Hereditární nádory prsu: nové geny, nová doporučení

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&

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Principy genetického testování

- Fáze 1994 – 2014

  - Testování vybraných genů u indikovaných pacientek
    - *BRCA1*
    - *BRCA2*
    - *PALB2*
    - *CHEK2*
    - *ATM*

  - Testování populačně specifických mutací u všech pacientek
    - c.181T>G v genu *BRCA1*
    - c.5266dup v genu *BRCA1*

Principy genetického testování

- Fáze NGS od roku 2014

ONKOGENETICKÝ PANEL CZECANCA, 226 GENŮ	viz CZECANCA.cz
AIP; ALK; **APC**; APEX1; **ATM**; ATMIN; ATR; ATRIP; AURKA; AXIN1; BABAM1; BAP1; **BARD1**; BLM; BMPR1A; BRAP; **BRCA1**; **BRCA2**; BRCC3; BRE; **BRIP1**; BUB1B; C11orf30; C19orf40; casp8; CCND1; CDC73; **CDH1**; CDK4; CDKN1B; CDKN1C; CDKN2A; CEBPA; CEP57; CLSPN; CSNK1D; CSNK1E; CWF19L2; CYLD; DCLRE1C; DDB2; DHFR; DICER1; DIS3L2; DMBT1; DMC1; DNAJC21; DPYD; EGFR; **EPCAM**; EPHX1; ERCC1; ERCC2; ERCC3; ERCC4; ERCC5; ERCC6; ESR1; ESR2; EXO1; EXT1; EXT2; EYA2; EZH2; FAM175A; FAM175B; FAN1; FANCA; FANCB; FANCC; FANCD2; FANCE; FANCF; FANCG; FANCI; FANCL; FANCM; FBXW7; FH; FLCN; GADD45A; GATA2; GPC3; GRB7; HELQ; HNF1A; HOXB13; HRAS; HUS1; CHEK1; **CHEK2**; KAT5; KCNJ5; KIT; LIG1; LIG3; LIG4; LMO1; LRIG1; MAX; MCPH1; MDC1; MDM2; MDM4; MEN1; MET; MGMT; **MLH1**; MLH3; MMP8; MPL; MRE11A; **MSH2**; MSH3; MSH5; **MSH6**; MSR1; MUS81; **MUTYH**; NAT1; **NBN**; NCAM1; NELFB; NF1; NF2; NFKBIZ; NHEJ1; NSD1; OGG1; **PALB2**; PARP1; PCNA; PHB; PHOX2B; PIK3CG; PLA2G2A; PMS1; **PMS2**; POLB; POLD1; POLE; PPM1D; PREX2; PRF1; PRKAR1A; PRKDC; **PTEN**; PTCH1; PTTG2; RAD1; RAD17; RAD18; RAD23B; **RAD50**; RAD51; RAD51AP1; RAD51B; **RAD51C**; **RAD51D**; RAD52; RAD54B; RAD54L; RAD9A; RB1; RBBP8; RECQL; RECQL4; RECQL5; RET; RFC1; RFC2; RFC4; RHBDF2; RNF146; RNF168; RNF8; RPA1; RUNX1; SBDS; SDHA; SDHAF2; SDHB; SDHC; SDHD; SETBP1; SETX; SHPRH; SLX4; SMAD4; SMARCA4; SMARCB1; SMARCE1; **STK11**; SUFU; TCL1A; TELO2; TERF2; TERT; TLR2; TLR4; TMEM127; TOPBP1; **TP53**; TP53BP1; TSC1; TSC2; TSHR; UBE2A; UBE2B; UBE2I; UBE2V2; UBE4B; UIMC1; VHL; WRN; WT1; XPA; XPC; XRCC1; XRCC2; XRCC3; XRCC4; XRCC5; XRCC6; ZNF350; ZNF365	

Principy genetického testování

- Fáze NGS

RENAL PANEL, 48 GENŮ
ACAN, ACTN4, ALB, BSND, C3, CASR, CD46, CFB, CFH, CFHR1, CFHR3, CFHR5, CFI, CLCNKA, CLCNKB, COL4A3, COL4A4, COL4A5, FGFR3, HNF1beta, IHH, INF2, KCNJ1, LMX1B, MCT8 (SLC16A2), NPHS2, NPPC, NPR2, PKD1, PKD2, PKHD1, SHOX, SLC12A1, SLC12A3, THBD, THRA, THRB, TMEM67, TRPC6, TRPS1, TSC1, TSC2, TSHR, nekódující oblast CNE3.9 (zesilovač SHOX)
LIPIDOVÝ PANEL, 10 GENŮ
APOB, APOE, CELSR2, HFE, LDLR, LDLRAP1, LIPA, NYNRIN, PCSK9, STAP1

Principy genetického testování

- Fáze vyšetřování celého exomu u všech pacientů od 2023

KLINICKÝ EXOM
4800 klinicky významných genů. Pouze po předchozí domluvě, vyšetření v rámci výzkumu.

Nejvýznamnější predispoziční geny pro karcinom prsu

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Breast Cancer Risk Genes — Association Analysis in More than 113,000 Women

Breast Cancer Association Consortium*

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

A Population-Based Study of Genes Previously Implicated in Breast Cancer

C. Hu, S.N. Hart, R. Gnanaolivu, H. Huang, K.Y. Lee, J. Na, C. Gao, J. Lilyquist,

32 247 osob

Nejvýznamnější predispoziční geny pro karcinom prsu

Table 1. Risk of Breast Cancer Overall Associated with Protein-Truncating Variants in 34 Genes in Population-Based Studies and All Studies.*

Gene	Population-Based Studies (48,826 patients and 50,703 controls)†				All Studies (60,466 patients and 53,461 controls)†	Prior Probability‡	BFDP
	No. of Carriers of Protein-Truncating Variants		Odds Ratio (95% CI)	P Value	P Value		
	Women with Breast Cancer	Controls					
ABRAXAS1	17	19	0.98 (0.50–1.94)	0.96	0.93	0.1	0.98
AKT1	3	6	0.47 (0.12–1.93)	0.29	0.14	0.1	0.94
ATM	294	150	2.10 (1.71–2.57)	9.2×10^{-13}	5.5×10^{-20}	0.8	1.3×10^{-18}
BABAM2	7	9	0.62 (0.23–1.71)	0.36	0.34	0.1	0.95
BARD1	62	32	2.09 (1.35–3.23)	0.00098	0.00011	0.2	0.0076
BRCA1	515	58	10.57 (8.02–13.93)	1.1×10^{-62}	3.7×10^{-65}	0.99	1.5×10^{-64}
BRCA2	754	135	5.85 (4.85–7.06)	2.2×10^{-75}	8.4×10^{-77}	0.99	3.1×10^{-76}
BRIP1	86	75	1.11 (0.80–1.53)	0.54	0.54	0.2	0.85
CDH1	11	12	0.86 (0.37–1.98)	0.72	0.58	0.2	0.94
CHEK2	704	315	2.54 (2.21–2.91)	3.1×10^{-39}	3.2×10^{-61}	0.99	1.3×10^{-60}
c.1100delC variant	548	245	2.66 (2.27–3.11)	1.1×10^{-33}	5.3×10^{-53}		
Other variants	156	70	2.13 (1.60–2.84)	3.0×10^{-7}	7.4×10^{-10}		
EPCAM	14	19	0.73 (0.36–1.49)	0.39	0.13	0.1	0.95
FANCC	71	65	1.26 (0.89–1.79)	0.20	0.20	0.1	0.87
FANCM	302	300	1.06 (0.90–1.26)	0.48	0.28	0.1	0.96
GEN1	31	43	0.66 (0.41–1.06)	0.088	0.18	0.1	0.95
MEN1	2	5	0.37 (0.07–1.97)	0.24	0.64	0.1	0.95
MLH1	5	9	0.58 (0.19–1.77)	0.34	0.55	0.1	0.95
MRE11	48	55	0.88 (0.59–1.32)	0.54	0.34	0.1	0.98
MSH2	13	13	1.06 (0.47–2.36)	0.89	0.80	0.1	0.92
MSH6	39	23	1.96 (1.15–3.33)	0.013	0.021	0.1	0.55
MUTYH	232	231	1.00 (0.83–1.21)	0.99	0.88	0.1	1.00
NBN	90	103	0.90 (0.67–1.20)	0.48	0.65	0.2	0.95
NF1	31	17	1.76 (0.96–3.21)	0.068	0.011	0.2	0.25
PALB2	274	55	5.02 (3.73–6.76)	1.6×10^{-26}	1.1×10^{-32}	0.99	2.9×10^{-32}
PIK3CA	3	12	0.21 (0.06–0.75)	0.016	0.19	0.1	0.94
PMS2	40	36	1.16 (0.73–1.85)	0.53	0.37	0.1	0.92
PTEN	14	6	2.25 (0.85–6.00)	0.10	0.0040	0.2	0.14
RAD50	120	121	1.08 (0.83–1.40)	0.57	0.45	0.1	0.95
RAD51C	54	26	1.93 (1.20–3.11)	0.0070	0.00026	0.3	0.0090
RAD51D	51	25	1.80 (1.11–2.93)	0.018	0.0018	0.3	0.044
RECQL	103	120	0.84 (0.64–1.10)	0.21	0.89	0.1	0.95

Table 2. Associations between Pathogenic Variants in Established Breast Cancer–Predisposition Genes and Risk of Breast Cancer.*

Breast Cancer–Predisposition Gene[1,2,7]	Case Patients (N=32,247)	Controls (N=32,544)	Odds Ratio (95% CI)†	P Value
	no. with pathogenic variant (%)			
ATM	253 (0.78)	134 (0.41)	1.82 (1.46–2.27)	<0.001
BARD1	49 (0.15)	35 (0.11)	1.37 (0.87–2.16)	0.18
BRCA1	275 (0.85)	37 (0.11)	7.62 (5.33–11.27)	<0.001
BRCA2	417 (1.29)	78 (0.24)	5.23 (4.09–6.77)	<0.001
CDH1	17 (0.05)	6 (0.02)	2.50 (1.01–7.07)	0.06
CHEK2	349 (1.08)	138 (0.42)	2.47 (2.02–3.05)	<0.001
NF1‡	19 (0.06)	11 (0.03)	1.93 (0.91–4.31)	0.09
PALB2	148 (0.46)	38 (0.12)	3.83 (2.68–5.63)	<0.001
PTEN	8 (0.02)	3 (0.01)	NA	NA
RAD51C	41 (0.13)	35 (0.11)	1.20 (0.75–1.93)	0.44
RAD51D	26 (0.08)	14 (0.04)	1.72 (0.88–3.51)	0.12
TP53‡	19 (0.06)	2 (0.01)	NA	NA
Total	1621 (5.03)	531 (1.63)	—	—

* The studies in the CARRIERS consortium that were included in this population-based analysis were BWHS, CPSII, CPS3, CTS, MCBCS, MEC, MMHS, NHS, NHSII, WCHS, WHI, and WWHS. NA denotes not applicable (too few events [<5] to calculate a stable odds ratio).
† Odds ratio estimates for any breast cancer were adjusted for study, age, family history of breast cancer, and race or ethnic group.
‡ Pathogenic variants in *NF1* and *TP53* were restricted to those with an alternate allele fraction (calculated as the number of alternate allele reads divided by the total number of reads at a specific genomic position) between 0.3 and 0.7.

Nejvýznamnější predispoziční geny pro karcinom prsu

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RAD51D	26 (0.08)	14 (0.04)	1.72 (0.88–3.51)	
TP53‡	19 (0.06)	2 (0.01)	NA	
Total	1621 (5.03)	531 (1.63)	—	

* The studies in the CARRIERS consortium that were included in this population-based analysis were BWH CPS3, CTS, MCBCS, MEC, MMHS, NHS, NHSII, WCHS, WHI, and WWHS. NA denotes not applicable ([<5] to calculate a stable odds ratio).
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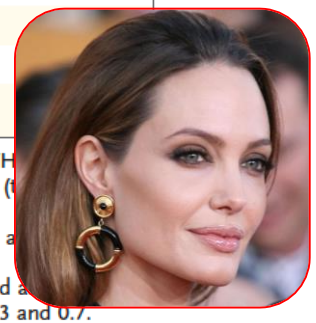


Nejvýznamnější predispoziční geny pro karcinom prsu

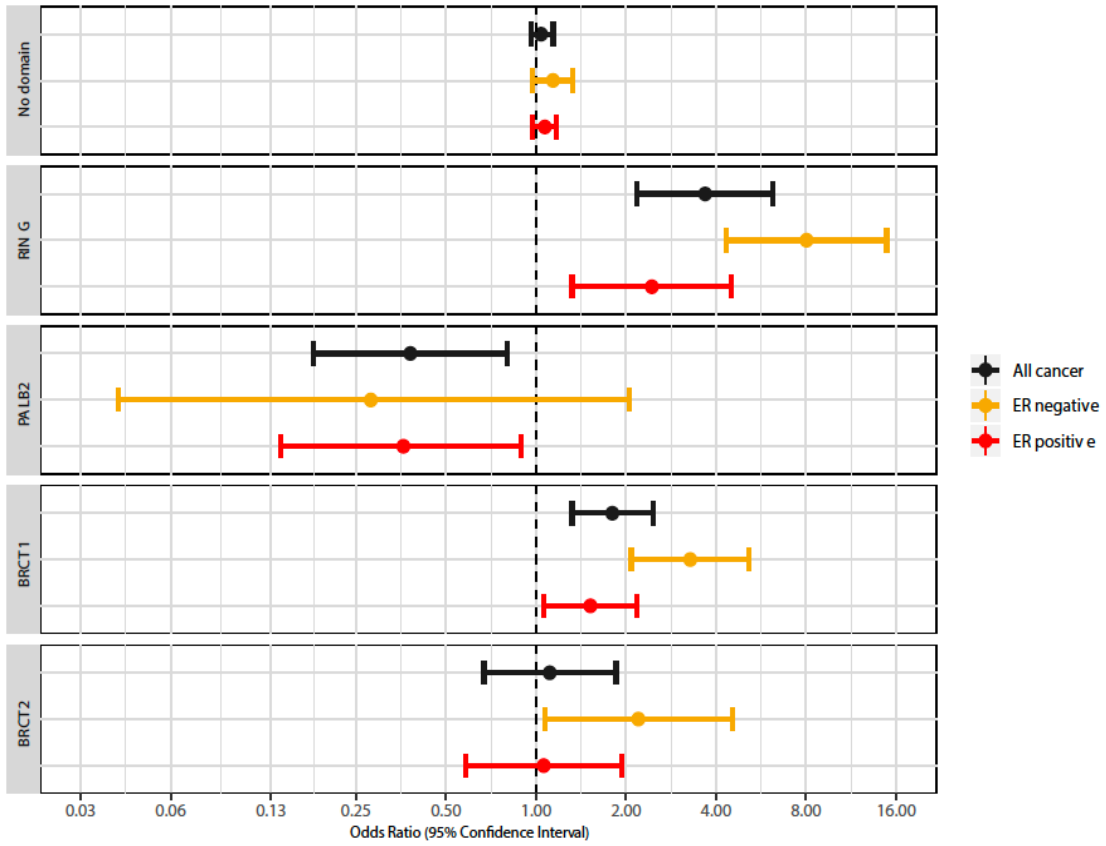
Table 2. Risk of Breast Cancer Overall Associated with Rare Missense Variants in 34 Genes in Population-Based Studies and All Studies.

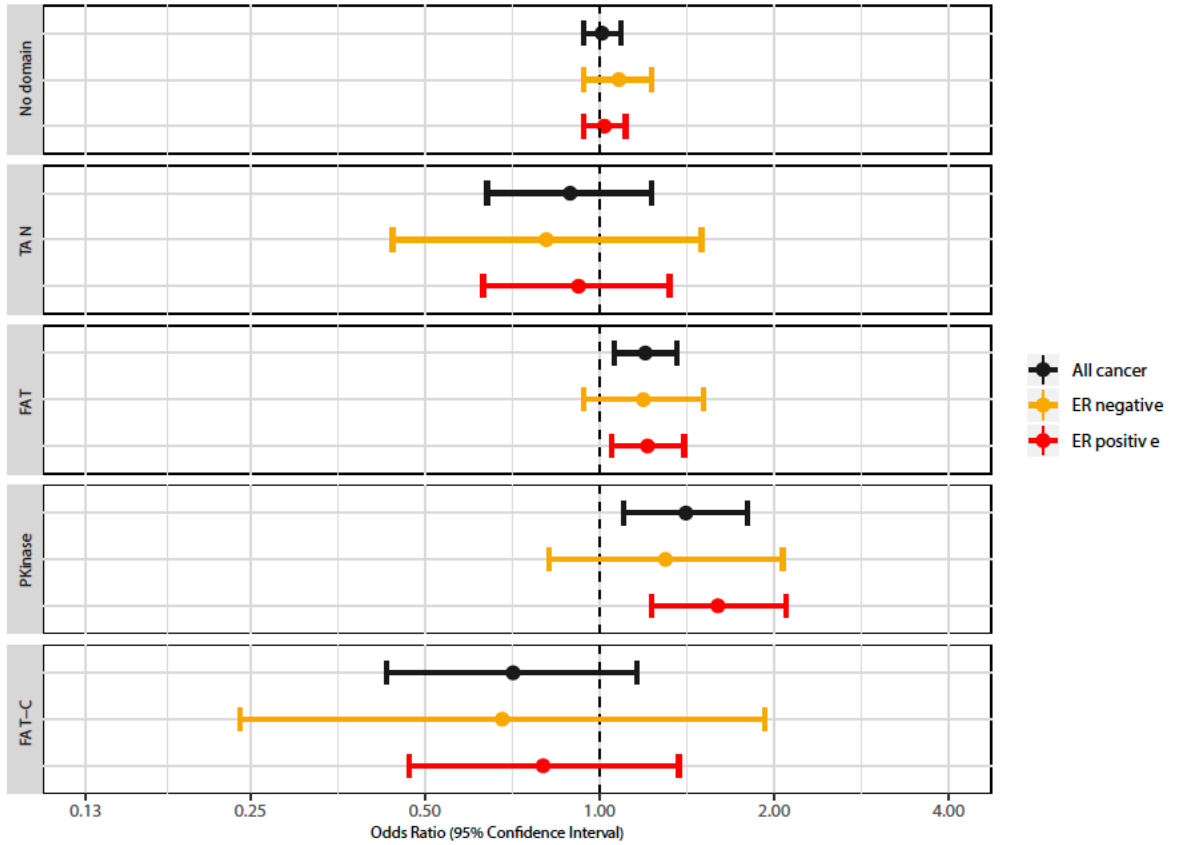
Gene	Population-Based Studies (48,826 patients and 50,703 controls)*				All Studies (60,466 patients and 53,461 controls)*
	No. of Carriers of Rare Missense Variants		Odds Ratio (95% CI)	P Value	P Value
	Women with Breast Cancer	Controls			
ABRAXAS1	233	242	1.04 (0.86–1.25)	0.70	0.40
AKT1	142	156	0.96 (0.76–1.21)	0.72	0.63
ATM	2411	2471	1.06 (1.00–1.13)	0.051	0.0010
BABAM2	167	170	1.01 (0.81–1.26)	0.91	0.63
BARD1	591	616	1.00 (0.89–1.12)	0.94	0.41
BRCA1	1393	1300	1.11 (1.02–1.20)	0.010	0.027
BRCA2	2831	3038	0.98 (0.93–1.04)	0.50	0.58
BRIP1	868	961	0.95 (0.86–1.04)	0.25	0.54
CDH1	682	668	1.10 (0.98–1.23)	0.096	0.042
CHEK2	895	697	1.42 (1.28–1.58)	2.5×10^{-11}	2.9×10^{-18}
EPCAM	290	328	0.97 (0.82–1.14)	0.69	0.43
FANCC	597	620	0.95 (0.85–1.07)	0.42	0.80
FANCM	1434	1566	0.95 (0.88–1.02)	0.17	0.85

R1699Q .. penetrace 20-30%

Některé mutace riziko vzniku malignit nezvyšují nebo zvyšují výrazně méně

Nejvýznamnější predispoziční geny pro karcinom prsu





BRCA1

ATM

Některé mutace riziko vzniku malignit nezvyšují nebo zvyšují výrazně méně

Nejvýznamnější predispoziční geny pro karcinom prsu

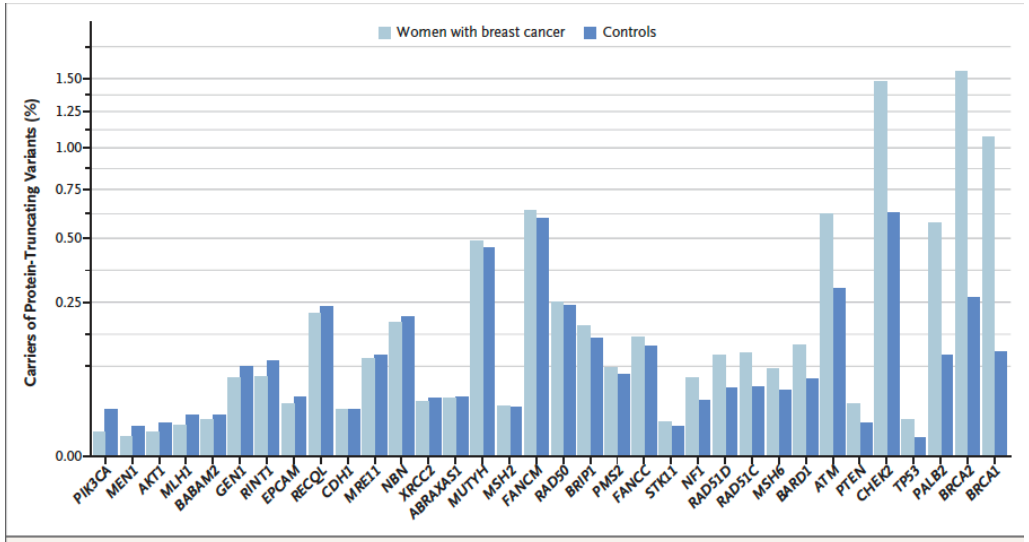


Figure 1. Frequency of Protein-Truncating Variants in 34 Genes in Population-Based Studies.

ATM	0,6%
BRCA1	1,02%
BRCA2	1,52%
CHEK2	1,48%
PALB2	0,55%
Celkem	**5,17%**

ATM	0,78%
BRCA1	0,85%
BRCA2	1,29%
CHEK2	1,08%
PALB2	0,46%
Celkem	**5,03%**

Incidence karcinomu prsu dle věku a predispozičních genů

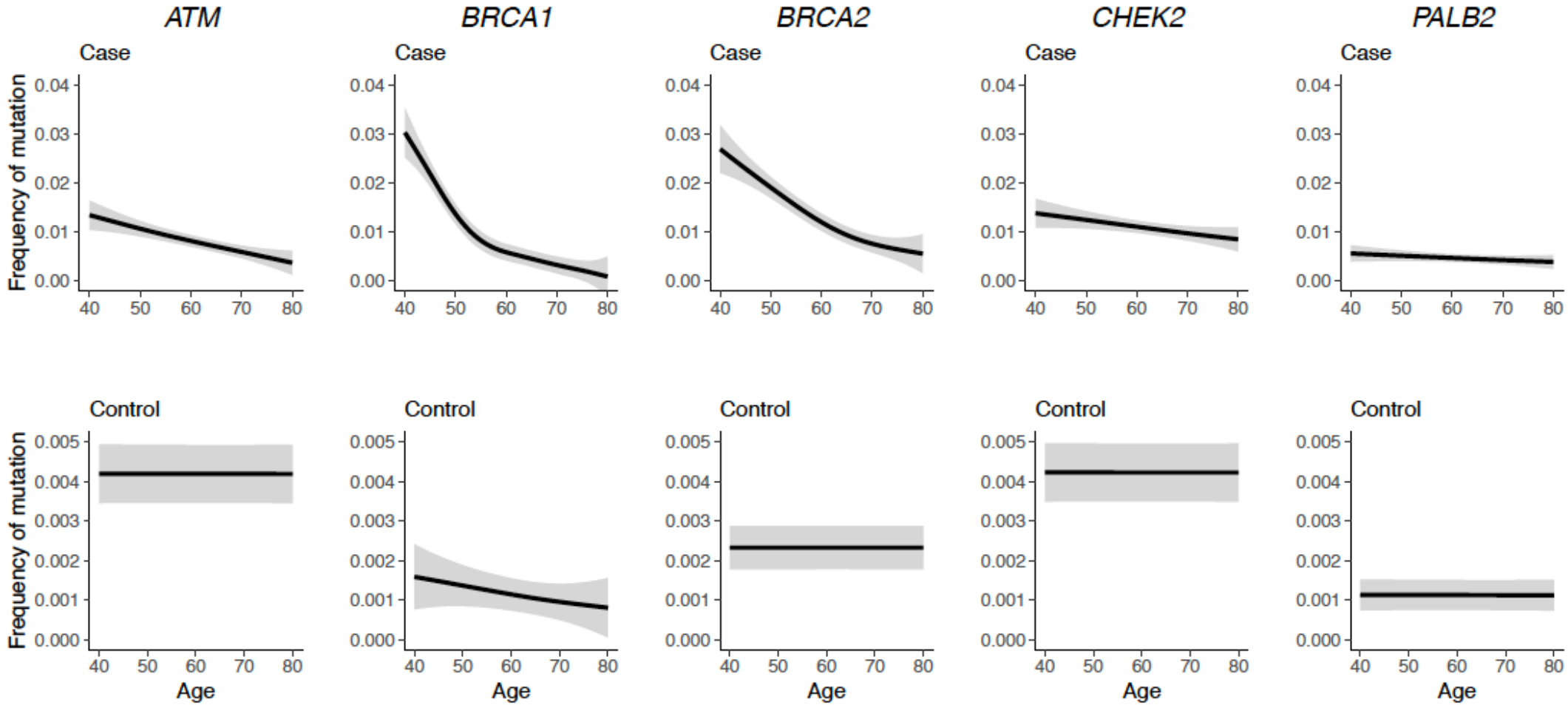


Figure S3: Frequency of PVs in the *ATM, BRCA1, BRCA2, CHEK2* and *PALB2* commonly mutated genes by age from the CARRIERS population-based study. Generalized additive model with smooth spline function for age (black line) was applied along with 95% confidence band (gray shading). Studies include BWHS, CPSII, CPS3, CTS, MCBCS, MEC, MMHS, NHS, NSHII, WCHS, WHI, and WWHS.

Penetrace predispozičních genů pro karcinom prsu

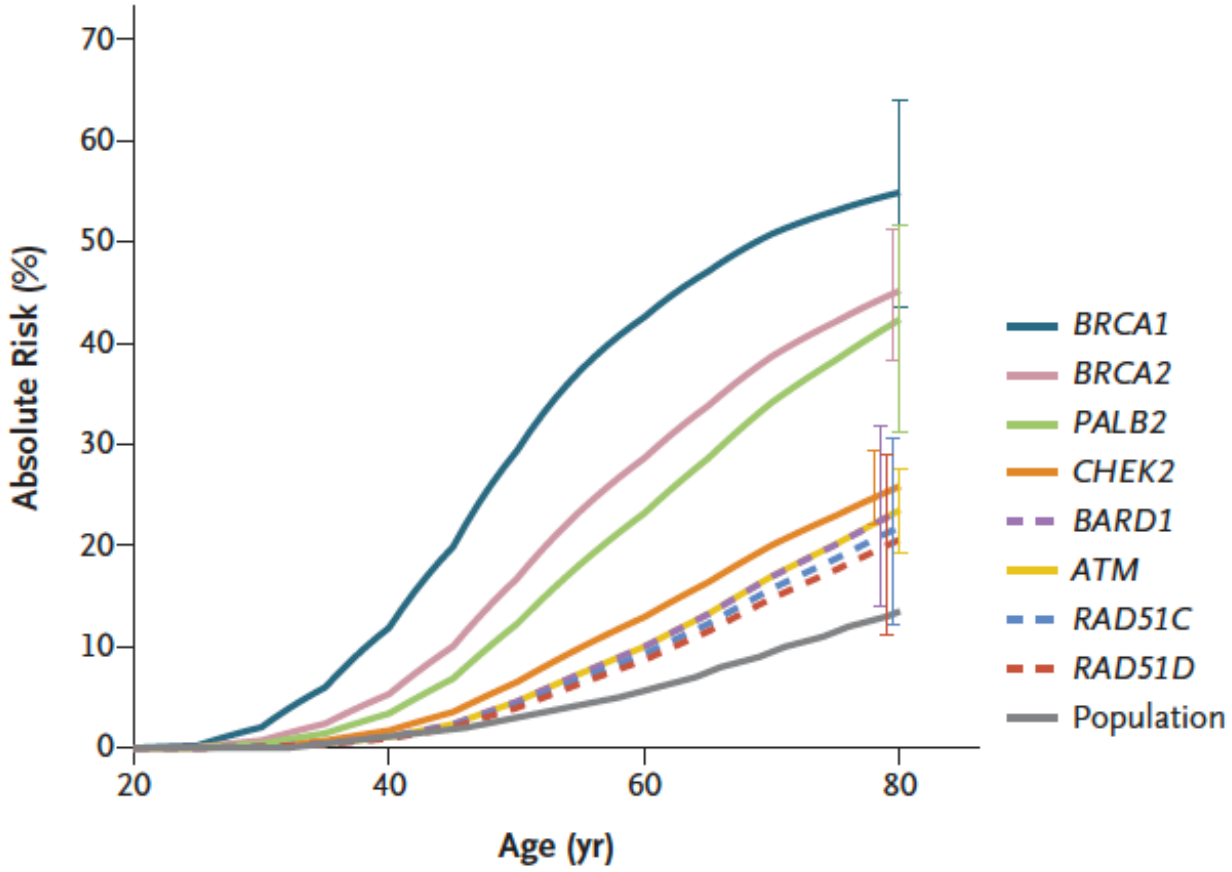


Figure 3. Estimated Absolute Risk of Breast Cancer Associated with Protein-Truncating Variants in 8 Genes.

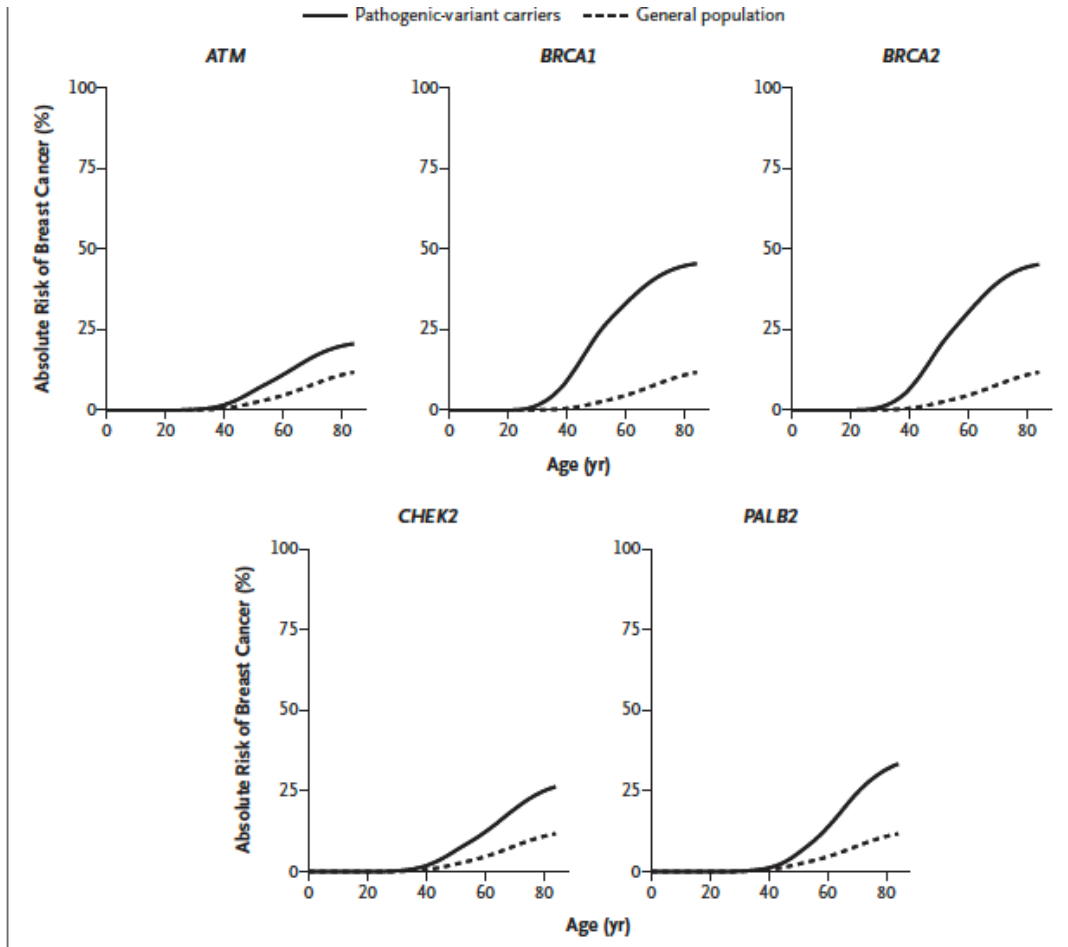


Figure 1. Population-Based Lifetime Absolute Risk of Breast Cancer Development According to Age and the Commonly Mutated Genes *ATM*, *BRCA1*, *BRCA2*, *CHEK2*, and *PALB2*.

The Cancer Risk Estimates Related to Susceptibility (CARRIERS) consortium studies that were included in the analysis of the absolute risk of breast cancer among pathogenic-variant carriers were the Cancer Prevention Study II, the Cancer Prevention Study 3, the California Teachers' Study, the Mayo Clinic Breast Cancer Study, the Multiethnic Cohort Study, the Mayo Mammography Health Study, the Nurses' Health Study, the Nurses' Health Study II, the Women's Circle of Health Study, the Women's Health Initiative, and the Wisconsin Women's Health Study. The analysis in the general population was performed with the use of age-specific breast cancer incidence data (restricted to non-Hispanic Whites) from the Surveillance, Epidemiology, and End Results 21 registries.

Penetrace predispozičních genů pro karcinom prsu dle věku v době diagnózy karcinomu prsu

Table S13: Associations between predisposition gene PVs and risk of breast cancer diagnosed at ≤ 50 years of age in the CARRIERS population-based study*

	# of PV (frequency)				
Gene	Case (N=5296)	Control (N=6042)	OR	95%CI	p-value
ATM	67 (1.27%)	28 (0.46%)	2.30	1,68	< 0.001
BARD1	9 (0.17%)	8 (0.13%)	0.94	1,44	0.90
BRCA1	144 (2.72%)	11 (0.18%)	16.14	4,61	< 0.001
BRCA2	135 (2.55%)	14 (0.23%)	11.79	3,97	< 0.001
CHEK2	74 (1.40%)	26 (0.43%)	2.64	2,35	< 0.001
PALB2	31 (0.59%)	11 (0.18%)	2.91	4,23	0.004
RAD51C	9 (0.17%)	5 (0.08%)	2.75	1,01	0.09

OR: Odds Ratio estimates for breast cancer were adjusted for study, age, and family history of breast cancer, and race/ethnicity.

*: Analyses of *CDH1, NF1, PTEN, RAD51D*, and *TP53* were not performed because of limiting numbers of PVs; included studies: BWHS, CPSII, CPS3, CTS, MCBCS, MEC, MMHS, NHS, NHSII, WCHS, WHI, and WWHS.

nad 50 let věku

BRCA1

- Zvýšené RR:
  - Prsu >60-70%
  - Ovarií 40-60%
  - Pankreatu 5%
  - Prostaty
- Chi. zákroky k diskuzi:
  - bilat. ME ve věku 30-40 let
  - adnexektomie ve věku 40(-45) let
  - kontralat. ME

BRCA2

- Zvýšené RR:
  - Prsu >60-70%
  - Ovarií 13-30%
  - Pankreatu 5-10%
  - Prostaty
  - Melanomu
- Chi. zákroky k diskuzi:
  - bilat. ME ve věku 30-40 let
  - adnexektomie ve věku 45-(50) let
  - kontralat. ME

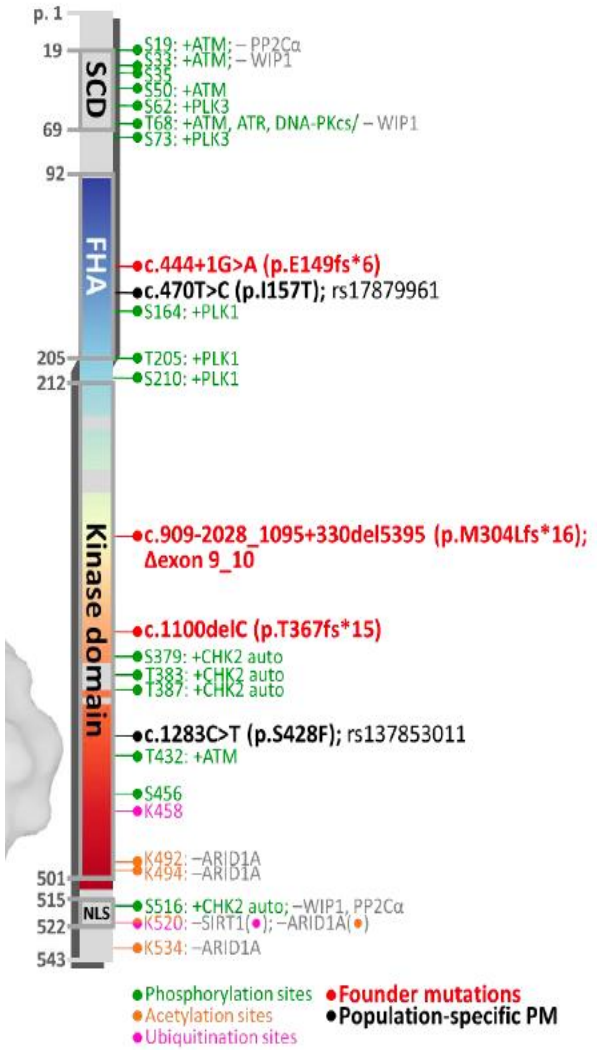
BRCA1

- Screening:
  - MRI / MMG / UZ 25-75 let
  - TVUZ 2x ročně
  - Nádorové markery +/-
- Terapie:
  - Pt deriváty
  - PARPi
- Chemoprevence

BRCA2

- Screening:
  - MRI / MMG / UZ 25-75 let
  - TVUZ 2x ročně
  - Nádorové markery +/-
- Terapie:
  - Pt deriváty
  - PARPi
- Chemoprevence

CHEK2



12 z 54 studií používá v metodice sekvenování celého genu

	I157T RR	1100delC	c.349A>G	c.444+1G>A
C18	1,48-2,0	-		
C50	1,4	separate analysis		
C61	1,7-2,7	1,6-3,29	1,9-7,7	1,58-4,7
C64	2,1	2,5-9,8		
C73	1,9-2,8	2,8-5,7		
NHL	2,86	-		

NENÍ POPSÁNO ZVÝŠENÉ RIZIKO VZNIKU KARCINOMU VAJEČNÍKŮ => NE PROF. ADNEXEKTOMIE !!

NENÍ POPSÁN PŘÍZNIVÝ EFEKT PROF. MASTEKTOMIE

ATM

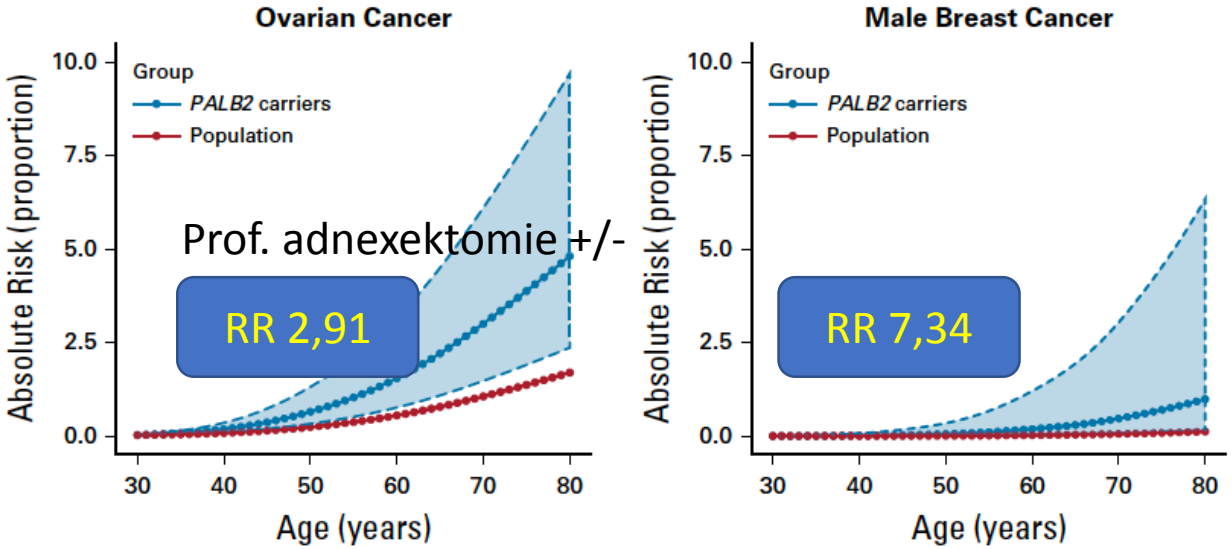
- Zvýšené RR:
  - Prsu 25-38%
  - Ovaria 3%
  - Pankreatu 5-10%

- Screening
  - C50, od 40 let, každoročně 1x

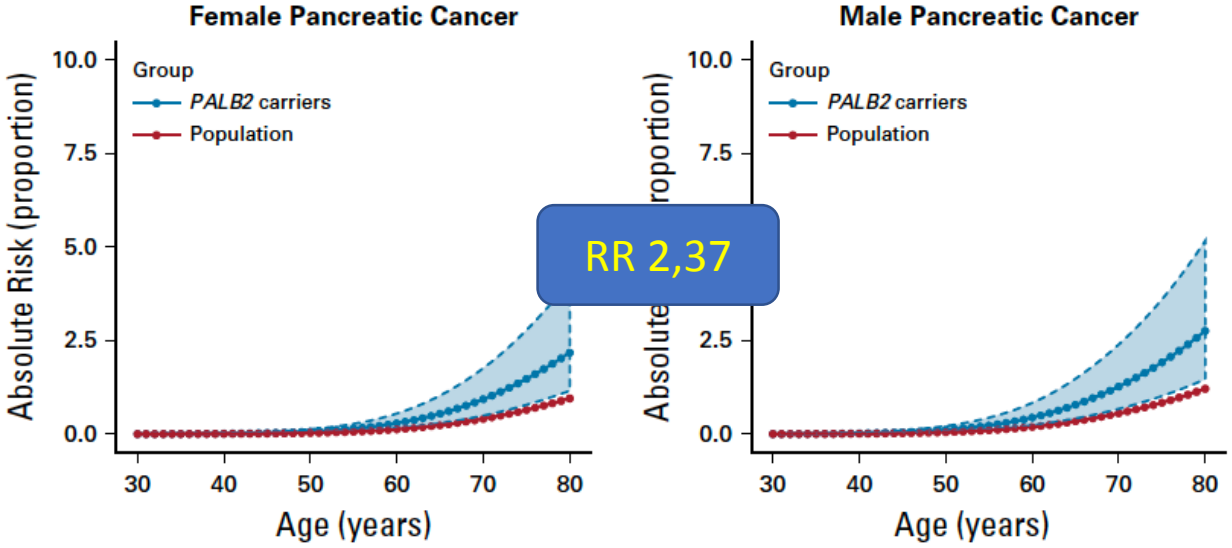
- Chi. zákroky k diskuzi:
  - Nejsou

- Ionizující záření?
  - Bez problémů

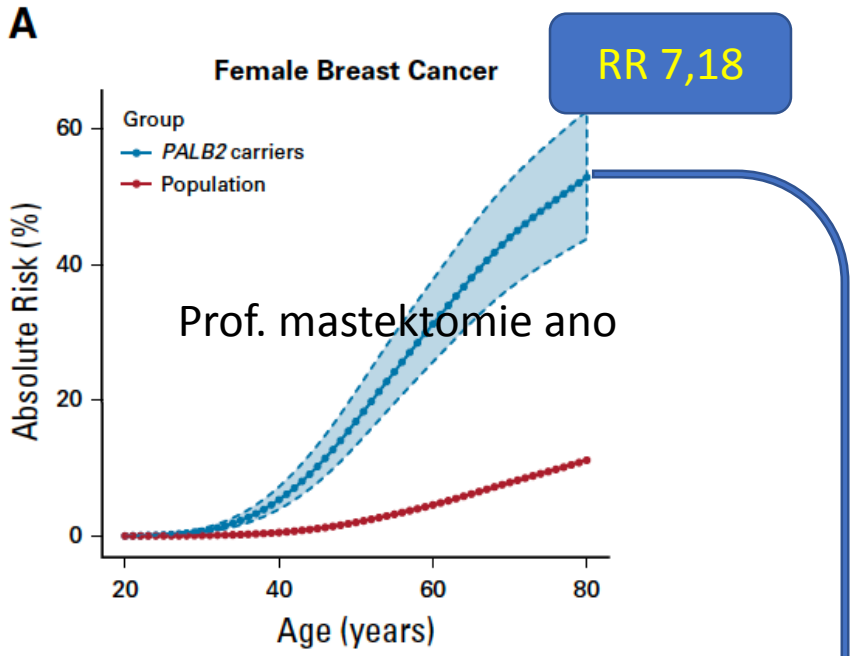
PALB2

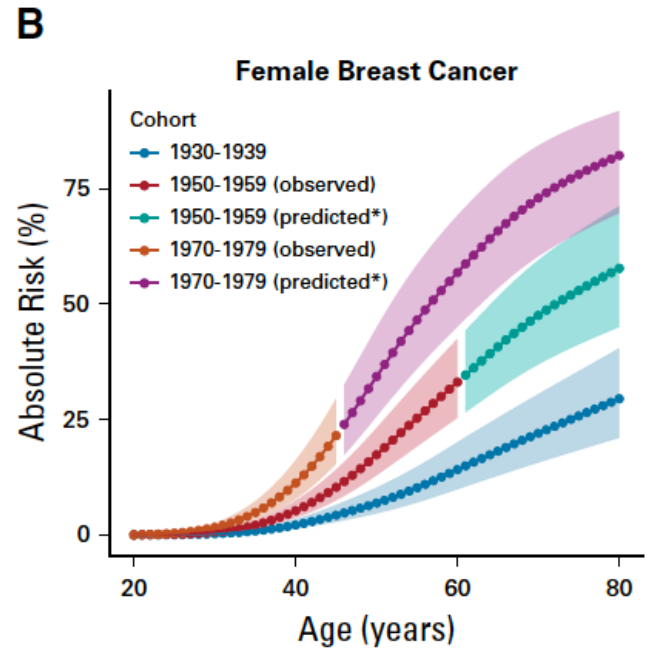

Ovarian Cancer
Group
PALB2 carriers
Population
Absolute Risk (proportion)
Age (years)
Prof. adnexektomie +/-
RR 2,91

Male Breast Cancer
Group
PALB2 carriers
Population
Absolute Risk (proportion)
Age (years)
RR 7,34


Female Pancreatic Cancer
Group
PALB2 carriers
Population
Absolute Risk (proportion)
Age (years)
RR 2,37

Male Pancreatic Cancer
Group
PALB2 carriers
Population
Age (years)


A
Female Breast Cancer
RR 7,18
Group
PALB2 carriers
Population
Absolute Risk (%)
Prof. mastektomie ano
Age (years)

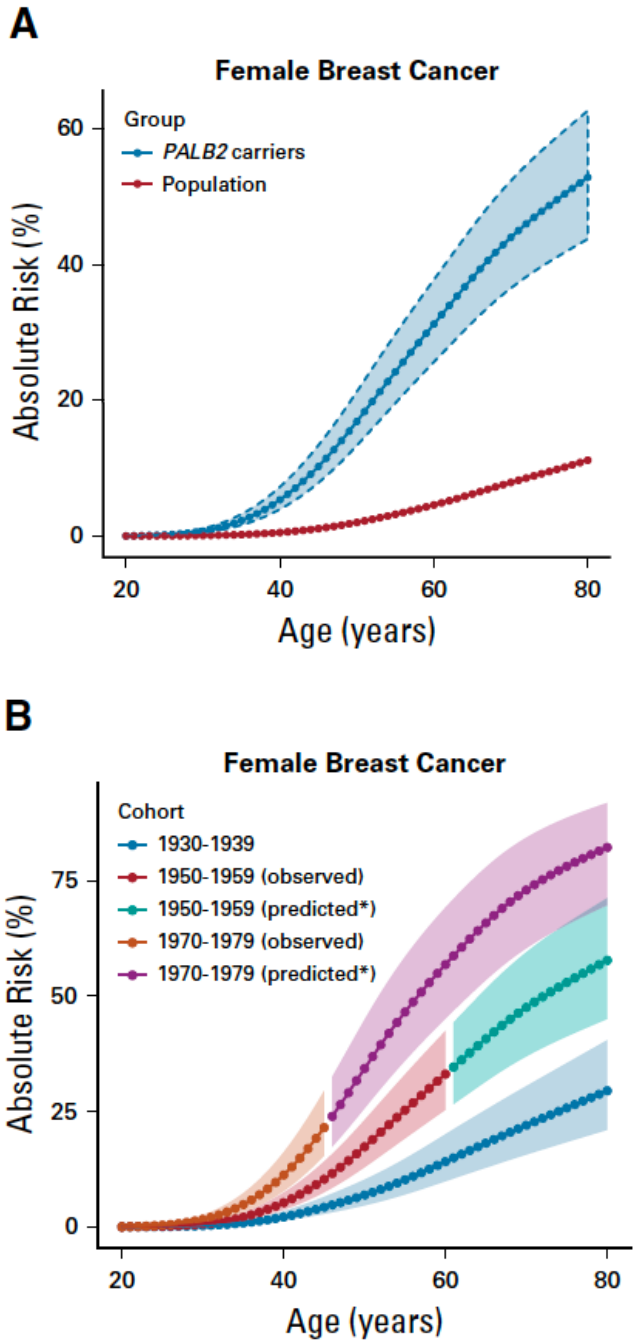

B
Female Breast Cancer
Cohort
1930-1939
1950-1959 (observed)
1950-1959 (predicted*)
1970-1979 (observed)
1970-1979 (predicted*)
Absolute Risk (%)
Age (years)

PALB2

Rodinná anamnéza ovlivňuje genovou penetraci

TABLE 3. Cumulative Risk of Developing Breast Cancer and Ovarian Cancer for Women With *PALB2* Pathogenic Variants by Family History

Cancer Type and Age (years)	Cumulative Risk of Developing Cancer for Women With *PALB2* Pathogenic Variants, % (95% CI)				
	Without Considering Family History	Mother Unaffected at Age 50 Years, Maternal Grandmother Unaffected at Age 70 Years	Mother Affected at Age 35 Years	Mother and Sister Affected at Age 50 Years	Mother and Maternal Grandmother Affected at Age 50 Years
Breast					
30	0.7 (0.5 to 1)	0.7 (0.5 to 1)	1 (1 to 2)	2 (1 to 2)	1 (1 to 2)
35	2 (2 to 3)	2 (1 to 3)	4 (3 to 6)	5 (4 to 6)	4 (3 to 5)
40	5 (4 to 7)	5 (4 to 7)	9 (7 to 12)	11 (9 to 13)	9 (7 to 12)
45	10 (8 to 13)	10 (7 to 12)	18 (14 to 22)	20 (17 to 24)	17 (14 to 21)
50	17 (13 to 21)	16 (13 to 20)	28 (23 to 34)	31 (27 to 36)	27 (23 to 32)
55	24 (20 to 30)	23 (19 to 28)	38 (32 to 45)	43 (38 to 48)	38 (32 to 43)
60	31 (26 to 38)	30 (25 to 36)	47 (40 to 55)	52 (47 to 58)	47 (41 to 53)
65	38 (32 to 46)	37 (30 to 44)	56 (48 to 63)	61 (55 to 67)	55 (49 to 62)
70	44 (37 to 52)	43 (35 to 51)	62 (54 to 71)	68 (61 to 74)	62 (55 to 69)
75	49 (41 to 59)	47 (39 to 57)	67 (58 to 76)	72 (66 to 79)	67 (59 to 74)
80	53 (44 to 63)	52 (42 to 62)	71 (62 to 80)	76 (69 to 83)	71 (63 to 79)



Závěr

- Hereditární vlohy k nádorům prsu způsobují vznik nádorů, které mají specifické vzorce vzniku, šíření a senzitivity k různým modalitám léčby
- Výsledky genetických analýz je třeba posuzovat v kontextu rodinné anamnézy, věku probandky, jejích přání a očekávání
- Výsledky genetického vyšetření je třeba interpretovat obezřetně a pečlivě
- Ženy s alteracemi predispozičních genů je třeba aktivně vyhledávat a věnovat jim odpovídající péči

Děkuji za pozornost