Bröstcancer

Utdrag ur nationellt vårdprogram: Kapitel 10, Ärftlig bröstcancer (och referenser)

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REGIONALA CANCERCENTRUM I SAMVERKAN

KAPITEL 10

Ärftlig bröstcancer

10.1 Bakgrund

Upptäckten av *BRCA1*, *BRCA2* och andra ärftliga hög- och medelpenetranta bröstcancergener har i hög grad ökat förståelsen för och påverkat handläggningen av familjer och individer med bröst- och äggstockscancerärftlighet. Analys av dessa gener kan användas för riskbedömning hos tidigare bröstfriska, men kan även ha betydelse vid val av behandling och uppföljning för patienter med manifest cancer. I avsaknad av påvisad sjukdomsassocierad variant (mutation) i sådan gen kan individens risk likväl vara högre än normalbefolkningens, men är i dessa fall typiskt som högst förhöjd till en klart lägre nivå än för bärare av en sjukdomsassocierad variant.

Kapitlet belyser i första hand konsekvenser av ärftlig bröstcancerrisk relaterat till ärftliga ”bröstcancergener”, men också andra relevanta risker, framför allt den ökade risk för äggstocks- och äggledarcancer som är associerad med sjukdomsassocierade varianter i *BRCA1* och *BRCA2*.

Evidensläget är generellt sett starkast för åtgärder associerade med sjukdomsassocierade varianter i *BRCA1* och *BRCA2*. I kapitlet (se tabell 1) sammanfattas även andra ärftliga riskfaktorer med rimlig evidensgrad för att sjukdomsassocierade varianter i angivna gener medför en måttligt till starkt förhöjd risk för bröstcancer, och föreslagna förebyggande åtgärder i enlighet med internationella riktlinjer.

Molekylärgenetisk screening kan principiellt initieras i två situationer:

1) **”Behandlingsutredning”** avser utredning i samband med ett nydiagnostiserat cancerfall. Syftet är att ge vägledning vid behandling av det enskilda cancerfallet. Behandlingsutredning kan initieras när som helst under behandlings- eller uppföljningsförloppet, och kan med fördel ske vid behandlande klinik, se avsnitt 10.2.3 under rubriken ”Molekylärgenetisk riskbedömning”.
   Vid positiv genetisk analys ska den testade individen eller en släkting erbjudas remiss till onkogenetisk mottagning för familjeutredning, vilket kan inkludera erbjudande om presymtomatisk testning till friska familjemedlemmar.
   Om genetisk analys utförs på tumörvävnad, så är en påvisad patogen variant antingen ärftlig eller förvärvad. Ärftlighet ska alltid bekräftas eller uteslutas genom analys av normalvävnad (blod). Det ska observeras att sensitiviteten avseende identifikation av sjukdomsassocierade varianter kan vara lägre vid analys av tumörvävnad, jämfört med blod.

2) Vid en ***”familjeutredning”*** är syftet i första hand att bedöma den framtida risken att insjukna i cancer i en familj med känd eller misstänkt cancerärftlighet. Utredningen initieras typiskt av en familjemedlem som reagerat på förekomst av cancerfall i familjen, och sker genom epidemiologisk riskvärdering, ofta i kombination med molekylärgenetisk testning. Denna typ av utredning sker i första hand vid onkogenetisk mottagning.

Patienter med cancer i bröst, äggstockar eller äggledare ska utfrågas avseende sin släktanamnes på både mödernet och fädernet. Ärftliga högriskgener är inte könsbundna, och sjukdomsassocierade varianter kan därför ärvas från en far likaväl som från en mor (autosomalt dominant nedärvning).

Faktorer i familjen som talar för ärftlighet är flera fall av bröstcancer i familjen, fall av bröstcancer vid låg ålder (< 40 år) och bilateral bröstcancer (se sammanfattning i 10.2). Vid sjukdomsassocierad variant i *BRCA1* eller *BRCA2* ses även förekomst av äggstocks- eller äggledarcancer, bröst- och äggstockscancer hos samma person, eller fall av manlig bröstcancer. Vid fall av så kallad ”trippelnegativ” bröstcancer finns en högre sannolikhet att finna en sjukdomsassocierad variant i *BRCA1* än vid annan bröstcancer. Fall av cancer i prostata och bukspottkörtel är också av särskilt intresse då dessa diagnoser förekommer i ökad frekvens hos individer med sjukdomsassocierad variant i *BRCA2*-genen. Vid ärftlig sjukdomsassocierad variant i *TP53*-genen föreligger en association med (mycket) ungt insjuknande i HER2-positiv bröstcancer.

10.1.1 Molekylärgenetisk utredning

Förekomst av sjukdomsassocierad variant i bröstcancerassocierad gen hos en individ kan ha stor betydelse för den framtida hälsan. Om alla bröstcancerpatienter med en variant ska identifieras måste sannolikt alla kvinnor med bröstcancer genomgå genetisk analys, och det är på sikt önskvärt att så blir fallet.

Gällande rutiner baseras på att begränsa genetisk analys till grupper med högre sannolikhet att identifiera en variant (se avsnitt 10.2). Rutinmässig genetisk analys vid misstänkt ärftlig bröstcancerrisk ska inkludera *BRCA1* och *BRCA2*, men kan även inkludera andra bröstcancerriskassocierade gener enligt tabell 1.

Utöver aktuella riktlinjer kan även andra erbjudas genetisk analys om särskilda skäl föreligger, till exempel om det finns ett begränsat antal kända kvinnor i familjen, eller vid Ashkenazi-judisk eller isländsk härkomst (populationer med starka så kallade foundereffekter), i händelse av avsaknad av kunskap om familjehistoria (t.ex. efter adoption), eller då ett positivt mutationssvar har omedelbar betydelse för val av behandling av en patient med manifest cancer. Genetisk analys i en tidigare otestad familj utförs i princip endast på individer med aktuell malignitet i den egna anamnesen.

I rekommendationerna avser ”bröstcancer” såväl invasiv bröstcancer som duktal cancer in situ (DCIS). ”Äggstockscancer” inkluderar äggledarcancer och primär peritoneal karcinomatos.

10.1.2 *BRCA1* och *BRCA2*

Det är rimligt att ange *livstidsrisken* för *bröstcancer hos kvinnor* vid sjukdomsassocierad variant i *BRCA1* eller *BRCA2* till 50–80 %. Livstidsrisken för *äggstockscancer* vid sjukdomsassocierad variant i *BRCA1* kan anges till 30–60 % respektive 10–25 % vid *BRCA2* (++++).

Populationsbaserade undersökningar visar i allmänhet, men inte alltid, lägre penetranssiffror [142-145] än studier som baseras på familjer som sökt på grund av ansamling av cancer i familjen [146, 147]. I en stor prospektiv studie som inkluderade 6 036 respektive 3 820 bärare av sjukdomsassocierade varianter i *BRCA1* och *BRCA2* uppskattades penetransen för bröstcancer hos bärare av sjukdomsassocierade varianter upp till 80 års ålder till 72 % (95 % KI 65–79 %) för *BRCA1* respektive 69 % (95 % KI 61–77 %) för *BRCA2*. För äggstockscancer uppskattades den till 44 % (95 % KI 36–53 %) respektive 17 % (95 % KI 11–25 %) [148].

Manlig bröstcancer: Risken för manlig bröstcancer är förhöjd hos *BRCA2*-mutationsbärare och uppgår vid 80 års ålder till cirka 7 % [149].

Kontralateral bröstcancer observeras oftare hos *BRCA1*- och *BRCA2*-mutationsbärare med bröstcancer än hos sporadiska fall (++++). I ett antal retrospektiva och prospektiva studier har den kumulativa incidensen, 10–20 år efter den initiala cancern, redovisats till 25–40 % för bärare av sjukdomsassocierade varianter. Den stora prospektiva studien som citeras ovan anger incidensen av kontralateral bröstcancer vid *BRCA1* till 40 % (95 % KI 35–45 %) och för *BRCA2* till 26 % (95 % KI 20–33 %) Det finns studier som antyder att tidigt insjuknande i en första bröstcancer är en riskfaktor för kontralateral bröstcancer hos bärare av patogena varianter i *BRCA1* och *BRCA2*, men resultaten är inte helt entydiga härvidlag [148, 150-154].

Lokalt återfall/ ny primär bröstcancer efter bröstbevarande bröstcancerbehandling av mutationsbärare: Ett stort antal studier har påvisat en högre risk för nya bröstcancerhändelser efter bröstbevarande bröstcancerbehandling. Incidenssiffrorna uppgår i dessa studier till 12–49 % vid uppföljning upp till 15 år [155-161] (+++).

Andra maligniteter associerade med BRCA1: Troligen föreligger utöver bröst- och äggstockscancer inga andra cancerrisker på en nivå som rutinmässigt bör föranleda riktade åtgärder med association till ärftlig sjukdomsassocierad variant i *BRCA1*. För diskussion om prostatacancer, se avsnitt 10.3.2.

Andra maligniteter associerade med BRCA2: Manliga bärare av sjukdomsassocierad variant i *BRCA2*-genen har 2–3 gånger ökad risk för prostatacancer [162] och 5–7 gånger ökad risk för tidigt debuterande prostatacancer [149]. Det föreligger även en ökad risk för pankreascancer hos *BRCA2*-mutationsbärare [163, 164].

10.1.3 *PALB2*

I en analys som inkluderade 362 medlemmar i 154 familjer från 13 centrum i västvärlden, med sjukdomsassocierade varianter i *PALB2,* beräknades bröstcancerrisken jämfört med den generella befolkningen i Storbritannien. Den absoluta kumulativa bröstcancerrisken beräknades till 14 % (95 % KI 9–20 %) vid 50 års ålder och 35 % (95 % KI 26–46 %) vid 70. Risken var tydligt högre hos kvinnor födda 1960 och senare jämfört med kvinnor födda 1940–1959 respektive före 1940 (kohorteffekt) och påverkades av om det förelåg fall av bröstcancer i den nära släkten. För kvinnor utan släkthistoria var den kumulativa insjuknanderisken vid 70 års ålder 33 % (95 % KI 25–44 %), medan den var 58 % (95 % KI 50–66 %) för de med minst två förstagradssläktingar med bröstcancerdiagnos vid 50 års ålder. Risken för bröstcancer är således kraftigt förhöjd jämfört med den generella befolkningen, i synnerhet i familjer med fall av bröstcancer med tidigt insjuknande i den nära släkten. Risken förefaller dock att vara något lägre än för *BRCA1*-mutationsbärare, men har beskrivits som ”överlappande” med risken för *BRCA2*-bärare. Det ska också observeras att det finns en kohorteffekt som gör att ovanstående risksiffror i dag kan vara i underkant. Man såg i studien ingen signifikant förhöjd risk för annan cancer utöver bröstcancer hos kvinnor [165]. En polsk studie indikerar likaledes en kraftigt förhöjd bröstcancerrisk hos bärare av *PALB2*-mutationer med en oddskvot på 4,39; 95 % KI 2,30–8,37, $p < 0,0001$ jämfört med sporadiska fall [166] (ökad bröstcancerrisk hos bärare av *PALB2*-mutationer ++++).

Data avseende kontralateral bröstcancerrisk och risk för samsidigt återinsjuknande efter bröstbevarande kirurgi är otillräckligt studerade hos bärare av sjukdomsassocierade varianter i *PALB2* [167].

I den svenska SWEA-studien där familjer med misstänkt bröst- och äggstockscancerärftlighet erbjöds paneltestning observerades sjukdomsassocierade varianter i *PALB2* i 0,78 % av de undersökta familjerna (opublicerade resultat). *PALB2* ingår i den svenska genpanelen vid rutinmässig molekylärgenetisk diagnostik vid misstänkt bröstcancerärftlighet.

10.1.4 Övriga gener associerade med kända tumörsyndrom (*TP53, PTEN, CDH1, STK11, NF1*)

Sjukdomsassocierade varianter i övriga kända högpenetranta bröstcancerassocierade gener är mycket ovanliga, och är ofta kopplade till ärftliga cancersyndrom med specifika kännetecken. Med utökad genetisk analys har man dock för dessa gener ibland identifierat sjukdomsassocierade varianter även i ”bröstcancerfamiljer” som inte uppfyller de klassiska syndromkriterierna, vilket kan innebära svåra gränsdragningar avseende klinisk handläggning. Tumörspecifika riskestimat är också osäkra på grund av inklusionsbias och små studier. Vid fynd av sjukdomsassocierad variant i någon av dessa gener ska familjen handläggas vid onkogenetisk mottagning med specialistkunskap kring ovanliga cancersyndrom.

Kortfattat har sjukdomsassocierade varianter i *TP53* associerats med Li-Fraumenis syndrom, vilket medför en mycket hög risk för ett flertal tumörformer inklusive pediatrisk cancer. Utöver tidigt insjuknande i (ofta HER2-positiv) premenopausal bröstcancer ses typiskt binjurebarkscancer, sarkom och hjärntumörer. Mutationer i *TP53* uppstår dock relativt ofta de novo, vilket innebär att en individ med *TP53*-mutation kan sakna släkthistoria [168, 169]. I den svenska SWEA-studien där familjer med misstänkt bröst- och äggstockscancerärftlighet erbjöds paneltestning observerades sjukdomsassocierade varianter i *TP53* i 0,75 % av de undersökta familjerna (opublicerade resultat). *TP53* ingår i den svenska genpanelen vid rutinmässig molekylärgenetisk diagnostik vid misstänkt bröstcancerärftlighet.

Sjukdomsassocierade varianter i *PTEN* har kopplats till *PTEN* hamartoma tumor syndrome (PHTS) som bland annat innefattar Cowdens syndrom. I dessa familjer ses utöver bröstcancer en tydligt ökad risk för sköldkörtelcancer och endometriecancer, och en mer måttligt ökad risk för koloncancer. Den ovanliga tumörformen cerebellärt dysplastiskt gangliocytom är i det närmaste patognomon, och det förekommer ofta även benigna förändringar inkluderande makrocefali, hud- och slemhinneförändringar och hamartomatösa intestinala polyper [168, 170].

STK11-mutationer kan medföra Peutz-Jeghers syndrom, där diagnosen ofta ställs utifrån symtomgivande typiska hamartomatösa intestinala polyper (så kallade Peutz-Jegher-polyper) i kombination med mukokutan pigmentering. Det föreligger även en ökad risk för i första hand bröst-, kolorektal-, ventrikel-, pankreas- och (icke-epitelial) ovarialcancer samt benigna könssträngstumörer (SCTAT) för kvinnor och Sertolicells-tumörer för män [168, 171].

CDH1-mutationer associeras med förhöjd risk för lobulär bröstcancer och diffus ventrikelcancer [168, 172].

Mutationer i *NF1* kopplas till neurofibromatos typ 1. Detta syndrom medför i allmänhet ett flertal symtom som inte är cancerrelaterade, och handläggning vid särskilt *NF1*-team rekommenderas. Kvinnor med *NF1*-mutation har en förhöjd bröstcancerrisk särskilt i åldersintervallet 30–50 år, och kvinnor och män med mutation har även en risk för bland annat gastrointestinala stromacellstumörer (GIST) och maligna perifera nervskidetumörer (MPNST) [168, 173].

I den ovan nämnda SWEA-studien förekom sjukdomsassocierade varianter i *PTEN*, *STK11* och *CDH1* i en mycket låg andel av de undersökta familjerna. *PTEN*, *STK11*, *CDH1* och *NF1* ingår

inte i den svenska genpanelen vid rutinmässig molekylärgenetisk diagnostisk vid misstänkt bröstcancerärftlighet, men kan beställas om den kliniska bilden talar för att syndrom associerat med sjukdomsassocierad variant i någon av dessa gener kan förekomma.

10.1.5 Gener associerade med måttligt förhöjd bröstcancerrisk (*CHEK2, ATM*)

Ett flertal gener har identifierats de senaste åren där sjukdomsassocierade varianter kopplats till en måttligt förhöjd risk att insjukna i bröstcancer (genomsnittlig livstidsrisk 20–30 %). För många av dessa gener är evidensläget fortfarande oklart, och i dagsläget bör flertalet av dessa gener inte ingå i kliniska genpaneler [174, 175]. Framför allt avseende generna *CHEK2* och *ATM* föreligger tillräckliga data för att med rimlig säkerhet kunna uttala sig om den associerade cancerrisken, även om flera större studier pågår (se även tabell 1).

Den relativt vanligt förekommande foundermutationen *CHEK2* 1100delC (och andra trunkerande mutationer i *CHEK2*), och trunkerande sjukdomsassocierade varianter i *ATM* uppvisar en likartad bröstcancerrisk, där livstidsrisken för bröstcancer hos mutationsbärande kvinnor i genomsnitt uppgår till 20–25 % [152, 176, 177]. Liksom för *BRCA1*/2, *PALB2* och andra bröstcancerassocierade gener modifieras dock risken av familjebilden, till stor del på grund av samverkande vanliga genetiska polymorfier, SNPs, så att en kvinna som har både en stark familjehistoria och en trunkerande variant i *CHEK2* eller *ATM* kan ha en livstidsrisk för bröstcancer som överstiger 35 % [178].

För kvinnor med bröstcancer och heterozygot bärarskap av *CHEK2* 1100delC finns evidens som talar för en mer allvarlig prognos samt en högre risk för kontralateral bröstcancer jämfört med fall som inte bär denna variant [179]. Den absoluta risken för kontralateral bröstcancer uppgår dock sannolikt inte till mer än 10–15 % [175]. I mycket ovanliga fall ses homozygot bärarskap av *CHEK2* 1100delC, och risken för kvinnlig bröstcancer är då sannolikt jämförbar med *BRCA1*/2-mutationsbärare [180].

De uppskattade bröstcancerriskerna enligt ovan gäller för trunkerande sjukdomsassocierade varianter. Missense-varianter (aminosyrautbyten) är oftast associerade med en klart lägre bröstcancerrisk, något som bland annat visats för den vanligt förekommande *CHEK2* I157T [181]. Det finns dock undantag från denna regel, och vissa ovanliga missense-varianter uppvisar en kliniskt signifikant risknivå. *ATM* c.7271T>G agerar dominant negativt, och kvinnliga bärare har en bröstcancerrisk som kan överstiga risken vid *BRCA1*-mutation [177, 182].

I den svenska SWEA-studien där familjer med misstänkt bröst- och äggstockscancerärftlighet erbjöds paneltestning observerades trunkerande mutationer i *CHEK2* och *ATM* i 3,5 % respektive 1,5 % av de undersökta familjerna, men missense-varianten *ATM* c.7271T>G har inte identifierats (opublicerade resultat). *CHEK2* och *ATM* ingår i den svenska genpanelen vid rutinmässig molekylärgenetisk diagnostik vid misstänkt bröstcancerärftlighet.

10.2 Utredning av misstänkt ärftlighet

10.2.1 Kriterier för utredning av misstänkt ärftlighet hos bröstcancerpatienter

Rekommendationer för vilka som bör genomgå cancergenetisk utredning inklusive molekylärgenetisk testning

- Bröstcancer ≤ 40 års ålder.
- Bröstcancer ≤ 50 år, om det i samma släktgren finns minst ett ytterligare fall av bröstcancer hos förstagradssläktingar eller andragradssläktingar. Bilateral bröstcancer räknas som två fall. Det andra fallet kan också vara äggstocks- eller äggledarcancer, tidig prostatacancer (före 65 års ålder) eller pankreascancer.
- Bröstcancer ≤ 60 år, om det i samma släktgren finns minst två ytterligare fall av bröstcancer hos förstagradssläktingar eller andragradssläktingar. Bilateral bröstcancer räknas som två fall. De andra fallen kan också vara äggstocks- eller äggledarcancer, tidig prostatacancer (före 65 års ålder) eller pankreascancer.
- Trippelnegativ bröstcancer ≤ 60 års ålder.
- Manlig bröstcancer oavsett ålder.
- Äggstockscancer inklusive äggledarcancer och primär peritoneal karcinomatos (icke-mucinös, icke-borderline) oavsett ålder.
- Äggstockscancer inklusive äggledarcancer och primär peritoneal karcinomatos oavsett ålder.
- I de fall man i *tumörvävnad* påvisat en sjukdomsassocierad variant krävs kompletterande analys av normalvävnad (blod) för att fastställa eller utesluta ärftlighet.
- I fall där positivt utfall av en genetisk analys skulle ha omedelbar betydelse för medicinsk behandling av patient med manifest cancer, oavsett familjehistoria.
- Kriterier uppfyllda för annat ärftligt syndrom där bröst-/äggstockscancer ingår.

10.2.2 Kriterier för utredning av misstänkt ärftlighet hos friska familjemedlemmar

Rekommendationer

- Om en sjukdomsassocierad variant (mutation) i *BRCA1*, *BRCA2* eller i annan gen associerad med en starkt förhöjd bröstcancerrisk påvisas i familjen kan man erbjuda presymtomatisk testning efter noggrann genetisk vägledning.
- Vid påvisande av sjukdomsassocierad variant i *ATM* eller *CHEK2,* som är förenad med en måttligt förhöjd bröstcancerrisk, bör erbjudande om presymtomatisk testning förbehållas kvinnliga förstagradssläktingar till associerade cancerfall.

10.2.3 Cancergenetisk utredning

Cancergenetisk utredning syftar till att identifiera individer med en från normalbefolkningen avvikande cancerrisk, vilket kan leda till att riktade åtgärder rekommenderas. Beslut om utökade kontroller utöver populationsscreening och eventuell riskreducerande kirurgi ska baseras på en

kvalificerad multidisciplinär bedömning som inkluderar släktträdet, eventuell molekylärgenetisk utredning samt en tolkning av vilken risk detta medför, samt potentiell nytta för individen.

Epidemiologisk riskbedömning: *Risken för primär bröstcancer* kan hos en bröstfrisk kvinna uppskattas baserat på släkthistoria, eventuellt genetiskt fynd och tumörfenotyp av i familjen förekommande cancerfall, med hjälp av epidemiologiska riskmodeller. I första hand rekommenderas BOADICEA [183] som värderar risk baserat på släkthistoria och tumörkarakteristika, och även kan ta hänsyn till molekylärgenetiska analysresultat. Gail- [184] och Tyrer-Cuzick-modellerna [185] tar även tar hänsyn till icke uppenbart ärftliga riskfaktorer.

Kontralateral bröstcancer kan uppstå efter suspekt ärftlig eller annan bröstcancer, och det är, i synnerhet ifall man överväger en kontralateral mastektomi, angeläget att försöka uppskatta denna sannolikhet, vilket kan ske med hjälp av BOADICEA-modellen.

En annan modell, kallad ”Manchestermodellen”, kan ge en grov uppfattning om den framtida bröstcancerrisken efter ett primärt bröstcancerinsjuknande. Modellen gör två antaganden: man utgår ifrån en årlig grundrisk om 0,5 % för insjuknande i kontralateral bröstcancer, och att en kvinna i snitt lever till 80 års ålder efter en bröstcancerdiagnos. För att kalkylera återstående kontralateral bröstcancerrisk i procent subtraherar man aktuell ålder från 80 och multiplicerar med 0,5 %. Vid sjukdomsassocierad variant i en ärftlig högpenetrant bröstcancergen multiplicerar man denna faktor med 4; vid bröstcancer i den nära släkten multiplicerar man med 2, och om den första bröstcancern var endokrint behandlad eller om kvinnan genomgått ooforektomi före 40 multiplicerar man med 0,5 [186]. Den kontralaterala bröstcancerrisken hos en kvinna med endokrint behandlad, östrogenreceptorpositiv bröstcancer vid 40 års ålder utan släkthistoria för bröstcancer skattas alltså enligt modellen till (80–40) * 0,5 * 0,5 = 10 %. En kvinna med ER-negativ bröstcancer vid 50 års ålder och en syster med bröstcancer får en skattad risk om (80–50) * 0,5 * 2 = 30 %. Metoden är inte prospektivt validerad men kan användas för att få en grov uppfattning om den kontralaterala bröstcancerrisken till exempel då en kontralateral mastektomi efterfrågas hos en kvinna utan molekylärgenetiskt fynd vid ärftlighetsutredning.

Molekylärgenetisk riskbedömning: Om individen eller familjen uppfyller kriterierna för genetisk analys rekommenderas att sådan erbjuds. Genetisk analys ska föregås av tydlig information (genetisk vägledning) för att säkerställa att den testade individen förstår aktuella implikationer av testresultatet för sig själv och för släkten. Sådan information kan med fördel lämnas i skriftlig form i samband med att blodprov tas på till exempel bröstkirurgisk eller onkologisk klinik vid behandlingsutredning. Genetisk undersökning ska i dessa fall omfatta *BRCA1* och *BRCA2*, och kan inkludera även andra gener associerade med ökad bröstcancerrisk enligt tabell 1.

Identifierade varianter graderas enligt en femgradig skala där 5 motsvarar säkert sjukdomsassocierade varianter (minst 99 % sannolikhet), 4 troligen sjukdomsassocierade varianter (95–99 %), 3 oklara varianter (VUS) (5–95 %), 2 troligen inte sjukdomsassocierade (0,1–5 % sannolikhet) respektive 1 icke sjukdomsassocierade (< 0,1 % sannolikhet) [187]. Endast varianter av grad 4–5 kan användas för kliniska beslut. Vid genetisk analys påträffas regelbundet varianter av oklar klinisk signifikans (VUS). Om dessa rapporteras ska det tydligt anges att de inte kan användas för individuell riskvärdering eller behandlingsbeslut. För att kunna erbjuda en högkvalitativ genetisk analys fordras dels en hög laboratoriemässig kvalitet, dels tillräcklig kompetens att bedöma den kliniska relevansen av påvisade genetiska varianter. Eftersom detektionsmetoderna successivt har förbättrats kan det finnas skäl att upprepa analysen i familjer som genomgått mutationsscreening med äldre tekniker. Om DNA inte är tillgängligt från någon

levande familjemedlem som behandlats för cancer ska man överväga att analysera DNA utvunnet från paraffininbäddat material från avliden släkting med en relevant canceranamnes.

Utfallet av en cancergenetisk utredning kan bli något av följande:

1. Den genetiska analysen visar en sjukdomsassocierad variant (variant av grad 4–5) i en bröstcancergen som är förenad med en ökad risk för att utveckla bröstcancer och eventuellt andra cancerformer. I familj med *högpenetrant* sjukdomsassocierad variant kan presymtomatisk testning efter genetisk vägledning erbjudas individer utan cancer. I familjer med mutation i *låg-/medelpenetrant* gen är presymtomatisk testning inte alltid meningsfull, om utfallet inte ändrar den kliniska handläggningen, men bör erbjudas kvinnliga förstagradssläktingar till fall med bröstcancerdiagnos. Fall i enlighet med 1 ska erbjudas remiss till onkogenetisk mottagning.
2. Resultatet visar en variant av oklar signifikans (VUS). Dessa varianter ska inte ligga till grund för beslut om riktade åtgärder, och i dessa fall kan presymtomatisk testning inte erbjudas, om inte evidensläget för varianten eventuellt ändras.
3. Screeningen påvisar inte någon avvikelse i bröstcancerassocierad gen. Ett sådant fynd utesluter inte helt att familjens medlemmar, inklusive den testade individen, kan ha en ärftligt ökad risk för bröstcancer och eventuellt andra maligna diagnoser. I avsaknad av positivt fynd vid genetisk analys bedöms den individuella risken med hjälp av en epidemiologisk modell. Vid mycket anmärkningsvärd familjehistoria kan man överväga remiss till onkogenetisk mottagning även om ingen sjukdomsassocierad variant påvisats vid analysen.

Presymtomatisk testning: I en familj med en påvisad sjukdomsassocierad variant ledande till en hög eller måttligt förhöjd bröstcancerrisk kan tidigare cancerfriska individer efter noggrann cancergenetisk vägledning erbjudas så kallad presymtomatisk testning. Analysen visar om vederbörande bär eller inte bär på den genetiska förändring som medför förhöjd cancerrisk. Om presymtomatisk testning är möjlig i familjen, är sådan obligat inför riskreducerande kirurgi. Vid förekomst av sjukdomsassocierad variant i gen kopplad till en måttligt förhöjd bröstcancerrisk är beslut om presymtomatisk testning svårare, då positivt fynd inte alltid påverkar den kliniska handläggningen. Presymtomatisk testning ska ske vid onkogenetisk mottagning.

10.3 Handläggning av personer med sjukdomsassocierad variant eller familjärt ökad risk

Rekommendationer vid kraftigt förhöjd risk (*BRCA1* eller *BRCA2*)

Individer som bär på en identifierad mutation i *BRCA1* eller *BRCA2* bör erbjudas möjlighet till klinisk kontakt från 25 till minst 74 års ålder:

- Genetisk vägledning på onkogenetisk mottagning för fördjupad information, och diskussion om utökad testning i familjen.
- Årlig bilddiagnostik (bröst) från 25 till cirka 74 års ålder, inkluderande bröst-MRT upp till cirka 55 års ålder.
- Information om möjlighet till riskreducerande mastektomi.
- Upprätta en regelbunden individuellt anpassad kontakt med gynekolog som kan ge information om riskreducerande salpingooforektomi och andra aktuella gynekologiska frågeställningar. Det är lämpligt att denna kontakt initieras vid cirka 30 års ålder.

- Riskreducerande salpingooforektomi rekommenderas för kvinnliga *BRCA1*- och *BRCA2*-mutationsbärare efter avslutad reproduktion, vid *BRCA1*-mutation vid cirka 35–40 års ålder, vid *BRCA2*-mutation vid cirka 40–50 års ålder.
- Efter riskreducerande salpingooforektomi hos en premenopausal kvinna utan tidigare bröstcancerdiagnos rekommenderas HRT (hormonersättning) upp till ungefär 50 års ålder.
- Manliga bärare av mutation i *BRCA2* ska erbjudas prostatacancerscreening från 40 års ålder tills kurativt syftande behandling inte längre skulle vara aktuell vid diagnos av prostatacancer (++).

Rekommendationer vid måttligt förhöjd risk (baserat på epidemiologisk riskbedömning med minst 20 % livstidsrisk, eller förekomst av sjukdomsassocierad variant i gen associerad med måttligt förhöjd risk)

- Årlig bilddiagnostik (bröst) från cirka 5 år före lägsta insjuknandeålder i familjen eller senast från 40 års ålder upp till cirka 74 års ålder.
- Vid uppföljning före 50 års ålder och vid mammografiskt täta bröst bör man, för ökad sensitivitet, komplettera med till exempel ultraljud (++) (C).
- Vid uppföljning före 40 års ålder är det rimligt att låta intervallet mellan undersökningarna vara ett år.
- För bröstfriska kvinnliga bärare av trunkerande variant i *CHEK2* eller *ATM*, som har en förstagradssläkting med bröstcancer, rekommenderas årlig mammografi i åldersintervallet 40 till 60 år, eller 10 år efter diagnos för kvinnor med bröstcancerdiagnos över 50 års ålder, därefter populationsscreening. Om det finns fall av bröstcancer före 45 års ålder i familjen rekommenderas screeningen erbjudas från 5 år före yngsta fallet i familjen.
- Risk för andra cancerformer (inklusive äggstockscancer) får bedömas från släktträdet samt eventuell påvisad sjukdomsassocierad variant. Remittera patienten till onkogenetisk mottagning vid behov.

Rekommendationer vid lätt förhöjd risk (baserat på epidemiologisk riskbedömning, motsvarande mindre än 20 % livstidsrisk)

- Mammografiscreening i populationsprogrammet.

Kunskapsläget och erfarenheten är störst vid riktad uppföljning av individer med mutation i *BRCA1* eller *BRCA2*. Aktuella rekommendationer vid uppföljning av kvinnor med kraftigt förhöjd risk utgår från det som rekommenderas hos *BRCA1/2*-mutationsbärare. Rekommendationer för bärare av patogena varianter i andra riskassocierade gener sammanfattas i tabell 1.

Tabell 1. I tabellen, som är modifierad från NCCN (NCCN Guidelines. Genetic/familial high-risk assessment: breast and ovarian, version 3,2019) [168], sammanfattas risknivå avseende cancer för bärare av sjukdomsassocierade varianter i andra riskassocierade gener utöver *BRCA1* och *BRCA2*, samt förslag till uppföljning. Rekommendationerna har inte evidensgraderats, eftersom det föreligger otillräckligt underlag för att värdera effekten av åtgärder. Förslagen utgår från aktuell risknivå. Observera att inklusion av en gen i denna lista inte innebär en rekommendation avseende huruvida testning bör utföras.

Gen	Bröstcancerrisk och förslag till uppföljning	Äggstockscancerrisk, handläggning	Övrig cancerrisk, handläggning
BRCA1	Starkt förhöjd risk. För handläggning, se ovan.	Starkt förhöjd risk. För handläggning, se ovan.	
BRCA2	Starkt förhöjd risk. För handläggning, se ovan.	Starkt förhöjd risk. För handläggning, se ovan.	Pankreas, prostata. För handläggning, se ovan.
TP53	Starkt förhöjd risk. Årlig bilddiagnostik av bröst från 20 års ålder. *TP53*-bärare bör om möjligt undvika joniserande strålning *vid uppföljning och behandling*,* framför allt i yngre åldrar och bör från 20 års ålder screenas omväxlande med MRT och ultraljud. Information om möjlighet till riskreducerande bröstkirurgi med omedelbar rekonstruktion.	Ingen säkert ökad risk.	Li-Fraumenis syndrom. Handläggning enligt separata riktlinjer, i första hand inom ramen för klinisk uppföljningsstudie*.
PALB2	Måttligt–starkt förhöjd risk. Årlig bilddiagnostik inkluderande MRT från 30 års ålder. Riskreducerande mastektomi kan övervägas baserat på aktuell släkthistoria.	Otillräcklig evidens avseende äggstockscancerrisk.	
PTEN	Sannolikt starkt förhöjd risk (osäkra riskestimat). Uppföljning med mammografi + MRT från 30–35 års ålder, eller 5–10 år före yngsta fallet i familjen. Information om möjlighet till riskreducerande mastektomi.	Ingen ökad risk.	*PTEN* Hamartoma Tumor Syndrome (PHTS, Cowdens syndrom). Handläggning enligt separata riktlinjer. Aktuella diagnoser inkluderar: uteruscancer, tyreoideacancer, kolorektal cancer och njurcancer.
CDH1	Sannolikt starkt förhöjd risk för lobulär bröstcancer (osäkra riskestimat). Uppföljning med mammografi + MRT från 30 års ålder. Riskreducerande mastektomi kan övervägas baserat på aktuell släkthistoria.	Ingen ökad risk.	Diffus ventrikelcancer. Handläggning enligt separata riktlinjer.

Gen	Bröstcancerrisk och förslag till uppföljning	Äggstockscancerrisk, handläggning	Övrig cancerrisk, handläggning
STK11	Sannolikt starkt förhöjd risk (osäkra riskestimat). Uppföljning med mammografi + MRT från 25 års ålder. Riskreducerande mastektomi kan eventuellt övervägas baserat på aktuell släkthistoria.	Förhöjd risk för icke-epitelial äggstockscancer.	Peutz-Jeghers syndrom. Handläggning enligt separata riktlinjer. Aktuella diagnoser inkluderar: kolorektal cancer, ventrikelcancer, tunntarmscancer, pankreascancer, gynekologisk cancer och testikelcancer.
NF1	Sannolikt måttligt förhöjd risk, med en tydlig riskökning främst i intervallet 30–50 år (osäkra riskestimat). Handläggning enligt separata riktlinjer.	Ingen ökad risk.	Neurofibromatos typ 1. Handläggning enligt separata riktlinjer.
ATM **(trunkerande mutationer)**	Måttligt förhöjd risk. För bröstfriska kvinnliga bärare av trunkerande variant i *ATM* rekommenderas årlig mammografi i åldersintervallet 40 till 60 år, eller 10 år efter diagnos för kvinnor med bröstcancerdiagnos över 50 års ålder, därefter populationsscreening. Om det finns fall av bröstcancer före 45 års ålder i familjen rekommenderas att screeningen erbjuds från 5 år före yngsta fallet i familjen.	Ingen ökad risk.	Otillräcklig evidens.
CHEK2 **(trunkerande mutationer)**	Måttligt förhöjd risk. För bröstfriska kvinnliga bärare av trunkerande variant i *CHEK2* rekommenderas årlig mammografi i åldersintervallet 40 till 60 år, eller 10 år efter diagnos för kvinnor med bröstcancerdiagnos över 50 års ålder, därefter populationsscreening. Om det finns fall av bröstcancer före 45 års ålder i familjen rekommenderas screeningen erbjudas från 5 år före yngsta fallet i familjen).	Ingen ökad risk.	Lätt förhöjd risk för kolorektalcancer. Ev. koloskopikontroller endast utgående från familjehistorien.

**Detta innebär att man bör undvika postoperativ strålbehandling om det kan undvikas till exempel som led i bröstbevarande behandling. Strålbehandling som led i kurativ bröstcancerbehandling bör emellertid ges.*

10.3.1 Bilddiagnostik

10.3.1.1 Mammografi

Minskningen av dödlighet är i storleksordningen 20–25 % [72] i hela populationen, och ännu högre bland dem som har deltagit i screeningen (++++) [19, 73, 74] (++++). Det är oklart om denna riskreduktion också gäller kvinnor med en ärftligt ökad risk, i synnerhet när de undersöks från en lägre ålder då sensitiviteten hos mammografi generellt sett är lägre [188]. Den mammografiska densiteten hos bärare av sjukdomsassocierad variant i *BRCA1* och *BRCA2* är inte högre än hos andra kvinnor, men det faktum att premenopausala kvinnor generellt sett har täta bröst är ett problem vid screening av kvinnor med ärftlig bröstcancerrisk, särskilt för dem under 40 års ålder [189-191].

10.3.1.2 Ultraljud och magnetresonanstomografi

Ultraljudsundersökning som tillägg till mammografiscreening medför en något ökad sensitivitet när det gäller att finna bröstcancer, framför allt hos kvinnor med mammografiskt täta bröst [188, 192] (+++). Ett antal studier av magnetresonanstomografi (MRT) talar för att denna metod erbjuder en markant ökad sensitivitet avseende bröstcancer i jämförelse med andra screeningmetoder hos yngre kvinnor med ärftlig bröstcancerrisk, men specificiteten är lägre (++++). Randomiserade data från mutationsbärare saknas, och sådana studier kommer knappast att kunna genomföras [193]. Av redovisade cancerfynd i dessa studier har majoriteten diagnostiserats i stadium 0 eller 1 [194-199], och i en icke-randomiserad jämförande studie observerades att kvinnor med ärftlig risk som undersöktes med MRT i tillägg till mammografi hade 70 % lägre risk att diagnostiseras med bröstcancer i stadium 2 eller högre [200] (+++). För översikt, se Warner 2018 [201].

10.3.2 Screening för annan cancer associerad med *BRCA1* respektive *BRCA2*

Det saknas stöd för att ovarialcancerscreening av *BRCA1/2*-bärare reducerar dödligheten i äggstockscancer (+) [202, 203], och i detta vårdprogram rekommenderas i första hand riskreducerande salpingooforektomi för *BRCA1*- och *BRCA2*-bärare efter avslutad reproduktion (++++ för dödlighetsreduktion). För detaljer, se Nationellt vårdprogram för Epitelial Äggstockscancer.

En nyligen publicerad metaanalys anger att män med mutation i *BRCA1* och *BRCA2* har en ökad risk för prostatacancer, vilket i första hand beror på en ökad risk associerat med sjukdomsassocierade varianter i *BRCA2* [162]. Ett flertal studier bekräftar att män med *BRCA2*-mutation har en förhöjd risk avseende i synnerhet tidigt prostatacancerinsjuknande jämfört med andra män (++++) [204-206]. Det vetenskapliga underlaget avseende ökad risk för prostatacancer vid *BRCA1*-mutation är tydligt svagare (+) [207]. Män med *BRCA2*-mutation ska rekommenderas PSA-screening från 40 års ålder, se Nationellt Vårdprogram för prostatacancer [208].

En ökad risk för pankreascancer är beskriven hos bärare av sjukdomsassocierad variant i *BRCA2* [163]. Den absoluta risken är dock låg, och nytta av screeningåtgärder är inte etablerad vid denna [209] (se nationella vårdprogrammet för pankreascancer [210] eller andra diagnoser).

10.3.3 Riskreducerande kirurgi

Vid riskreducerande eller profylaktisk mastektomi (PM) genomförs vanligen en omedelbar rekonstruktion. Risken för bröstcancer är relaterad till bland annat bröstkörtelmassan, och retrospektiva och prospektiva data talar för att man vid profylaktisk mastektomi hos friska kvinnor reducerar bröstcancerrisken med minst 90 %. Detta gäller både *BRCA1*- och *BRCA2*-bärare liksom individer med en på epidemiologisk grund definierad riskökning [211-214] (++++) avseende reduktion av bröstcancerincidens hos bärare av sjukdomsassocierad variant).

Det saknas specifika data för kvinnor med sjukdomsassocierade varianter i andra bröstcancergener, men det finns ingen anledning att tro att den riskreducerande effekten skulle avvika i dessa fall. Effekten avseende bröstcancerspecifik och total överlevnad är oklar (+) [215]. En riskreducerande mastektomi med omedelbar rekonstruktion är en medicinskt motiverad åtgärd för kvinnor som har en kraftigt ökad bröstcancerrisk (till exempel mutationsbärare *BRCA1*, *BRCA2* och *TP53*) och som så tydligt önskar det, men underlag för att rekommendera detta saknas för individer med en måttligt förhöjd bröstcancerrisk. För detaljer kring rekonstruktion i samband med riskreducerande kirurgi, se avsnitt 13.9 Rekonstruktiv kirurgi.

10.3.3.1 Riskreducerande salpingooforektomi i samband med ärftlig bröstcancerrisk

Riskreducerande salpingooforektomi hos tidigare bröstfriska:
En riskreducerande salpingooforektomi (SOE) minskar effektivt risken för att insjukna i äggstockscancer [203, 216, 217] (++++). Efter en sådan operation kvarstår dock en viss risk att drabbas av primär peritoneal karcinomatos. I en studie inträffade detta i 4–5 % av fallen efter 20 års uppföljning [218], i en annan i 1,2 % respektive 1,8 % av fallen efter cirka 4 års uppföljning hos *BRCA1*-mutationsbärare utan respektive med tidigare bröstcancerdiagnos. Detta kan jämföras med en äggstockscancerincidens under motsvarande uppföljningstid om cirka 6 % hos dem som inte opererats [214]. Vid riskreducerande operation är det av största vikt att äggledarna tas bort eftersom dessa inte sällan är ursprunget för tumörutvecklingen [219].

Kvinnor med sjukdomsassocierad variant i *BRCA1* eller *BRCA2* samt potentiella bärare (icke-testade förstagradssläktingar till identifierade bärare) bör ha en regelbunden gynekologisk kontakt, dock inte nödvändigtvis årligen. Syftet är bland annat att kunna föra en diskussion om framtida riskreducerande kirurgi och finna en lämplig tidpunkt för ingreppet.

En profylaktisk salpingooforektomi bör utföras laparoskopiskt och av en van gynekologisk kirurg som är väl förtrogen med äggstockscancer. Hela ovariet inklusive hilus och äggledare ska avlägsnas. Noggrann histologisk analys med seriesnittning ska utföras.

Cirka 5 % ockult cancer har påvisats hos *BRCA*-mutationsbärare vid profylaktisk kirurgi [217, 219, 220]. En prospektiv kohortstudie som inkluderade sammanlagt 2 482 mutationsbärare i Europa och Nordamerika visade att de som genomgått en riskreducerande salpingooforektomi hade en signifikant lägre dödlighet i såväl äggstockscancer (HR 0,21, 95 % KI 0,06–0,80) som bröstcancer (HR 0,44, 95 % KI 0,26–0,76) som avseende alla dödsorsaker (HR 0,40, 95 % KI 0,26–0,61) [214]. Mycket likartade resultat ses i en annan prospektiv kohortstudie inkluderande 3 936 cancerfriska *BRCA*-mutationsbärare från Nordamerika och Europa [217] (++++ avseende reduktion i äggstockscancerincidens, +++ avseende dödlighetsreduktion). I denna studie sågs ingen effekt avseende reducerad bröstcancerrisk för de kvinnor som tagit bort äggstockarna efter 50 års ålder (HR 1,36, 95 % KI 0,26–7,05), men däremot en halverad bröstcancerrisk i gruppen som opererats med SOE före 50 års ålder (HR 0,51, 95 % KI 0,32–0,82). I en studie som inkluderade 3 722 mutationsbärare (*BRCA1* och *BRCA2*) sågs endast en effekt av ooforektomi

på bröstcancerrisken hos *BRCA2*-mutationsbärare under 50 år (HR 0,18, 95 % KI 0,05–0,63), däremot ingen signifikant effekt hos *BRCA1*-mutationsbärare (HR 0,79, 95 % KI 0,55–1,13) [221].

Tidigare bröstfriska kvinnor som genomgått riskreducerande salpingooforektomi premenopausalt bör efter ingreppet erbjudas hormonersättning i syfte att lindra klimakteriella symtom, till exempel fram till 50 års ålder, utan att detta tycks påverka bröstcancerrisken på ett tydligt negativt sätt.

Riskreducerande salpingooforektomi efter tidigare bröstcancerdiagnos:
I en prospektiv kohortstudie som inkluderade sammanlagt 2 561 tidigare bröstcancerpatienter som var bärare av sjukdomsassocierade varianter i *BRCA1* och *BRCA2* observerades efter en uppföljning om cirka 5 år en minskad dödlighet motsvarande en HR på 0,32 (95 % KI 0,26–0,39) (++++ för reduktion av dödlighet efter riskreducerande salpingooforektomi hos patient med tidigare *BRCA*-associerad bröstcancer [214].

10.3.4 Medicinsk prevention med tamoxifen och aromatashämmare av bröst- och ovarialcancer

Selektiva östrogenreceptormodulerare ses i en stor metaanalys inkluderande över 83 000 bröstcancerfriska kvinnor med normal till måttligt ökad risk för sjukdomen reducera risken att insjukna i bröstcancer med 38 % (HR 0,62, 95 % KI 0,56–0,69) [63]. Även aromatashämmare har studerats i en stor metaanalys och ses reducera incidensen av hormonreceptorpositiv bröstcancer med 53 % (HR 0,468, 95 % KI 0,346–0,634) [222] (++++ för reducerad cancerincidens). Det beräknade antalet individer som måste behandlas för att förebygga ett fall av bröstcancer var 42 (numbers needed to treat) i den citerade metaanalysen. Data som avser effekt på överlevnad saknas. För individer med sjukdomsassocierade varianter i *BRCA1* eller *BRCA2* saknas specifika data som ges stöd för en rimlig nytta-riskrelation vid denna typ av kemoprevention (+).

P-pillerbruk har en skyddande effekt på ovarialcancerinsjuknande i en för ärftlighet oselekterad population, vilket visas i en metaanalys av epidemiologiska studier som inkluderade 23 257 ovarialcancerfall och 87 303 kontroller. Effekten av 5 års bruk var en riskreduktion på 29 % (95 % KI 23–34 %) av ovarialcancerincidensen under de närmaste 10 åren efter avslutad exponering [223]. En metaanalys av sex studier som inkluderade högriskindivider (*BRCA*-bärare och individer med hög risk baserat på familjehistoria) visade ett liknande resultat [224], med en riskreduktion om 42 % (OR 0,58, 95 % KI 0,46–0,53). (++++ för reducerad ovarialcancerincidens efter p-pillerbruk). Det ska påpekas att man i denna metaanalys såg en icke-signifikant relativ riskökning avseende bröstcancerrisk om 21 % (OR 1,21, 95 % KI 0,93–1,58).

10.4 Handläggning av bröstcancerpatienter med sjukdomsassocierad variant i högpenetrant bröstcancergen

10.4.1 Riskreducerande kirurgi

Rekommendationer

- I samband med bröstcancerdiagnos hos en kvinna med sjukdomsassocierad variant i *BRCA1*, *BRCA2* eller annan högpenetrant bröstcancergen: Information om möjlighet till mastektomi som alternativ till bröstbevarande kirurgi.
- Bröstcancerfrisk kvinna med mutation i högpenetrant bröstcancergen efter tidigare bröstcancerdiagnos: Möjlighet till kontralateral (bilateral) mastektomi med omedelbar rekonstruktion.
- Riskreducerande salpingooforektomi rekommenderas för kvinnliga *BRCA1*- och *BRCA2*-mutationsbärare efter avslutad reproduktion, vid *BRCA1*-mutation vid cirka 35–40 års ålder, vid *BRCA2*-mutation vid cirka 40–50 års ålder. Observera att rekommendationen gäller även efter kurativ bröstcancerbehandling.

10.4.1.1 Kontralateral riskreducerande mastektomi vid primär bröstcancer

Bärare av sjukdomsassocierad variant i *BRCA1 eller BRCA2*

Vid kontralateral mastektomi (kontralateral profylaktisk mastektomi, kPM), hos kvinnor som tidigare opererats för bröstcancer ser man på samma sätt relativa riskreduktioner avseende bröstcancerincidens på minst 90 % (++++) [225, 226]. Vid kPM efter tidigare bröstcancerinsjuknande hos *BRCA1/2*-bärare finns prospektiva och retrospektiva kohortstudier som talar för en signifikant överlevnadsvinst av ingreppet. En kanadensisk studie av bröstcancerfall i stadium 1–2 visar en riskreduktion avseende total överlevnad motsvarande en HR för total överlevnad på 0,52 (95 % KI 0,29–0,93), och en skillnad i absoluta tal efter 20 år på 21 %-enheter. Andelen riskreducerande salpingooforektomier var högre bland de som genomgick kPM (72 vs 42 %) men föll inte ut prognostiskt i multivariatanalys. En prospektiv holländsk studie som framför allt inkluderar patienter i stadium 0–2 visar på ett HR för totalöverlevnad på 0,49 (95 % KI 0,29–0,82) och en absolut effekt efter 15 år om 12 %-enheter. Andelen patienter som genomgått riskreducerande salpingooforektomi var högre bland de som genomgick kPM, men antalet fall av ovarialcancer var lågt i båda grupperna (2 vs 4 %). Antalet kontralaterala bröstcancerinsjuknanden var 2 % bland de kontralateralt opererade vs 19 % för de som inte genomgått ingreppet. Det finns alltså underlag att betrakta sjukdomsassocierad variant i *BRCA1* och *BRCA2* som en prediktiv faktor för nytta avseende total överlevnad av kontralateral riskreducerande mastektomi (+++).

Individer med negativ molekylärgenetisk undersökning avseende högpenetranta gener

Bortsett från individer med mutation i högpenetranta bröstcancergener saknas det evidens att fastställa en risknivå vid vilken en kontralateral mastektomi kan vara indicerad. Vid en eventuell sådan bedömning måste utöver den aktuella kontralaterala risken (se avsnitt 10.2.3 ovan), även prognosen avseende den diagnostiserade bröstcancern beaktas. I den övervägande majoriteten av fall av sporadisk bröstcancer saknas indikation för ett kontralateralt avlägsnande av bröstvävnad i syfte att öka den bröstcancerspecifika överlevnaden. Om en sådan frågeställning uppkommer ska sannolikheten för mutation i *BRCA1, 2* och andra högpenetranta bröstcancergener bedömas, och

mutationsscreening erbjudas om indikation för testning föreligger. För bärare av sjukdomsassocierad trunkerande variant i *CHEK2* och *ATM* saknas specifik evidens för nytta avseende kontralateral riskreducerande bröstkirurgi, men kan på en individuell basis diskuteras. Om sådan åtgärd övervägs ska faktorer som förekomst av bilateral sjukdom i familjen, och tidigt insjuknande i familjen vägas in i bedömningen (+).

I fall som är negativa vid molekylärgenetisk undersökning ska bedömning underställas multidisciplinär bröstkonferens med beaktande av till exempel Manchestermodellen, BOADICEA eller annan objektiv modell samt prognosen efter tidigare cancerdiagnos.

10.4.1.2 Bröstbevarande kirurgi vs mastektomi vid ärftlig bröstcancer

Man ser i en systematisk översikt att kvinnor opererade med bröstbevarande kirurgi i samband med *BRCA1/2*-associerad bröstcancer har en högre risk att insjukna i återfall i samma bröst jämfört med kvinnor med sporadisk bröstcancer. De absoluta risknivåerna uppgår efter 10 år till 12–41 % vilket kan jämföras med 4–24 % hos sporadiska kontroller. Någon skillnad i överlevnad kunde inte påvisas [227].

Genomgången strålbehandling kan påverka de tekniska förutsättningarna för genomförande av implantatbaserad rekonstruktion efter en framtida mastektomi. Mastektomi som alternativ till bröstbevarande behandling kan innebära att man vid lymfkörtelnegativ sjukdom kan undvika postoperativ strålbehandling och på så sätt underlätta genomförandet av bröstrekonstruktion.

10.4.2 Medicinsk behandling

Rekommendationer

- För patienter med metastatisk *BRCA1*/2-associerad bröstcancer bör PARP-hämmare (+++) eller platinumbaserad cytostatikabehandling (++) erbjudas som ett tidigt behandlingsalternativ. För bakgrund: se kapitlet om medicinsk behandling vid spridd bröstcancer, avsnitt 18.4 samt 0.

KAPITEL 28

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KAPITEL 29

Vårdprogramgruppen

29.1 Vårdprogramgruppens sammansättning

Den nationella arbetsgruppen består av en representant per regionalt cancercentrum samt en ordförande som utsetts av RCC i samverkan. Gruppen har eftersträvat multiprofessionalitet med representanter för de olika vårdnivåer som är engagerade i patientens vårdflöde. Utöver detta har patientföreträdare deltagit.

29.2 Vårdprogramgruppens medlemmar

Ordförande
Jonas Bergh, professor i onkologi, Karolinska Institutet, överläkare Bröstcentrum, Tema cancer, Karolinska Universitetssjukhuset, Solna

Regionala representanter
Norr
Anne Andersson, medicine doktor, överläkare, Onkologiska kliniken, Norrlands Universitetssjukhus, Umeå

Stockholm Gotland
Theodoros Foukakis, docent, överläkare, Bröstcentrum, Tema cancer, Karolinska Universitetssjukhuset och Institutionen för onkologi-patologi, Karolinska Institutet, Solna

Syd
Niklas Loman, docent, överläkare, Verksamhetsområde Hematologi, Onkologi och Strålningsfysik; Skånes Universitetssjukhus, Lund

Sydöst
Eva Vikhe Patil, överläkare, Bröstkirurgi, Universitetssjukhuset i Linköping, Linköping

Uppsala Örebro
Antonios Valachis, docent, överläkare, Onkologiska Kliniken, Universitetssjukhuset, Örebro

Väst
Dan Lundstedt, medicine doktor, överläkare, Jubileumskliniken, Sahlgrenska Universitetssjukhuset, Göteborg

Övriga representanter – kapitelförfattare

Anne Andersson, överläkare, Cancercentrum, onkologi, Norrlands Universitetssjukhus, Umeå

Malin Backman, medicine doktor, Institutionen för neurolobiologi, vårdvetenskap och samhälle, Karolinska Institutet, Solna

Jenny Bergqvist, medicine doktor, överläkare, Bröstcentrum Capio S:t Görans Sjukhus, Stockholm

Yvonne Brandberg, professor, psykolog, Institutionen för onkologi-patologi, Karolinska Institutet, Solna

Hans Ehrencrona, docent, överläkare, VO Klinisk genetik och patologi, Labmedicin, Region Skåne

Irma Fredriksson, medicine doktor, överläkare, Bröstcentrum Kirurgi, Karolinska Universitetssjukhuset samt Institutionen för Molekylär medicin och Kirurgi, Karolinska Institutet, Solna

Johan Hartman docent, specialist klinisk patologi, Avdelningen för Onkologi-Patologi, Karolinska Institutet, Solna

Malin Laurell Lövefors, funktionsenhetschef, Mammografiavdelningen FO Thoraxradiologi/Bröst, Karolinska Universitetssjukhuset, Solna

Barbro Linderholm, docent, överläkare, Onkologiska Kliniken, Sahlgrenska Universitetssjukhuset, Göteborg

Maria Mani, docent, överläkare, VO Käk- och Plastikkirurgiska kliniken, Akademiska sjukhuset, Uppsala

Greger Nilsson, medicine doktor, överläkare, Onkologiska enheten, Visby Lasarett samt Onkologiska kliniken Gävle sjukhus, Visby/Gävle

Helena Olofsson, medicine doktor/PhD, överläkare, sektionschef klinisk patologi, Linjeansvarig och överläkare i bröstpatologi, Klinisk Patologi, Akademiska laboratoriet, Akademiska sjukhuset, Uppsala

Charlotta Wadsten, medicine doktor, överläkare, Kirurgkliniken, Sundsvalls Sjukhus, Sundsvall

Yvonne Wengström, professor, legitimerad onkologisjuksköterska, Institutionen för neurobiologi, Vårdvetenskap och Samhälle för Omvårdnad, Karolinska Institutet, Solna

Fredrik Wärnberg, professor, Kirurgkliniken, Akademiska sjukhuset, Uppsala

Sophia Zackrisson, överläkare, docent, universitetslektor i diagnostisk radiologi, VO Bild- och funktion, Skånes Universitetssjukhus Malmö samt Institutionen för translationell medicin, Lunds Universitet, Malmö/Lund

29.3 Jäv och andra bindningar

Kopior av hela gruppens jävsdeklarationer, inklusive föreläsaruppdrag, går att få från Regionalt cancercentrum Stockholm-Gotland.

SweBCG har sedan många år på årlig basis uppdaterat jävsdeklarationerna för alla medlemmar. Jävsdeklarationerna för respektive författare finns tillgängliga på SweBCG:s webbplats (www.swebcg.se). Individuella jävsdeklarationer har tagits in för författare som inte varit medlemmar i SweBCG.