が発症した卵巣がんに対しては，通常の卵巣がんと同様の治療が行われている。一方，*BRCA1/2* 遺伝子変異を有する腫瘍に対して，その特徴を利用した分子標的治療薬が期待されている。PARP 阻害剤は，一本鎖 DNA 切断の重要な修復過程である塩基除去修復に関わる DNA 修復酵素として機能する PARP(Poly ADP ribose polymerase)を阻害する薬剤である。PARP 阻害剤を投与すると，通常は *BRCA* 遺伝子の存在により DNA 修復が行われるが，*BRCA* 遺伝子の機能が低下している腫瘍に対しては，合成致死のメカニズムにより細胞死に至らしめるため，がん特異的に治療できると考えられている[44]。PARP 阻害剤の効果は，*BRCA1/2* の生殖細胞変異を有するがんのみならず，体細胞変異や *BRCA1/2* の発現低下による“BRCAness”の特徴を有するがんに対しても効果があると考えられている。現在，国内外で PARP 阻害剤を用いた臨床試験が進行している[45]。PARP 阻害剤の適応を判断するコンパニオン診断の開発と共に，卵巣がんやトリプルネガティブ乳がんに対しての実臨床への応用が期待される。

## 4．*BRCA1/2* 遺伝子変異陰性者への対応

濃厚な家族歴があるにもかかわらず *BRCA1/2* 遺伝子変異が同定されなかった場合，1)実施した遺伝子検査では検出できない変異がある，2)*BRCA1/2* 遺伝子ではない遺伝子が関係している，3)家系内に遺伝性素因はあるが，変異を調べた患者は散発がんであった，4)環境要因が関与している，5)がんの集積は偶然であった，などの可能性を考えておく必要がある[46]。

## おわりに

近年，HBOC やリスク低減手術への社会的な関心が増えるなかで，産婦人科診療において HBOC 患者と関わる機会が今後ますます増えていくことが予想される。HBOC のリスクが高いと思われる女性に対しては，必要に応じて遺伝カウンセリングを紹介することが求められる。現在のところ RRSO が施行可能な施設は限られているが，各施設の倫理委員会の承認を得て準備を進めている施設が増えている。また産婦人科医として HBOC 患者に対して行う診療は，遺伝的リスク評価，RRSO のみならず，スクリーニング，経口避妊薬による化学予防，RRSO 後の HRT など，多岐にわたることを認識する必要がある。

一方で，わが国においては，遺伝性腫瘍に対する遺伝カウンセリング，*BRCA1/2* 遺伝子検査，RRSO に関する治療費は保険収載されておらず，すべて自費診療で行われているという問題がある。変異陽性ハイリスクでありながら，費用が直接的な障壁となり，遺伝子検査，その後の治療を行うことを躊躇する患者が存在することは，RRSO によってもたらされるがんのリスク低減効果を考えると，今後の課題とすべきであると考える。

また，日本人における遺伝子変異の情報や浸透率などの情報はいまだ十分ではなく，欧米の情報を用いて診療にあたっているのが現状である。わが国においても，遺伝腫瘍に対するデータベースの構築や研究が行われているが，遺伝性腫瘍は多領域に関連することから，今後は組織横断的な取り組みが必要である。

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第 66 回日本産科婦人科学会・学術講演会

教育講演 1

# 遺伝性婦人科腫瘍

慶應義塾大学医学部産婦人科学教室

教授　青木　大輔

# Hereditary Gynecologic Cancer

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## はじめに

一般に癌の発生には遺伝因子と環境因子の両者が関与する．ところが一部の家系では卵巣癌や子宮体癌などの血縁腫瘍歴が多発することが知られている．遺伝性に発生する卵巣癌としては，乳癌や卵巣癌あるいは卵管癌，腹膜癌が血縁者に発生する遺伝性乳癌卵巣癌(hereditary breast and ovarian cancer；HBOC)が代表である．一方，遺伝性の子宮体癌としては子宮体癌や消化器癌ときには卵巣癌が血縁者に多発する Lynch 症候群が代表的である．HBOC あるいは Lynch 症候群は常染色体優性遺伝の遺伝形式をとることから，家系内の複数の世代間で関連癌罹患者が存在し，詳細な家族歴の聴取がその発見の端緒となることが多い．これら遺伝性婦人科腫瘍の取り扱いはプライマリ・ケアを含む実地臨床の課題であることを理解していただければ幸いである．

## 遺伝性乳癌卵巣癌の原因遺伝子

HBOC の原因遺伝子としては，1994 年に本邦の三木らが乳癌家系の遺伝子解析を通して同定した *BRCA1* と[1]，その後に報告された *BRCA2* が知られている[2]．HBOC は *BRCA1* または *BRCA2* (*BRCA1/2*)遺伝子の生殖細胞系列変異が原因の遺伝性疾患であり，*BRCA1/2* 遺伝子変異保持者(mutant carrier)の家系では乳癌や卵巣癌(卵管癌や原発性腹膜癌を含む)など関連腫瘍への罹患者が複数存在し，膵臓癌，前立腺癌，男性乳癌のリスクも高い．

HBOC は常染色体優性遺伝の遺伝形式をとる．そのため子供が親の遺伝子変異を受け継ぐ可能性は 50% であるが，多くの遺伝性腫瘍と同様に遺伝子変異を有していても浸透率(癌が発症する確率)は 100% ではない．*BRCA1* 遺伝子変異を有する女性の 35% から 60% は 70 歳までに *BRCA* 関連婦人科癌(卵巣癌，卵管癌あるいは原発性腹膜癌)に罹患する可能性があり，これは一般女性母集団と比較し 35 倍から 40 倍の相対危険度に相当する[3)~5)]．

Key Words: Hereditary breast and ovarian cancer, Lynch syndrome, BRCA1/2, Mismatch repair genes, Microsatellite instability, Genetic counseling, Risk-reducing salpingo oophorectomy

今回の論文に関連して，開示すべき利益相反状態はありません．

【表1】 HBOCに対する遺伝性癌リスク評価（hereditary cancer risk assessment）の専門的知識をもつ医療提供者へ紹介する際の指標として考慮すべき臨床的パラメーター[6]

| |
|---|
| Consider hereditary cancer risk assessment for HBOC syndrome caused by mutations in BRCA1 or BRCA2 genes, if: |
| *Affected individual with at least one of the following:* |
| Breast cancer at ≤40 yr |
| Premenopausal breast cancer (≤50 yr) and a close relative[a] with premenopausal breast cancer (≤50 yr) |
| Premenopausal breast cancer (≤50 yr) and a close relative[a] with ovarian, male breast, or pancreatic cancer at any age |
| Postmenopausal breast cancer (>50 yr) with two close relatives[a] diagnosed with breast cancer at any age (particularly if at least one cancer was diagnosed at ≤50 yr) |
| Breast cancer at ≤50 yr and Ashkenazi Jewish descent |
| Postmenopausal breast cancer (>50 yr), Ashkenazi heritage, and at least one close relative[a] diagnosed with breast cancer at any age (particularly if diagnosed at ≤50 yr) |
| Ovarian, fallopian, or primary peritoneal cancer at any age |
| Cancer at any age and a known familial mutation |
| Two breast primaries, including bilateral disease |
| Ovarian, fallopian, or primary peritoneal cancer and breast cancer at any age |
| *Unaffected individual with:* |
| A first- or second-degree relative who meets any of the above criteria |

[a]A close relative is defined as a first-degree (one who is one meiosis away from a particular individual in a family, such as a parent, sibling, offspring), second-degree (one who is two meioses away from a particular individual in a pedigree, such as a grandparent, grandchild, uncle, aunt, nephew, niece, half-sibling), or third-degree relative (one who is three meioses away from a particular individual in a pedigree, such as a great-grandparent, biologic first cousin).
*Abbreviation:* HBOC, hereditary breast/ovarian cancer.

## 遺伝性乳癌卵巣癌における家族歴聴取とリスク評価ならびに遺伝カウンセリング

来院理由として「家系に乳癌や卵巣癌が多いので来院した」というケースはHBOCの可能性があり，詳細な家族歴聴取を行う必要がある．HBOCは血縁内に関連腫瘍歴の人が複数存在する，若年発症の乳癌や卵巣癌，同時性/異時性の同側/両側の乳癌，同時性/異時性で乳癌と卵巣癌の重複発症，など常染色体優性遺伝の特徴を反映していることが多い．また男性乳癌も伴うことがある．これらの特徴のうち1つでもあてはまる場合には，HBOCの可能性を念頭に置く必要がある．表1には提唱されているプライマリ・ケアの現場から遺伝診療部門へ紹介すべき臨床的パラメーターを示した[6]．

また米国予防医学専門委員会(U.S. preventive services task force；USPSTF)は，癌の未発症者に対して，プライマリ・ケア医が遺伝カウンセリングへ紹介する前に一般外来におけるHBOCのリスク評価(アセスメント)を推奨する一方，BRCA関連癌の家族歴のない女性に対してルーチンな遺伝カウンセリングや遺伝子検査は推奨しないとしている[7]．しかしながら，卵巣癌全体の10～15%の例がHBOCであるといわれており，婦人科実地臨床においては卵巣癌の診療中にHBOCの患者に遭遇している可能性があるともいえる．そのため当該患者の遺伝性癌リスクを正確に評価するために家族歴の聴取が不可欠である．

さらに，遺伝性腫瘍の臨床的特徴としては，散発性(sporadic)腫瘍と比較して，若年発症，同時性・異時性の重複癌を伴うほか，乳腺などでは両側性に発症するということがある．HBOC関連卵巣癌も同様の性格を有することが知られている．*BRCA1/2*変異陽性卵巣癌の検討では，同遺伝子変異陰性の卵巣癌と比較し，grade1やⅠ期のものが有意に少なく，進行癌で「high-grade serous」が特徴であると報告されている[8][9]．わが国では2008年に，日本人を対象とする*BRCA1/2*遺伝子検査の有用性を評価する多施設共同研究が行われ，患者の既往歴と家族歴から推定される変異陽性率が解析された．これにより日本人においても欧米と同等もしくはそれ以上の割合で*BRCA1/2*変異保

持者が存在することが明らかになっている[10].

HBOCの遺伝カウンセリングの実際では，上述のようなクライエントの既往歴，家族歴やリスク因子等を詳細に聴取し，乳癌や卵巣癌発症についてのリスク評価を行う．またHBOCに関する医学的な情報提供を行った後，遺伝子検査，がん予防法，クライエントに応じた治療法などについて話し合い，クライエントの自己決定を支援する必要がある．さらにサーベイランスや治療のために他の診療科，施設，メディカルスタッフとのコーディネートを行うことも重要である．このように十分な遺伝カウンセリングを行った後に，*BRCA1/2*遺伝子検査は遺伝子変異を有する可能性が高い例に対して検査希望者に対して行う．

## *BRCA1/2* 遺伝子検査の実際

*BRCA1/2*遺伝子検査は家系内の乳癌や卵巣癌を発症した人からまず検査を開始することが望ましい．同検査は生殖細胞系列の遺伝子変異を調べるものであり，通常と同様に採血を行い，末梢血由来血液の白血球細胞からDNAを抽出して解析する．アシュケナジー系ユダヤ人などの一部の集団を除いては，hot spotが存在しない(特定の塩基において高頻度に*BRCA1/2*の変異を認めない)ため，全遺伝子を解析しなくてはならない．エクソンの欠失や重複など大きな変異がある場合には，シークエンスにより変異を同定することができない場合があるので注意が必要である．その場合には，MLPA法で解析を行う必要がある．本邦における*BRCA1/2*遺伝子検査は(株)ファルコバイオシステムズが米国Myriad社から受託する形で解析を行っている．*BRCA1*は24エクソン，*BRCA2*は27エクソンを有する大きな遺伝子であるが，全コーディングエクソン配列を解析するスクリーニング検査の結果，発端者に*BRCA1/2*遺伝子変異がみつかった場合，その血縁者に対しては発端者と同じ部位に変異があるかのみ調べることとなる(シングルサイト検査)．*BRCA1*あるいは*BRCA2*のいずれかに生殖細胞系列の病的変異が検出された場合，HBOCと診断される．スクリーニング検査を行った場合の結果の解釈は，暫定的な判定も含めると「病的変異(deleterious)」，「病的変異疑い(possibly deleterious)」，「病的意義が未確定な遺伝子変異(uncertain)」，「遺伝子多型と思われる(favor polymorphism)」「遺伝子変異を認めず」の5種類である．「病的変異(deleterious)」あるいは「病的変異疑い(possibly deleterious)」が検出された場合には，HBOCと診断し医学的管理を推奨する根拠となる．「病的意義が未確定な遺伝子変異(uncertain)」は学術的には「variant of uncertain significance：VUS」とされ，Myriad社の報告では，VUSは2%程度で検出されると発表されている．検査を行う前には，VUSが検出される可能性など検査の限界についても説明しておく必要がある[11].

## *BRCA1/2* 遺伝子変異保持者に対する管理およびリスク低減卵巣卵管摘出術について

女性の生涯における卵巣癌発症率は約1.4%であるといわれている[3]．一方，*BRCA1/2*遺伝子変異保持者(mutation carrier)では卵巣癌が高率に発生するものの，前述したように，全変異保持者が乳癌や卵巣癌を発症するわけではないが(不完全浸透)，一般女性母集団と比較すると発症リスクははるかに高率である[3)~5)].

そこで*BRCA1/2*遺伝子変異保持者に対しては，その後のがん予防法を伝える必要がある．がん予防法には，がんになることを防ぐ「一次予防」と，がんを早期に発見することより死亡を防ぐ「二次予防」がある．現在のところ卵巣癌全般に対する有効なスクリーニング方法は示されておらず，経腟超音波検査，血清CA-125測定等は卵巣癌スクリーニング方法として感度，特異性とも限界があり，死亡率減少効果は認められていない[12]．なお通常の婦人科医による「がん検診」は子宮頸癌の早期検出を目的としており卵巣癌の発見を念頭に置いているわけではないことを情報提供する必要がある．

このように*BRCA1/2*遺伝子変異保持者に対する二次予防法が確立されていない現時点では，*BRCA1/2*遺伝子変異保持者に対するがん一次予防法としてリスク低減卵巣卵管摘出術(risk-

reducing salpingo-oophorectomy；RRSO)が最も確実性の高い卵巣癌予防策である．RRSOは卵巣癌発症のリスク低減だけではなく乳癌の発症リスクも低減する．乳癌死，婦人科癌関連死，および全死亡率をそれぞれ90%，95%，76%低下させたことが報告されている[13]．これらの報告から米国NCCN(The National Comprehensive Cancer Network)のガイドラインでもRRSOが推奨されている[14]．

乳癌についてはRRSOのほかにリスク低減乳房切除術(risk-reducing mastectomy；RRM)という選択肢がある．しかしながらRRMによって乳癌の発症率を90%程度下げるという報告があるものの，生命予後を改善するか否かはいまだ明らかになっておらず，未発症のHBOCに対して外科的介入を行うとすればまず選択すべきはRRSOであり，すでに本邦の乳癌診療ガイドラインでも2011年改訂よりHBOCの項目を設けてRRSOについて明記されている．2013年版にはRRSOに関して「リスク低減卵巣卵管切除術により卵巣癌卵管癌の発症リスクを減少できるだけでなく，乳癌発症リスクが減少することは確実である」さらに「リスク低減卵巣卵管切除術により総死亡率を減少させることはほぼ確実である」と記載されている[15]．

閉経前にRRSOを実施する場合は，骨粗鬆症による骨折や脂質異常症に起因する動脈硬化，その後発症する脳血管疾患や心血管疾患発症の高危険群になる．このようなRRSO後のヘルスケアに関する課題についても施行前に伝えるべきである．またRRSOを施行された*BRCA*遺伝子変異保持者の病理検査においては卵管を含めた全割切片による詳細な検索が必要である．その結果，高頻度にoccult cancerがみつかり[16]，その多くは遠位部卵管であったことが報告されている．このことは，一部の卵巣癌の発生母地が実は卵管であるという最近の議論を裏付ける事実としても重要視されている[17)~20)]．一方，RRSOを施行した*BRCA1/2*遺伝子変異保持者を術後20年間フォローアップしたところ腹膜癌(intra-abdominal carcinomatosis)の発生する累積危険率が3.5%以上であるという報告がある[21]．したがってRRSO後の病理検査でoccult cancerがみつかることがあること，将来，腹膜癌が発生する可能性があることから術後もサーベイランスが必要なこと，などについてカウンセリングの段階で伝えておく必要がある．

またRRSOを選択しない女性では35歳以降もしくは家系でもっとも早い発症年齢に基づいておおよそ半年ごとに経腟超音波検査とCA-125測定を行うことを考慮することになる．

## 遺伝性乳癌卵巣癌に関連する卵巣癌の治療

HBOC関連卵巣癌に対する治療法は，現在のところ散発性卵巣癌と同様に標準的手術と術後化学療法が基本である．最近，*BRCA1/2*変異陽性の卵巣癌に関してはPARP阻害薬の有効性が期待されることから注目されている[22]．通常，DNAに切断という傷が入った場合，BRCA1/2とPARP-1(poly-adenosine diphosphate-ribose polymerase 1)が修復を担う．*BRCA*遺伝子の機能が低下している癌細胞では二本鎖DNAの切断を修復する機能が欠損しており，DNA修復はもっぱらPARP-1に依存することになることから，PARP阻害薬を投与することで合成致死のメカニズムにより細胞死が引き起こされ，癌特異的に治療できるという作用機序が明らかにされている[23]．したがって，PARP阻害剤の効果は，*BRCA1/2*に生殖細胞変異を有する場合だけでなく，体細胞変異やBRCA1/2の発現低下によるいわゆる"BRCAness"の状態を有する癌細胞に対しても効果があると考えられている[24]．PARP阻害薬の臨床試験は現在進行中である．

## Lynch症候群の原因遺伝子

Lynch症候群は，従来，家族性非ポリポーシス大腸癌(hereditary non-polyposis colon cancer；HNPCC)といわれていた疾患で，若年発症の大腸癌と子宮体癌(子宮内膜癌)に特徴づけられる遺伝性癌症候群である[25]．Lynch症候群は常染色体優性遺伝の遺伝形式をとる．そのため子供が親の遺伝子変異を受け継ぐ可能性は50%であり，Lynch症候群家系では，一般集団と比較して大腸癌や子

【表2】 Lynch症候群例の70歳までに癌を発症するリスクと一般集団との比較[26]

| Cancer Type | General Population Risk | Lynch Syndrome (*MLH1* and *MSH2* heterozygotes) | |
|---|---|---|---|
| | | Risk | Mean Age of Onset |
| Colon | 5.50% | 52%-82% | 44-61 years |
| Endometrium | 2.70% | 25%-60% | 48-62 years |
| Stomach | <1% | 6%-13% | 56 years |
| Ovary | 1.60% | 4%-12% | 42.5 years |
| Hepatobiliary tract | <1% | 1.4%-4% | Not reported |
| Urinary tract | <1% | 1%-4% | ～55 years |
| Small bowel | <1% | 3%-6% | 49 years |
| Brain/central nervous system | <1% | 1%-3% | ～50 years |
| Sebaceous neoplasms | <1% | 1%-9% | Not reported |

宮体癌の発症リスクが高い．表2にLynch症候群例の70歳までに癌を発症するリスクを一般集団と比較して示した[26]．Lynch症候群女性の子宮体癌生涯発症リスクは25～60%であると報告されており，一般集団における同発症リスクと比較して有意に高い[27)~29)]．また卵巣癌，胃癌，胆道系癌，腎盂・尿管癌，小腸癌，脳腫瘍も，一般集団と比較して発症リスクが高い．

1990年代初頭に，Lynch症候群家系では*MLH1*, *MSH2*, *MSH6*および*PMS2*遺伝子等のDNAミスマッチ修復(DNA mismatch repair gene：MMR)遺伝子に変異を有することが発見された．とくに*MLH1*および*MSH2*遺伝子変異はLynch症候群患者の90%以上で認められ[30]，また*MSH6*遺伝子変異を有する家系では子宮体癌の発症リスクが高いと報告されている[31]．

## Lynch症候群における家族歴聴取とリスク評価ならびに遺伝カウンセリング

HBOCと同様，Lynch症候群においても家族歴の聴取は重要である．Lynch症候群の臨床的なクライテリアとして，アムステルダムクライテリアⅡが採用されることが多い(表3)[29]．改訂前の同基準においては大腸癌にのみ照準を合わせていたが，新基準は大腸癌以外の関連腫瘍(大腸癌，子宮内膜癌，卵巣癌，小腸癌，胃癌，腎盂・尿管癌，胆道系癌など)もその診断基準に含まれるようになった．臨床診断基準に基づく診断の正確さは家族歴聴取の正確さに依存している．そのため病理診断結果，家族のスクリーニングの状況や手術の既往，さらに大腸ポリープの既往を調査することが診断の精度を高めるのに有用となる．アムステルダムクライテリアに合致しない場合でも，関連癌の若年発症例や多重多発癌を発症している場合にはLynch症候群の可能性を考慮する必要がある．

【表3】 アムステルダムクライテリアⅡ（以下の項目をすべて満たす必要がある）[29]

| |
|---|
| 関連腫瘍(大腸・直腸癌，子宮内膜癌，胃癌，小腸癌，肝胆道癌，腎盂癌，尿管癌)を有する家族が3名以上あり，そのうち1名は他の2名の一度近親者である |
| 連続する2世代で罹患している |
| 50歳以前にHNPCC関連腫瘍と診断された者が1名以上いる |
| 家族性大腸ポリポーシスが否定されている |

日本産科婦人科学会婦人科腫瘍委員会では「本邦における遺伝性子宮内膜癌の頻度とその病態に関する小委員会」(平成17～18年度，委員長：宇田川康博，平成19～20年度，委員長：青木大輔)を設置し，本邦における新アムステルダムクライテリアを満たす子宮体癌の頻度を検討した．調査に参加した10施設で血縁腫瘍歴調査を継続的に実施した結果，全子宮体癌2,457症例中34例(1.38%)に新アムステルダムクライテリアを満たす子宮体癌が存在することを明らかにした．さらにLynch症候群関連子宮体癌では散発性体癌と比較して，若年発症例，高分化型類内膜腺癌例，I

期例，重複癌存在例が有意に高頻度であることを報告している[32]．

2007年には米国のSociety of Gynecologic Oncologyにより，子宮体癌患者がLynch症候群に該当するか否かのリスク評価が推奨される要件としてはどのようなものかあるかについて，委員会声明が提示された[33]．プライマリ・ケア医や産婦人科腫瘍医にとって，子宮体癌の患者がLynch症候群に該当するかを判断するにあたっては，1)若年発症，2)同時性・異時性癌，3)家族歴等のパラメーターが重要となり，当該例では遺伝診療部門で遺伝的リスク評価を行うことが適切であるとしている．

Lynch症候群に対する遺伝カウンセリングでは，HBOCの場合と同様にクライエントの既往歴，家族歴やリスク因子等を詳細に聴取して，関連癌発症についてのリスク評価を行う．またLynch症候群に関する医学的な情報提供を行った後に遺伝子検査やがん予防法，さらにクライエントに応じた治療法などについて話し合いを行うことで，最終的にクライエントの自己決定を支援する．サーベイランスや治療のために他の診療科，施設，メディカルスタッフとのコーディネートを行うことも重要であることはHBOCと同様である．

*MMR*遺伝子検査は，癌のリスク評価を行ったうえで遺伝子変異を有する可能性が高い例に対して十分な遺伝カウンセリングを行った後に，検査希望者に対して行う．

## Lynch症候群の診断と*MMR*遺伝子検査

*MMR*遺伝子変異は生殖細胞系列の遺伝子変異を調べるものであり，末梢血の白血球細胞由来のDNAを解析することによって*MMR*に属する*MLH1*, *MSH2*, *MSH6*, *PMS2*遺伝子の変異の有無を明らかとする．

Lynch症候群関連の遺伝子検査として，腫瘍組織を用いたマイクロサテライト不安定性(microsatellite instability；MSI)検査もあげられる．マイクロサテライト領域とはDNAの中で塩基配列が繰り返す領域のことであり，このような領域はミスマッチ修復機構の機能低下によってDNA複製時に反復回数のエラーが生じやすい．同検査では腫瘍部位と非腫瘍部位でマイクロサテライトの反復回数の違いをとらえるものである．MSI検査は本邦において2007年より「悪性腫瘍遺伝子検査(2,000点)」として保険収載されている．MSIを検出するための領域(マイクロサテライトマーカー)として，BAT25, BAT26, D2S123, D5S346, D17S250の5種が採用されることが多い．なおMSIは*MMR*遺伝子の生殖細胞系列の遺伝子変異によるもののほか，*MMR*遺伝子のメチル化や体細胞変異によっても陽性を示すことに留意が必要である．

さらにパラフィン包埋切片を対象としてMLH1, MSH2, MSH6およびPMS2のタンパク発現を免疫組織化学的に検出することも可能である．しかしながらそれらのタンパクの発現低下を認めた場合，*MMR*遺伝子の生殖細胞系列の遺伝子変異によるものか，同遺伝子のメチル化による発現低下によるものであるかの区別は，遺伝子検査を行わない限り困難である．

## Lynch症候群の管理とリスク低減手術

表4にLynch症候群家系のハイリスク例に推奨される管理法を示した[34]．このように診療科横断的なサーベイランス体制が必要であるが，遵守するためには困難も多いようである．ダナファーバー癌研究所のサーベイランス実態調査は，Lynch症候群例に経腟超音波法と子宮内膜組織診を毎年受けるように推奨している．しかしながら，半数のみしかこれらの検査を受けていなかったと報告している[35]．

近年，*MMR*遺伝子変異保持者に対して子宮全摘出術と両側付属器切除術を行う，リスク低減手術を推奨する報告がなされた．Schmelerらは*MLH1*, *MSH2*および*MSH6*のいずれかに生殖細胞系列の遺伝子変異を有する女性をリスク低減手術施行例と非施行例に分けて後方視的に検討した結果，リスク低減手術施行例では子宮内膜癌，卵巣癌ともに発生を認めなかったが，リスク低減手術非施行女性の33%に子宮内膜癌が，5.5%に卵

【表4】 Lynch症候群家系のハイリスク例に推奨される管理[34]

| 介入 | 推奨事項 |
|---|---|
| 大腸内視鏡検査 | 20～25歳から1～2年ごと，あるいは家系内で最も若年で診断された年齢より10歳若い年齢のうち早く基準を満たした時より始める<br>*MSH6*遺伝子異常の家系では30歳から開始する |
| 子宮内膜組織診 | 30～35歳より毎年施行 |
| 経腟超音波検査 | 30～35歳より毎年施行 |
| 尿細胞診 | 25～35歳より1～2年ごとに施行 |
| 病歴と身体所見検査，指導とカウンセリング | 21歳より毎年施行 |
| 大腸切除術 | 一次予防としては推奨しないが，癌と診断された場合には亜全摘術を行う |
| 子宮全摘出術および卵巣摘出術 | 出産後のオプションとして話し合う |

巣癌が発生したと報告していることから，挙児希望のないLynch症候群女性に対して子宮全摘出術および両側卵巣卵管摘出術を推奨している[36]．

## その他の婦人科遺伝性腫瘍

遺伝性腫瘍の多くは多臓器に癌が発生する．したがって，遺伝性腫瘍の一環として婦人科領域の腫瘍が発生することがある．Peutz-Jeghers症候群は，口唇や頬面膜の色素斑，多発する消化管ポリープを特徴とする*STK11*遺伝子の変異による常染色体優性遺伝性疾患であり，婦人科関連腫瘍としては，卵巣に性策間質性腫瘍や子宮頸部の最小偏倚型粘液性腺癌あるいは分葉状内頸部腺過形成[37]が発生する．Cowden症候群は*PTEN*遺伝子の変異によって発生する多発性過誤腫症候群であり，乳房，甲状腺などに良性ないし悪性腫瘍が生じる遺伝性疾患で子宮体癌の発生が知られている．

## おわりに

米国では*BRCA1/2*遺伝子変異が認められた35歳以上の女性170例のうち，98例(58%)がRRSOを受けたという報告がある[38]．一方，本邦においてはHBOCに対してRRSOを施行することが多くの施設に普及しているとは言い難い．その理由として遺伝診療部門を設置している医療機関や*BRCA*遺伝子検査可能施設が限られている，遺伝カウンセリング，遺伝子検査，RRSOが保険診療では認められていない，さらに婦人科医療スタッフが日常診療の中でリスク評価を十分に行っているとは言い難い状況などが影響していると考えられる．

最近，筆者らはテキサス大学MDアンダーソン癌センター婦人科腫瘍学部門のKaren H. Luによって監修されたHereditary Gynecologic Cancer：Risk，Prevention and Managementを翻訳する機会にめぐまれた[6][39]．本邦と米国とでは医療提供体制が異なるものの婦人科領域の遺伝性腫瘍に関して包括的に述べられているので参考にしていただければ幸いである．

遺伝性腫瘍に対して，こういった予防的治療は元より，カウンセリングや遺伝子検査などの医療介入がなされた場合でも，当事者やその血縁者には少なからぬ心理的，社会的，および健康上の問題が発生しうると考えられる．しかもそれらは一生涯に渡る可能性が高い．したがってカウンセリングや遺伝子検査を開始する時点から十分に倫理的配慮が整っていると判断できる施設での実施が要求され，受診開始時から生涯に渡るサポートを可能にする包括的医療体制を確立することは当事者や血縁者のみならず，検査を受診するもの，受診を検討するものにとっても益するところが大であり米国の体制は参考になる．本邦においてもこういった医療基盤の整備の推進は，子宮体癌に加えて卵巣癌，卵管癌，腹膜癌といった現在，早期発見が困難でかつ難治性とされている婦人科悪性疾患に対しても新たな医療的アプローチを展開するために不可避な過程であるといえよう．

## 文　献


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# Features of ovarian cancer in Lynch syndrome (Review)

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**Abstract.** Lynch syndrome is a hereditary ovarian cancer with a prevalence of 0.9-2.7%. Lynch syndrome accounts for 10-15% of hereditary ovarian cancers, while hereditary breast and ovarian cancer syndrome accounts for 65-75% of these cancers. The lifetime risk for ovarian cancer in families with Lynch syndrome is ~8%, which is lower than colorectal and endometrial cancers, and ovarian cancer is not listed in the Amsterdam Criteria II. More than half of sporadic ovarian cancers are diagnosed in stage III or IV, but ≥80% of ovarian cancers in Lynch syndrome are diagnosed in stage I or II. Ovarian cancers in Lynch syndrome mostly have non-serous histology and different properties from those of sporadic ovarian cancers. A screening method for ovarian cancers in Lynch syndrome has yet to be established and clinical studies of prophylactic administration of oral contraceptives are not available. However, molecular profiles at the genetic level indicate that ovarian cancer in Lynch syndrome has a more favorable prognosis than sporadic ovarian cancer. Inhibitors of the phosphatidylinositol 3-kinase/mammalian target of the rapamycin pathway and anti-epidermal growth factor antibodies may have efficacy for the disease. To the best of our knowledge, this is the first review focusing on ovarian cancer in Lynch syndrome.

## Contents



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*Key words:* lynch syndrome, ovarian cancer, surveillance, chemoprevention, risk-reducing surgery

## 1. Introduction

Ovarian cancer is a gynecological malignancy with a poor prognosis. Signs and symptoms of ovarian cancer are less apparent in comparison with those in endometrial cancer, and early detection is difficult due to the anatomical location of the ovaries in the abdominal region. Early ovarian cancer often occurs in the abdominal area, but only 30% of cases are diagnosed in stage I or II and the majority of ovarian cancer is diagnosed at an advanced stage (1).

Ovarian cancer is conventionally viewed as familial, and epidemiologically the risk of development is 2- to 6-fold higher in females that have a first-degree relative with ovarian cancer, suggesting a strong link with their genetic background (2). Hereditary ovarian cancer may be classified into hereditary breast-ovarian cancer syndrome (including site-specific ovarian cancer and breast/ovarian cancer predisposition) and Lynch syndrome (3), while other pathogeneses account for ≤2% of hereditary ovarian cancer. Although breast cancer susceptibility gene 1 (BRCA1) and BRCA2, which have been identified as causative genes in hereditary breast-ovarian cancer, are involved in 65-75% of hereditary ovarian cancers, Lynch syndrome accounts for 10-15% of hereditary ovarian cancers (4). Lynch syndrome is an autosomal dominant hereditary cancer family syndrome that was previously referred to as hereditary non-polyposis colorectal cancer (HNPCC) (5). The present review focuses on the recent findings regarding the association between Lynch syndrome and hereditary ovarian cancer.

## 2. Etiology and diagnosis of Lynch syndrome

Patients with Lynch syndrome have high risks of familial endometrial cancer, urinary tract cancer, and small intestinal cancer. In 1999, the International Collaborative Group-HNPCC published the revised Amsterdam Criteria (AC) I as the international clinical criteria for Lynch syndrome (AC II) (Table I) (5). Lynch syndrome is mainly caused by germline mutations in DNA mismatch repair (MMR) genes. These MMR genes, including mutL homolog 1 (MLH1), mutS homolog 2 (MSH2),

Table I. Clinical criteria for Lynch syndrome (HNPCC) (5).

| |
|---|
| Classic ICG-HNPCC Criteria (Amsterdam Criteria I, 1990) |
| There should be at least three relatives with colorectal cancer, and all the following criteria should be present. |
| i) One should be a first-degree relative of the other two. |
| ii) At least two successive generations should be affected. |
| iii) At least one colorectal cancer should be diagnosed before age 50. |
| iv) Familial adenomatous polyposis should be excluded. |
| v) Tumors should be verified by pathological examination. |
| Revised ICG-HNPCC Criteria (Amsterdam Criteria II, 1999) |
| There should be at least three relatives with a Lynch/HNPCC-associated cancer (cancer of the colorectum, endometrium, small bowel, ureter or renal pelvis). |
| i) One should be a first-degree relative of the other two. |
| ii) At least two successive generations should be affected. |
| iii) At least one of the relatives with cancers associated with HNPCC should be diagnosed before age 50. |
| iv) Familial adenomatous polyposis should be excluded in the colorectal cancer case(s) if any. |
| v) Tumors should be verified by pathological examination. |

ICG, International Collaborative Group; HNPCC, hereditary non-polyposis colorectal cancer.

Table II. Revised Bethesda Guidelines for Lynch syndrome (9).

| |
|---|
| Tumors from individuals should be tested for MSI in the following situations: |
| i) Colorectal cancer diagnosed in a patient who is <50 years of age. |
| ii) Presence of synchronous, metachronous colorectal, or other HNPCC-associated tumors[a], regardless of age. |
| iii) Colorectal cancer with the MSI-H histology diagnosed in a patient who is <60 years of age[b]. |
| iv) Colorectal cancer diagnosed in one or more first-degree relatives with an HNPCC-related tumor, with one of the cancers being diagnosed under age 50 years. |
| v) Colorectal cancer diagnosed in two or more first- or second-degree relatives with HNPCC-related tumors, regardless of age. |

[a]LS-related tumors include colorectal, endometrial, gastric, ovarian, pancreatic, ureteral and renal pelvis, biliary tract, and brain (usually glioblastoma as observed in Turcot syndrome) tumors, sebaceous gland adenomas and keratoacanthomas in Muir-Torre syndrome, and carcinoma of the small bowel. [b]Presence of tumor-infiltrating lymphocytes, Crohn's-like lymphocytic reaction, mucinous/signet-ring differentiation, or medullary growth pattern. HNPCC, hereditary non-polyposis colorectal cancer; MSI, microsatellite instability.

MSH3, MSH6, postmeiotic segregation increased 1 (PMS1) and PMS2, are tumor-suppressor genes involved in the repair of errors that occur during DNA replication (6). While mutations in MLH1 and MSH2 account for 90% of cases of Lynch syndrome, MSH6 and PMS2 mutations occur in in 7-10% and <5% of cases, respectively (7,8). Patients with Lynch syndrome have a monoallelic germline mutation in one of these genes. When the other allele is somatically mutated, the two alleles are inactivated and normal expression of the MMR protein is lost. This causes a phenomenon referred to as microsatellite instability (MSI). Microsatellites are multiple tandem repeats of 1-6 nucleotides in the genome. MMR proteins repair abnormalities in microsatellite repeat numbers that occur during DNA replication. In cells without MMR proteins, this repair is not usually performed and MSI develops due to an accumulation of abnormal microsatellite repeats (6). This aberrant MMR system leads to the development of various types of cancer, including colorectal, endometrial, small intestinal, renal pelvis, ureteral, gastric and ovarian cancers. A definite diagnosis of Lynch syndrome requires the fulfillment of AC II or the Revised Bethesda Guidelines (Table II), high MSI or the abnormal immunostaining of MMR proteins and confirmation of a germline mutation of an MMR gene (9).

## 3. Characteristics of ovarian cancer in Lynch syndrome

Lynch syndrome has a prevalence of 0.9-2.7% and accounts for 10-15% of hereditary ovarian cancers (10). The lifetime risks and age at onset of Lynch syndrome-associated cancers are presented in Table III. The lifetime risk of ovarian cancer for females in families with Lynch syndrome is 8% (95% confidence interval, 5.8-10.3), which is significantly higher than the 1.4% risk of ovarian cancer in the general population (10,11). The age at onset of ovarian cancer in Lynch syndrome is 42-49 years and that of sporadic ovarian cancer is 60-65 years (12-14). Although Lynch syndrome is diagnosed based on the germline mutations of MMR genes, 50% of cases are diagnosed at the onset of endometrial and ovarian cancer,

Table III. Lifetime risks and age at onset in Lynch syndrome-associated cancers (10,11).

| Cancer type | General population lifetime risk, % | Lynch/HNPCC lifetime risk, % | Age at onset, years |
|---|---|---|---|
| Colon | 5.5 | 43-48 | 44-61 |
| Endometrium | 2.6 | 40-62 | 27-72 |
| Ovary | 1.4 | 5.8-10.3 | 42-49 |

HNPCC, hereditary non-polyposis colorectal cancer.

as 'sentinel' cancers (15). This is clinically valuable in the identification of Lynch syndrome among young females with endometrial or ovarian cancer. However, the AC II criteria (Table I) do not include ovarian cancer as a sentinel cancer, and careful establishment of a family history by gynecologists or gynecological oncologists is required in these cases.

A study by Vasen *et al* (16) found a significantly higher lifetime risk of the development of ovarian cancer in 10.4% of MSH2 mutation carriers, compared with an ~3-fold lower risk of 3.4% in MLH1 mutation carriers (P=0.003). The study also reported a small difference in the mean age of onset between the MSH2 mutation carriers (45 years; range, 37-58 years) and the MLH1 mutation carriers (51 years; range, 35-75 years) (16). By contrast, the onset of ovarian cancer is also more frequent (33%) in families with an MSH6 mutation, although the lifetime risk of this mutation has not been established (17). The majority of ovarian cancers in Lynch syndrome are well- or moderately-differentiated and at the International Federation of Gynecology and Obstetrics stage I or II at diagnosis. In a large-scale analysis of 80 patients registered between 1936 and 1997, 61% of cases were at stage I, 23% at stage II, 14% at stage III and 2% at stage IV; and a number of the cases were early-stage ovarian cancer (14). Synchronous endometrial cancer was identified in 21.5% of these cases (14).

Sporadic ovarian tumors are pathologically subdivided into epithelial, gender cord stromal and germ cell tumors, with epithelial tumors being the most common. Among the epithelial tumors, high-grade serous carcinoma is the most common, and other subtypes include clear cell carcinoma (CCC), mucinous carcinoma and transitional cell carcinoma. In a retrospective study of ovarian cancer in Lynch syndrome, Watson *et al* (14) analyzed the clinical records of 79 patients with ovarian cancer from 11 countries. Of these patients, 44 were members of families with known Lynch syndrome mutations and the remaining patients had a family history corresponding to Lynch syndrome. Epithelial tumors were identified in 74 cases, including serous, mucous, endometrioid and mixed-type carcinomas and CCC. Non-epithelial ovarian tumors were also identified in 5 cases, and there were 2 cases each of granulosa cell, gender cord and endodermal sinus tumors and dysgerminoma. Immunohistochemical screening of MSH2, MLH1, MSH3, MSH6, PMS1 and PMS2 and MSI analysis was not performed. Thus, it cannot be concluded with certainty that these non-epithelial ovarian tumors were associated with Lynch syndrome.

Several studies, including the immunohistochemical examination and MSI analysis of MMR genes in ovarian cancer (18-23), have reported a wide variety of epithelial tumors associated with a high MSI status, such as malignant Müllerian mixed tumor, CCC, mucinous tumor, endometrioid tumor and mixed-type carcinomas. However, the association of pure high-grade serous carcinoma with high MSI caused by the germline mutation of MMR genes is unclear. In a large-scale study, Rosen *et al* (21) did not identify a case with high MSI among 168 cases of pure high-grade serous carcinoma. High-grade serous carcinoma is almost the sole histological type of hereditary ovarian cancer in hereditary breast-ovarian cancer syndrome with BRCA mutation (24,25). For ovarian cancer caused by MMR mutation, Crijnen *et al* (26) found non-serous adenocarcinoma in seven of 19 cases (37%) and Watson and Lynch (27) found this type in 31 of 48 cases (65%). Thus, various histological types of ovarian cancer are caused by MMR mutation, while serous adenocarcinoma is the main histological type of ovarian cancer caused by BRCA mutation. This indicates that hereditary breast-ovarian cancer and ovarian cancer in Lynch syndrome may have different properties.

In an examination of prognosis, Grindedal *et al* (28) found that the 5-, 10-, 20- and 30-year survival rates of ovarian cancer in Lynch syndrome were 82.7, 80.6, 78 and 71.5%, respectively. Crijnen *et al* (26) compared the prognoses of 26 patients with ovarian cancer and Lynch syndrome that fulfilled AC II criteria or had MMR mutations with those of 52 age- and stage-matched patients with sporadic ovarian cancer. The 5-year survival rates were 64.2 and 58.1%, respectively, and they did not differ significantly (P=0.56). However, this may have been due to the similar effects of platinum-based chemotherapy and it was concluded that a further prospective study was required. Cancer cells with MMR mutations cannot undergo apoptosis *in vitro* and are resistan to platinum drugs (29,30). However, an analysis of clinical data showed that the sensitivity of ovarian cancer with MMR gene mutations to platinum-based chemotherapy was similar to that of sporadic ovarian cancer (31). Various mechanisms may underlie resistance to platinum-based agents, including genetic or epigenetic changes of MMR genes, and further *in vitro* and *in vivo* studies are required.

## 4. Surveillance and prevention of ovarian cancer in Lynch syndrome

Appropriate methods for the surveillance of gynecological cancers in females of familes with a history of Lynch syndrome have not been fully established. The current guidelines are presented in Table IV (32). Annual endometrial sampling and transvaginal ultrasound in gynecological examinations are

Table IV. Recommended management for at-risk members of families with Lynch syndrome (33).

| Type of intervention | Recommendation |
|---|---|
| Screening colonoscopy | Every 1-2 years beginning at age 20-25 years (age 30 years in MSH6 families), or 10 years younger than the youngest age at diagnosis in the family, whichever comes first |
| Endometrial sampling | Every year beginning at age 30-35 years |
| Transvaginal ultrasound for endometrial and ovarian cancer | Every year beginning at age 30-35 years |
| Urinalysis with cytology | Every 1-2 years beginning at age 25-35 years |
| History and examination with detailed review of systems, education, and counseling regarding Lynch syndrome | Every year beginning at age 21 years |
| Colorectal resection | For persons with a diagnosed cancer or polyp not resectable by colonoscopy, subtotal colectomy favored with preferences of well-informed patient activity elicited |
| Hysterectomy or oophorectomy | Discuss as an option after childbearing |

MSH6, mutS homolog 6.

recommended, although the level of evidence is not high. It is also unclear at what age screening for gynecological cancers should commence. This age should be determined based on the cumulative incidence of cancers in a family history of ovarian and endometrial cancers. In a review of retrospective studies, the ages of cancer onset and cumulative incidences in 90 families with Lynch syndrome, based on AC II criteria registered at the Royal Melbourne Hospital, were compared with those in the general population (33). The mean age at diagnosis of ovarian cancer was 48.3 years, and the cumulative incidences of the cancer were 0.2% at age 30, 0.5% at 35, and 0.7% at 40 years. Thus, effective screening for ovarian cancer is preferably commenced prior to age 30, since the initiation of screening between age 30 and 35 would result in 3-7% of gynecological cancers being overlooked.

Cancer antigen 125 (CA125) may be the most useful tumor marker for the detection of ovarian cancer. The CA125 tumor antigen is a glycoprotein found in the coelomic epithelium during the development of the majority of non-mucous ovarian cancers. The antigen is detected using a monoclonal antibody. One benefit of CA125 detection is that there is little elevation of the level at 10-60 months prior to the clinical diagnosis of ovarian cancer (34). A retrospective study conducted using the JANUS serum bank showed that half of the serum samples collected 18 months prior to the diagnosis of ovarian cancer had CA125 levels >35 U/ml (the normal level), providing a sensitivity of 50% (34,35). In asymptomatic and postmenopausal females, the positive predictive value was 2% for detecting ovarian cancer using CA125 alone (36,37). Furthermore, in a large-scale ovarian cancer screening study of 22,000 subjects using CA125 alone, the sensitivity was 58% and the specificity was 98.5% (38). The specificity is extremely significant for ovarian cancer screening. The specificity of CA125 is limited as CA125 can be elevated in non-malignant and malignant diseases, including fibroid, endometriosis, menses, endometrial cancer and breast cancer, as well as other diseases, such as cirrhosis, congestive cardiac failure, diverticulitis and pancreatitis (39,40). Thus, the CA125 level may provide a false-positive or -negative finding in screening for early detection and risk prediction of ovarian cancer in the general population, and thus is of limited practical utility. A combination of ultrasound and CA125 detection has also been found to be of limited value in ovarian cancer screening. Thus, the US Preventative Services Task Force indicated that routine screening for ovarian cancer with ultrasound, serum tumor markers or internal examination cannot be recommended, and that obtaining the best health care is the most practical approach (37,41).

Although screening for ovarian cancer with ultrasound and CA125 may not be useful in the general population, it has been shown to be effective in the high-risk population with a BRCA1/2 mutation (42). BRCA mutation carriers are recommended to undergo screening with CA125 and transvaginal ultrasound twice a year, starting at age 30-35 or 5-20 years prior to the age at which a relative was diagnosed with ovarian cancer (42,43). Although there is no consensus on the benefits of screening for ovarian cancer, zlarge-scale prospective trials exploring the benefits of screening for ovarian cancer in high-risk women are now in progress (44). There has been no clinical study with a focus on screening for hereditary ovarian cancer in females from families with Lynch syndrome and similar guidelines for these females have not been established. As aforementioned, the majority of ovarian cancers in Lynch syndrome are found at a relatively early stage and are frequently accompanied by endometrial cancer. Clarification of the pathology and clinical course is required to establish the optimal screening procedure for ovarian cancer in Lynch syndrome.

## 5. Chemoprevention of Lynch syndrome

The Concerted Action Polyp Prevention (CAPP2) trial was performed as a multinational collaborative prospective study of the chemoprevention of Lynch syndrome. Aspirin (600 mg/day) and resistant starch (30 g/day) were randomly administered and

the chemopreventive effects on colorectal cancer were compared in MLH1 and MSH2 mutation carriers. The study concluded that aspirin reduced the incidence of colorectal cancer by 50% in females with Lynch syndrome (45). A CAPP3 study using a reduced dose of aspirin is planned. These results indicate that aspirin may also have a preventive effect for ovarian cancer in Lynch syndrome. Numerous case-control studies have investigated the chemoprevention of ovarian cancer in the general population, including use of Cancer and Steroid Hormone data collected by the Surveillance, Epidemiology, and End Results program. These results showed that the use of oral contraceptives reduces the development of endometrial and ovarian cancers by 50% (46,47). The effects of oral contraceptives on the prevention of ovarian cancer in Lynch syndrome are not clear, but their efficacy in females with a BRCA1/2 mutation, another high-risk population for ovarian cancer, indicates that oral contraceptives may reduce the incidence of Lynch syndrome-associated ovarian cancer (48-51). More studies are required to identify the efficacy of chemoprevention against Lynch syndrome-associated ovarian cancer.

## 6. Risk-reducing surgery for the prevention of Lynch syndrome

Risk-reducing gynecological surgery is another option for the prevention of ovarian cancer in Lynch syndrome. In 1997, the Cancer Genetics Studies Consortium reviewed evidence regarding prophylactic hysterectomy and bilateral salpingo-oophorectomy (BSO) for risk reduction, and published a consensus statement concluding that there was insufficient evidence to recommend that females with Lynch syndrome should undergo prophylactic surgery to reduce the risk of gynecological cancer (52). Despite this lack of evidence, hysterectomy with BSO has been indicated to be a reasonable preventive strategy for females with Lynch syndrome following completion of childbearing (53-55).

A study by Schmeler *et al* (56) provided evidence for the benefits of risk-reducing gynecological surgery in females with Lynch syndrome. A retrospective comparison was performed in 315 females with a documented germline mutation in MLH1, MSH2 or MSH6, including 61 females who had undergone prophylactic hysterectomy or had a benign disorder and had undergone hysterectomy with or without BSO, and 210 age-matched females who had not undergone this procedure. There were no cases of endometrial or ovarian cancer among the females who had undergone prophylactic surgery, but endometrial cancer developed in 69 females (33%) and ovarian cancer in 12 females (5.5%) among those who had not undergone prophylactic surgery. Females who had undergone prophylactic hysterectomy (61 females) and women who had undergone prophylactic BSO (47 females) were matched with mutation-positive women who had not undergone the procedure in question (210 females for the analysis of endometrial cancer and 223 for the analysis of ovarian cancer). Thus, risk-reducing surgery completely prevented new onset of endometrial and ovarian cancers in the cohort. The median age at diagnosis was 46 years for endometrial cancer and 42 years for ovarian cancer. These results are consistent with those obtained in previous studies of females with Lynch syndrome, with a mean age at diagnosis of 48-49 years for endometrial cancer (57,58) and 42 years for ovarian cancer. These results support the performance of a risk-reducing hysterectomy with BSO in females with Lynch syndrome after the age of 35 or once childbearing is completed (56).

Lindor *et al* (32) discussed the recommendations for the care of individuals with an inherited predisposition to Lynch syndrome based on a review of the data and the opinions of specialists. In the study, risk-reducing hysterectomy and BSO was suggested for females at age ≥35 years after childbearing, with hereditary counseling prior to surgery, including a discussion of the risks of the surgery, benefits and technical restrictions. Chen *et al* (59) compared three arms of annual gynecological examination, annual screening (transvaginal ultrasound + endometrial biopsy + CA125 level) and risk-reducing hysterectomy and BSO in a theoretical cohort of 10,000 females with Lynch syndrome to determine management strategies for preventing gynecological cancers. This analysis indicated that 75 surgeries would be required to save one life, in comparison with the screening arm. However, for cancer prevention, only 28 and 6 risk-reducing surgeries were required to prevent one case of ovarian and endometrial cancer, respectively. These results provide evidence that risk-reducing hysterectomy and BSO can reduce mortality from cancer and the incidence of cancer in females with Lynch syndrome.

The incidence of primary peritoneal cancer following risk-reducing BSO in females with a BRCA mutation is 0.8-1.0% (60,61). Primary peritoneal cancers have also been reported in females with Lynch syndrome who received risk-reducing BSO and long-term follow-up is required in these patients (62). In addition, females with Lynch syndrome are at a high risk of developing cancers metachronously or synchronously (54,63). Once females with Lynch syndrome are affected with colorectal cancer, it is highly possible that they may develop endometrial or ovarian cancer. Similarly, in females with Lynch syndrome who are first diagnosed with endometrial or ovarian cancer, it is highly possible that they may develop colorectal cancer. In a study of 117 females with Lynch syndrome who developed dual cancers, Lu *et al* (55) identified 16 cases (14%) of colon cancer and gynecological cancer (endometrial or ovarian cancer) that were diagnosed simultaneously. Of the remaining 101 women, 52 (51%) with an initial diagnosis of endometrial or ovarian cancer, and 49 (49%) with an initial diagnosis of colon cancer. In a similar study in 41 females (13%), Schmeler *et al* (58) found a synchronous diagnosis of colon cancer and endometrial or ovarian cancer in three cases and metachronous diagnosis in 38 cases. Of these 41 cases, 21 (51%) had gynecological cancer diagnosed following surgical treatment for colon cancer. Risk-reducing hysterectomy and BSO in these cases would have prevented gynecological cancer, which indicates that this risk-reduction surgery could be performed in females undergoing colorectal cancer surgery.

The disadvantages of risk-reducing hysterectomy and BSO include surgical complications and premature menopause. The common complications are bleeding, infection and injuries to the urinary tract and bowel. These complications have been found in 1-9% of females with a benign disease following hysterectomy and BSO (56). In premenopausal females, risk-reducing BSO results in premature menopause, with symptoms including hot flashes, vaginal dryness, sexual dysfunction, sleep disturbance and an increased risk of osteo-

porosis (56). A number of these conditions can be managed with hormonal or non-hormonal medications and there is no risk of uterine body cancer. Furthermore, an estrogen preparation can be used following hysterectomy and BSO. Parker *et al* (64) compared females who underwent oophorectomy at the time of hysterectomy for benign disease with females who underwent ovarian conservation. In the study, females undergoing oophorectomy prior to 55 years of age have an 8.58% excess mortality by age 80, compared with 3.92% excess mortality in those undergoing oophorectomy prior to age 59. These findings do not necessarily apply to Lynch syndrome, and risk-reducing hysterectomy and BSO are reasonable options for females with Lynch syndrome, particularly those who are >35 years after childbearing. The risk-reduction for cancers, risks associated with surgery, side-effects and uncertainty of screening for gynecological cancers should be explained in patient counseling prior to surgery. Females undergoing colorectal cancer surgery should receive risk-reducing hysterectomy and BSO simultaneously.

## 7. Genetics and epigenetics of ovarian cancer in Lynch syndrome

Lynch syndrome-associated ovarian cancers mostly have non-serous histology and ~82-84% are found in stage I or II, whereas only 30% of sporadic cancers are present in stage I or II (14). This aspect of ovarian cancer in Lynch syndrome is significantly different from findings for sporadic ovarian cancer and hereditary breast-ovarian cancer syndrome with BRCA1/2 mutation. In a recent comparison of patients with Lynch syndrome-associated ovarian cancer (n=20) and sporadic ovarian cancer (n=87), Niskakoski *et al* (65) found differences in genetic and epigenetic mutations in the analysis of p53, KRAS/BRAF, phosphatidylinositol 3-kinase, catalytic subunit α (PIK3CA) and cyclin-dependent kinase inhibitor 2B (CDKN2B) (tumor-suppressor genes), and long interspersed nucleotide element 1 (LINE1). PIK3CA is a cancer gene coding p110α, a catalytic subunit of PI3K (66). PIK3 and the mammalian target of rapamycin (mTOR) lie downstream of the Ras signaling pathway, which is activated in numerous tumors. The PIK3/mTOR pathway is directly activated by the mutation of PIK3CA and contributes to canceration. CDKN2B synthesizes a cyclin-dependent phosphoenzyme inhibitor (67) that forms a complex with CDK4 or CDK6 and inhibits the activation of CDK in G1 phase. Transcription of CDKN2B is activated by hypomethylation during canceration and CDKN2B in particular, plays an important role in the carcinogenesis of breast cancers. LINE1 is a retrotransposon with reverse transcriptase activity (68). LINE1 is usually methylated and inactivated, but can be demethylated and transcribed during canceration.

Niskakoski *et al* (65) examined mutations of p53, KRAS/BRAF and PIK3CA, and hypomethylation in CDKN2B and LINE1 in Lynch syndrome-associated ovarian cancer and sporadic ovarian cancer. In a clear contrast to sporadic cases, p53 and KRAS/BRAF mutations were absent in Lynch syndrome cases. The rates of p53 mutation differed significantly at 0% (0/20) in Lynch syndrome cases vs. 37% (32/87) in sporadic ovarian cancer (P<0.0001), and KRAS/BRAF mutations showed a similar trend of 0% (0/20) vs. 8% (7/87). Similar results have been found in colorectal cancer in Lynch syndrome (69). Among histological types of sporadic ovarian cancer, p53 mutations were found at a frequency of 85% (17/20) in serous adenocarcinoma and at significantly lower frequencies of 30% (8/27) in endometrioid adenocarcinoma (P=0.00029) and 18% (7/39) in clear cell adenocarcinoma (P<0.0001). PIK3CA mutations were found in 30% (6/20) of Lynch syndrome-associated cases of ovarian cancer, similar to the rates in endometrioid adenocarcinoma (36%; 10/28) and clear cell adenocarcinoma (36%; 14/39) in sporadic ovarian cancer. Among the histological types of sporadic ovarian cancer, PIK3CA mutation was significantly higher in endometrioid adenocarcinoma (P=0.013) and clear cell adenocarcinoma (P=0.011) compared with serous adenocarcinoma. mTOR inhibitors may be useful for the treatment of cases with a PIK3CA mutation (65). Hypomethylation of CDKN2B and LINE1 was significantly increased in sporadic ovarian cancers compared with Lynch syndrome cases (both P<0.0001). LINE1 is important in advanced stages of ovarian cancer (69) and this result is consistent with the favorable prognosis of ovarian cancer in Lynch syndrome.

## 8. Conclusion

There are few clinical studies on ovarian cancer in Lynch syndrome due to the small number of patients and relative lack of recognition of this disease. However, differences among histological types, stages at diagnosis and survival rates have been described. These findings indicate that ovarian cancer in Lynch syndrome has different properties from those of sporadic ovarian cancer and hereditary breast-ovarian cancer syndrome, which are other forms of hereditary ovarian cancer. The findings in Niskakoski *et al* (64) provide strong evidence for these differences. The absence of p53 and KRAS/BRAF mutations in ovarian cancer in Lynch syndrome is similar to the hereditary features of colorectal cancer in Lynch syndrome. Anti-epidermal growth factor antibodies may have efficacy for this form of colorectal cancer and may also be useful for ovarian cancer in Lynch syndrome (69). Cases with PIK3CA mutations may be treated effectively using mTOR inhibitors. Further clinical studies and investigation of the genetics of ovarian cancer in Lynch syndrome are required to improve risk assessment, screening and development of novel drugs for this disease.

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