**Introduction**

In the hierarchy of epidemiological evidence on causes of cancer, longitudinal studies (either nested case–control or case–cohort studies) are second only to randomized trial evidence [1, 2]. The Finnish Maternity Cohort (FMC) was established in 1983 to provide a resource for such studies. All women in Finland are at their 12th week of pregnancy offered screening for congenital infections (hepatitis B, HIV, and syphilis). The residual serum samples are stored in the FMC [3]. There is a separate legal basis for the collection and scientific use of FMC (The law of the National Institute for Health and Welfare 668/2008). Since 2001, a nationwide informed consent system based on the opt-out principle with negligible drop out has been in operation.

An example of pioneering cancer research based on the FMC are longitudinal studies documenting that exposure to human papillomavirus (HPV) types 16 and 18 causes an excess risk for later development of both cervical, other anogenital and oropharyngeal cancers [4–6]. FMC's serial samples have been useful for disentangling the temporal order of events in carcinogenesis, for example, antagonistic interaction of different HPV types [7], and disclosing smoking as an independent risk factor of cervical cancer [8]. The prediagnostic serial samples also enable studies on the sensitivity and specificity of biomarkers for future cancer diagnosis and screening [9]. High-quality data on the gestational date of the sample collection enable studies on hormones and cancer [10]. The FMC is positioned as an international Open Access resource. Linkage of personal identifiers with the nationwide, population-based Finnish Cancer Registry and other population-based health and trial registries establishes a unique study base for longitudinal studies [11].

**METHODS**

**Cancer Registry follow-up for 17 million person-years of a nationwide maternity cohort**

Matti Lehtinen1,2,3, Heljä-Marja Surcel3,4,5, Kari Natunen1,3, Eero Pukkala1,6 & Joakim Dillner2,3

1University of Tampere, Tampere, Finland
2Karolinska Institute, Stockholm, Sweden
3European Science Infrastructure Services EEIG, Stockholm, Sweden
4National Institute for Health & Welfare, Helsinki, Finland
5Biobank Borealis of Northern Finland, Oulu University Hospital, Oulu, Finland
6Finnish Cancer Registry, Institute for Statistical and Epidemiological Cancer Research, Helsinki, Finland

**Abstract**

Population-based Finnish Maternity Cohort (FMC) comprises 2M first trimester sera collected from 1M women during 33 years. Informed consent is by the opt-out principle, and linkages with cancer and population registries provide a base for over time and over generation studies. Follow-up for 17M person-years by the end of 2014 can identify 39,700 cases of invasive cancer and 18,900 cases of premalignant breast and cervix lesions, and basal cell carcinoma diagnosed after serum sampling. For women with multiple pregnancies, serial samples taken before cancer diagnosis are available. Offspring of the women have developed more than 4000 cancers. For 100,000 individuals, samples taken during the pregnancies of both their mothers and grandmothers enable familial cancer studies. FMC continues to collect samples, and surveillance of exposures or interventions like vaccination programs is feasible. In summary, the FMC is a unique, accessible biobank for epidemiological, biomarker, and surveillance studies on cancer.

---

**Keywords**
Biobank, cancer causes, cohort, epidemiology, tumor markers

---

**Correspondence**
Matti Lehtinen, University of Tampere, 33014 Tampere, Finland. Tel: +358405437862; Fax +358 3 2100004; E-mail: matti.lehtinen@uta.fi

**Funding Information**
NCI contract: HHSN261201300016C
Received: 4 September 2017; Accepted: 10 September 2017

Cancer Medicine 2017; 6(12):3060–3064
doi: 10.1002/cam4.1222
Table 1. Estimated numbers of incident invasive cancer cases in the Finnish Maternity Cohort 1983–2014.

| Primary site                      | ICD-10 code | After first sample \((N = 953,000)\) | After second sample \((N = 604,000)\) | After third sample \((N = 240,000)\) |
|-----------------------------------|-------------|--------------------------------------|-------------------------------------|-----------------------------------|
| All sites                         | C00–96, D32–33, D42–43, D45–47, D76 | 39,700                              | 19,900                              | 6800                              |
| Mouth, pharynx                    | C00–14      | 490                                  | 220                                 | 85                                |
| Lip                               | C00         | 10                                   | 5                                   | 1                                 |
| Tongue                            | C02         | 110                                  | 50                                  | 5                                 |
| Mouth, other                      | C03–06      | 110                                  | 50                                  | 15                                |
| Salivary glands                   | C07–08      | 110                                  | 50                                  | 20                                |
| Pharynx                           | C01, C09–14 | 130                                  | 55                                  | 20                                |
| Digestive organs                 | C15–26      | 3900                                 | 1900                                | 700                               |
| Esophagus                         | C15         | 65                                   | 30                                  | 10                                |
| Stomach                           | C16         | 550                                  | 280                                 | 95                                |
| Small intestine                   | C17         | 110                                  | 55                                  | 20                                |
| Colon                             | C18         | 1400                                 | 700                                 | 250                               |
| Rectum, rectosigmoid, anus        | C19–20      | 790                                  | 380                                 | 130                               |
| Liver                             | C22         | 135                                  | 50                                  | 20                                |
| Gallbladder, bile ducts           | C23–24      | 140                                  | 60                                  | 20                                |
| Pancreas                          | C25         | 530                                  | 230                                 | 85                                |
| Other digestive organs            | C26         | 30                                   | 10                                  | 0                                 |
| Respiratory organs                | C30–39      | 1050                                 | 420                                 | 130                               |
| Nose, sinuses                     | C30–31      | 35                                   | 15                                  | 5                                 |
| Larynx, epiglottis                | C32         | 15                                   | 5                                   | 2                                 |
| Lung, trachea                     | C33–34      | 980                                  | 350                                 | 110                               |
| Mediastinum, pleura               | C38         | 10                                   | 8                                   | 4                                 |
| Bone                              | C40–41      | 90                                   | 40                                  | 10                                |
| Melanoma of the skin              | C43         | 2200                                 | 1200                                | 430                               |
| Skin, nonmelanoma                 | C44         | 400                                  | 180                                 | 60                                |
| Mesothelioma                      | C45         | 20                                   | 9                                   | 3                                 |
| Autonomic nervous system           | C47         | 10                                   | 4                                   | 0                                 |
| Soft tissues                      | C48–49      | 280                                  | 140                                 | 60                                |
| Breast                            | C50         | 18,400                               | 9200                                | 3000                              |
| Female genital organs             | C51–58      | 3800                                 | 1700                                | 550                               |
| Cervix uteri                      | C53         | 1130                                 | 630                                 | 260                               |
| Corpus uteri                      | C54         | 1100                                 | 400                                 | 130                               |
| Uterus, other                     | C55, C58    | 20                                   | 5                                   | 1                                 |
| Ovary                             | C56         | 1100                                 | 500                                 | 150                               |
| Other female genital              | C51–52, C57 | 280                                  | 110                                 | 25                                |
| Placenta                          | 15          | 4                                    | 2                                   |
| Urinary organs                    | C64–68      | 900                                  | 400                                 | 160                               |
| Kidney                            | C64         | 620                                  | 290                                 | 120                               |
| Bladder and urinary tract         | C65–68      | 270                                  | 110                                 | 40                                |
| Eye                               | C69         | 70                                   | 30                                  | 10                                |
| Brain, central nervous system     | C70–72, D32–33, D42–43 | 2500                               | 1400                                | 500                               |
| Thyroid gland                     | C73         | 2300                                 | 1300                                | 520                               |
| Other endocrine glands            | C74–75      | 50                                   | 20                                  | 5                                 |
| Ill defined or unknown            | C76, C80    | 300                                  | 130                                 | 40                                |
| Lymphoid and hematopoietic tissue | C81–96, D45–47, D76 | 2600                               | 1300                                | 430                               |
| Hodgkin lymphoma                  | C81         | 350                                  | 180                                 | 55                                |
| Non-Hodgkin lymphoma              | C82–86, C96, D76 | 1200                               | 600                                 | 200                               |
| Myeloma                           | C90         | 220                                  | 100                                 | 25                                |
| Leukemia                          | C91–95      | 600                                  | 300                                 | 90                                |

196% of the Finnish pregnant women between 1983 and 2016 have consented to participate in the FMC. As the women can withdraw consent at will the numbers should be considered as estimates.
Material and Methods

At the end of 2016 the FMC comprised 2.0 million serum samples from about 1 million women. As the congenital screening is repeated on each pregnancy, serial samples are available for about 50% of the women. Moreover, there are approximately 100,000 pairs of mothers and daughters, who both have donated sera to the FMC for scientific research.

We estimated the numbers of incident cancer cases in the FMC (Table 1). Cancer incidence in the FMC is similar to that in the general female population for all cancer types [11], with the exception of endometrial cancer which is decreased (43%) due to protection from pregnancy. Thus, it was possible to estimate the number of cancer cases by multiplying the person-years generated by women in FMC by the end of year 2014 with cancer incidence rate in the Finnish female population in each 5-year age category (www.cancerregistry.fi).

Results

There are approximately 40,000 prospectively occurring cases of cancer within 17.2 million person-years of follow-up up to 2014. During the first 5 years after pregnancy, the number of new cancer cases is moderate but increases when the women become older. Breast cancer comprised almost half of all incident invasive cancer cases identified (18,400 cases, Table 1).

The next 10 most common cancer types were as follows: thyroid cancer (2300 cases), melanoma (2200 cases), colorectal cancers (2190 cases), lymphomas (1550 cases), cervical cancer (1130 cases), endometrial cancer (1100 cases).
cases), ovarian cancer (1100 cases), lung cancer (980 cases), kidney cancer (620 cases), and leukemia (600 cases). Noninvasive cancers include 10,000 cases of in situ cervical cancer, 7400 cases of basal cell carcinomas, and 1500 cases of in situ breast carcinomas.

The number of childhood cancer cases in the offspring of the FMC donors (4000 cases) is sizeable (Table 2). Especially, the numbers of childhood leukemias and lymphomas (altogether more than 1600 cases) are high (Table 2).

**Discussion**

Cancer incidence in the FMC is similar to that in the general female population for all cancer types [11], with the exception of endometrial cancer which is decreased (43%) due to protection from pregnancy. With only 20 women opting out in 2017, the population-based nature of FMC remains virtually intact.

In addition to longitudinal studies on cancer etiology and screening studies, the resource is also potentially useful for studies on genetic cancer risk. However, the first trimester serum samples contain measurable amounts of fetal DNA, which needs to be controlled for in genetic studies [12]. Because the FMC is nationwide and contains samples from 94% of all Finnish pregnant women [11], very large-scale over-generation studies can be designed by linking the identities of the mothers to their offspring and/or relatives [13]. Due to the long history of the FMC, prospects for studying congenital causes of cancer in the offspring of the women in FMC are also good.

Ongoing FMC projects include studies of the possible role of the same microbiome, that is, similar serological signature for mothers and daughters with the same cancer for the same types of *Chlamydia trachomatis* [14], HPV [7], *Helicobacter pylori*, or *Streptococcus galolyticus* in familial cervical, colorectal, and stomach cancers, respectively.

The FMC sample collection can also support clinical trials and surveillance purposes, including cancer control. For example, we are currently comparing the long-term stability of antibody responses induced by either quadrivalent or bivalent vaccines against HPV among women who participated as adolescents in large randomized albeit population-based trials of these vaccines [15]. By linking the clinical trial files to the FMC files, it has been possible to identify serum samples collected up to 14 years postvaccination. Evaluation of vaccine-induced antibody response in yet-to-be-identified breakthrough cases makes search for correlates of protective immunity feasible.

This cohort profile describes the basic characteristics of the FMC and provides some examples of its potential use. The FMC is also a role model in strict safe guarding of integrity and compliance with data protection laws. While linkages of course need to be performed with identifiable data, once the samples are retrieved they are pseudonymized and it is not possible to link the research data to an identifiable individual. To promote the use of the FMC as an international resource for epidemiological cancer research, an international nonprofit company (ESIS EEIG) specializing in assisting international researchers with the data and samples they need has been founded and is available to facilitate the formal and logistic process to obtain access to the samples and data that international cancer research may need (www.esis.fi).

**Acknowledgments**

We thank P. Koskela, who originally established the FMC Biobank.

**Conflicts of Interest**

None declared.

**References**

1. Hill, A. B. 1965. The environment and disease: association or causation. Proc. R. Soc. Med. 58:295–300.
2. Doll, R., and R. Peto. 1981. Causes of cancer. J. Natl. Cancer Inst. 166:1191–1308.
3. Koskela, P., T. Anttila, B. Bjorge, A. Brunsvig, J. Dillner, M. Hakama, et al. 2000. *Chlamydia trachomatis* infection is a risk factor for cervical cancer. Int. J. Cancer 85:35–39.
4. Dillner, J., M. Lehtinen, T. Bjorge, T. Luostarinen, L. Youngman, E. Jellum, et al. 1997. A prospective seroepidemiological study of human papillomavirus infection as a risk factor for cervical cancer. J. Natl. Cancer Inst. 89:1293–1299.
5. Bjorge, T., J. Dillner, T. Anttila, V. Abeler, A. Engeland, T. Hakulinen, et al. 1997. A prospective seroepidemiological study of human papillomavirus and non-cervical anogenital cancers. BMJ 315:646–649.
6. Mork, J., A.-K. Lie, E. Glatthe, S. Clark, G. Hallmans, E. Jellum, et al. 2001. A prospective study on human papillomavirus as a risk factor for head and neck cancer. N. Engl. J. Med. 344:1125–1231.
7. Luostarinen, T., P. Namujju, M. Merikukka, H. M. Surcel, T. Hakulinen, J. Dillner, et al. 2013. Order of prevalent/incident sexually transmitted infections and the risk of CIN grade 3. Int. J. Cancer 133:1756–1760.
8. Kapeu, A., L. Youngman, E. Jellum, J. Dillner, M. Hakama, P. Koskela, et al. 2009. Smoking is an independent risk factor of cervical cancer. Am. J. Epidemiol. 169:480–488.
9. Lehtinen, M., P. Koskela, H. Ögmundsdottir, A. Bloigu, J. Dillner, M. Gudnadottir, et al. 2003. Maternal
herpesvirus infections and risk of acute lymphoblastic leukaemia in the offspring. Am. J. Epidemiol. 158:207–213.

10. Fortner, R., H. Schock, R. Kaaks, M. Lehtinen, E. Pukkala, H. Å. Lakso, et al. 2017. Human chronionic gonadotropin and maternal breast cancer: a nested case-control study in the Finnish Maternity Cohort. Can. Res. 77:134–141.

11. Pukkala, E., A. Anderssen, G. Berglund, R. Gislefoss, V. Gudnason, G. Hallmans, et al. 2007. Nordic biological specimen banks as basis for studies of cancer causes and control – more than 2 million sample donors, 25 million person years and 100,000 prospective cancers. Acta Oncol. 46:286–307.

12. Sjöholm, M. I., G. Hoffman, S. Lindgren, J. Dillner, and J. Carlson. 2005. Comparison of archival plasma and formalin-fixed paraffin-embedded tissue for genotyping in hepatocellular carcinoma. Cancer Epidemiol. Biomarkers Prev. 14:251–255.

13. Lehtinen, M., M. Pawlita, K. Zumbach, M. Hakama, E. Jellum, P. Koskela, et al. 2003. Evaluation of antibody response to human pilomavirus early proteins in women who developed cervical cancer 1-20 years later. Am. J. Obstet. Gynecol. 88:49–55.

14. Anttila, T., P. Saikku, P. Koskela, A. Bloigu, J. Dillner, I. Ikaheimo, et al. 2001. Serotypes of Chlamydia trachomatis and risk for cervical squamous cell carcinoma. JAMA 285:46–51.

15. Lehtinen, M., and J. Dillner. 2013. Clinical HPV vaccination trials and beyond. Nat. Rev. Clin. Oncol. 10:400–410.