On hereditary ovarian cancer
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ENGLISH SUMMARY

Although most cases of ovarian cancer are sporadic, about 20% are associated with a genetic predisposition, most often related to a BRCA1/2 mutation. Women with a BRCA1/2 mutation (Hereditary Breast and Ovarian Cancer Syndrome) have a highly increased risk of breast and ovarian cancer. While the cumulative risk of ovarian cancer by age 75 in the general population is estimated to range from 0.4% to 1.3%, risk estimates range from 31% to 59% for BRCA1 mutation carriers, and from 6% to 18% for BRCA2 mutation carriers.

BRCA1/2 are tumor suppressor genes with important functions in cell cycle control and response to DNA damage by homologous recombination. The identification of women with a BRCA1/2 mutation has potential clinical benefits. First, identifying these individuals is very important for early cancer diagnosis or prevention. Concerning their increased breast cancer risk, BRCA1/2 mutation carriers are offered intensive breast cancer screening or bilateral risk reducing mastectomy. For ovarian cancer there is no effective screening method and mutation carriers are advised to have risk reducing salpingo-oophorectomy (RRSO). RRSO can reduce the ovarian cancer risk by up to 96% when performed at the appropriate age, before the incidence rises. Among women who already developed cancer, information over a BRCA-mutation status is relevant not only for their relatives, but recently also for themselves, for guiding treatment options, since patients with BRCA1/2 deficient tumors have been reported to respond better to certain therapies, such as Poly(ADP-ribose) polymerase (PARP)-inhibitors. PARP is a protein that, together with BRCA1/2, plays a role in DNA repair by homologous recombination. PARP inhibitors cause an increase in DNA single-strand breaks which, during replication, become irreparable DNA double-strand breaks in BRCA1/2 defective cells. Therefore, patients with BRCA1/2 deficient tumors are hypersensitive to therapy with PARP inhibitors (synthetic lethality).

Because of the potential clinical benefits of identifying BRCA1/2 mutation carriers, there are several guidelines for the genetic risk evaluation of patients suspected to have Hereditary Breast and Ovarian Cancer Syndrome. Most recent international guidelines in developed countries recommend that all women diagnosed with invasive epithelial ovarian cancer are offered genetic testing, irrespective of age, histological subtype and family history. However, this recommendation is not always followed, for several reasons. There are large inequities on access to health care around the world, especially when concerning highly specialized services such as genetic testing. Hence, while most high-income countries follow the recommendation of offering genetic testing and counseling for all ovarian cancer patients, in low- and middle-income countries these services are often not available for the majority of women.

The overall aim of this thesis is to improve care of BRCA1/2 mutation carriers both in high- and in low-/middle-income countries. For that, we explored three aspects of hereditary ovarian cancer associated with BRCA1/2 mutations. First we focused on the identification of BRCA1/2 mutation carriers among ovarian cancer patients in a setting of limited resources. Subsequently, we explored the variation in ovarian cancer risk among BRCA1/2 mutation carriers, investigating possible sources of variation in this risk. Finally, we directed our
attention to the long term follow-up of women who had RRSO, investigating the possible consequences of this procedure, especially on bone health and cholesterol profile.

PART I

In low- and middle-income countries like Brazil, available resources are often not sufficient for offering genetic evaluation to all ovarian cancer patients. Therefore, PART I of this thesis aimed to assess the genetic profile of Brazilian women with ovarian cancer and to optimize a selection of patients with the highest mutation risk for genetic testing, in a setting of limited resources. So far, no studies had evaluated the entire coding sequence of BRCA1/2 for mutations on a cohort of patients selected solely on basis of an ovarian cancer diagnosis in Brazil, and epidemiological information on the demographic, clinical and genetic characteristics of ovarian cancer patients in the Brazilian population was lacking. The 3 chapters that compose PART I are based on a consecutive cohort of women undergoing treatment or follow up for ovarian cancer at the Instituto do Câncer do Estado de São Paulo, a reference center for cancer treatment in Brazil. Between October 2012 and February 2015 patients were consecutively invited to participate based solely on a diagnosis of ovarian cancer, with no restrictions concerning age at diagnosis or family history of cancer.

In chapter 2 the risk profile and family histories of cancer of the first 51 consecutive ovarian cancer patients included in the study were described. For each patient, probability of identifying a BRCA1/2 mutation was assessed with the Manchester score, a scoring system based on the number of relatives affected with cancer and their age at diagnosis. The association between clinical/demographic characteristics of these women and the probability of hereditary ovarian cancer (i.e. higher than 10% risk of BRCA1/2 mutation according to Manchester score) was investigated. In this small study we observed that 12 out of the 51 patients presented an estimated risk higher than 10% of having a BRCA1/2 mutation. Furthermore, having comorbidities (such as hypertension, diabetes, dyslipidemia or hormonal disorders) was associated with a lower estimated risk of having a mutation.

The frequency and spectrum of BRCA1/2 mutations vary considerably among populations with different ethnic backgrounds. Because there were no previous studies focused on hereditary ovarian cancer in the Brazilian population, which is a genetically heterogeneous population, information on the prevalence and spectrum of BRCA1/2 mutations among ovarian cancer patients from Brazil were lacking. Chapter 3 describes the BRCA1/2 mutation profile of a cohort of 100 consecutive unselected Brazilian ovarian cancer patients seen at a reference center for cancer treatment between October 2012 and February 2015. Fourteen different BRCA1/2 mutations were detected in 19 of these women. The frequency of mutations in this patient group was relatively high when compared to other studies in the Brazilian population, however previous studies had different criteria for selection of study participants and none had focused specifically on ovarian cancer patients. When compared to studies focused on ovarian cancer patients in other populations, the prevalence of a BRCA1/2 mutation reported in this study was also relatively high, emphasizing the importance of BRCA1/2 mutation analysis in ovarian cancer patients in Brazil.

The relatively high prevalence of BRCA1/2 mutations observed in chapter 3 suggests
that the recommendation of offering genetic evaluation to all women diagnosed with ovarian cancer should also be implemented in Brazil. However, due to the limited resources available, it is challenging to follow this recommendation for all ovarian cancer patients in the public health care system. Therefore, chapter 4 aimed at optimizing the selection of patients for genetic testing when available resources are limited. Several algorithms have been developed to estimate the probability of identifying a \( BRCA1/2 \) mutation in an individual. We evaluated the accuracy of four of the most widely used of these algorithms (BOADICEA, BRCAPRO, Myriad and Manchester Score) in the cohort of ovarian cancer patients described in chapter 3, also investigating whether other factors could be added to these algorithms to improve their accuracy. BOADICEA performed better than the other 3 algorithms, indicating a high probability of mutation for 24 women, 14 of which indeed had a \( BRCA1/2 \) mutation. However, with BOADICEA, five of the 19 mutation carriers would have been missed (sensitivity 73%). Furthermore, later menarche was significantly associated with the \( BRCA1/2 \) mutation status and adding information on it to the evaluated algorithms tended to improve their performances. The use of algorithms for estimating mutation-carrier probability could reduce the number of tests to be performed by up to 76%, and this could therefore be a valuable tool for the implementation of genetic testing in settings where available resources do not allow testing of all women diagnosed with ovarian cancer. However, still a quarter of the mutation carriers among ovarian cancer patients would be missed and offering genetic testing to all ovarian cancer patients (except the mucinous type) even in limited resources setting should be the aim.

PART II

Because of their highly increased risk of ovarian cancer, women in whom a \( BRCA1/2 \) mutation is identified are advised to have RRSO before the age at which ovarian cancer incidence starts to significantly rise (age 35-40 in \( BRCA1 \) and 40-45 in \( BRCA2 \) mutation carriers), after child bearing has been completed. RRSO has severe implications for most of these women’s quality of life and hence it is of utmost importance to provide them with precise risk estimates to support the difficult decisions they must make regarding (timing of) RRSO. Currently, counseling is based on age-related risk estimates derived from cohort studies of \( BRCA1/2 \) mutation carriers. However, previous studies indicate that ovarian cancer risks vary considerably among \( BRCA1/2 \) mutation carriers. It has been suggested that the type of family history of cancer and the mutation position on the gene are associated with variation in ovarian cancer risks in \( BRCA1/2 \) mutation carriers. Part II of this thesis evaluates these two possible sources of (age related) risk variation aiming at providing women a more personalized risk estimate.

Chapter 5 investigates the combined impact of mutation position on the gene and type of cancer family history on the ovarian cancer risk of women from families with \( BRCA1/2 \) mutations in the northern part of the Netherlands. Mutations within the central regions of \( BRCA1 \) are associated with higher risks of ovarian cancer than mutations in other portions of the gene, even when taking information on the family history of cancer into account. For women from \( BRCA2 \) families, the type of cancer family history had a stronger impact.
on ovarian cancer risks, and this impact remained stable when taking the mutation position on the gene into account. Because the study described on chapter 5 only included women from a genetically homogeneous population from the northern Netherlands, we conducted another study, including a larger cohort of BRCA1/2 mutation carriers from a nationwide Dutch cohort study (chapter 6). In this study we further investigated whether the association between family history and ovarian cancer risk could be explained by the mutation position on the gene. A family history of breast cancer was significantly associated with lower ovarian cancer risks both among BRCA1 and BRCA2 mutation carriers. After taking information on mutation position on the gene into account, the observed associations were still comparably strong, although no longer significant. Hence, the mutation position on the gene does not completely explain the association between family history of cancer and ovarian cancer risks.

PART III

Because there are no effective screening methods for ovarian cancer, women with BRCA1/2 mutations are offered a RRSO just before ovarian cancer incidence starts to rise (35-40 years for BRCA1 and 40-45 years for BRCA2). When performed at premenopausal age, RRSO causes an acute and premature onset of menopause which has unwanted consequences for women’s health. PART III of this thesis investigates the long term health consequences of premenopausal RRSO.

In chapter 7 we investigated the impact of premenopausal RRSO on the cholesterol profile of women with hereditary increased risk of ovarian cancer, comparing them with age-matched women who never had an oophorectomy. Although women who had RRSO had an overall healthier lifestyle, with a lower prevalence of smoking and higher rates of participation in sports, RRSO was associated with a more atherogenic cholesterol profile, e.g. higher levels of non-HDL cholesterol and lower levels of HDL cholesterol compared to age-matched controls.

In chapter 8 the impact of surgical menopause on bone health was investigated. Although natural menopause is associated with lower bone mineral density and a higher risk of fractures, previous studies investigating the impact of surgical menopause on bone health had reached inconsistent results. Therefore we performed a systematic review and meta-analyses of the available literature on the topic. BMD was significantly lower in women who had surgical menopause than in premenopausal age-matched women. However, according to existing literature, when compared to natural menopause, surgical menopause has no evident impact on BMD and on fracture prevalence.

Finally, chapter 9 outlines a general discussion of the studies comprised in this thesis, highlighting its main conclusions. Overall, this thesis provides important information for health care providers involved in the identification and counseling of BRCA1/2 mutation carriers. The evidence provided by this thesis can contribute to the implementation of genetic testing in countries with limited resources, to the understanding of the variation in ovarian cancer risk in BRCA1/2 mutation carriers, and to increasing awareness over the potential long term consequences of RRSO. These results can contribute to improving the care of BRCA1/2 mutation carriers in high- as well as low-/middle-income countries.
Hoewel de meeste gevallen van eierstokkanker sporadisch zijn, zijn ongeveer 20% geassocieerd met een genetische aanleg, meestal een BRCA1/2-mutatie. Vrouwen met een BRCA1/2-mutatie hebben een sterk verhoogd risico op borst- en eierstokkanker (erfelijk borst- en eierstokkankersyndroom). Het cumulatieve risico op eierstokkanker op 75-jarige leeftijd in de algemene bevolking ligt naar schatting tussen de 0,4% en 1,3%, terwijl de risico’s voor BRCA1-mutatiedraagsters tussen de 31% en 59% en voor BRCA2-mutatiedraagsters tussen de 6% en 18% liggen.

BRCA1 en -2 zijn tumorsuppressorgenen met een belangrijke functies in de controle van de cellercyclus en het herstel van DNA-schade met behulp van homologe recombinatie. Het vaststellen van een BRCA1/2-mutatie bij vrouwen kan klinische voordelen hebben. Ten eerste is het identificeren van deze vrouwen van belang voor de vroege diagnose en het voorkómen van kanker. Vanwege hun verhoogde risico op borstkanker, wordt aan BRCA1/2-mutatiedraagsters intensieve borstkankerscreening of bilaterale risicoreducerende mastectomie aangeboden. Voor eierstokkanker is er geen effectieve screeningsmethode en mutatiedraagsters wordt geadviseerd om risicoreducerende salpingo-oophorectomie (RRSO) te ondergaan. RRSO kan het risico op eierstokkanker met 96% verminderen, mits tijdig uitgevoerd, voordat de incidentie van eierstokkanker stijgt. Ook bij vrouwen bij wie kanker is vastgesteld, is informatie over een BRCA1/2-mutatie relevant, niet alleen voor hun familieleden, maar ook voor de behandelopties bij henzelf. Recente studies laten zien dat patiënten met BRCA1/2-deficiënte tumoren beter reageren op bepaalde therapieën, waaronder Poly (ADP-ribose) polymerase (PARP) -remmers. PARP is een eiwit dat samen met BRCA1/2 een rol speelt bij het repareren van DNA-schade door homologe recombinatie. PARP-remmers veroorzaken een toename in enkelstrengs DNA-breuken die daarna, tijdens replicatie, in BRCA1/2-deficiënte cellen onherstelbare DNA-dubbelstrengsbreuken worden (synthetische letaliteit).

Vanwege de mogelijke voordelen van het identificeren van BRCA1/2-mutatiedraagsters, zijn er verschillende richtlijnen om vrouwen met een verhoogd risico op erfelijk borst- en ovariumkankersyndroom te herkennen. De meest recente internationale richtlijnen in ontwikkelde landen adviseren om erfelijkheidsonderzoek aan te bieden aan alle vrouwen met epitheliale eierstokkanker, ongeacht diagnoseleeftijd, histologisch subtype en familiegeschiedenis. Dit advies wordt echter niet altijd gevolgd. Wereldwijd is er ongelijkheid in de toegang tot gezondheidszorg, vooral als het gaat om zeer specialistische zorg, zoals erfelijkheidsonderzoek. Hoewel de meeste hoge-inkomenslanden het advies voor erfelijkheidsonderzoek in alle patiënten met eierstokkanker volgen, is deze zorg vaak niet beschikbaar voor vrouwen in landen met lage en middeninkomens.

Het algemene doel van dit proefschrift is het verbeteren van de zorg voor BRCA1/2-mutatiedraagsters, zowel in hoge als in lage-/middeninkomenslanden. Daarvoor hebben we drie aspecten van erfelijke eierstokkanker in BRCA1/2-mutaties onderzocht. Als eerste richtten we ons op de identificatie van BRCA1/2-mutatiedraagsters in patiënten met eierstokkanker in een omgeving met beperkte middelen. Vervolgens hebben we de variatie in
het eierstokkankerrisico onder BRCA1/2-mutatiedraagsters onderzocht en mogelijke bronnen van deze variatie. Tenslotte hebben we aandacht besteed aan de nazorg voor vrouwen met RRSO en de mogelijke consequenties van deze procedure, met name op het gebied van botgezondheid en cholesterolprofiel.

**DEEL I**

In lage- en middeninkomenslanden zoals Brazilië zijn de beschikbare middelen vaak onvoldoende om erfelijkheidsonderzoek aan te bieden aan alle patiënten met eierstokkanker. Daarom was het doel van DEEL I van dit proefschrift om het genetische profiel van Braziliaanse vrouwen met eierstokkanker vast te stellen en om in deze omgeving met beperkte middelen de selectie van patiënten voor erfelijkheidsonderzoek met het grootste mutatierisico te optimaliseren. Tot dan toe waren er geen studies waarin de volledige BRCA1/2-genen werden onderzocht op mutaties in een niet-geselecteerd cohort van eierstokkankerpatiëntes in Brazilië en epidemiologische informatie over de demografische, klinische en genetische eigenschappen van eierstokkankerpatiëntes in deze bevolking ontbrak. De drie hoofdstukken in DEEL I zijn gebaseerd op een cohort van vrouwen dat werd behandeld of gevolgd na eierstokkanker bij het Instituto do Câncer do Estado de São Paulo, een referentiecentrum voor kankerbehandeling in Brazilië. Tussen oktober 2012 en februari 2015 werden alle eierstokkankerpatiëntes uitgenodigd om deel te nemen, ongeacht diagnoseleeftijd of familiegeschiedenis van kanker.

In hoofdstuk 2 werden het risicoprofiel en familiegeschiedenis van kanker beschreven voor de eerste 51 opeenvolgende eierstokkankerpatiëntes geïncludeerd in de studie. Voor elke patiënt werd de kans op het vinden van een BRCA1/2-mutatie geschat met de Manchester-score, gebaseerd op het aantal familieleden met kanker en hun diagnoseleeftijd. De associatie tussen de klinische en demografische kenmerken van deze vrouwen en een hoge kans op erfelijke eierstokkanker (i.e. een risico op een BRCA1/2-mutatie hoger dan 10% volgens de Manchester-score) werd onderzocht. In deze kleine studie vonden we dat voor 12 van de 51 patiënten het geschatte risico op een BRCA1/2-mutatie hoger was dan 10%. Het hebben van comorbiditeit (zoals hoge bloeddruk, diabetes, dyslipidemie of hormonale stoornissen) was geassocieerd met een lager geschat risico op een BRCA1/2-mutatie.

De frequentie en het spectrum van BRCA1/2-mutaties variëren sterk tussen populaties met verschillende etnische achtergronden. Omdat er geen eerdere studies waren naar erfelijke eierstokkanker in de genetisch heterogene Braziliaanse bevolking, ontbrak informatie over de prevalentie en het spectrum van BRCA1/2-mutaties in Braziliaanse eierstokkankerpatiëntes. Hoofdstuk 3 beschrijft het BRCA1/2-mutatieprofiel van 100 opeenvolgende niet-geselecteerde Braziliaanse eierstokkankerpatiëntes uit bovenbeschreven cohort. In 19 van deze vrouwen werden 14 verschillende BRCA1/2-mutaties vastgesteld. De mutatiefrequentie in deze patiëntengroep was relatief hoog in vergelijking met eerdere studies in de Braziliaanse populatie, maar deze hadden verschillende selectiecriteria voor de studiepopulatie en waren niet specifiek gericht op eierstokkankerpatiëntes. In vergelijking met studies gericht op eierstokkankerpatiëntes in andere populaties, was de prevalentie van BRCA1/2-mutaties in onze studie ook relatief hoog. Deze bevinding onderstrept het belang
van BRCA1/2-mutatieanalyse bij eierstokkankerpatiëntes in Brazilië.

De relatief hoge prevalentie van BRCA1/2-mutaties in hoofdstuk 3 suggereert dat het advies om erfelijkheidsonderzoek aan te bieden aan alle vrouwen met eierstokkanker ook in Brazilië moet worden geïmplementeerd. Door de beperkte middelen in de publieke gezondheidszorg is het echter moeilijk om dit advies te volgen. Daarom is hoofdstuk 4 gericht op het optimaliseren van de selectie van patiënten voor erfelijkheidsonderzoek bij beperkte middelen. Er bestaan verschillende algoritmen om de kans op het vinden van een BRCA1/2-mutatie in een individu te schatten. We evalueerden de nauwkeurigheid van vier van de meest gebruikte algoritmen (BOADICEA, BRCAPRO, Myriad en Manchester-score) in het cohort van eierstokkankerpatiëntes beschreven in hoofdstuk 3. Ook onderzochten wij of de toevoeging van andere factoren aan deze algoritmen hun nauwkeurigheid kon vergroten. BOADICEA voldeed beter dan de andere drie algoritmen en gaf een hoge kans op het vinden van een BRCA1/2-mutatie voor 24 vrouwen, van wie 14 daadwerkelijk een BRCA1/2-mutatie hadden. Echter, vijf van de 19 mutatiedraagsters zouden zijn gemist (sensitiviteit 73%). Een latere menarche was geassocieerd met BRCA1/2-mutatiestatus en toevoeging van deze parameter aan de geëvalueerde algoritmen verbeterde hun prestaties. Het gebruik van algoritmen om het mutatierisico te schatten zou het aantal te verrichten BRCA1/2-testen met 76% kunnen terugbrengen en kan waardevol zijn bij de implementatie van erfelijkheidsonderzoek in een setting waar genetisch testen van alle eierstokkankerpatiëntes door beperkte middelen niet mogelijk is. Echter, een kwart van de mutatiedraagsters onder eierstokkankerpatiëntes zou hierbij gemist worden. Het aanbieden van erfelijkheidsonderzoek voor alle eierstokkankerpatiënten (behalve het mucineuze type), zou het doel moeten zijn, zelfs bij beperkte middelen.

DEEL II

Vanwege hun sterk verhoogde risico op eierstokkanker, wordt aan vrouwen bij wie een BRCA1/2-mutatie is vastgesteld, geadviseerd om RRSO te ondergaan voor de leeftijd waarop de incidentie van eierstokkanker aanzienlijk stijgt (35-40 jaar in BRCA1- en 40-45 in BRCA2-mutatiedraagsters), nadat de kinderwens is voltooid. RRSO heeft ernstige gevolgen voor kwaliteit van leven van deze vrouwen en daarom is het belangrijk om hen nauwkeurige risicoschatting te verstrekken ter ondersteuning van de moeilijke beslissingen die zij moeten nemen met betrekking tot (de timing van) RRSO. In de huidige praktijk is de counseling gebaseerd op leeftijdsgerelateerde risicoschattingen verkregen uit cohortstudies van BRCA1/2-mutatiedraagsters. Echter, meerdere studies wijzen erop dat risico’s van eierstokkanker aanzienlijk verschillen tussen BRCA1/2-mutatiedraagsters. Waarschijnlijk hangen type familiegeschiedenis van kanker en de mutatiepositie op het gen samen met variatie in eierstokkankerrisico’s in BRCA1/2-mutatiedraagsters. DEEL II van dit proefschrift evalueert deze twee mogelijke bronnen van (leeftijdsgerelateerde) risicovariatie, om meer gepersonaliseerde risicoschattingen mogelijk te maken.

Hoofdstuk 5 onderzoekt de gecombineerde invloed van mutatiepositie op het gen en type familiegeschiedenis van kanker op het eierstokkankerrisico in vrouwen met BRCA1/2-mutaties in Noord-Nederland. Mutaties binnen de centrale regio’s van BRCA1 zijn geassocieerd met hogere risico’s op eierstokkanker dan mutaties in andere delen van
het gen, zelfs wanneer rekening wordt gehouden met type familiegeschiedenis van kanker. Voor vrouwen met *BRCA2*-mutaties had het type familiegeschiedenis van kanker een sterkere invloed op het eierstokkankerrisico, en deze invloed bleef stabiel wanneer rekening werd gehouden met de mutatiepositie op het gen. Omdat in hoofdstuk 5 alleen vrouwen uit een genetisch homogene populatie uit Noord-Nederland waren geïncludeerd, hebben we een vervolgstudie uitgevoerd in een groter cohort *BRCA1/2*-mutatiedraagsters uit een landelijke Nederlandse cohortstudie (hoofdstuk 6). In deze studie onderzochten we of de associatie tussen de familiegeschiedenis en eierstokkankerrisico kan worden verklaard door de mutatiepositie op het gen. Een familiegeschiedenis van borstkanker was geassocieerd met lagere eierstokkankerrisico’s bij zowel *BRCA1* als *BRCA2*-mutatiedraagsters. Na correctie voor mutatiepositie op het gen, waren de waargenomen associaties nog steeds even sterk, hoewel niet langer significant. Daarom verklaart de mutatiepositie op het gen de associatie tussen de familiegeschiedenis van kanker- en eierstokkankerrisico’s niet volledig.

**DEEL III**

RRSO op premenopauzale leeftijd veroorzaakt een acuut en vroegtijdig begin van de menopauze die ongewenste gevolgen heeft voor de gezondheid van vrouwen. DEEL III van dit proefschrift onderzoekt de lange-termijn-gevolgen van premenopauzale RRSO.

In hoofdstuk 7 onderzochten we de invloed van premenopauzale RRSO op het cholesterolprofiel van vrouwen met een erfelijk verhoogd risico op eierstokkanker, vergeleken met leeftijdsgenotes zonder RRSO. Hoewel vrouwen met RRSO een gezondere levensstijl hadden (minder rokers en hogere participatiecijfers in sport), was RRSO geassocieerd met een meer atherogeen cholesterolprofiel met hogere niet-HDL-cholesterolconcentraties en lagere HDL-cholesterolconcentraties vergeleken met leeftijdsgenotes zonder RRSO.

In hoofdstuk 8 werd de invloed van de chirurgische menopauze op botgezondheid onderzocht. Hoewel de natuurlijke menopauze geassocieerd wordt met een lagere botmineraaldichtheid (BMD) en een hoger risico op fracturen, rapporteerden eerdere studies naar de botgezondheid na chirurgische menopauze inconsistentere resultaten. Daarom hebben we een systematische review en meta-analyse van de beschikbare literatuur over dit onderwerp uitgevoerd. BMD was significant lager in vrouwen met chirurgische menopauze dan in premenopauzale leeftijdsgenoten. Volgens de bestaande literatuur heeft de chirurgische menopauze echter geen duidelijke invloed op BMD en op fractuurrisico ten opzichte van de natuurlijke menopauze.

Tot slot schetst hoofdstuk 9 een algemene discussie over de studies in dit proefschrift, waarbij de belangrijkste conclusies worden onderstreept. Dit proefschrift bevat belangrijke informatie voor zorgverleners die betrokken zijn bij de identificatie en begeleiding van *BRCA1/2*-mutatiedraagsters. Het bewijs in dit proefschrift kan bijdragen aan de implementatie van genetisch testen in landen met beperkte middelen, het begrijpen van de variatie in het risico op eierstokkanker bij *BRCA1/2*-mutatiedraagsters en om het bewustzijn over de potentiële lange termijn gevolgen van RRSO te vergroten. Deze resultaten kunnen bijdragen aan de verbetering van de zorg voor *BRCA1/2*-mutatiedraagsters in zowel hoge- als lage- en middeninkomenslanden.
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ABOUT THE AUTHOR

Natalia Teixeira was born on January 21st 1990 in Sao Paulo, Brazil, as daughter of Luis A. Teixeira and Marilene C. T. Teixeira. In February 2008 she started her Medical education in the Faculty of Medicine at the University of Sao Paulo. Since her early stages of Medical school she developed a growing interest for scientific research, enrolling in extracurricular research activities since her first semester. In July 2010, she participated in the Summer School Oncology for Medical Students, at the University of Groningen, in the Netherlands. The summer school stimulated her interest in medical research even further, and, in 2011, she returned to Groningen for a one-year exchange program, during which she participated in a research project entitled “Ovarian cancer in BRCA1/2 mutation carriers: the impact of mutation position and family history on the cancer risk,” under the supervision of Prof. G.H. (Truuske) de Bock and Prof. M.J. (Marian) Mourits. She developed a great interest in BRCA1/2 associated ovarian cancer, and after her exchange year in Groningen, she decided to pursue a MD-PhD position to continue her investigation on the topic.

From 2012 to 2014, in addition to the rotations of her final years of Medical school, she participated in a research project entitled “BRCA1/2 mutations in ovarian cancer patients in Brazil,” under the supervision of Prof. GH de Bock, Prof. MJ Mourits, Prof. MAAK Folgueira and Dr. MDPE Diz. In November 2014, she obtained her medical degree at the University of Sao Paulo, and in February 2015, she was awarded a grant from the Graduate School of Medical Sciences of the University of Groningen to continue her research on hereditary ovarian cancer at the department of Epidemiology at the University Medical Center Groningen. From February 2015 to March 2017, she conducted the final part of her PhD project, under the supervision of Prof. GH de Bock, Prof. MJ Mourits and Dr. JC Oosterwijk. The results of her PhD project are presented in this thesis, which was submitted in May 2017 and will be defended on October 23rd 2017.