them to all doctors (specialists and interns in general practice) working at each health centre. From this, 52 complete responses were collected. Participants were not identifiable by name at any point during the collection of data, and participation was voluntary.

Survey design

The survey first asked for information about the experience and role of each participant. It then consisted of questions around the professional's knowledge of risk calculators, including which risk calculators they were familiar with and use, followed by clinical scenarios (appendix 1). Each case detailed previous biopsy results, PSA, digital rectal examination observations, estimated size of the prostate (from the digital rectal examination) and results of transrectal ultrasound, where information was available.

Initially, all cases were presented without the calculated risk of PCa/csPCa and participants selected which cases they would refer to urology. After this stage, the predicted risk of PCa and csPCa, based on the RPCRC was shown, and participants were asked to again select cases for referral.

Statistical analysis

The statistical analysis was carried out using IBM® SPSS® Statistics 25. The measurements 'would you refer for prostate biopsy?' before and after the cancer risk was shown were analysed individually for each case and the method used was the McNemar's test. The McNemar's test is a non-parametric hypothesis test which is used for analysing two paired groups, as in the present case: before vs. after groups. It takes into account the matched pairs which have changed, randomly or not, from 'Yes' to 'No' and vice versa. The two following hypotheses were used:

· H0 (Null Hypothesis): the knowledge of the cancer risk does not affect the decision of the participants about the biopsy requirement.

· H1 (Alternative Hypothesis): the knowledge of the cancer risk affects the decision of the participants about the biopsy requirement.

It is important to emphasize that the matched pairs which did not change from ‘Yes’ to ‘No’ and from ‘No’ to ‘Yes’ were not considered relevant information for this analysis. The p-values less than 0.05 was considered as statistically significant.

RESULTS

Of the 52 participants, 85% were female and 15% male (Fig.1). Practitioners were either specialists (69%) or interns (31%) in general practice (Fig. 2). They had a range of experience, from 0 to over 30 years, with the majority having 0-5 years of experience (Fig.3).

When asked if they use risk calculators for prostate cancer, 92% of participants answered 'No' (Fig.4). Practitioners were also questioned on their knowledge of risk calculators. The majority (92%) hadn't heard of the options provided (Fig. 5), and 100% stated that they do not use any of the risk calculators listed (Fig.6).

The following results show whether GPs would refer each patient for a biopsy after knowing the risk for prostate cancer.

Case 1

Before the risk of prostate cancer was shown, 77% of practitioners would refer the patient for biopsy (Fig.7). Afterwards, this increased to 100% (Fig.8).
0 practitioners changed from 'Yes' to 'No'; 12 practitioners changed from 'No' to 'Yes'. The p-value of $p < 0.001$ indicates that there is significant difference in the GP's decision after knowing the cancer risk (Tables I and II).

Case 2

Before the risk of prostate cancer was shown, 23% of practitioners would refer the patient for biopsy (Fig.7). Afterwards, this increased to 54% (Fig.8).
4 practitioners changed from 'Yes' to 'No'; 20 practitioners changed from 'No' to 'Yes'. The p-value of $p = 0.002$ indicates that there is significant difference in the GP's decision after knowing the cancer risk (Tables III and IV).

Case 3

Before the risk of prostate cancer was shown, 100% of practitioners would refer the patient for biopsy (Fig.7). Afterwards, this decreased to 85% (Fig.8).
8 practitioners changed from 'Yes' to 'No'; 0 practitioners changed from 'No' to 'Yes'. The p-value of $p = 0.008$ indicates that there is significant difference in the GP's decision after knowing the cancer risk (Tables V and VI).

Case 4

Before the risk of prostate cancer was shown, 62% of practitioners would refer the patient for biopsy (Fig.7). Afterwards, this decreased to 23% (Fig.8).
20 practitioners changed from 'Yes' to 'No'; 0 practitioners changed from 'No' to 'Yes'. The p-value of $p < 0.001$ indicates that there is significant difference in the GP's decision after knowing the cancer risk (Tables VII and VIII).

Case 5

Before the risk of prostate cancer was shown, 85% of practitioners would refer the patient for biopsy (Fig.7). Afterwards, this decreased to 54% (Fig.8).
16 practitioners changed from 'Yes' to "NO; 0 practitioners changed from 'No' to 'Yes'. The p-value of $p < 0.001$ indicates that there is significant difference in the GP's decision after knowing the cancer risk (Tables IX and X).

Case 6

Before the risk of prostate cancer was shown, 92% of practitioners would refer the patient for biopsy (Fig.7). Afterwards, this decreased to 39% (Fig.8).
28 practitioners changed from 'Yes' to 'No'; 0 practitioners changed from 'No' to 'Yes'. The p-value of $p < 0.001$ indicates that there is significant difference in the GP's decision after knowing the cancer risk (Tables XI and XII).

As noted, all the p-values were statistically significant, leading to the rejection of the null hypothesis in all 6 cases. In a general view, the increase of 'Yes' answers were noticed only for 2 cases (Case 1 and Case 2), corresponding to 33.3% of the data set.

DISCUSSION

The major findings of this study were that the big majority (92.3%) of general practitioners don't use risk calculators for prostate cancer in their daily practice and report not knowing about any of the seven risk calculators detailed in the survey.

These findings could be due to the guidelines for Portuguese general practitioners – the 'Norms of Clinical Orientation' – which do not refer to or recommend the use of risk prediction models like risk calculators for patient selection for biopsy. The guidelines recommend that men with PSA levels above 10ng/mL, or between 4ng/mL and 10ng/mL with a free PSA below 25%, should be referred to urology for biopsy.[18]

However, the use of risk calculators is recommended by the European Association of Urology[13] as it has been shown that using individualised risk prediction calculators with other available prebiopsy information (such as digital rectal examination results and estimated prostate volume) in the urology setting can result in a considerable reduction of unnecessary, potentially harmful and costly biopsies.[19,20,21,22,23]

Our study also showed a change in attitude (i.e. referral for biopsy) after knowing the risk for prostate cancer in all cases presented, with 66.7% of the cases showing a shift from biopsy referral to non-referral, which would lead to a reduction in the number of unnecessary biopsies performed. Consequently, the implications for patients and the health service would be significant, saving stress, discomfort and risk of complications for the former, and time and money for the latter. Our results corroborate a recent study set in a primary health care facility, where GPs used the Rotterdam Prostate Cancer Risk Calculator (RPCRC) to help in their decision whether or not to refer patients for a biopsy. The results showed that risk stratification could prevent almost half of referrals of men to the urologist, with an overall positive predictive value of 79% and an overall negative predictive value of 96% for prostate cancer.[24]

A tool for decision making on referral for prostate biopsy in the primary care setting was recently developed. This tool utilises a range of data, including PSA, percentage

of free PSA and comorbidity, predicting the gain in life expectancy from treatment. It also provides recommendations regarding referral for prostate biopsy. All of these tests are accessible by general practitioners. Using this tool together with a multivariable risk calculator that includes digital rectal examination findings and prostate volume can achieve an even higher clinical impact.[25] Even though this tool still needs further validation, it can be seen as a promising resource for general practitioners and may reduce the overdiagnosis and overtreatment caused by opportunistic PSA testing.

Furthermore, GPs experience uncertainties with prostate cancer screening, as it still is a controversial topic.[26] There are risk calculators available as apps for mobile phones and others available through a web browser, such as the RPCRC (http://www.prostatecancer-riskcalculator.com). If the lack of usage of risk calculators is due to difficulty accessing them, utilising technology to make tools more accessible and user friendly could have a significant impact on their integration into the daily practice of GPs. The use of risk calculators may help practitioners make informed decisions and reduce some of this burden of uncertainty.

Strengths and limitations

This study invited GPs to participate voluntarily and anonymously: this would strengthen the likelihood of obtaining truthful data. The design of the study is such that it can be easily replicated at little cost to researchers and/or participants. The quantitative nature of results mean that the data is relatively easy to analyse, which allows more scope for exploring further lines of enquiry.

It must be noted that results of this study cannot necessarily be generalised, since the sample size was small and participants were all from one health centre group. More accurate results could be gained by replicating the study with a larger sample. This would also allow for identification of regions where GPs are using risk calculators and, to follow on from this, an analysis of the reasons for these regional variations.

Care must also be taken when drawing conclusions from results of online surveys as the validity of answers cannot be completely guaranteed. There is also the possibility of duplicate responses.

Since participation in the study was voluntary, practitioners with strong opinions may have been more likely to take part, potentially resulting in some selection bias. This cannot be proved or disproved but, if the study were repeated on a larger scale, these effects would likely be diluted.

Recommendations

It can be inferred that, if large proportions of practitioners in Portugal aren't using risk calculators, it is a result of lack of awareness, understanding, training or time.

Awareness

The General Health Directory (Direção Geral de Saúde) could publish guidance to GPs, in the 'Norms of Clinical Orientation': these updated guidelines could communicate an expectation that risk calculators for prostate cancer should be used as a tool for making an informed decision. They could also specify recommended risk calculators so that practitioners are aware of what is available to them.

Understanding

Since prostate cancer is the most prevalent cancer in men globally, and the most frequently diagnosed form of cancer in Western Europe, it is clear that prostate cancer should be a training priority. As there is a particular issue around overdiagnosis, GPs need to understand the value of risk calculators in addressing this problem.

Training

As well as understanding why risk calculators are beneficial, GPs should also receive training (whether at conferences, seminars, in-house or online) in how to use them effectively. This should include instruction on how to interpret the results.

Time/integration into daily practice

If tackling the overdiagnosis of prostate cancer was to be made a priority, GPs would naturally receive time to develop their knowledge and understanding of risk calculators. To support practitioners to integrate risk calculators into their daily practice, applications could be readily accessible from within the electronic medical records system.

APPENDICES

Appendix 1: Survey

QUESTIONÁRIO: Uso de Calculadoras de risco para Cancro da Próstata por médicos de Medicina Geral e Familiar

1.Sexo:
- Feminino
- Masculino

2.Função:
- Especialista em MGF
- Interno de Formação Específica (MGF)
- Interno de Formação Específica (outra)
- Interno de Formação Geral
- Outra

3.Experiência:
- <5 anos
- 5-10 anos
- 11-20 anos
- 21-30 anos
- >30 anos

4.Usa Calculadoras de Risco para Cancro da Próstata?
- Sim
- Não

5.Quais Calculadoras de Risco conhece?
- RPCRC/ERSPC
- PCPT
- Karakiewicz
- ProstataClass
- Sunnybrook
- Finne
- Chun
- Nenhuma das anteriores

6.Quais Calculadoras de Risco usa?
- RPCRC/ERSPC
- PCPT
- Karakiewicz
- ProstataClass
- Sunnybrook
- Finne
- Chun
- Nenhuma das anteriores

7. Apenas usando os dados da tabela, qual/quais casos referenciaria para Especialidade Hospitalar?

Caso	Biópsia prévia negativa	PSA	Toque retal	Tamanho estimado por toque retal	Ecografia transretal
1	Não	2	Com alterações	-	30cc, heterogénea
2	Não	4	Normal	-	2cc, normal
3	Não	4	Com alterações	>50cc	-
4	Não	7	Normal	-	80cc, normal
5	Não	25	Normal	-	50cc, normal
6	Não	30	Normal	-	80cc, normal

- Caso 1
- Caso 2
- Caso 3
- Caso 4
- Caso 5
- Caso 6
- Nenhum

8. Sabendo o risco de Ca Próstata, qual/quais casos referenciaria para Especialidade Hospitalar?

Caso	Biópsia prévia negativa	PSA	Toque retal	Tamanho estimado por toque retal	Ecografia transretal	Risco de Ca Próstata	Risco de Ca Próstata clinicamente significativo
1	Não	2	Com alterações	-	30cc heterogénea	30%	16%
2	Não	4	Normal	-	2cc, normal	30%	7%
3	Não	4	Com alterações	>50cc	-	17%	8%
4	Não	7	Normal	-	80cc, normal	9%	2%
5	Não	25	Normal	-	50cc, normal	16%	5%
6	Não	30	Normal	-	80cc, normal	10%	2%

- Caso 1
- Caso 2
- Caso 3
- Caso 4
- Caso 5
- Caso 6
- Nenhum

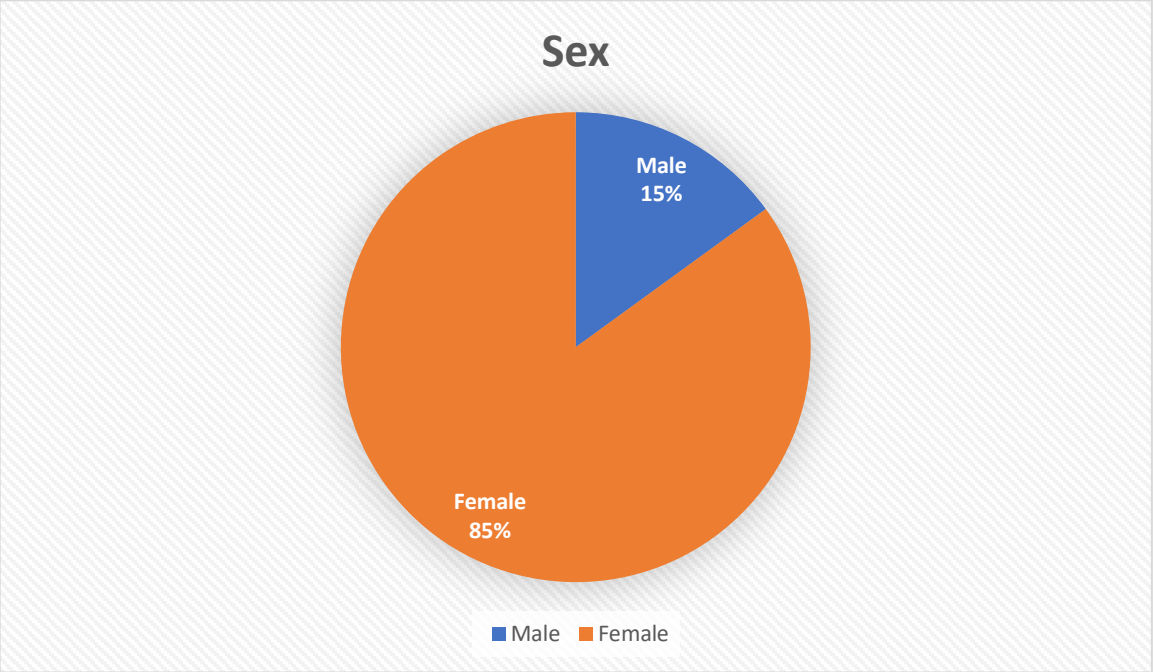

Figure 1 – Sex of participants

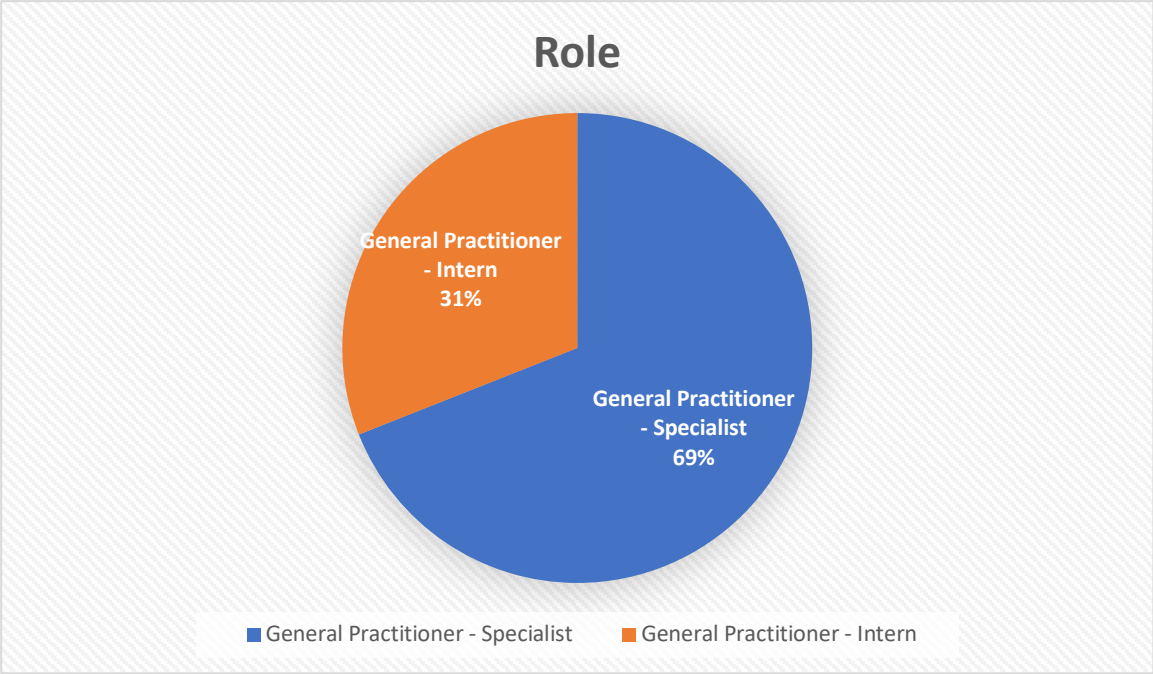

Figure 2 – Role of participants

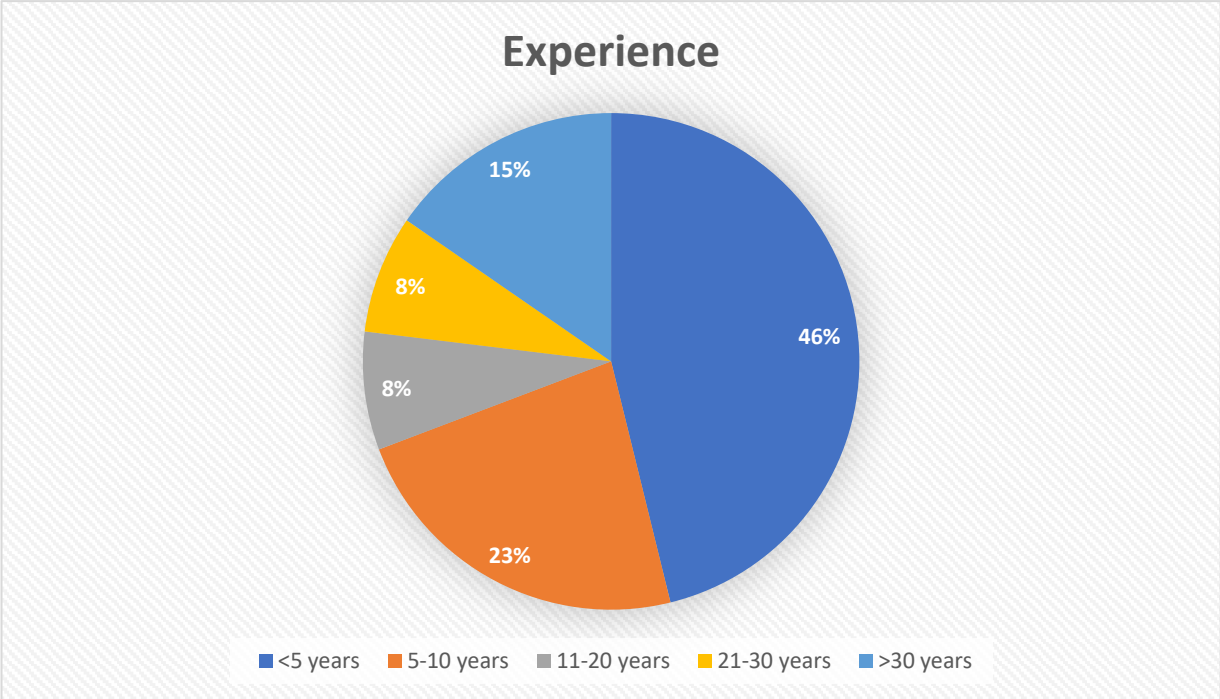

Figure 3 – Experience of participants

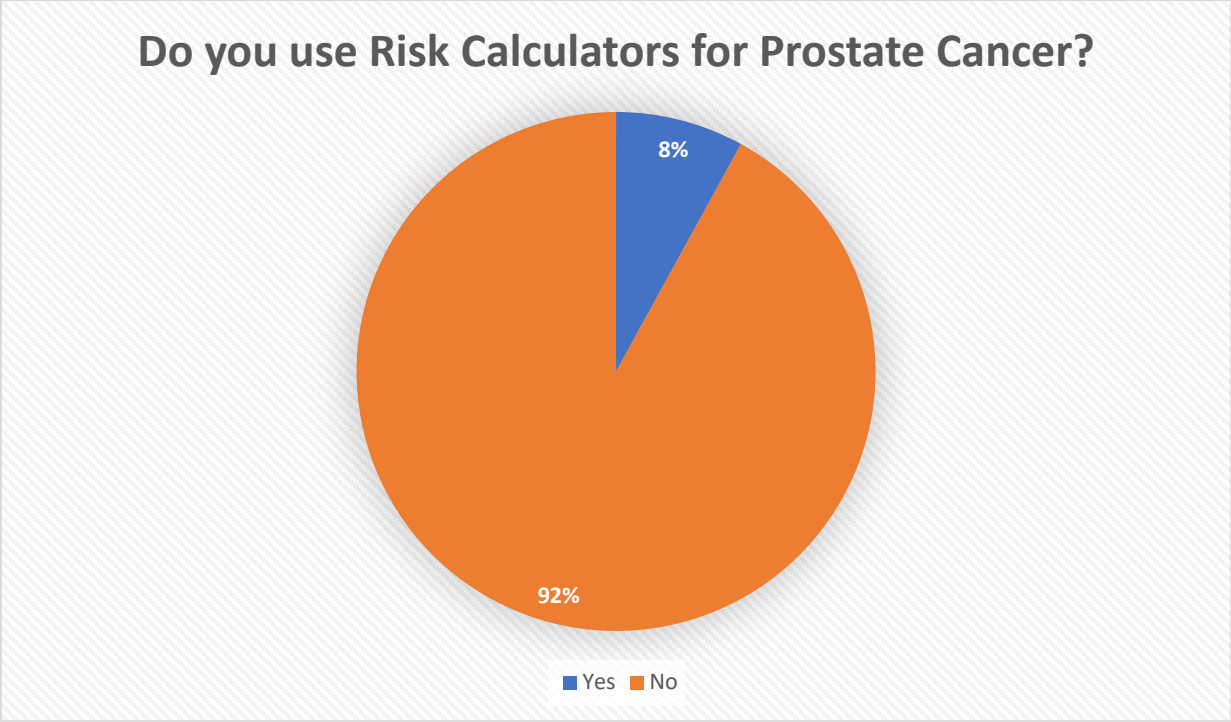

Figure 4 – Quantification of the use of risk calculators

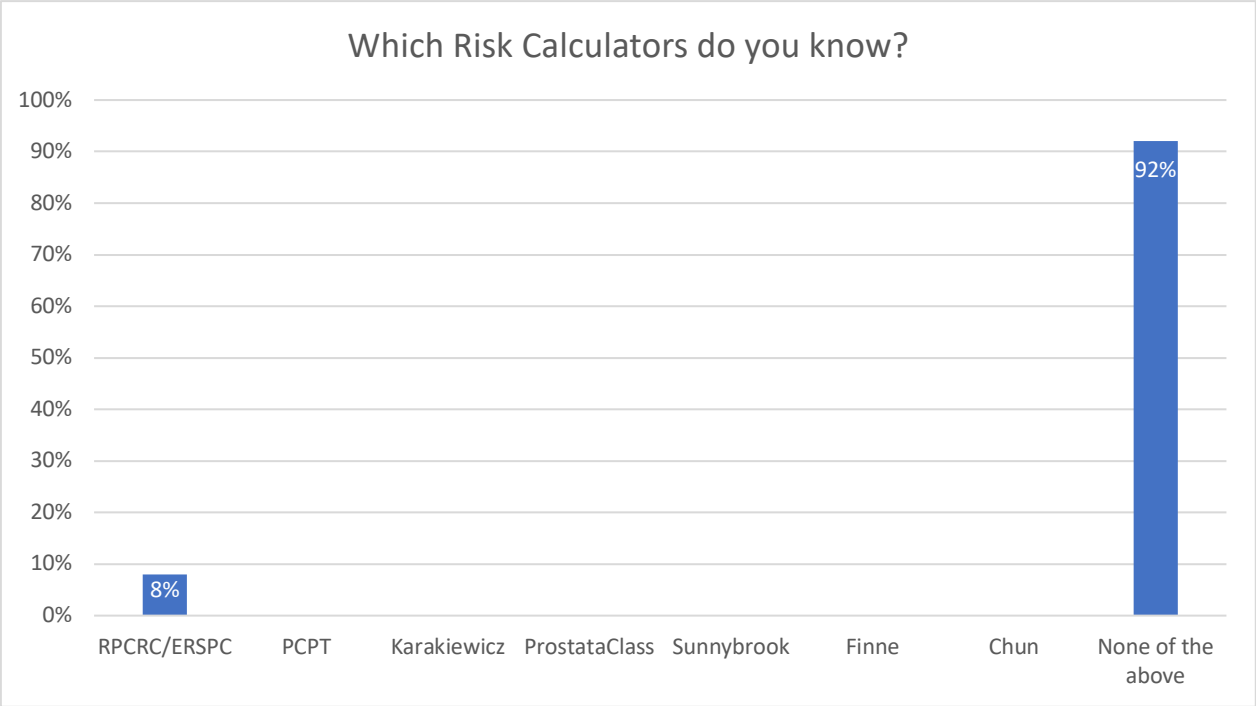

Figure 5 – Knowledge of risk calculators

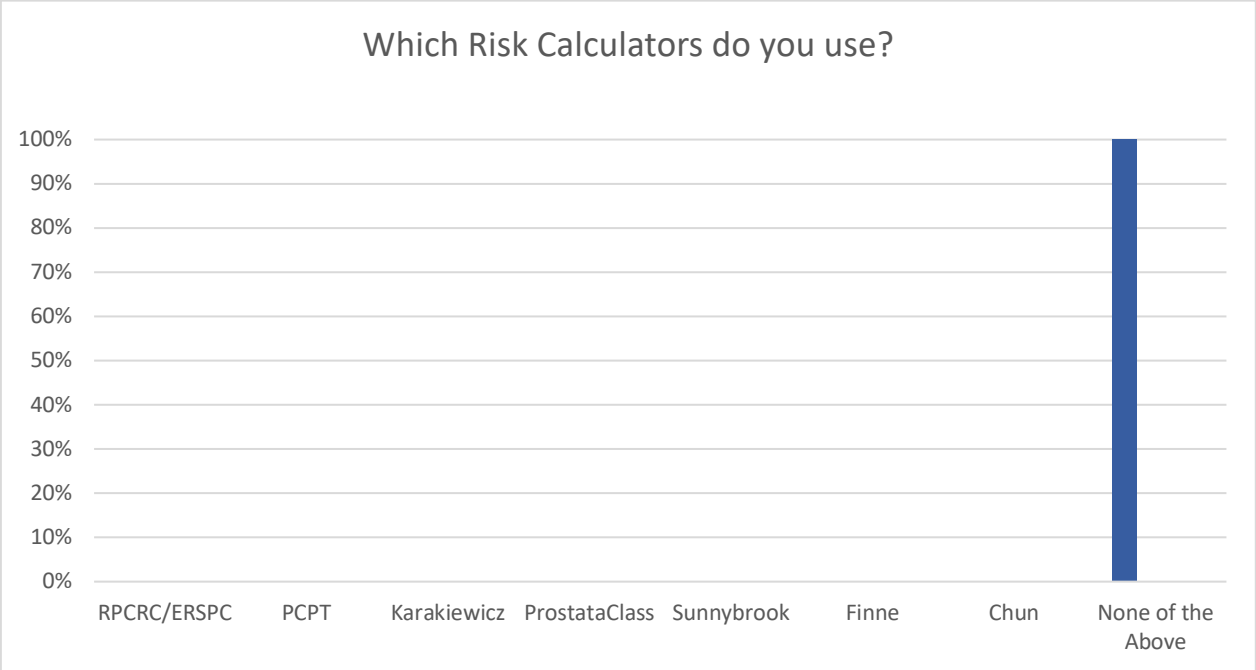

Figure 6 – Risk Calculators used by the participants

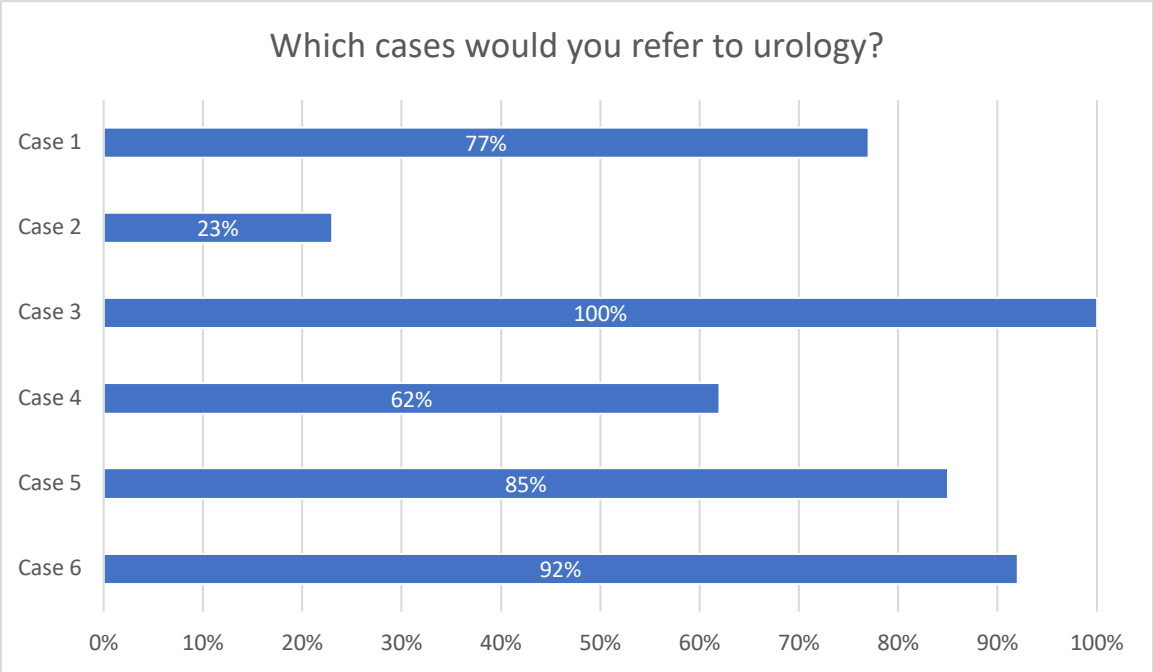

Figure 7 – Percentage of participants who would refer each case before knowing the calculated risk for prostate cancer

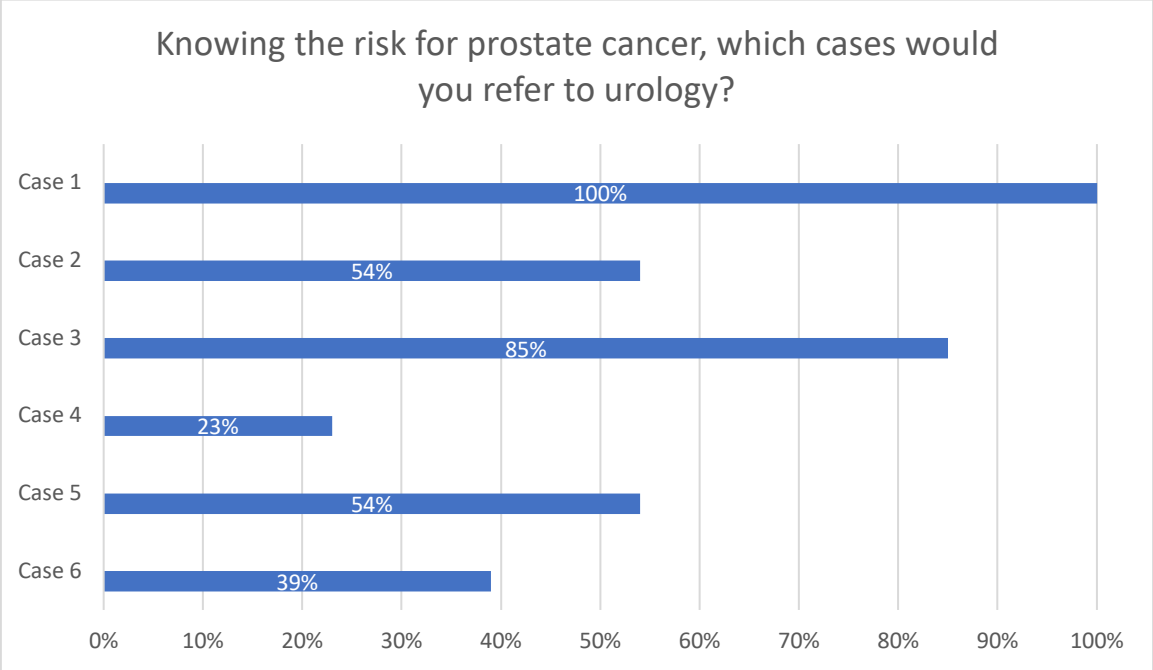

Figure 8 – Percentage of participants who would refer each case after knowing the calculated risk for prostate cancer

Table I and Table II – McNemar's test for Case 1

Would you refer for a biopsy? & Would you refer for a biopsy after knowing the risk for prostate cancer?

Would you refer for a biopsy?	Would you refer for a biopsy after knowing the risk for prostate cancer? No	Yes
No	0	**12**
Yes	**0**	40

Test Statistics[a]

	Would you refer for a biopsy? & Would you refer for a biopsy after knowing the risk for prostate cancer?
N	52
Exact Sig. (2-tailed)	,000[b]

a. McNemar Test

b. Binomial distribution used.

Table III and Table IV – McNemar's test for Case 2

Would you refer for a biopsy? (before knowing the risk for prostate cancer) & Would you refer for a biopsy after knowing the risk for prostate cancer?

Would you refer for a biopsy? (before knowing the risk for prostate cancer)	Would you refer for a biopsy after knowing the risk for prostate cancer?	
	No	Yes
No	20	**20**
Yes	**4**	8

Test Statistics[a]

	Would you refer for a biopsy? (before knowing the risk for prostate cancer) & Would you refer for a biopsy after knowing the risk for prostate cancer?
N	52
Exact Sig. (2-tailed)	***,002***[b]

a. McNemar Test

b. Binomial distribution used.

Table V and Table VI – McNemar's test for Case 3

Would you refer for a biopsy? (before knowing the risk for prostate cancer) & Would you refer for a biopsy after knowing the risk for prostate cancer?

Would you refer for a biopsy? (before knowing the risk for prostate cancer)	Would you refer for a biopsy after knowing the risk for prostate cancer?	
	No	Yes
No	0	**0**
Yes	**8**	44

Test Statistics[a]

	Would you refer for a biopsy? (before knowing the risk for prostate cancer) & Would you refer for a biopsy after knowing the risk for prostate cancer?
N	52
Exact Sig. (2-tailed)	***,008***[b]

a. McNemar Test

b. Binomial distribution used.

Table VII and Table VIII – McNemar's test for Case 4

Would you refer for a biopsy? (before knowing risk for prostate cancer) & Would you refer for a biopsy after knowing the risk for prostate cancer?

Would you refer for a biopsy? (before knowing risk for prostate cancer)	Would you refer for a biopsy after knowing the risk for prostate cancer?	
	No	Yes
No	20	**0**
Yes	**20**	12

Test Statistics[a]

	Would you refer for a biopsy? (before knowing risk for prostate cancer) & Would you refer for a biopsy after knowing the risk for prostate cancer?
N	52
Exact Sig. (2-tailed)	,000[b]

a. McNemar Test

b. Binomial distribution used.

Table IX and Table X – McNemar's test for Case 5

Would you refer for a biopsy? & Would you refer for a biopsy after knowing the risk for prostate cancer?

Would you refer for a biopsy?	Would you refer for a biopsy after knowing the risk for prostate cancer?	
	No	Yes
No	8	**0**
Yes	**16**	28

Test Statistics[a]

	Would you refer for a biopsy? & Would you refer for a biopsy after knowing the risk for prostate cancer?
N	52
Exact Sig. (2-tailed)	,000[b]

a. McNemar Test

b. Binomial distribution used.

Table XI and Table XII – McNemar's test for Case 6

Would you refer for a biopsy? & Would you refer for a biopsy after knowing the risk for prostate cancer?

Would you refer for a biopsy?	Would you refer for a biopsy after knowing the risk for prostate cancer?	
	No	Yes
No	4	**0**
Yes	**28**	20

Test Statistics[a]

	Would you refer for a biopsy? & Would you refer for a biopsy after knowing the risk for prostate cancer?
N	52
Chi-Square[b]	26,036
Asymp. Sig.	***,000***

a. McNemar Test

b. Continuity Corrected

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