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**Project title:**
**Lung and breast cancer prevention by an integrated intervention of maternal smoking cessation and breastfeeding**

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**Lung and breast cancer prevention by an integrated intervention of maternal smoking cessation and breastfeeding**

**INVESTIGATORS**

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**ABSTRACT (300 words maximum)**

The elevated risk of lung cancer due to cigarette or cigar smoking can be largely reversed by long-term smoking cessation. Pregnancy is a unique opportunity to quit smoking. However, most quitters return to smoking ("relapse") after delivery. Sufficient breastfeeding protects against breast cancer. But smokers tend to not breastfeed. Our team has successfully developed two separate interventions for smoking cessation during pregnancy and breastfeeding maintenance, respectively. However, only 50% of quitters in our sample remain smoking abstinent at 6 months postpartum, and only 21% of quitters still breastfeed at 6 months postpartum. Observational research suggests smoking abstinence and breastfeeding reinforce each other. These reciprocal associations (a positive feedback loop) have not yet been leveraged in the design of more effective interventions.

We are proposing the first randomized controlled trial to integrate maternal smoking cessation and breastfeeding interventions to enhance both cancer prevention behaviors. We will recruit 40 daily smoking women in their 1st or 2nd trimester of pregnancy (≤28 weeks) from local obstetric clinics, communities, and social media. They will be randomized into either the intervention (N=20) or control group (N=20). The two groups will complete the same number of sessions (6 during pregnancy and 3 postpartum), but focus on different topics. Specifically, the control group will receive instructions on general pregnancy and infant care. The intervention group will receive instructions on general pregnancy and infant care, plus an integrated multicomponent intervention that promotes both smoking cessation and breastfeeding (i.e., education and counseling, monitoring and feedback, and contingent financial incentives). Two female Certified Lactation Counselors (interventionists) will be trained to run study sessions during home visits. Interventionists will provide additional support via phone and text messaging until 6 months postpartum. Main outcomes include smoking abstinence and breastfeeding rates at 6 months postpartum within the duration of this award.



**Key words (5 max)**

Smoking cessation; Breastfeeding; Lung cancer; Breast cancer; Pregnancy


**Project description for general scientific audience**

We are proposing the first randomized controlled trial to integrate maternal smoking cessation and breastfeeding interventions to enhance both cancer prevention behaviors. We will recruit 40 daily smoking pregnant women, start integrated intervention during pregnancy and continue until 6 months postpartum.

**This study involves human subjects only.**

**This study does not involve vertebrate animals.**

**SPECIFIC AIMS**

**Aim 1:** to develop a protocol for training and mentoring Certified Lactation Counselors to implement an integrated intervention of maternal smoking cessation and breastfeeding. *We hypothesize Certified Lactation Counselors can be trained to implement our intervention protocol with high fidelity.*

**Aim 2:** to examine the efficacy of an integrated intervention of maternal smoking cessation and breastfeeding on smoking abstinence rates. *We hypothesize smoking abstinence rates at delivery and 6 months postpartum will be higher in the intervention group than the control group. Among successful quitters during pregnancy in the intervention group, we expect smoking abstinence rate at 6 months postpartum will be higher than the rate that we previously observed when our smoking cessation intervention was delivered alone.*

**Aim 3:** to examine the efficacy of our integrated intervention on breastfeeding rates. *We hypothesize breastfeeding rate at 6 months postpartum in the intervention group will be higher than the control group. We also expect breastfeeding rate at 6 months postpartum in the intervention group will be higher than the rate that we previously observed among smokers when our breastfeeding intervention was delivered alone.*

## 1. BACKGROUND AND SIGNIFICANCE

**1.1 Smoking cessation and lung cancer.** Prevention of lung cancer is a top public health priority. Among U.S. women, lung cancer is the second most common cancer (102,625 new cases in 2014) and the leading cause of cancer death (70,667 deaths in 2014).[1] Cigarette smoking is a well-established cause for lung cancer, causing 87% of lung cancer deaths in the U.S.[2] Fortunately, the elevated risk of lung cancer due to smoking can be largely reversed by long-term smoking cessation.[3-5] Pregnancy is a unique opportunity for women to quit smoking. About 23% of U.S. women smoke at conception and 54% of them report quitting smoking during pregnancy.[6] But most women who quit smoking during pregnancy return to smoking ("relapse") after delivery, e.g., 45% and 81% relapse by 6 and 12 months postpartum, respectively.[7,8] Temporary smoking abstinence only during pregnancy may have limited benefits against lung cancer, as the risk of lung cancer seems to begin to decrease after 2 years of abstinence.[3] However, there is little demonstrated success in preventing long-term postpartum smoking relapse using existing interventions.[9]

**1.2 Breastfeeding and breast cancer.** Among U.S. women, breast cancer is the most common cancer (236,968 new cases in 2014) and the second most common cause of death from cancer (41,211 deaths in 2014).[1] Sufficient breastfeeding is a protective factor against breast cancer,[10] besides its well-known nutritional and immunological benefits to the breastfed child.[11] There is a dose-response inverse association between lifetime breastfeeding duration and risk of breast cancer: the longer breastfeeding lasts, the lower the risk of breast cancer.[10,12] According to a large meta-analysis, the relative risk of breast cancer decreases by 4.3% for every 12 months of lifetime breastfeeding. Accordingly, National Cancer Institute (NCI) encourages women to breastfeed for 12 months or longer to reduce risk of breast cancer.[13] The European Code against Cancer also recommends that, ''*Breastfeeding reduces the mother's cancer risk. If you can, breastfeed your baby*''.[14]

**1.3 Rationale for an integrated intervention of maternal smoking cessation and breastfeeding.** Interestingly, maternal smoking abstinence and breastfeeding can strongly reinforce each other, which has been demonstrated by two lines of research. First, smokers tend to not initiate breastfeeding or have shorter breastfeeding duration (e.g., a mean of 11 vs 28 weeks[15]) than non-smoking mothers,[15-18] which can further increase their already elevated cancer risk due to smoking. Possible reasons include concerns of contaminated breast milk by smoking,[19,20] smoking-related lactation inhibition,[21-25] and the infant's refusal of breast milk from smokers due to altered flavor[26] and/or nutrient composition.[22,27,28] In contrast, smoking cessation during pregnancy is associated with increased breastfeeding intention and practices.[29-32] Secondly, successful breastfeeding is associated with 30-60% lower risk of postpartum smoking relapse,[7,33,34] which may be attributed to breastfeeding-related emotional benefits. Breastfeeding mothers have lower perceived stress[35-37] and less negative affect (e.g., depression[38-40] and anger[38]) than formula-feeding mothers. High levels of postpartum stress and negative affect are common triggers of postpartum smoking relapse. However, the reciprocal associations (a positive feedback loop) between maternal smoking abstinence and breastfeeding reported in previous *observational* studies have been not considered in existing *interventions* yet. An integrated intervention may achieve larger effects than traditional interventions that targeted each separately.

**1.4 Our supportive work.** Our team has developed and tested an effective multicomponent smoking cessation intervention for pregnant smokers **(PI, Wen)**.[41] As high as 63% (19/30) of our participants quit smoking successfully during pregnancy,[41] compared to 6% among pregnant smokers receiving usual care in a reference population.[42] Participants' intention of exclusively breastfeeding has been doubled by our smoking cessation intervention (39.1% at post-test vs 19.4% at pre-test).[43] Quitters are 3.5 times (75% vs 20%) more likely to initiate breastfeeding than persistent smokers.[44] But only a small proportion of our participants remain

smoking abstinent (50%) or breastfeeding (21%) at 6 months postpartum, indicating the need of sustained postpartum support for relapse prevention and breastfeeding. In addition, we have developed an effective intervention to maintain breastfeeding among low-income mothers (**PI, Washio**): the breastfeeding rate at 6 months postpartum was 72% in the intervention group, compared to 0% in the usual care group.[45]

**1.5 Clinical-translational relevance and impacts.** This phase 2A clinical trial (proof-of-concept) will test the feasibility and preliminary impact of an integrated intervention of maternal smoking cessation and breastfeeding. It potentially advances this important field from the *observational* to *intervention* phase.

## 2. APPROACH

**2.1 Study design.** We are proposing the first randomized controlled trial to integrate maternal smoking cessation and breastfeeding interventions from pregnancy to 6 months postpartum (**Table 1**).

***Table 1. Study design (W-week, M-month)***

| Recruitment | Randomization | Home-based, CLC-delivered intervention | | Outcomes |
|---|---|---|---|---|
| 1st & 2nd trimesters of pregnancy (≤28 w) | After baseline assessment | Pregnancy (6 weekly visits) | Postpartum (3 bi-monthly visits) | 6 months postpartum |
| 40 daily pregnant smokers | Intervention (N=20) | Integrated smoking cessation & breastfeeding intervention* + Instructions on general pregnancy and infant care | | 1. Smoking abstinence 2. Breastfeeding |
| | Control (N=20) | Instructions on general pregnancy and infant care | | |

*Education and counseling, monitoring and feedback, and contingent financial incentives

**2.2 Recruitment and screening**. We will recruit 40 daily smoking pregnant women from Erie County and Niagara County, NY (36,731 births in 2014-2016[46]). Recruitment flyers will be distributed in local obstetric clinics, communities, and Facebook. Eligible participants must be at least 18 years old, at ≤28 weeks of gestation to ensure adequate time for interventions, and daily smoking cigarettes and/or cigars in the past 7 days verified by urine cotinine testing. Exclusion criteria include being diagnosed with cancer, current heavy alcohol use, current use of marijuana and illegal drugs, uncontrolled mental disorders, with medical conditions contraindicating breastfeeding, and being strongly against breastfeeding.

**2.3 Randomization**. After baseline assessments, the 40 eligible participants will be randomized into either the intervention (N=20) or control group (N=20). A sequence of random numbers in blocks of 2 will be used to ensure equal numbers of participants for each group over time.

**2.4 Intervention** 2.4.1 Intervention group: integrated intervention of smoking cessation and breastfeeding. The intervention group will receive an integrated intervention of smoking cessation and breastfeeding: education and counseling, monitoring and feedback, and contingent financial incentives.[41]

*Intervention schedule*. Participants need to complete 6 weekly prenatal visits and 3 bi-monthly postpartum visits (1, 3, 6 months) at their own home. Two female Certified Lactation Counselors (CLCs) will be trained as interventionist to run these home visits. Each home visit will last for about 60 minutes, which will be divided between smoking cessation intervention and breastfeeding promotion intervention. Interventionists will provide additional support via phone and text messaging until 6 months postpartum.

*Theories-based intervention*. Our integrated intervention of smoking cessation and breastfeeding is guided by two theories: the Health Belief Model (HBM) [47,48] and Contingency Management (CM).[49] According to the HBM, an individual behavior (e.g., smoking cessation) depends upon several factors: perceived susceptibility (e.g., smoking-related risk of low birth weight), perceived severity (e.g., cost and burden to raise a low-birth-weight infant), perceived benefits (e.g., saving money for baby items, removal of guilt of harming the baby), perceived barriers (e.g., daily stress and fear of nicotine withdrawal symptoms), self-efficacy (e.g., smoking craving management), and cues to action (e.g., fetal ultrasound scan).[50] CM uses stimulus control and consequences to change behaviors. Positive behavior (e.g., smoking abstinence) is encouraged by providing reinforcing consequences (e.g., financial incentives), while the undesired behavior (e.g., continuous smoking or relapse) is discouraged by withholding reinforcing consequences or providing punitive measures.

*Intervention component #1: Education and counseling*. Our educational materials include readings and video-taped lectures that address several perceptions in the Health Belief Model through information on negative consequences of smoking and non-breastfeeding, benefits of quitting smoking and breastfeeding, barriers to quit smoking or breastfeed and related strategies. At each visit, participants will first take a quiz with 10 multiple-choice questions on assigned educational materials, and receive a $5 reward for passing it (two attempts). Then, the interventionist will conduct behavioral counseling that focusing on self-efficacy enhancement through 1) planning for quitting smoking, progress review, feedback, craving analysis, and relapse prevention; and 2) making an individualized breastfeeding plan and addressing concerns including previous unsuccessful experience if applicable. After delivery, interventionists will help participants to initiate breastfeeding as soon as possible, and solve everyday problems during breastfeeding practices.

*Intervention component #2: Monitoring and feedback*. We will use the Internet and related technology (e-Health) to facilitate daily monitoring of smoking and breastfeeding behaviors. At the first prenatal intervention visit, participants will receive a free personal smartphone-based iCO™ Smokerlyzer breath carbon monoxide (CO) monitor (Bedfont Scientific Ltd, Kent, UK) and be instructed to test their CO level at home every day. This device has high validity.[51] Breath CO is a sensitive biomarker reflecting recent smoking levels and provides timely feedback on smoking reduction or cessation. Maternal breath CO levels will also be converted into the fetal carboxyhaemoglobin (%COHb) OR "fetal blood CO". A high fetal %COHb indicates fetal hypoxia (lack of oxygen), which can serve as a strong cue to action, i.e., smoking cessation. After delivery, participants will receive a free smartphone-based wireless baby weight scale ("Hatch Baby Grow", Hatch Baby, Inc, Menlo Park, CA) to monitor their breastfeeding by weighing their baby before and after each breastfeeding, which can provide accurate information on how much breast milk that the baby consumes. The two smartphone Apps will automatically transmit results to interventionists who can remotely monitor each participant's progress and provide timely feedback and assistance.

*Intervention component #3: Contingent financial incentives.* During pregnancy, if a participant reports smoking abstinence and all her daily breath CO levels since the last visit are within non-smoking range (≤4 parts per million or ppm), she will receive a financial incentive that starts at $10 at the second prenatal intervention visit and escalates by $5/visit in next 4 weekly prenatal visits.[41] After delivery, participants will receive incentives for breastfeeding if they are able to nurse or to provide breast milk by pumping in the presence of the interventionist. Contingent incentives will start at $20/visit at the 1-month postpartum visit and increase by $10/visit at the 3-month and 6-month postpartum visits.[45]

2.4.2 Control group: instructions on general pregnancy and infant care. Participants in the control group will receive usual prenatal care from physicians, nurses, or social workers. They will receive best standard care on smoking cessation and breastfeeding, including referral to the New York State Smokers' Quitline[52] and the Special Supplemental Nutrition Program for Women, Infants, and Children (WIC).[53] Several efforts will be made to balance attention and compensation between two groups. First, participants in the control group will complete the same frequency and duration of visits as their counterparts in the intervention group. Instead of focusing on smoking cessation and breastfeeding, they will receive instructions on general pregnancy and infant care. Specifically, they will review educational materials with quizzes ($5 reward/quiz), and receive counseling guided by two authoritative books: "*Your Pregnancy and Childbirth: Month to Month*" published by the ACOG[54] and "*Caring for Your Baby and Young Child: Birth to Age 5*" published by the AAP,[55] respectively. These materials will be also given to the intervention group but without quizzes or counseling. Secondly, the control group will earn a total amount of financial compensation ($25/prenatal visit and $30/postpartum visit) that is similar to the intervention group, regardless of smoking status and feeding practice.

2.4.3 Adherence and retention of participants. Adherence to intervention will be assessed by the number of completed visits, completed activities at each visit, passed quizzes, and self-monitoring of breath CO levels and infant feeding via smart-phone Apps.[56] If we lose contact, we will reach out to the 3 contact people that participants indicated at enrollment.

2.4.4 Training the interventionists. The interventionists need to complete 70-hour training (**Table 2**). In Step 1, they will study educational materials on smoking cessation and breastfeeding, the 5As model (ask, advise, assess, assist, arrange) for smoking cessation,[57] behavioral change theories (HBM[47,48] and CM[49]), and counseling skills. In Step 2, they need to complete ethical and compliance training (CITI) for being involved in human research. They will also learn to follow research protocols, use visit instructions/checklists, run breath CO and urine cotinine tests, use wireless devices and small-phone apps to monitor breath CO and infant feeding, and ensure safety during home visits. In Step 3, they will observe 5 smoking cessation and breastfeeding intervention visits in the PI's clinic. In Step 4, they will run 5 clinic-based visits under supervision. In Step 5, they will practice 5 home visits along with the PI and Project Coordinator. Careful evaluation of interventionists' readiness will be conducted via exams and trial runs.

***Table 2. Schedule for interventionist training***

| Training content | Trainer | Location | Time |
|---|---|---|---|
| 1. Knowledge, theories, and skills | PI and Co-Is | PI's clinic and online | 40 hours |
| 2. Research ethics, tools, and safety | PI's research staff | PI's clinic and online | 10 hours |
| 3. Clinic visit observation (5 visits) | PI's research staff | PI's clinic | 5 hours |
| 4. Clinic visit practice (5 visits) | PI's research staff | PI's clinic | 5 hours |
| 5. Home visit practice (5 visits) | PI and PI's research staff | Participants' home | 10 hours |

2.4.5 Monitoring intervention (fidelity). Step-by-step instructions with a 10-item checklist will be used for each visit. The interventionists will take pictures of test sheets during home visits for later confirmation. Home visits will be audio-recorded for quality assurance and 20% will be randomly sampled for review. The

interventionists and research staff will attend biweekly group meetings to review participants' process and share work experiences. Fidelity of intervention delivery will be used for quality improvement.[58]

**2.5 Outcome measures.** 2.5.1 Maternal smoking status. The interventionist will administer a timeline follow-back interview[59] at enrollment to assess the participant's use of cigarettes, cigars, vapor and electronic cigarettes since conception. Based on their recorded daily numbers of cigarettes and cigars smoked after enrollment, we will classify smoking abstinence status in the past 7 days (7-day point-prevalence).[60,61] The self-reported smoking abstinence will be biochemically confirmed by urine cotinine tests (<50 ng/mL[62]) using LC-MS/MS assays (Kaleida Health Lab, Buffalo, NY) at the end of pregnancy and 6 months postpartum. Participants will be informed that use of nicotine replacement therapy (NRT, e.g., gums and patches), electronic cigarettes, or other nicotine-containing products will interfere with urine cotinine tests.

2.5.2 Breastfeeding intention and practices. During pregnancy, participants will report breastfeeding intention using questionnaires modified from the Infant Feeding Practices Study II.[63] During postpartum, mothers will report feeding methods, frequency and duration of breastfeeding and/or formula use every month until 6 months postpartum. Breastfeeding status will be visually verified by a female researcher, looking for one of the following indicators of successful breastfeeding in the infant: audible swallowing, a regular suck/swallow/breath pattern, or visible milk in the infant's mouth after they are not latched anymore.[45] For mothers who pump milk, staff will observe pumping combined with the resulting milk being fed to the infant.

**2.6 Covariates**. Covariates of interest include socio-demographics, health motivation,[64] parity, pregnancy intention,[65,66] gestational age at enrollment,[67] baseline smoking frequency, intention to quit smoking, partner smoking, perceived stress,[68] negative affect,[69,70] breastfeeding intention, and breastfeeding experience.

**2.7 Statistical analysis**. We will calculate the fidelity score for each intervention visit using a 10-item visit checklist. Trajectories of fidelity scores will be fitted with mixed models with interventionist, visit sequence number, and their interaction term (intervention*visit sequence number) being independent variable (**Aim 1**). Smoking abstinence (**Aim 2**) and breastfeeding **(Aim 3**) rates at 6 months postpartum will be analyzed by Chi-squared tests and multivariable logistic regression models. Independent variables in the model will include group (intervention vs control), fidelity of intervention delivery, and unbalanced covariates at enrollment. The timing of termination of breastfeeding (weaning) will be analyzed with Cox regression. We will use Intent-to-Treat analysis by including all women as assigned at randomization. Multiple imputation with 20 replicates will be used to impute missing data.[71]

**2.8 Sample size**. Based on our smoking interventions[29,41,60] and reported associations (~50% reduction) between breastfeeding and smoking relapse,[7,33,34] we estimate smoking abstinence rate at 6 months postpartum to be 23.1% (=30% smoking cessation by the end of pregnancy x [100% - 23% postpartum relapse rate]) in the intervention group versus 5.5% (=10% x [100% - 45%]) in the control group. Accordingly, we need 55 participants per group (110 in total) to detect difference in smoking abstinence with 80% power at a significance level of 0.05 (**Aim 2**). Based on our breastfeeding intervention[45] and reported associations (~50% reduction) between smoking and breastfeeding,[29-32,44] we estimate breastfeeding rate at 6 months postpartum to be 31% (=30% quitters x 80% breastfeeding rate + 70% persistent smokers x 10% breastfeeding rate) in the intervention group versus 17% (=10% x 80% + 90% x 10%) in the control group. Accordingly, we will need 126 participants per group (252 in total) to detect difference in breastfeeding rate in a larger R01 (**Aim 3**). Therefore, in this pilot study, recruiting 20 participants per group (a total of 40) will be sufficient to test feasibility and preliminary impact of our integrated intervention.

## 3. STUDY TIMELINE AND MILESTONES

| TASKS | Month | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 | 11 | 12 |
| IRB approval (in advance) | | | | | | | | | | | | |
| Materials and training staff | X | | | | | | | | | | | |
| Recruitment | X | X | X | X | X | | | | | | | |
| Prenatal intervention | | X | X | X | X | X | X | | | | | |
| Postpartum intervention | | | | X | X | X | X | X | X | X | X | X |
| Process & outcome evaluation | | X | X | X | X | X | X | X | X | X | X | X |
| Data analysis | | | | | | | | | | | X | X |
| Reports & manuscripts | | | | | | | | | | | | X |

## 4. ROLE OF PILOT STUDY IN SECURING EXTRAMURAL FUNDING

Preliminary data collected from this pilot study will be used to support re-submission of our NIH R01 grant application (1R01CA230255-01; NCI). Reviewers in the 1st submission rated our novel idea of integrating intervention positively with 2 of 3 reviewers giving a score of 1 for innovation criterion (see the attached **Summary Statement**). Primary concerns included the lack of piloting on efficacy of integrated intervention, unclear role of run-in period and feasibility of biological sample collection. These methodological concerns can be effectively addressed by this pilot study.