

1-246	前立腺がん
(タイトル)	Prostate cancer in US Air Force veterans of the Vietnam war.
(著者)	Pavuk M, Michalek JE, Ketchum NS.
(書誌事項)	J Expo Sci Environ Epidemiol. 2006;16(2):184-90.
(対象と方法)	対象は、米国 1962 年-1971 年に Vietnam で行われた Ranch Hand 作戦(RH)と、同時期に Southeast Asia に従軍していた退役軍人(SEA)1497 人。1987 年に採決した血清中 TCDD を測定。(5 年毎に 4 回採血したサブサンプルにより算出した半減期により、20 年の cumulative TCDD 曝露も推定)。1982 年～2003 年 12 月末までの追跡調査で、医療記録により 140 例の前立腺がん罹患を確認。
(結果)	枯葉剤使用なし群 SEA に対して、作戦従事した(RH) TCDD 血清レベル低、高群の多変量調整 RR は、それぞれ 1.02, 1.22 (95%CI; 0.79-1.89, trend P =0.42)と関連なし。1969 年以前(TCDD がより高濃度)に従軍していたものに限っては、それぞれ 1.00, 2.27 (1.11-4.66, trend P=0.04)と有意に上昇(41 症例)。1969 以降では、関連なし。従軍 2 年未満で、血清レベル高群が有意に上昇するも(2.15; 1.03-4.48)、2 年以上では関連なし(1.05; 0.59-1.90)。20 年 cumulative TCDD 曝露は、SEA と RH それぞれ低レベル群を参照として、高レベル群の RR を計算。いずれのグループでも累積曝露量による有意な上昇は見られず(SEA; 1.10, 95%CI; 0.69-1.75, RH; 1.32, 95%CI; 0.75-2.34)。
(研究デザイン)	前向きコホート研究
(アウトカム)	前立腺がん
(曝露評価法)	血清、軍務記録
(国地域集団)	米国退役軍人コホート
(曝露要因)	TCDD (2,3,7,8-tetrachlorodibenzo-p-dioxin)

1-47	前立腺がん
(タイトル)	Nested case-control study of occupational chemical exposures and prostate cancer in aerospace and radiation workers.
(著者)	Krishnadasan A, Kennedy N, Zhao Y, Morgenstern H, Ritz B.
(書誌事項)	Am J Ind Med. 2007;50(5):383-90.
(対象と方法)	基本集団は、1950-92年に核施設、航空宇宙産業の工場に勤務する労働者の前向きコホート研究対象者10,714人。症例は、1988年1月から1999年12月までに前立腺がん罹患(8州のがん登録)した男性362例。対照は、年齢・就業開始年・診断年齢・就労産業でマッチさせた1805例。就業記録等によって職業性の化学物質曝露量を推定。
(結果)	各化学物質曝露の多変量調整ORは、非曝露群に対して、中低曝露群・最高曝露群それぞれ、Hydrazine; 0.84, 0.83 (0.49-1.4, trend P=0.39)、PAHs; 0.93, 1.2 (0.71-2.1, trend P=0.63)、Benzene; 0.84, 1.5 (0.79-2.8, trend P=0.83)と関連が見られなかったが、TCE曝露については、OR=1.3, 2.1 (1.2-3.9, trend P=0.02)と、有意に高かった。
(研究デザイン)	コホート内症例対照研究
(アウトカム)	前立腺がん
(曝露評価法)	就業記録等による職業性曝露
(国地域集団)	米国カリフォルニア州 (radiation cohort, aerospace cohort; Los Angeles)
(曝露要因)	Hydrazine, TCE (trichloroethylene), PAHs (polycyclic aromatic hydrocarbons), Benzene

1-109	前立腺がん
(タイトル)	Occupational risk factors for prostate cancer and benign prostatic hyperplasia: a case-control study in Western Australia.
(著者)	Fritschi L, Glass DC, Tabrizi JS, Leavy JE, Ambrosini GL.
(書誌事項)	Occup Environ Med. 2007;64(1):60-5.
(対象と方法)	人口ベースの症例対照研究。基本集団は、Western Australia の 45-75 才男性。症例は、2001 年 1 月-2002 年 8 月に前立腺がん(がん登録)に新規罹患した 606 人。対照は、年齢をマッチさせた 471 人。曝露要因は、アンケートによる職業歴と電話インタビューによって Organophosphate, Organochlorines, Phenoxy herbicides, Other herbicides, Other pesticides, Any pesticides, Synthetic fertilisers, PAH などの曝露を評価。
(結果)	非曝露群に対する曝露群の年齢調整 OR (95%CI)は、Organophosphate; 0.69 (0.43-1.12), Organochlorines; 0.76 (0.33-1.75), Phenoxy herbicides; 1.00 (0.61-1.63), Other herbicides; 1.03 (0.62-1.66), Other pesticides; 0.69 (0.34-1.37), Any pesticides; 1.02 (0.69-1.50), Synthetic fertilisers; 0.99 (0.74-1.32), PAH; 1.01 (0.78-1.30), Any PAH; [低曝露群] 1.11, [高曝露群] 1.02 (0.67-1.53)と、いずれも有意なリスク上昇を認めたものはなし。
(研究デザイン)	症例対照研究 人口ベース
(アウトカム)	前立腺がん
(曝露評価法)	職業歴に関する調査票と電話インタビュー
(国地域集団)	オーストラリア
(曝露要因)	Organophosphate, Organochlorines, Phenoxy herbicides, Other herbicides, Other pesticides, Any pesticides, Synthetic fertilisers, PAH (polycyclic aromatic hydrocarbons)

1-128	前立腺がん
(タイトル)	A case-control study of farming and prostate cancer in African-American and Caucasian men.
(著者)	Meyer TE, Coker AL, Sanderson M, Symanski E.
(書誌事項)	Occup Environ Med. 2007;64(3):155-60.
(対象と方法)	人口ベースの症例対照研究。基本集団は、South Carolina 住民の 65-79 才男性。症例は、1999 年-2001 年に前立腺がん(がん登録)に新規罹患した 405 人。対照は、Health Care Financing Administration Medicare Beneficiary File から年齢・人種・地域をマッチした 392 人を抽出。曝露要因は、電話インタビューにより農業従事歴とその職務内容などを評価。
(結果)	農業従事歴なし群に対する農業従事歴ありの多変量調整 OR は、1.4 (95%CI; 1.1-1.9)と有意に高かったが、従事年数カテゴリー毎の OR では、≤4 年;1.5, 5-9 年; 1.4, 10-20 年; 1.5, ≥21 年; 1.1 (95%CI ;0.7-1.9, trend P=0.51)と、年数に応じた OR の上昇は見られなかった。 農業従事歴なし群に対する、職務経験のなし群, あり群の OR(95%CI)は、Mixed/ applied pesticides; 1.0, 1.6 (1.2-2.2), Handle hay, grain, silage; 1.4, 1.4 (1.1-1.9), Harvest tobacco; 1.4, 1.4 (0.9-2.0), Plant/ pick crops, till soil; 1.4, 1.4 (1.1-1.9), Pick cotton; 2.1, 1.1 (0.8-1.6), Repair pesticide equipment; 1.5, 1.3 (0.8-2.0)であった。Mixed/ applied pesticides 職務あり群の OR が有意に高かった。
(研究デザイン)	症例対照研究 人口ベース
(アウトカム)	前立腺がん
(曝露評価法)	職業歴に関する電話インタビュー
(国地域集団)	米国のサウスカロライナ州
(曝露要因)	Ever farmed, Years of farming, Mixed/ applied pesticides, Handle hay, grain, silage, Harvest tobacco, Plant/ pick crops, till soil, Pick cotton, Repair pesticide equipment

1-81	前立腺がん
(タイトル)	Evaluation of ecological and in vitro effects of boron on prostate cancer risk (United States).
(著者)	Barranco WT, Hudak PF, Eckhert CD.
(書誌事項)	Cancer Causes Control. 2007;18(1):71-7.
(対象と方法)	対象は、米国テキサス州の 24 地区。評価指標は、地区ごとの 1997-2001 年の前立腺がん罹患率と死亡率 (Texas Cancer Registry)。地区ごとの Groundwater Database of the Texas Water Development Board により boron, selenium レベルを評価。
(結果)	単回帰分析で、boron は前立腺がん罹患率・死亡率と負の関連を示したが ($R=0.63$, $R=0.598$)、selenium は有意な関連を認めなかった ($R=0.144$, $R=0.154$)。
(研究デザイン)	地域相関研究
(アウトカム)	Texas Cancer Registry 前立腺がん罹患率、死亡率
(曝露評価法)	Groundwater Database of the Texas Water Development Board.
(国地域集団)	米国テキサス州の 24 地区
(曝露要因)	boron, selenium (chemo-preventive)

1-227	精巣がん
(タイトル)	In utero exposure to persistent organic pollutants in relation to testicular cancer risk.
(著者)	Hardell L, Bavel B, Lindstrom G, Eriksson M, Carlberg M.
(書誌事項)	Int J Androl. 2006;29(1):228-34.
(対象と方法)	<p>病院ベースの症例対照研究。基本集団は、スウェーデン男性の母親 89 人。症例は、1997-2000 年に精巣がん罹患した 58 人 (スウェーデンの 5 つの病院) の母親のうち 44 人。対照は、スウェーデン住基台帳より年齢をマッチして (5 歳階級) ランダムに抽出した精巣がんのない男性 61 人の母親のうち 45 人。1997-2000 年に、本人の生活習慣等に加え、母親からも採血を行い、さらに産婦人科系の経歴についてアンケートをとった。</p> <p>曝露要因は母親の血中濃度により評価 (対照群母親の血中濃度中央値をカットオフポイントとして採用、高群の低群に対するオッズ比を求めた)。</p>
(結果)	<p>年齢・BMI 調整後の、母親の血中 PCBs 濃度、HCB 濃度高い群では、精巣がんのオッズ比が有意に高かった [PCBs: OR= 3.8 (95%CI: 1.4-10), HCB: OR= 4.4 (95%CI: 1.7-12)]。</p> <p>p,p'-DDE と Chlordane は、母親の血中濃度と有意な関連は認められなかった。PBDE は有意に高いオッズ比を示した [OR=2.5 (95%CI: 1.02-6.0)]。</p> <p>※精巣がん患者本人の群と対照群とで、有意な違いはなかった (らしい)。</p>
(研究デザイン)	症例対照研究 病院ベース
(アウトカム)	精巣がん
(曝露評価法)	母親の血液
(国地域集団)	スウェーデン
(曝露要因)	PCBs, p,p'-DDE (dichlorodipenyldichloroethylene), Chlordane, HCB (hexachlorobenzene), PBDEs (polybrominated diphenylethers)

2-6	子宮内膜症
(タイトル)	Endometriosis Among Women Exposed to Polybrominated Biphenyls
(著者)	Hoffman CS, Small CM, Blanck HM, Tolbert P, Rubin C, Marcus M.
(書誌事項)	Ann Epidemiol. 2007;17(7):503-10.
(対象と方法)	対象は、1970年代後半に18才以上の女性で構成された米国ミシガンPBBコホートを 使用し、1997年に1530名の登録者から血清PBBを測定した1046名を対象と した。測定時期やデータの欠落などにより、最終的に943名を対象に、インタビュ ーと自己回答調査法を行った。解析は、カプランマイヤー曲線とPBB、PCBレベル と子宮内膜症との関連をCoxハザードモデルで解析した。
(結果)	対象のうち79名(9%)が子宮内膜症であった。PBB曝露が低レベル群(<or=1 parts per billion [ppb])を基準としたとき、中レベル群(1-4 ppb) (hazard ratio [HR] = 0.72; 95% confidence interval [CI], 0.39-1.31) と高レベル群(>or=4 ppb) (HR = 0.90; 95% CI, 0.51-1.59) では、子宮内膜症の発生率が低かった。PCB曝露では、 中レベル群 (5-8 ppb) (HR = 1.67; 95% CI, 0.91-3.10) と高レベル群(>or=8 ppb) (HR = 1.68; 95% CI, 0.95-2.98) で、低レベル群(<or=5 ppb)に比較し、発 生率が上昇していた。 PBB曝露との関連は明らかにされなかったが、血清PCBレベルに関する知見は、先 行研究と一致していた。
(研究デザイン)	前向きコホート (The Michigan Female Health Study)
(アウトカム)	子宮内膜症
(曝露評価法)	血清、自己回答調査法とインタビュー
(国地域集団)	米国ミシガン州
(曝露要因)	polybrominated biphenyls (PBBs), polychlorinated biphenyls (PCBs)

2-19	子宮内膜症
(タイトル)	Impaired NK-cell-mediated cytotoxic activity and cytokine production in patients with endometriosis: a possible role for PCBs and DDE.
(著者)	Quaranta MG, Porpora MG, Mattioli B, Giordani L, Libri I, Ingelido AM, Cerenzia P, Di Felice A, Abballe A, De Felip E, Viora M.
(書誌事項)	Life Sci. 2006;79(5):491-8.
(対象と方法)	子宮内膜症や良性腫瘍と診断された18~45歳の18名の女性で、10名 (raparo 下にて子宮内膜症と診断) を症例、8名を対照とした。子宮内膜症を持つ患者の、NK cell や IL-1 beta、IL-12 などの免疫機能と免疫機能を異常制御すると知られている PCBs と p,p'-DDE の血清レベルの違いを検証する。解析は Student's t-test で行い、 $p < 0.05$ を有意とした。
(結果)	免疫機能に関しては、子宮内膜症の患者では、増殖性 response と IgG 産生は異常制御を起こしていなかったが、NK 細胞活性は、有意にダウンレギュレーションを起こしていた。さらに IL-1 beta と IL-12 産生のダウンレギュレーションは、対照群に関して有意に起きていた。PCBs と p,p'-DDE の血清レベルは、症例群のほうで有意に高かった。特に症例の total PCBs 濃度は 330 ng/g fat であり、対照は 160 ng/g fat であった。また、p,p'-DDE 濃度は、症例群で 770 ng/g fat であり、対照群で 310 ng/g fat であった。さらに、健康な人の PBMC を使って、PCBs や p,p'-DDE を観察していくと、NK cell cytotoxic 活性と IL-1 beta や IL-12 産生のダウンレギュレーションが、明らかにみられた。これらの知見は、特定の免疫パラメーターの変化と PCBs や DDE レベルの上昇と子宮内膜症と関連があることが示唆された。
(研究デザイン)	症例対照研究・病院
(アウトカム)	子宮内膜症
(曝露評価法)	血清
(国地域集団)	イタリア
(曝露要因)	NK 細胞活性とサイトカイン産生 PCBs (118, 138, 153, 180) , p,p'-DDE

2-18	子宮内膜症
(タイトル)	High plasma concentrations of polychlorinated biphenyls and phthalate esters in women with endometriosis: a prospective case control study.
(著者)	Reddy BS, Rozati R, Reddy S, Kodampur S, Reddy P, Reddy R.
(書誌事項)	Fertil Steril. 2006;85(3):775-9.
(対象と方法)	インド南部地方の Mahavir 病院で子宮内膜症と診断された 85 名と同病院に不妊治療で来院し子宮内膜症のない患者 135 名を対照とした。症例は、stage I ~IVのサブグループに分類した。それらの血清から polychlorinated biphenyls (PCBs) と phthalate esters (PEs) の濃度を比較し、子宮内膜症との関連を検証した。分析は、ANOVA にて解析し、 $p < 0.05$ を有意とした。
(結果)	PCBs(1,5,29,98,)では、stage で有意な違いが見られた ($F=55.57, 7.29, 71.87, 30.64$)。PCBs(47,54,171,200/201)では、違いが見られなかった。また di-n-butyl phthalate($F=48.88$), butyl benzyl phthalate($F=42.76$), DEHP($F=28.81$), di-n-octyl phthalate($F=94.88$)において、stage で有意な違いが見られたが、diethyl phthalate と dimethyl phthalate では、差が見られなかった。
(研究デザイン)	症例対照研究・病院
(アウトカム)	子宮内膜症
(曝露評価法)	血清
(国地域集団)	インド
(曝露要因)	PCBs(1,5,29,98,47,54,171,200/201), PEs(di-n-butyl phthalate, butyl benzyl phthalate, bis-2-ethyl hexyl phthalate[DEHP], di-n-octyl phthalate, diethyl phthalate, dimethyl phthalate),

2-14	子宮内膜症
(タイトル)	Association of phthalate esters with endometriosis in Indian women.
(著者)	Reddy BS, Rozati R, Reddy BV, Raman NV.
(書誌事項)	BJOG. 2006;113(5):515-20.
(対象と方法)	49名の子宮内膜症を持った不妊症患者を症例に、年齢をマッチングさせた子宮内膜症はないが他の原因による不妊症患者 38名 (group I)と子宮内膜症や他の婦人科疾患がなく避妊手術をした患者 21名(group II)を対照にした。これらの対象の血清中の Phthalate esters(PEs) 濃度を測定し、子宮内膜症の発生との関連を検証した。
(結果)	子宮内膜症を持った症例は、明らかに di-n-butyl phthalate (DnBP)($0.44 \pm 0.41 \mu\text{g/ml}$), butyl benzyl phthalate (BBP)($0.66 \pm 0.61 \mu\text{g/ml}$), di-n-octyl phthalate (DnOP)($3.32 \pm 2.17 \mu\text{g/ml}$), diethyl hexyl phthalate (DEHP)($2.44 \pm 2.17 \mu\text{g/ml}$)濃度が、対照 (group I (0.08 ± 0.14 ; 0.12 ± 0.20 ; 0 ; 0.50 ± 0.80); group II (0.15 ± 0.21 ; 0.11 ± 0.22 ; 0 ; 0.45 ± 0.68))に比べ高かった。PEs 濃度と子宮内膜症の進行度とは違いとは有意な関連がみられた (DnBP: $r=+0.73$, $P < 0.0001$; BBP: $r=+0.78$, $P < 0.0001$; DnOP: $r=+0.57$, $P < 0.0001$, DEHP: $r=+0.44$, $P < 0.0014$)。 PEs は子宮内膜症の発生要因と関連があることが示唆された。
(研究デザイン)	症例対照研究・病院 (Department of Reproductive Medicine, Bhagawan Mahavir Medical Research Centre, Maternal Health and Reproductive Institute and Department of Analytical R&D, Hetero Research Foundation, Hyderabad, Andhra Pradesh)
(アウトカム)	子宮内膜症
(曝露評価法)	血清 gas chromatography.
(国地域集団)	インド
(曝露要因)	PEs(di-n-butyl phthalate [DnBP], butyl benzyl phthalate [BBP], di-n-octyl phthalate [DnOP], diethyl hexyl phthalate [DEHP])

2-13	子宮内膜症
(タイトル)	Environmental and host-associated risk factors in endometriosis and deep endometriotic nodules: a matched case-control study.
(著者)	Heilier JF, Donnez J, Nackers F, Rousseau R, Verougstraete V, Rosenkranz K, Donnez O, Grandjean F, Lison D, Tonglet R.
(書誌事項)	Environ Res. 2007;103(1):121-9.
(対象と方法)	年齢をマッチングした症例対照研究。症例は、Deep endometriotic nodules(DEN)88名、endometriosis88名、対照は同病院の婦人科に受診し CA-125 値が<35U/ml の 88 名。食事摂取の質問 (FFQ) を含んだ質問紙調査法と <i>ortho</i> -PCBs と dioxins を測定し、ANOVA にて解析した。
(結果)	DEN では、飲酒摂取が毎日の群において OR: 5.82 [95%CI : 1.20-28.3] であり、仕事の活動量が少ない群で OR: 4.58 (95%CI 1.80-11.62) であった。PE では、仕事の活動量が少ない群で OR: 5.61 (95%CI 1.90-16.60) であった。タンポン使用や職業、環境曝露などの有機塩酸化合物との関連はみられなかった。食品摂取に関しても、有意なリスクは見られなかった。特定の食品と PCDD/PCDFs や WHO-PCBs、 <i>ortho</i> -PCBs との関連をみると、PCDD/PCDFs は関連が見られなかったが、魚肉や豚肉などの食品摂取において、WHO-PCBs と <i>ortho</i> -PCBs 量に有意な差がみられた ($p < 0.01$)。本研究では、サンプルサイズが小さく、検出力に影響したかもしれないが、病理学的には違いはあるもののエストロゲン由来という意味で PE と DEN の両者は、リスクの関連や予防する因子が類似していることが推察された。
(研究デザイン)	症例対照研究・病院
(アウトカム)	子宮内膜症
(曝露評価法)	面接による質問紙調査法、血清
(国地域集団)	ベルギー
(曝露要因)	dioxin , <i>ortho</i> -PCBs

2-5	子宮内膜症
(タイトル)	Interaction between cytochrome P450 gene polymorphisms and serum organochlorine TEQ levels in the risk of endometriosis.
(著者)	Tsuchiya M, Tsukino H, Iwasaki M, Sasaki H, Tanaka T, Katoh T, Patterson DG Jr, Turner W, Needham L, Tsugane S.
(書誌事項)	Mol Hum Reprod. 2007;13(6):399-404. Epub 2007 Apr 20.
(対象と方法)	不妊治療を行っている 20-45 歳の日本人女性 138 名。ラパロスコピー検査にて、子宮内膜症なしをコントロール(59名)、stages I-II を早期(31名)、stages III-IV を進行性(48名)のサブグループに分類。ゲノタイプ CYP1A1 Ile462Val と CYP1B1 Leu432Val polymorphisms を持つグループにおいて dioxin や PCB toxic equivalency (TEQ) レベルによる子宮内膜症の進行性との関連をロジスティック解析にて解析した。
(結果)	CYP1A1 462Val 対立遺伝子を持った群で、dioxin レベルの高い群において進行性の子宮内膜症のリスクが低くなる傾向であった(調整 OR=0.13, 95%CI: 0.02-0.76) (P for interaction = 0.08)。PCB TEQ は、CYP1A1 においては関連がなかったが、CYP1B1 Leu432Val polymorphism では、PCB TEQ レベルの高い群において進行性子宮内膜症のリスクが有意に高かった。(調整 OR=2.36, 95%CI: 0.56-10.0)(P for interaction = 0.05)。CYP1A1 と CYP1B1 polymorphisms は、有機塩酸化合物の曝露と子宮内膜症の進行との関連に影響する可能性がある。
(研究デザイン)	断面研究
(アウトカム)	子宮内膜症
(曝露評価法)	血清 ; gas chromatography/high-resolution isotope dilution mass spectrometry. 白血球; PCR-RFLP
(国地域集団)	日本
(曝露要因)	CYP1B1 と CYP1A1 の対立遺伝子を持つグループ。 Dioxin, PCB toxic equivalency (TEQ)

2-21	子宮内膜症
(タイトル)	Increased levels of polychlorobiphenyls in Italian women with endometriosis.
(著者)	Porpora MG, Ingelido AM, di Domenico A, Ferro A, Crobu M, Pallante D, Cardelli M, Cosmi EV, De Felip E.
(書誌事項)	Chemosphere. 2006;63(8):1361-7.
(対象と方法)	2000年4月から2004年1月の期間、ラパロスコピー検査にて子宮内膜症が疑われたり、良性の婦人科疾患と診断されたローマに在住する154名の女性。最終的に、40名を子宮内膜症のある症例、40名を良性の婦人科疾患の対照とした。これらの対象は、20-40歳までの未産、現在その他の疾患に罹患していない、1年以内の体重増加が10kg以上でないことを条件とした。血清中の polychlorobiphenyls (PCBs)濃度と dioxine 濃度を測定し、Mann-whitney's U-test にて比較した。また、全対象80名の血中 PCB 濃度を3グループに分類し、症例と対照のオッズ比を算出した。
(結果)	子宮内膜症のある女性において血中 PCBs 濃度が高かった(症例: Σ PCBs410 ng g(-1), lipid base,対照: 250 ng g(-1), lipid base $p < 0.001$, 高位群 OR: 4.0, CI 95% 1.3-13; $p = 0.0003$)。ダイオキシン様の PCBs(105, 118, 156, 167) と非ダイオキシン様 PCBs (101, 138, 153, 170, 180)では、対照に比べ症例で血中濃度が高かった。本研究結果より、子宮内膜症のある女性における PCB 濃度の上昇が示され、特にダイオキシン様や非ダイオキシン様のタイプが含まれていることもわかった。今後は、メカニズムの解明が必要である。
(研究デザイン)	断面研究
(アウトカム)	子宮内膜症
(曝露評価法)	血清、質問紙調査法
(国地域集団)	イタリア、ローマ
(曝露要因)	PCBs28,52, 105, 118, 156, 167,101, 138, 153, 170, 180

研究成果の刊行に関する一覧表

書籍

著者氏名	論文タイトル名	書籍全体の 編集者名	書籍名	出版社名	出版地	出版年	ページ

雑誌

著者氏名	論文タイトル名	発表誌名	巻名	ページ	出版年
Tsuchiya M, Miura T, Hanaoka T, <u>Iwasaki M</u> , Sasaki H, Tanaka T, Nakao H, <u>Kato H</u> , Ikenoue T, Kabuto M, <u>Tsugane S</u> .	Effect of soy isoflavones on endometriosis: interaction with estrogen receptor 2 gene polymorphism.	Epidemiology	18	402-408	2007
Tsuchiya M, Tsukino H, <u>Iwasaki M</u> , Sasaki H, Tanaka T, <u>Kato H</u> , Patterson DG Jr, Turner W, Needham L, <u>Tsugane S</u> .	Interaction between cytochrome P450 gene polymorphisms and serum organochlorine TEQ levels in the risk of endometriosis.	Mol Hum Reprod	13	399-404	2007
Itoh H, <u>Iwasaki M</u> , Hanaoka T, Sasaki H, Tanaka T, <u>Tsugane S</u> .	Urinary bisphenol-A concentration in infertile Japanese women and its association with endometriosis: a cross-sectional study.	Environ. Health Prev. Med.	12	258-264	2007
Tsukino H, Ohmori H, Kohshi K, Yamano Y, <u>Kato H</u> .	Molecular epidemiology and urothelial cancer.	J UOEH	29	265-289	2007

著者氏名	論文タイトル名	発表誌名	巻名	ページ	出版年
<u>Katoh T</u> , Yamano Y, Tsuji M, Watanabe M	Genetic polymorphisms of human cytosol glutathione S-transferases and prostate cancer.	Pharmacogenomics	9	93-104	2008
<u>Iwasaki M</u> , Inoue M, Otani T, Sasazuki S, Kurahashi N, Miura T, Yamamoto S, <u>Tsugane S</u>	Plasma Isoflavone Level and Subsequent Risk of Breast Cancer Among Japanese Women: A Nested Case-Control Study From the Japan Public Health Center-Based Prospective Study Group.	J Clin Oncol.		Mar 3; [Epub ahead of print]	2008

Effect of Soy Isoflavones on Endometriosis Interaction With Estrogen Receptor 2 Gene Polymorphism

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and Shoichiro Tsugane*

Background: Progression of endometriosis is considered estrogen-dependent. Dietary soy isoflavones may affect the risk of endometriosis, and polymorphisms in estrogen receptor genes may modify this association. We examined associations among soy isoflavone intake, estrogen receptor 2 (*ESR2*) gene polymorphisms and risk of endometriosis.

Methods: We recruited women age 20–45 years old who had consulted a university hospital for infertility in Tokyo, Japan in 1999 or 2000. A total of 138 eligible women were diagnosed laparoscopically and classified into 3 subgroups: control (no endometriosis), early endometriosis (stage I–II) and advanced endometriosis (stage III–IV). We measured urinary levels of genistein and daidzein as markers for dietary intake of soy isoflavones, and genotyped *ESR2* gene *RsaI* polymorphisms.

Results: Higher levels of urinary genistein and daidzein were associated with decreased risk of advanced endometriosis (P for trend = 0.01 and 0.06, respectively) but not early endometriosis. For advanced endometriosis, the adjusted odds ratio for the highest quartile group was 0.21 (95% confidence interval = 0.06–0.76) for genistein and 0.29 (0.08–1.03) for daidzein, when compared with the lowest group. Inverse associations were also noted between urinary isoflavones and the severity of endometriosis (P for trend = 0.01 for genistein and 0.07 for daidzein). For advanced endometriosis, *ESR2* gene *RsaI* polymorphism appeared to modify the effects of genistein (P for interaction = 0.03).

Conclusions: Dietary isoflavones may reduce the risk of endometriosis among Japanese women.

(*Epidemiology* 2007;18: 402–408)

Soy isoflavones are phytoestrogens found in soybeans. Phytoestrogens are plant-derived nonsteroidal compounds that possess estrogen-like biologic activities. These compounds reportedly display weak estrogenic and antiestrogenic properties.^{1–3} The 2 primary isoflavones found in soy are genistein and daidzein. Structural similarities allow isoflavones to bind to estrogen receptors.⁴

It has been hypothesized that soy isoflavones may play a role in the etiology of estrogen-related diseases and several epidemiologic studies have been conducted; however, findings have been complicated and inconsistent.^{5–7} A prospective study in Japan, where isoflavone intake is known to be relatively high, showed a protective effect on postmenopausal breast cancer.⁵ On the other hand, a nested case–control study in the United Kingdom, where intake is relatively low, showed that serum and urinary isoflavone levels were associated with increased breast cancer risk.⁶ A recent meta-analysis found a small reduction in breast cancer risk associated with soy intake.⁷ However, the authors suggested that the results should be interpreted cautiously due to potential exposure misclassification, confounding, lack of a dose-response pattern and the possibility of adverse effects of soy constituents.

Endometriosis is a benign, proliferative disease in which tissue similar to endometrial tissue is found outside the uterus—usually in the pelvic cavity, but sometimes in distant organs. Endometriosis is commonly accompanied by pelvic pain and infertility. Both genetic and environmental factors may contribute.⁸ The reported prevalence of largely asymptomatic endometriosis found in women undergoing tubal ligation is about 4%, ranging from 1% to 7%.⁹ Progression of endometriosis is considered estrogen-dependent.¹⁰ Soy isoflavones might thus be expected to affect the risk and severity of endometriosis. However, few studies have investigated the effects of soy isoflavones on endometriosis.

Several studies have recently described associations between estrogen receptor (*ESR*) gene polymorphisms and endometriosis.^{11–13} Genistein and daidzein reportedly display much greater affinity for *ESR2* than for *ESR1*,¹⁴ suggesting

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that the estrogenic or antiestrogenic properties of soy isoflavones may occur preferentially through ESR2. Although functional variability of ESR2 gene polymorphisms could feasibly be associated with response to soy isoflavones, whether ESR2 gene polymorphisms exert altered phenotypic effects on endometriosis through interactions with soy isoflavones is not known.

The present study investigated whether urinary genistein and daidzein are associated with risk and severity of endometriosis, and whether polymorphisms in the ESR2 gene are associated with response to soy isoflavones.

METHODS

Study Protocol and Ethics

This study was part of a case-control study conducted on a Japanese population to investigate associations between genetic and environmental factors in endometriosis.¹⁵ We recruited consecutive female patients age 20 to 45-year-old who attended the Department of Obstetrics and Gynecology at Jikei University School of Medicine Hospital for infertility in 1999 or 2000. Since pregnancy commonly results in complete resolution of minimal or mild endometriosis, women who had given birth or lactated were ineligible, leaving a total of 159 women who met the criteria. After excluding 15 women who did not give consent, 5 who did not undergo blood screening or laparoscopic examination, and 1 whose DNA sample was not available, a total of 138 women were available for the study (participation rate = 87%). No participants had undergone therapy before laparoscopic examination.

All study protocols were approved by the Institutional Review Boards of Jikei University, National Cancer Center and National Institute for Environmental Studies. All participants provided written informed consent before laparoscopic examination.

Before the laparoscopic examination, participants were interviewed by a single trained interviewer using a structured questionnaire to collect information on demographic factors, age, height, weight, medical history for themselves and their families, reproductive and menstrual history, oral contraceptive use, food- and alcohol-consumption frequency, and smoking history.

Participants collected first morning urine sample using a paper cup and plastic tube, and gave a fasting blood sample before the laparoscopic examination. Blood samples were divided into plasma and buffy layers. All biologic samples were stored at -80°C until analysis.

Diagnosis of Endometriosis

Laparoscopy is necessary for definitive diagnosis of endometriosis. In the present study, all participants underwent diagnostic laparoscopy, and stage of endometriosis was determined by trained gynecologists in accordance with the revised classifications of the American Fertility Society.¹⁶ Endometriosis was absent in 59 women (43%), Stage I in 21 women (15%), Stage II in 10 women (7%), Stage III in 23 women (17%) and Stage IV in 25 women (18%). Current theories of endometriosis suggest that what is defined as

minimal/mild endometriosis may actually represent a normal physiologic process. Furthermore, a lack of consistency between laparoscopic and histologic diagnosis has been reported, particularly for minimal/mild endometriosis.¹⁷ Considering the more severe stages as a separate category thus appears logical.¹⁸ Based on surgically or pathologically confirmed disease status, we classified cases into 2 subgroups: early (Stage I–II) or advanced endometriosis (stage III–IV). Women without endometriosis were defined as controls.

Determination of Soy Isoflavone Levels

Urinary levels of soy isoflavones offer a useful biomarker for dietary intake and plasma concentration of isoflavones.^{19–21} The present study measured urinary levels of genistein and daidzein as markers for dietary intake of soy isoflavones. A total of 30 mL of first-morning urine was collected before laparoscopic examination. Genistein and daidzein levels were analyzed using high-performance liquid chromatography with a coulometric array detector in accordance with the modified methods of Gamache and Acworth.²²

Concentrations of genistein and daidzein were determined by linear regression of peak height for each standard, and were adjusted according to recovery rate of the internal standard. The regression coefficient of peak height and concentration calculated for soy isoflavones revealed a linearity range of 0–8.0 $\mu\text{g/mL}$, with correlation coefficient values >0.995 . Voltametric response for the standard solution displayed coefficients of variation of 2.7%–8.4% for intraday variation and 11.1%–12.2% for interday variation. Recovery rates of soy isoflavones in urine samples ranged between approximately 85% and 100%. Detection limits were 3.22 ng/mL for genistein and 4.14 ng/mL for daidzein.

Concentrations of urinary genistein and daidzein were adjusted by urinary creatinine concentration to correct for variability in urine dilution ($\mu\text{mol/g Cre}$). All measurements were performed by investigators blinded to case-control status.

Genotyping of ESR2 Gene Polymorphism

The ESR2 *RsaI* polymorphism, comprising a G-to-A change at nucleotide 1082 in exon 5, was genotyped using polymerase chain reaction (PCR) restriction fragment length polymorphism methods.²³ Blood samples were obtained before laparoscopic examination. Genomic DNA samples were extracted from peripheral white blood cells using a standard protease K method. PCR products were digested using 5 U of *RsaI* restriction enzyme at 37°C for 8 hours, then electrophoresed on a 3% agarose gel containing ethidium bromide.

In this study, ESR2 *RsaI* polymorphism is represented by the *r* and *R* alleles, with *R* indicating the presence of corresponding restriction sites, and *r* indicating the absence of restriction sites. For quality control, blinded control samples were inserted to validate genotyping identification procedures. Concordance for blinded samples was 100%. Genotyping was conducted by investigators blinded to case-control status.

Statistical Analysis

To assess differences between cases and controls, basic characteristics and possible risk factors for endometriosis were compared using Student *t* test and the χ^2 test. Spearman correlation coefficients between urinary level of genistein and daidzein were calculated. We calculated odds ratios (ORs) and 95% confidence intervals (CIs) for urinary levels by an unconditional logistic regression model following classification into medians or quartiles based on control distribution. Linear trends for ORs were tested in the unconditional logistic regression model by treating the categories as ordinal variables. We evaluated trends for median values according to disease stage to assess associations between urinary levels of genistein and daidzein and disease stage.

To compare observed and expected genotype frequencies, we tested for Hardy-Weinberg equilibrium by using an exact test. *ESR2 RsaI* polymorphism was classified into 2 subgroups according to the presence of corresponding restriction sites: *r/r* genotype; and *R/r* + *R/R* genotype. ORs and 95% CIs were calculated for associations between *ESR2 RsaI* polymorphism and endometriosis using the unconditional logistic regression model.

To investigate whether the *ESR2 RsaI* genotype modified the effect of urinary levels of genistein or daidzein, we calculated ORs and 95% CIs of endometriosis according to a combination of subgroups for the *ESR2 RsaI* genotype and urinary isoflavones, using the unconditional logistic regression model. A low level of urinary isoflavones in combination with *R/r* + *R/R* genotype was considered as the reference group. Interactions between *ESR2 RsaI* polymorphism and urinary isoflavones in the risk of endometriosis were tested with the Wald test using product terms between urinary genistein or daidzein and genotypes.

The present study was designed to have 80% power to detect a decrease in risk of two-thirds at the 5% level of significance. All statistical tests were based on 2-tailed probabilities. We adjusted ORs and 95% CIs for possible confounding factors of endometriosis, namely age (continuous), menstrual cycle (continuous), and duration of menstrual bleeding (less than 7 days or 7 days or more).^{9,10} We used SPSS for Windows software version 11.0 (SPSS JAPAN, Tokyo, Japan) for statistical analyses.

RESULTS

Baseline Characteristics and Possible Risk Factors for Endometriosis

Table 1 shows baseline characteristics and possible risk factors for endometriosis in controls and cases. No important differences in mean age or body mass index were identified between groups. Distribution of menstrual bleeding, hypermenorrhea, and smoking also did not differ substantially. The advanced endometriosis group had a shorter mean menstrual cycle length than controls (controls, 30.7 ± 6.1 days; advanced endometriosis, 28.3 ± 3.0 days) and was more likely to have menstrual cramps and dyspareunia.

TABLE 1. Baseline Characteristics and Possible Risk Factors for Endometriosis

Baseline Characteristics	Controls (n = 59)	Endometriosis	
		Early (Stage I–II) (n = 31)	Advanced (Stage III–IV) (n = 48)
Age (yrs); mean ± SD	33.1 ± 4.1	32.3 ± 3.2	32.6 ± 3.7
Body mass index (kg/m ²); mean ± SD	21.0 ± 3.4	20.6 ± 2.1	20.2 ± 2.1
Menstrual cycle (d); mean ± SD	30.7 ± 6.1	29.6 ± 3.6	28.3 ± 3.0
Menstrual bleeding; no. (%)			
<7 days	42 (71)	21 (68)	35 (73)
≥7 days	15 (25)	6 (19)	10 (21)
Missing	2 (3)	4 (13)	3 (6)
Hypermenorrhea; no. (%)			
No	39 (66)	20 (65)	29 (60)
Yes	18 (31)	7 (23)	15 (31)
Missing	2 (3)	4 (13)	4 (8)
Menstrual cramps; no. (%)			
No	10 (17)	2 (6)	1 (2)
Yes	47 (80)	25 (81)	44 (92)
Missing	2 (3)	4 (13)	3 (6)
Dyspareunia; no. (%)			
No	31 (53)	12 (39)	10 (21)
Yes	25 (42)	14 (45)	34 (71)
Missing	3 (5)	5 (16)	4 (8)
Smoking status; no. (%)			
Never	38 (64)	19 (61)	29 (60)
Current or ever-smoker	19 (32)	8 (26)	15 (31)
Missing	2 (3)	4 (13)	4 (8)

Effect of Urinary Isoflavones on Endometriosis

Table 2 shows risk of endometriosis according to median or quartile levels of urinary isoflavones. In controls, median isoflavone level was 3.24 $\mu\text{mol/g}$ Cre for genistein and 4.01 $\mu\text{mol/g}$ Cre for daidzein. The Spearman correlation coefficient between genistein and daidzein was 0.84. Urinary genistein and daidzein levels were inversely associated with advanced endometriosis (*P* for trend = 0.01 and 0.06, respectively) but not with early endometriosis. For advanced endometriosis, the adjusted odds ratio for the highest quartile group was 0.21 (95% CI = 0.06–0.76) for genistein and 0.29 (0.08–1.03) for daidzein when compared with the lowest group.

Table 3 shows the trends of median values for urinary isoflavones according to disease stage. An inverse relationship with stage of endometriosis was observed for both genistein levels (*P* for trend = 0.01) and daidzein levels (*P* for trend = 0.07).

Associations Between *ESR2 RsaI* Polymorphism and Endometriosis

Table 4 shows the genotypic distribution of *ESR2 RsaI* polymorphism and associations with risk of endometriosis. The *ESR2 RsaI r/r* genotype was predominant. Allele fre-

TABLE 2. Association between Urinary Isoflavone Level and Risk of Endometriosis

Urinary Isoflavone	No. Controls	Endometriosis			
		Early (Stage I–II)		Advanced (Stage III–IV)	
		No.	OR (95% CI)*	No.	ORs (95% CI)*
Genistein ($\mu\text{mol/g}$ creatinine)					
<1.60 [†]	14	7	1.00	22	1.00
1.60–3.23	15	12	1.86 (0.49–7.09)	13	0.65 (0.21–2.01)
3.24–6.49	15	7	0.82 (0.18–3.80)	7	0.40 (0.12–1.34)
≥ 6.50	15	5	0.63 (0.14–2.89)	6	0.21 (0.06–0.76)
<i>P</i> for trend			0.34		0.01
Low level (<3.24) [†]	29	19	1.00	35	1.00
High level (≥ 3.24)	30	12	0.50 (0.18–1.39)	13	0.35 (0.14–0.87)
Daidzein ($\mu\text{mol/g}$ creatinine)					
<1.94 [†]	14	5	1.00	16	1.00
1.94–4.00	15	7	1.87 (0.41–8.57)	15	0.84 (0.26–2.73)
4.01–7.94	15	12	2.16 (0.49–9.41)	10	0.65 (0.20–2.09)
≥ 7.95	15	7	1.33 (0.30–5.97)	7	0.29 (0.08–1.03)
<i>P</i> for trend			0.73		0.06
Low level (<4.01) [†]	29	12	1.00	31	1.00
High level (≥ 4.01)	30	19	1.21 (0.45–3.27)	17	0.49 (0.21–1.15)

*Adjusted for age (continuous); menstrual cycle (continuous); and duration of menstrual bleeding (less than 7 days or 7 days or more).

[†]Reference category.

TABLE 3. Median Values[†] of Urinary Isoflavone Level and Stage of Endometriosis

Urinary Isoflavone	Controls (n = 59)	Early (Stage I–II) (n = 31)	Advanced (Stage III–IV) (n = 48)	<i>P</i> for Trend*
Genistein ($\mu\text{mol/g}$ creatinine)	3.2 (1.6–6.5)	2.6 (1.7–5.2)	1.7 (0.6–4.1)	0.01
Daidzein ($\mu\text{mol/g}$ creatinine)	4.0 (1.9–8.0)	4.9 (2.6–7.6)	2.6 (1.0–5.0)	0.07

*Jonckheere-Terpstra test.

[†]Median (25th–75th percentile).

quencies of *ESR2 RsaI* polymorphism were 0.77 for the *r* allele and 0.23 for the *R* allele. In addition, the distribution of *ESR2 RsaI* polymorphism was in Hardy–Weinberg equilibrium ($P = 0.26$). The *ESR2 RsaI r/r* genotype was associated

with reduced risk of early endometriosis compared with the *R/r + R/R* genotype (OR = 0.30; CI = 0.11–0.85). The association was weaker for advanced endometriosis (0.67; 0.29–1.55).

TABLE 4. Association Between *ESR2 RsaI* Polymorphism and Risk of Endometriosis

Genotype*	No. Controls	Early (Stage I–II)		Advanced (Stage III–IV)	
		No.	OR (95% CI) [†]	No.	OR (95% CI) [†]
<i>R/r + R/R</i> [‡]	26	21	1.00	26	1.00
<i>r/r</i>	33	10	0.30 (0.11–0.85)	22	0.67 (0.29–1.55)

*Exact test for Hardy–Weinberg equilibrium: $P = 0.26$.

[†]Adjusted for age (continuous); menstrual cycle (continuous); and duration of menstrual bleeding (less than 7 days or 7 days or more).

[‡]Reference category.

Interactions Between *ESR2 RsaI* Polymorphism and Urinary Isoflavones in the Risk of Endometriosis

Table 5 shows ORs and 95% CIs of endometriosis for combinations of *ESR2 RsaI* genotype and urinary isoflavone levels. Compared with subjects with the *ESR2 RsaI R/r + R/R* genotype and a low genistein level, ORs of advanced endometriosis were lower among the 3 other groups. The adjusted OR was 0.10 (95% CI = 0.02–0.48) for subjects with *ESR2 RsaI R/r + R/R* genotype with high genistein level; 0.32 (0.10–1.04) for subjects with *ESR2 RsaI r/r* genotype with low genistein level; 0.27 (0.08–0.92) for subjects with *ESR2 RsaI r/r* genotype with high genistein

TABLE 5. Interactions Between *ESR2* *RsaI* Polymorphism and Urinary Isoflavone in the Risk of Endometriosis

Genotype	Urinary Isoflavone ($\mu\text{mol/g}$ creatinine)	No. Controls	Early (Stage I–II)		Advanced (Stage III–IV)	
			No.	OR (95%CI)*	No.	OR (95%CI)*
	Genistein					
<i>R/r</i> + <i>R/R</i>	Low [†]	11	11	1.00	22	1.00
<i>R/r</i> + <i>R/R</i>	High	15	10	0.88 (0.23–3.38)	4	0.10 (0.02–0.48)
<i>r/r</i>	Low	18	8	0.54 (0.15–1.93)	3	0.32 (0.10–1.04)
<i>r/r</i>	High	15	2	NC	9	0.27 (0.08–0.92)
<i>P</i> for interaction				NC		0.03
	Daidzein					
<i>R/r</i> + <i>R/R</i>	Low [†]	15	10	1.00	19	1.00
<i>R/r</i> + <i>R/R</i>	High	11	11	1.28 (0.33–4.96)	7	0.35 (0.09–1.34)
<i>r/r</i>	Low	14	2	0.18 (0.03–1.09)	12	0.56 (0.18–1.78)
<i>r/r</i>	High	19	8	0.44 (0.12–1.61)	10	0.39 (0.13–1.20)
<i>P</i> for interaction				0.58		0.45

*Adjusted for age (continuous); menstrual cycle (continuous); and duration of menstrual bleeding (less than 7 days or 7 days or more).

[†]Reference category.

NC, estimates were not calculated due to missing data.

level. A significant interaction was noted between *ESR2* *RsaI* polymorphism and genistein levels in risk of advanced endometriosis (*P* for interaction = 0.03). Interactions between *ESR2* *RsaI* polymorphism and genistein level were not observed in early endometriosis. Although a similar pattern was observed for ORs of both early and advanced endometriosis for the combinations of *ESR2* *RsaI* genotype and urinary daidzein level, these may have been due to chance.

DISCUSSION

The present study showed an inverse association between urinary isoflavones and the risk of advanced endometriosis. This association was stronger for genistein than daidzein. In addition, there was statistical evidence for interaction between urinary genistein and *ESR2* gene polymorphisms.

The reduced risk of endometriosis following ingestion of soy isoflavones may be attributable to antiestrogenic properties of these compounds. A previous study showed that prolonged exposure to genistein results in decreased levels of estrogen receptor mRNA in addition to decreased response to estradiol stimulation.²⁴ Plasma levels of isoflavones can be 10,000- to 100,000-fold higher than those of estradiol.²⁵ When the relative binding affinity of 17 β -estradiol was set at 100 in solid-phase competition experiments, relative binding affinity for *ESR2* was 87 for genistein and 0.5 for daidzein.¹⁴ Although the elimination half-life from blood and urine is reportedly 7–8 hours for both genistein and daidzein,²⁶ long-term soy diets may modify the physiologic effects of estrogens. Given these facts, a lower prevalence of endometriosis might be expected in Japanese populations compared with Western countries, as with breast cancer. Nevertheless, the prevalence of endometriosis in the Japanese general population remains unclear due to the need for surgical diagnosis.

Our finding showed that the strength of association was stronger for genistein than for daidzein. One possible explanation is the difference in their binding affinities to *ESR2*. A second possibility is based on the difference in metabolism between genistein and daidzein. Daidzein can be metabolized to equol and *O*-desmethylangolites by intestinal bacteria, and these metabolites are absorbed, enter the circulation, and are excreted in urine. Although equol has been suggested to possess stronger estrogenic properties than genistein, some individuals are capable of equol production whereas others are not, probably because of differences in gut microflora. This difference might play a role in the weaker associations for daidzein than genistein.²⁷

ESR2 plays important roles in endometrial function, in addition to the well-known role of *ESR1* in endometrial proliferation and differentiation.²⁸ The *ESR2* *RsaI* polymorphism does not cause amino acid changes, but may well be associated with altered ligand-binding affinity or transcriptional activity. Genes containing single nucleotide polymorphisms (SNPs) can cause different structural folds in mRNA,²⁹ and these mRNA variants may possess different biologic functions during interactions with other cellular components. Altered estrogen or soy isoflavone signal transduction thanks to *ESR2* gene polymorphisms may be directly responsible for interindividual susceptibility to and severity of endometriosis.

The present study found evidence of an interaction between urinary genistein and *ESR2* gene polymorphisms. Isoflavones may play a more effective role among the *ESR2* *RsaI* *R/r* + *R/R* genotype than the *r/r* genotype, although the latter itself is likely to be protective for endometriosis. This result should be interpreted cautiously, however, because of the relatively small number of subjects—a major limitation of