Broadening Risk Profile in Familial Colorectal Cancer Type X; increased risk for five cancer types in the national Danish cohort

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Abstract

Background

Familial colorectal cancer type X (FCCTX) is a phenotypically defined subset of hereditary colorectal cancer with unknown and potentially heterogeneous genetic aetiology. FCCTX has been characterized as a colorectal cancer-specific syndrome, which we herein challenge by estimating the risk for extra-colorectal cancer in the Danish FCCTX cohort.

Methods

Through the national hereditary non-polyposis colorectal cancer (HNPCC) register, 213 families fulfilling the Amsterdam I criteria and showing retained mismatch repair (MMR) function were identified. In here, sex and age-specific incidence rate ratios (IRR) were calculated for 30 extra-colorectal cancer types in comparison with the general Danish population.

Results

In total, 494 extra-colorectal cancers developed with significantly increased risks for cancers of the urinary tract, breast, stomach, pancreas, and eye tumours. The age groups at increased risks were 30-49 years for gastric cancer, 30-69 years for female breast cancer, 50-69 years for ocular melanoma and above age 70 for pancreatic cancer and urothelial cancer.

Conclusions

Danish FCCTX families show an increased risk of several extra-colorectal cancer types. This observation may indicate unidentified disease-predisposing genetic variants in this phenotypically defined subset of hereditary colorectal cancer and calls for awareness during genetic counselling and follow-up.

Background

Heredity is estimated to explain ~20% of the colorectal cancer diagnoses and covers a complex genetic landscape (Valle, 2017). Though several rare high-risk alleles have been identified, a large fraction of families with seemingly inherited colorectal cancer diagnoses remains genetically undefined. In here families, who meet the Amsterdam I criteria for Lynch syndrome, but with no signs of mismatch repair (MMR) deficiency, i.e. a mismatch-repair stable phenotype and/or retained MMR protein expression, are

referred to as familial colorectal cancer type X (FCCTX) (Lindor et al., 2005; Vasen et al., 2013). This subset constitutes 40% of the families that fulfil the Amsterdam I criteria and belong to the hereditary non-polyposis subgroup of hereditary cancer (Valle, 2014). The genetic aetiology of FCCTX is most likely heterogenous and may include rare pathogenic germline variants in e.g. heterozygous *MUTYH*, *CHEK2*, *BRCA2*, *POLE*, *POLD1*, *SEMA4A*, *BMPR1A*, *RPS20* or *OGG1* or modifying single nucleotide polymorphisms in *SEMA4A, EXO1, TGFBR1,* or *NUDT1* (Bellido et al., 2016; Dominguez-Valentin et al., 2018; Garre et al., 2011, 2015; Hansen et al., 2015; Nieminen et al., 2011, 2014; Schulz et al., 2014; Xicola et al., 2016).

Besides the MMR proficient molecular phenotype, FCCTX-associated colorectal cancers have been distinguished from the genetically defined cancer syndrome, Lynch syndrome, by a predilection for tumour development in the distal colon and the rectum, a high adenoma/carcinoma rate and a lower risk of synchronous and metachronous colorectal cancer (Dove-Edwin et al., 2006; Klarskov et al., 2012; Mueller-Koch et al., 2005; Shiovitz et al., 2014). The risk of colorectal cancer is lower than in Lynch syndrome with a relative risk (RR) of 0.5, but higher than the general population with a standardized incidence ratio of 2.3 (Benatti et al., 2001; Lindor et al., 2005). Current literature suggests that FCCTX is a colorectal cancer-only syndrome, which provide the basis for current recommendations of surveillance with regular colonoscopy starting 5-10 years prior to the youngest case in the family in families classified as FCCTX (Benatti et al., 2001; Lindor et al., 2005; Mueller-Koch et al., 2005; Valle et al., 2007).

We challenged this notion through risk assessment of 30 different extra-colorectal cancer types in the Danish FCCTX cohort compared to the Danish general population and to the national Lynch syndrome cohort and found increased risk of five extra-colorectal cancer types, i.e. urothelial cancer, female breast cancer, gastric cancer, pancreatic cancer, and ocular melanoma.

Methods

The national Danish hereditary non-polyposis colorectal cancer (HNPCC) register contains ~6000 families with suspected or verified hereditary colorectal cancer reported to the register by genetic counsellors, surgeons, pathologists, and genetic diagnostic laboratories. Families have been included based on a suspicious family history of colorectal cancer, fulfilment of the Amsterdam I or II criteria (Vasen et al., 2013), or identification of disease-predisposing variants in genes linked to hereditary colorectal cancer. Based on family history, the register subclassifies families according to genotypic and phenotypic subsets (Lindberg et al., 2017). The Danish HNPCC register identifies all family members in the Danish Civil Registration System, regardless of cancer history, based on data collected from clinical files and health care registers.

Patient selection

Families classified as FCCTX (n=213) were eligible for the study. FCCTX was defined as fulfilment of the Amsterdam I criteria with no signs of MMR deficiency. The Amsterdam I criteria are defined as at least three relatives with histologically verified colorectal cancer in two generations with one individual being a first-degree relative of the other two and at least one individual diagnosed below the age of 50 (Vasen et

al., 1991). MMR proficiency was characterized by retained MMR protein expression and/or a microsatellite stable phenotype and/or a gene test showing no MMR mutations in at least one of the three colorectal cancer patients included in the Amsterdam I triad.

A maximum of one tumour with MLH1/PMS2 protein loss in the family was accepted if this was in conjunction with a *BRAF* mutation and/or *MLH1* promotor hypermethylation (N=4) or normal MMR expression was found in ³1 tumour from a family member (N=16). Loss of MSH2/MSH6 protein expression was not allowed, while loss of MSH6 only was observed in two cases and allowed motivated by normal genetic test result in the same individual (N=1) or normal MMR protein expression in another tumour in the same family (N=1). Variants of unknown significance were included only when normal MMR protein expression was verified in a tumour from the same patient (N=2). Of the 252 Amsterdam I positive families reviewed, 213 fulfilled the criteria for MMR proficiency. Individuals affected with colorectal cancer and their first- and second-degree relatives were eligible for the study.

Data processing

Data on primary extra-colorectal cancer diagnoses were obtained from the population-based Danish Cancer Registry. This registry has close to complete coverage based on mandatory double reporting from pathologists and clinicians (Storm, 1988; Storm et al., 1997). Benign tumours, carcinoma *in situ*/dysplasia, and basal cell carcinomas of the skin were excluded. Patients with more than one primary cancer in different organs were allowed to contribute to the tissue-specific risk estimates, while synchronous/metachronous cancer in the same organ or in the same side of paired organs were not allowed. Data on vital status were obtained from the Danish Civil Registration System.

To determine the risk relative to the general population, we used a population-based cohort obtained from the Nordcan database (Engel, G. et al., 2016). This cohort contains data on age-specific cancer events and person years at-risk in the Danish background population during the time period from January 1st, 1978 to December 31st, 2013 with stratification for year of diagnosis, sex, age, and disease. The Nordcan database classifies malignancies into 36 groups. The FCCTX-associated cancers could be matched to 30 of these after exclusion of cancer in the colon, rectum and anal canal, unspecified cancers, specified cancer (grouped by Nordcan), and 2 rare specified malignancies without cases in the FCCTX cohort. All cancers and person years at-risk identified in the Danish FCCTX cohort and the previously published Danish Lynch syndrome cohort were removed from the Nordcan data set (Therkildsen et al., 2017). To correct for potential ascertainment bias, we performed a subgroup analysis in a cohort surveilled for colorectal cancer, reflecting prospective data, with inclusion of cancers diagnosed following the first colonoscopic surveillance session in the family and exclusion of diagnoses and person years at-risk prior to this date. The study was granted acceptance from the Danish Data Protection Agency. According to Danish regulations, registry studies are not subject to ethical review.

Statistical analyses

Person years at-risk and cancer events in the FCCTX cohort and in the population-based Nordcan cohort were stratified and aggregated into 4 age groups (0-29 years, 30-49 years, 50-69 years and 70 years or above) using the %STRATIFY SAS macro, which removes individuals from the at-risk group if cancer is diagnosed within the study period, and SAS software, version 9.4 (SAS Institute Inc., Cary, NC, USA) (Rostgaard, 2008). Person years at-risk were determined as the period from date of birth or start of study period (January 1st, 1978), whichever came last, to date of diagnosis of any type of cancer, date of death or end of study period (December 31st, 2013), whichever came first.

Stratified and aggregated data were transferred into R 3.2.3 (R Core Team, 2019, *A Language and Environment for Statistical Computing*. Vienna, Austria: R Foundation for Statistical Computing: URL https://www.R-project.org/). Incidence rates (IRs) were calculated as the number of events divided by person years at-risk in each age group. Incidence rate ratios (IRRs) were calculated as the ratio between the IRs in the FCCTX cohort and the population-based cohort. Since FCCTX is part of the HNPCC subgroup of hereditary colorectal cancer and are classified according to the same clinical criteria, i.e. the Amsterdam criteria, we also estimated IRs relative to the previous IRs published in the Danish Lynch syndrome cohort (Therkildsen et al., 2017). Confidence intervals (95% CI) and p values were calculated using the exact conditional Poisson test. All p values were two-sided and significance levels were adjusted for multiple testing using Bonferroni correction for estimation in the 4 age groups (i.e. significance was reached when $p < 0.0125$).

Results

The FCCTX cohort comprised 213 families, including 646 individuals with a colorectal cancer, 1,982 first-degree relatives and 1,044 second-degree relatives. These individuals contributed with 110,767 person-years at-risk and during this time 966 individuals developed 1,079 cancers, including 494 extra-colorectal cancers and 585 colorectal cancers (Supplementary table 1). The most prominent cancer types observed were breast cancer (N=104), prostate cancer (N=51), urothelial cancer (N=45), and lung cancer (N=40). Prospective analyses were based on 223 individuals in surveillance from 109 families, who contributed with 903,448 person years at-risk. In this subgroup that considered only cancers that developed after the initiation of surveillance in the family, 160 cancers, including 26 breast cancers, 21 urothelial cancers and 19 prostate cancers, were diagnosed (Supplementary table 1).

Compared to a population-based cohort, the FCCTX cohort revealed significantly increased risks for five cancer types, i.e. breast cancer, urothelial cancer, pancreatic cancer, gastric cancer, and ocular melanoma with variable peak incidence ages identified in the different tumour types (Figure 1, Table 1, Supplementary table 2). Significantly increased IRRs were observed for breast cancer in the age groups from age 30 until 69 years (IRR for age 30-49: 1.71, 95% CI 1.02-2.68, $p = 0.0070$ and IRR for age 50-69: 1.54, 95% CI 1.06-2.14, $p = 0.0030$), while gastric cancer showed an IRR of 5.87 (95% CI 1.57-15.02, $p = 0.0007$) for the age group 30-49 years. Urothelial cancer and pancreatic cancer developed at significantly increased IRRs of 2.10 (95% CI 1.26-3.30, $p = 0.0003$) and 2.21 (95% CI 1.12-4.38, $p = 0.0023$), respectively, in the oldest age cohort, above age 70. In total, five eye tumours developed in age group 50-

69 years, all of which were classified as ocular melanomas, giving an IRR of 7.73 (95% CI 1.76-21.45, p = 0.0006) (Figure 1, Table 1).

The increased risks of extra-colorectal cancers applied to all FCCTX individuals with similar risk levels in first-degree and second-degree relatives compared to the relatives affected with colorectal cancer (Supplementary Figure 1). In the prospective analysis, significantly increased risks applied to urothelial cancer and ocular melanoma with an IRR of 2.94 (95% CI 1.34-5.54, p=0.0004) above age 70 for urothelial cancers and an IRR of 13.81 (95% CI 1.68-49.32, p = 0.0015) for ocular melanomas (Table 2).

At least one individual with breast cancer was observed in 85 FCCTX families. If the criteria for genetic testing for hereditary breast and ovarian cancer were considered, 35 of these families fulfilled at least one of the criteria previously described (Zeichner et *al*., 2016). Likewise, gastric cancer was found in 18 FCCTX families, of which two families fulfilled the clinical criteria for genetic testing previously published (Ford and Chun, 2012; van der Post et *al*., 2015). As we did not have genetic data on variants in the *BRCA1*/*BRCA2* genes predisposing for hereditary breast and ovarian cancer or the *CDH1* gene predisposing for hereditary diffuse gastric cancer, we excluded these families from the FCCTX cohort. The sensitivity analysis decreased the IRRs to non-significant levels for breast cancer, gastric, pancreatic and urothelial cancer, except for breast cancer age 30-49 where the IRR significantly decreased to 0.19 (95% CI: 0.02-0.67, p = 0.0002), from a previous increased IRR. Eye tumours remained significantly increased with similar IRR (Table 3).

Compared to Lynch syndrome, FCCTX families showed significantly lower risks in at least one age group for eight different tumour types, i.e. endometrial cancer, ovarian cancer, urothelial cancer, kidney cancer, gastric cancer, cancer of the small bowel, non-melanoma skin tumours and brain tumours (Table 4). For urothelial cancer and skin cancer this observation was consistent from age 30+. The risk of urothelial cancer in FCCTX showed IRRs of 0.06-0.31 (p-values <0.0009) compared to Lynch syndrome and the risk of skin cancer showed IRRs of 0.11-0.24 (p<0.005) (Table 4). For the other tumour types this difference particularly applied to the peak ages of these cancer types in Lynch syndrome, i.e. age 30-69 years (Table 4). No difference in risks of breast cancer, eye tumours and pancreatic cancer were found between the FCCTX and Lynch syndrome cohorts for all age groups (Supplementary table 4).

Discussion

Increased awareness of hereditary colorectal cancer and improved access to genetic diagnostics implies that a growing number of families with a phenotype suggesting hereditary cancer with an undefined genotype are identified. FCCTX represents one of these subsets where refined risk estimates are relevant to develop evidence-based surveillance recommendations. Lindor et al., described a standardized incidence ratio for colorectal cancer of 2.3 in a cohort of 71 FCCTX families and did not identify any significantly increased risk of extra-colorectal cancer (Lindor et al., 2005). Based on this observation, FCCTX is considered a colorectal cancer-only syndrome with surveillance generally recommended to be confined to colonoscopy with 5-year intervals starting 5-10 years prior to the first case in the family.

Surveillance programs for colorectal cancer have been optimized with documentation of more efficient detection of precursor lesions and early-stage tumours (RR 0.2-0.3) (Hatfield et al., 2018). Reduced risk of mortality from colorectal cancer and increased life expectancy implies that individuals with FCCTX may be at risk of extra-colorectal tumour types during this increased lifetime. Our data, based on all 213 FCCTX families in the national Danish HNPCC-register, challenges the present view on FCCTX as a colorectal cancer-only syndrome and demonstrate significantly increased incidence rates for five extra-colorectal cancer types with urothelial cancer remaining significant in the colorectal cancer-surveilled cohort (Figure 1, Table 1, Table 2).

We demonstrate an increased risk of urothelial cancer from age 70 in FCCTX with IRRs of 2.1 in the entire FCCTX cohort and 2.9 in the surveilled subset compared to the risk in an age- and sex matched Danish population (Tables 1 and 2). The risk of urothelial cancer in FCCTX was significantly lower than in Lynch syndrome with IRRs of 0.1-0.3 (Table 4). Except for Lynch syndrome, urothelial cancer has not been linked to hereditary colorectal cancer (Gu and Wu, 2011). One possibility would be undiagnosed Lynch syndrome cases e.g. MMR gene variants that allow for retained MMR function and normal MMR protein expression. Alternatively, a subset of FCCTX could harbour mutations in genes linked to urothelial cancer development, e.g. *FGFR3*, *TP53* or *HRAS* (Zhang and Zhang, 2015). To this point, 42/45 urothelial cancer in the FCCTX cohort developed in the urinary bladder, which stands in contrast to a predilection for tumours in the upper urinary tract in Lynch syndrome (Joost et al., 2015). Unfortunately, it was not possible to discriminate between upper and lower urinary tract cancers in the population-based cohort since the Nordcan database does not differentiate between these sites.

The increased risk of gastric cancer with an IRR of 5.9 in the age group 30-49 years could potentially signify a genetic subset that confers heredity for this cancer type. About 10-20% of gastric cancer is caused by heredity with confirmed causes in 1-3%, predominantly linked to the hereditary diffuse gastric cancer caused by pathogenic variants in the *CDH1* gene (van der Post et al., 2019). Only two of the 18 FCCTX families in our cohort in which gastric cancer developed fulfilled the criteria currently applied for genetic diagnostics due to early-onset cases in the families (Chun and Ford, 2012; van der Post et al., 2015). When we excluded these families from the FCCTX cohort the risk was, as expected, reduced and was not significant. The co-occurrence of gastric and colorectal cancer in Amsterdam I positive families calls for further studies but may be explained by polygenetic defects resulting in a severe cancer phenotype in some FCCTX families. Addition of *CDH1* in the genetic testing of FCCTX families might genetically classify a small fraction of the FCCTX families.

The increased risks of breast cancer with IRRs 1.5-1.7 in the age group 30-69 years and pancreatic cancer with an IRR of 2.2 after age 70 support the suggestion of disease-predisposing variants in *BRCA2,* causing the observed malignancies in a small subset of FCCTX families (Garre et al., 2015). We also identified an IRR of 10.2 for early-onset ovarian cancer. Various guidelines exist for referring individuals to genetic diagnostics in hereditary breast and ovarian cancer (Zeichner et al., 2016). In addition to fulfilling the Amsterdam I criteria, 35 out of the 213 FCCTX families also fulfilled the clinical genetic testing criteria for hereditary breast and ovarian cancer. Exclusion of these families from the FCCTX cohort decreased

the risk of breast and pancreatic cancer to a nonsignificant level for the age groups 50-69 and 70+, and the risk for breast cancer flipped to a significantly decreased IRR when comparing to the population-based cohort for the age group 30-49 years (Table 3). Whether the increased risk of breast cancer and colorectal cancer in these families can be explained solely by *BRCA2* germline mutations or by polygenetic defects or environmental factors remains to be elucidated. Though the families included in this study had not been systematically screened for hereditary breast and ovarian cancer, our data support a role for hereditary breast and pancreatic cancer in FCCTX, and application of broader diagnostic genetic panels that also cover the *BRCA2* gene may, based on our data, have a potential to identify disease-predisposing mutations in some FCCTX families.

The five eye tumours identified in the Danish FCCTX cohort were all malignant melanomas. Uveal melanoma is predominantly sporadic but between 2-5% have been estimated to be caused by familial or hereditary predisposition. Autosomal dominant inheritance of pathogenic *BAP1* gene variants have been observed in 47% of uveal melanomas, while pathogenic *EIF1AX* variants have been found in 14-20% of the cases (Harbour et al., 2010; Helgadottir and Höiom, 2016). BAP1-associated uveal melanomas are diagnosed in the age of 30-59 years and are associated with cutaneous melanomas and renal cell carcinomas, while *EIF1AX* gene variants are associated with thyroid and ovarian cancer (Harbour et al., 2010; Helgadottir and Höiom, 2016). In our cohort, uveal melanomas presented in the age span from 54-69 years and 2 of 5 cases occurred in patients with previous cutaneous melanomas. These data encourage awareness of family history during the genetic counselling and diagnostic testing.

Comparison between the risk of extra-colorectal cancer in the FCCTX cohort with the national Danish Lynch syndrome cohort, revealed differences as well as similarities. Urothelial cancer and skin cancer showed significantly lower risk levels in FCCTX compared to Lynch syndrome with IRRs of 0.06-0.31 and 0.11-0.24, respectively (Table 4). Increased risks and reminiscent risk profiles applied to breast cancer, gastric cancer and pancreatic cancer. These similarities are also supported by other studies on the risk of upper gastrointestinal cancer in Lynch syndrome (Engel et al., 2012; Kastrinos et al., 2009; Win et al., 2012). Surveillance for cancer of the upper gastrointestinal tract is not recommended in FCCTX, but the increased risk observed may suggest awareness with consideration of *Helicobacter Pyroli* screening and eradication in FCCTX similarly to the recommendations in Lynch syndrome (Ishaq and Nunn, 2015; Vasen et al., 2013; Win et al., 2012).

Studies have shown that compared to Lynch syndrome, FCCTX confers a lower risk for colorectal cancer (11-20% vs 58-75%), a higher age at onset (60 vs 45 years), a different predominant tumour locations (distal vs proximal) and a worse prognosis (Choi et al., 2019; Lindor et al., 2005; Nejadtaghi et al., 2017; Zetner and Bisgaard, 2017). In FCCTX, colonoscopic screening is generally recommended with 5-year intervals starting 5-10 years before the earliest colorectal cancer diagnosis in the family, though surveillance patterns are likely more variable in FCCTX than in Lynch syndrome. The recent demonstration of excess cancer-related deaths in FCCTX compared to Lynch syndrome and short intervals to second primary colorectal cancer suggests that clinical management in FCCTX needs to be optimized (Choi et al., 2019).

Conclusions

Our observation of increased risks with distinct and variable incidence patterns in relation to age for five extra-colorectal cancer types in FCCTX needs validation but challenges the present view of FCCTX as a colorectal cancer-only syndrome. The consistently increased risk of urothelial cancer motivates further investigation to obtain more detailed insights into risk profiles and tumour types with the aim to identify possible disease-predisposing genes. The demonstration of increased risks for breast cancer and pancreatic cancer could suggest that genetic variants in *BRC*A2 may explain some FCCTX families. The FCCTX cohort may be a suitable target for application of broader panels during genetic diagnostics. Further characterization and subdivision of FCCTX are needed to define discriminatory features, provide more robust risk estimates and recommend relevant and cost-effective surveillance to individuals at increased risk.

Abbreviations

FCCTX, familial colorectal cancer type X, HNPCC, hereditary non-polyposis colorectal cancer; IR, incidence rate; IRR, incidence rate ratio; MMR, mismatch repair; *MLH1*, mutL homolg 1; *MSH2*, mutS homolog 2; *MSH6*, mutS homolog 6; *PMS2*, PMS1 homolog 2; *BRAF*, B-Raf protooncogene; *MUTYH*, mutY DNA glucosylase; *CHEK2*, checkpoint kinase 2; *BRCA1*, breast cancer 1; *BRCA2*, breast cancer 2; *POLE*, DNA polymerase epsilon; *POLD1*, DNA polymerase delta 1; *SEMA4A*, semaphorin 4A; *BMPR1A*, bone morphogenetic protein receptor type 1A; *RPS20*, ribosomal protein S20; *OGG1*, 8-oxoguanine DNA glycosylase; *EXO1*, exonuclease 1; *TGFBR1*, transforming growth factor beta receptor 1; *NUDT1*, nudix hydrolase 1; *CDH1*, Cadherin 1; *FGFR3*, fibroblast growth factor receptor 3; *TP53*, tumour protein p53; *HRAS*, H-Ras protooncogene; *BAP1*, BRCA1 associated protein 1; *EIF1AX*, eukaryotic translation initiation factor 1A X-linked.

Declarations

Ethics approval and consent to participate: The study was approved by the Danish Data Protection Agency (AHH-2014-042). According to the Danish regulations, anonymized registry studies are not subjected to ethical review.

Consent for publication: Not applicable.

Availability of data and material: Detailed data can be shared upon request for meta-analyses or other scientific purposes.

Competing interests: The authors have no competing interests to declare.

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Authors' contributions: MN and CT were responsible for the study design and wrote the first draft. LJL contributed to the concept and collected data from the Danish Cancer Society and verified all the tumour diagnoses in the cohort. LSH processed the data in SAS including the %STRATIFY macro analyses. CT and TK performed the statistical analyses in R. MR commented on the manuscript and assisted with the statistical analyses. All authors have approved the final version and agreed with submission to the British Journal of Cancer.

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Tables

Due to technical limitations, the tables are only available as a download in the supplemental files section.

Table 1. Age-dependent incidence rate ratios of different cancer types comparing the entire FCCTX cohort to the age and sex-matched population-based cohorts.

Table 2. Age-dependent incidence rate ratios comparing the surveilled FCCTX cohort and the population-based cohorts.

Table 3. Age-dependent incidence rate ratios of specific cancer types in the FCCTX cohort without the 37 families that fulfilled the criteria for genetic testing for hereditary breast and ovarian cancer or hereditary gastric cancer conpared to the age and sex-matched population-based cohort.

Table 4. Age-dependent incidence rate ratios of different cancer types comparing the entire FCCTX cohort with the Lynch syndrome cohort.

Figures

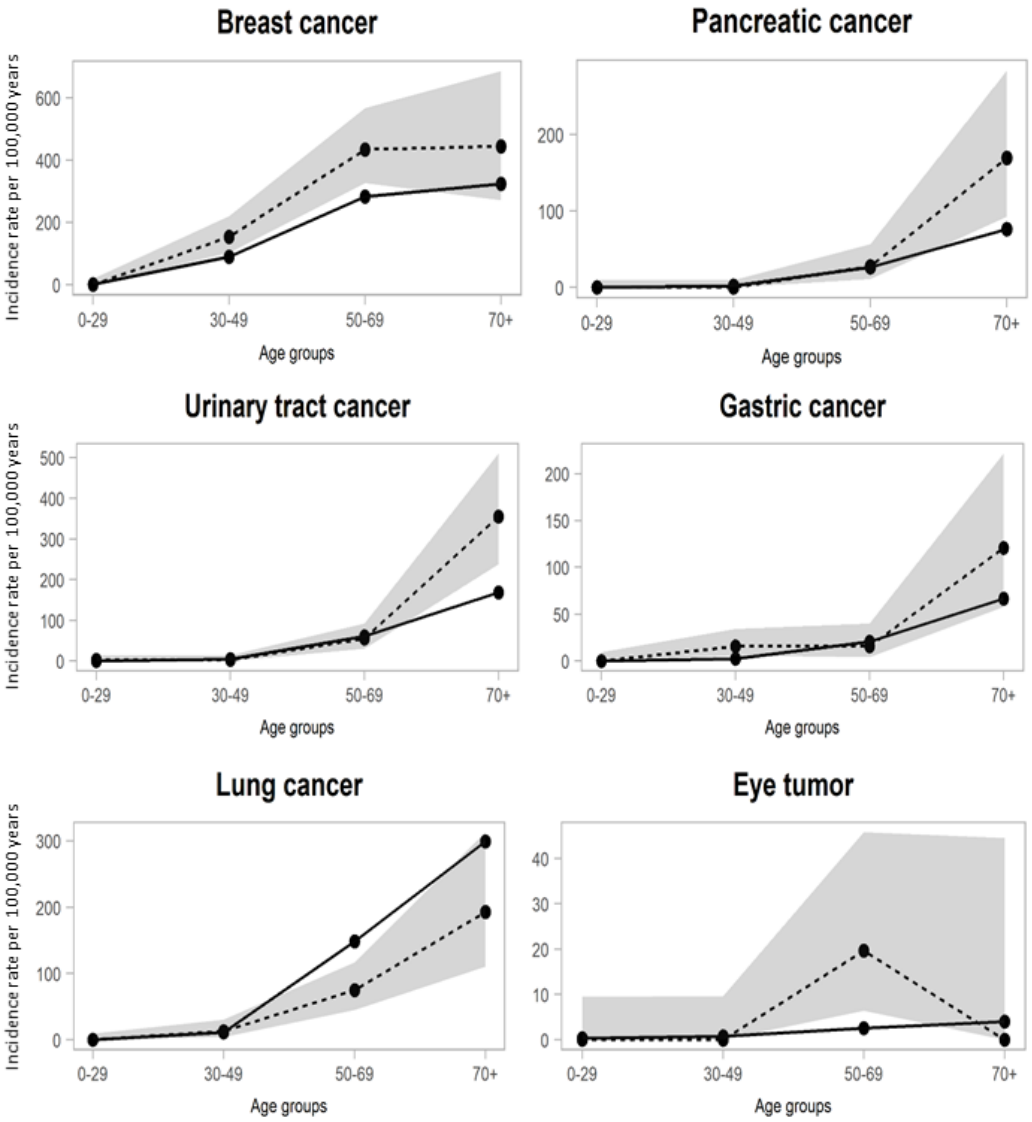

Figure 1

Age-dependent incidence rates and 95% confidence intervals for five cancer types with significantly increased incidence rate ratios in at least one age group in FCCTX (dotted lines) compared to the general population (solid lines).

Supplementary Files

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- Supplementarytable2.pdf
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- Table4.xlsx
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