

平 28 年 度 委 託 研 究 開 発 成 果 報 告 書

I. 基本情報

事業名： (日本語) 革新的がん医療実用化研究事業
(英語) Practical Research for Innovative Cancer Control

研究開発課題名： (日本語) 「個人の生活習慣等の環境要因と遺伝的リスクを考慮した科学的根拠に基づき効率的な乳がん予防法の開発研究」
(英語) Development of evidence-based breast cancer prevention program considering individual environmental and genetic risk factors.

研究開発担当者 (日本語) 愛知県がんセンター研究所 部長 松尾恵太郎
所属 役職 氏名： (英語) Aichi Cancer Center Research Institution, Division Chief,
Keitaro Matsuo

実施期間： 平成28年4月1日 ～ 平成29年3月31日

分担研究開発課題名

(日本語) リスク予測モデルの構築における症例対照研究実施と統合、累積リスクを用いたフィードバック方法の開発、介入観察研究による予防介入効果の評価
(英語) Conducting case-control studies to build risk prediction model, Development of risk feedback method using cumulative risk based on the model, and evaluation of effect of intervention study.

研究開発分担者 所属 役職 氏名

(日本語) 愛知県がんセンター研究所 室長 伊藤秀美
(英語) Aichi Cancer Center Research Institute, Section Head, Hidemi Ito

分担研究開発課題名

(日本語) リスク予測モデルの構築における症例対照研究実施とリスク予測モデルの前向きコホート研究における外的妥当性の評価
(英語) Conducting a case-control studies at Nagano to build risk prediction model, and validation of the model in prospective cohort study.

研究開発分担者 所属 役職 氏名

(日本語) 国立がん研究センター社会と健康研究センター 部長 岩崎基

(英語) National Cancer Center, Division Head, Motoki Iwasaki

分担研究開発課題名

(日本語) リスク予測モデルの構築における症例対照研究実施

(英語) Conducting a case-control studies at Kagoshima to build risk prediction model.

研究開発分担者 所属 役職 氏名

(日本語) 鹿児島大学 准教授 郡山千早

(英語) Kagoshima University, Associate Professor, Chihaya Koriyama

分担研究開発課題名

(日本語) リスクフィードバックによる行動変容の介入観察研究と予防介入フィールド設定のためのニーズ調査実施

(英語) Conduction of interventional study on behavior change based on risk feedback and needs survey for prevention study field.

研究開発分担者 所属 役職 氏名

(日本語) 愛知県がんセンター研究所 主任研究員 細野覚代

(英語) Aichi Cancer Center Research Institution, Researcher, Satoyo Hosono

分担研究開発課題名

(日本語) 予防介入方法の開発、リスクフィードバックによる行動変容の介入観察研究

(英語) Development of preventive intervention method and conduction of interventional study

研究開発分担者 所属 役職 氏名

(日本語) 徳島大学 教授 井本逸勢

(英語) Tokushima University Professor, Issei Imoto

分担研究開発課題名

(日本語) 遺伝的・環境リスクの人口寄与危険割合の検討と予防介入フィールド設定のためのニーズ調査実施

(英語) Estimation of population attributable fraction of genetic and environmental risk factors and needs survey for preventive intervention study field.

研究開発分担者 所属 役職 氏名

(日本語) 国立がん研究センター がん対策情報センター 室長 片野田耕太

(英語) National Cancer Center, Section Head, Kota Katanoda

分担研究開発課題名

(日本語) 介入後のリスク・行動変容による乳がん罹患・死亡低減効果の予測

(英語) Estimation of effect of intervention for risk behavioral modification on breast cancer incidence and mortality

研究開発分担者 所属 役職 氏名

(日本語) 国立がん研究センター がん対策情報センター 研究員 堀芽久美

(英語) National Cancer Center, Researcher, Megumi Hori

II. 成果の概要 (総括研究報告)

和文

本研究開発では、日本における乳がんの死亡・罹患を減少させるための個別化予防法を開発することを目的とする。そのため、大きく以下の二つに取り組む。(1) 複数の易罹患性遺伝子座、遺伝性乳がん関連遺伝子変異、生殖要因といった固定リスクと、生活習慣などの変動リスクを組み合わせ、乳がんのリスク予測モデルを開発する。(2) リスク予測モデルに基づくリスク層別化乳がん一次・二次予防プログラムを開発する。

本年度(1)に関しては、3つの症例対照研究(愛知県がんセンター、長野、鹿児島大学)に基づき、既存全ゲノム関連解析研究より選んだ22遺伝子多型、ハーモナイゼーション後の質問票に基づく環境要因を用いたリスク予測モデルを構築した。これに基づき、日本人集団における乳がんに関する累積罹患率の推定を終えた。

前述の3つの症例対照研究から得られたリスク予測モデルの検証に関して、前向きコホート研究(多目的コホート研究)での質問調査票のハーモナイゼーションを終え、前述の22遺伝子多型の測定を同コホート集団に対して実施し、検証解析を実施した。

さらに本年度は、新たに愛知県がんセンターの症例対照研究集団を対象にBRCA1, BRCA2, TP53, PTEN, STK11, PALB2, CHEK2, CDH1, ATMの遺伝性乳がん関連遺伝子変異の次世代シーケンサーによる検討に着手した。愛知県がんセンター症例対照研究対象者に対して、研究の詳細を通知した後、オプトアウト形式での同意手続きを実施した。また、平行して次世代シーケンサーを用いたアンプリコンシーケンシングアッセイを確立した。NGS頻度が高い易罹患性遺伝子座、頻度が低い遺伝性乳がん関連遺伝子変異、環境要因を横並びで評価する国内初めてのものであり、散発性乳がんと家族性乳がんが混在するわが国の乳がん対策を考える上で重要な知見を構築できる見込みである。

(2)として実施する観察介入研究に関しては、(1)と平行してリスク提示コンテンツ、説明用のコンテンツの作成を終えた。説明用のコンテンツは、映像コンテンツなども取りそろえ、将来的な大規模な介入への展開可能性を考慮したものを作成した。介入観察研究の研究プロトコルを作成し、倫理審査を受け、UMINへの研究登録を終えた。次年度からの介入観察研究の体制が整った。

(1)と(2)の結果に基づき経済的・社会的な影響をシュミレーションするために必要な項目の設定を行った。経済的評価を行う上で必要なレセプト調査に関する倫理審査終了後、レセプト調査を実施している。また社会的な影響を評価するためのシュミレーションに着手している。

英文

This research project aimed to develop evidence-based breast cancer prevention program considering individual environmental and genetic risk factors among Japanese. The project contains two specific sub-projects: 1) to develop risk prediction model applying information of environment, common genetic variation, and rare risk-related gene alterations, 2) to develop breast cancer primary/secondary prevention program based on the model in 1).

In this fiscal year, we have developed a risk prediction model based on data from three case-control studies conducted at Aichi, Nagano and Kagoshima with use of 22 single nucleotide polymorphisms (SNPs) and environmental factors based on harmonized questionnaire items. Further, we estimated cumulative risk of breast cancer based on risk strata.

To validate above mentioned risk prediction model, we made independent evaluation based on the data from a prospective cohort study (Japan Public Health Center-based study) with 22 SNPs and harmonized environmental factors.

To extend utility of the prediction model, we launched another sub-project integrating heritable breast cancer related gene information in the model. We chose BRCA1, BRCA2, TP53, PTEN, STK11, PALB2, CHEK2, CDH1, ATM for targeted exome sequence by next generation sequencer. To enable this, we contacted subjects in the case-control study conducted at Aichi Cancer Center to obtain consent for experimental evaluation of nine genes listed. We have already finished assay system for the project.

About second sub-project, we have already completed preparation of materials for risk presentation and subjects recruitment for our intervention study. These materials are prepared for the larger intervention study. Our intervention program was designed as a randomized-controlled study to evaluate its efficiency in change risk reduction behavior for breast cancer by informing individual breast cancer risk based on SNPs and environmental risk factor. Protocol was approved by ethics committee and was registered to study registration system by UMIN.

We are also conducting simulation to evaluate possible economical and public health impact of our intervention.

III. 成果の外部への発表

(1) 学会誌・雑誌等における論文一覧（国内誌 0 件、国際誌 13 件）

1. Wen W, Shu XO, Guo X, Cai Q, Long J, Bolla MK, Michailidou K, Dennis J, Wang Q, Gao YT, Zheng Y, Dunning AM, García-Closas M, Brennan P, Chen ST, Choi JY, Hartman M, Ito H, Lophatananon A, Matsuo K, Miao H, Muir K, Sangrajrang S, Shen CY, Teo SH, Tseng CC, Wu AH, Yip CH, Simard J, Pharoah PD, Hall P, Kang D, Xiang Y, Easton DF, Zheng W. Prediction of breast cancer risk based on common genetic variants in women of East Asian ancestry. **Breast Cancer Res.** 2016;18:124.

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(2) 学会・シンポジウム等における口頭・ポスター発表

1. がんリスクを推測する - 遺伝情報を交えた個別化予防、口頭、松尾恵太郎、第54回日本癌治療学会、横浜、2016/10/20, 国内

2. Breast cancer risk of active and passive smoking in post-menopausal women by hormone receptor and HER2 status. ポスター、郡山千早、秋葉澄伯、第 75 回日本癌学会学術総会、横浜、2016/10/8、 国内
3. 地域がん登録データに基づく乳癌の長期予後の検討、ポスター、吉村 章代、澤木 正孝、服部 正也、石黒 淳子、権藤 なおみ、小谷 はるる、瀧 由美子、片岡 愛弓、岩田 広治、第 24 回日本乳癌学会学術総会、東京、2017/6/17、 国内
4. Impact of germinal center-associated nuclear protein polymorphisms on breast cancer risk and prognosis in a Japanese population. ポスター、Kotani H, Ito H, Kuwahara K, Kuzushima K, Iwata H, Tsunoda N, Nagino M, Tanaka H, Matsuo K. 39th Annual San Antonio Breast Cancer Symposium, San Antonio, USA、2016/12/9、 国外
5. Building a simulation model for estimating individual female breast cancer incidence based on genetic and lifestyle-related risk factors. Hori M, Ito H, Matsuo K, Katanoda K. Marrakesh, Morocco, 2016/10/20, 国外

(3) 「国民との科学・技術対話社会」に対する取り組み

1. がんを予防する、松尾恵太郎、国際ロータリー 2 7 1 0 地区インターシティーミーティング、松尾恵太郎、2017/3/5、 国内
2. 遺伝性乳がんー遺伝子検査でわかること、井本逸勢、第 31 回日本助産学会学術集会、あわぎんホール（徳島市）、2017/3/18、 国内

(4) 特許出願

該当無し

平成28年度医療研究開発推進事業費補助金

(革新的がん医療実用化研究事業) 成果報告書

I. 基本情報

事業名： (日本語) 革新的がん医療実用化研究事業
(英語) Practical Research for Innovative Cancer Control

補助事業課題名： (日本語) 個人の生活習慣等の環境要因と遺伝的リスクを考慮した科学的根拠に基づく効率的ながん予防法の開発研究
(英語) Development of evidence-based breast cancer prevention program considering individual environmental and genetic risk factors.

補助事業担当者 (日本語) 国立保健医療科学院 医療・福祉サービス研究部
主任研究官 白岩 健

所属 役職 氏名： (英語) National Institute of Public Health Department of Health and
Welfare Services Senior Researcher, TAKERU SHIROIWA

実施期間： 平成28年4月1日 ～ 平成29年3月31日

II. 成果の概要（総括研究報告）

研究開発分担者の片野田・堀氏と共同で医療経済評価において使用する予後予測モデルと、費用推計が必要な健康状態について検討した。また、左記の健康状態におけるレセプトを用いた費用推計について、昨年度検討した結果に基づき、愛知県がんセンターにおいて 300 名の患者(① Stage 0、② Stage 1、③ Stage 2、④ Stage 3、⑤ Stage 4 ⑥ BSC (best supportive care))からレセプトデータを取得した。レセプトデータは対象患者を同定後に、個人情報情報を削除して国立保健医療科学院内に保存した。

補助事業代表者：愛知県がんセンター・研究所 部長・松尾恵太郎 総括研究報告を参照。

III. 成果の外部への発表

- (1) 学会誌・雑誌等における論文一覧（国内誌 件、国際誌 件）
なし
- (2) 学会・シンポジウム等における口頭・ポスター発表
なし
- (3) 「国民との科学・技術対話社会」に対する取り組み
なし
- (4) 特許出願
なし