UNIVERSITÀ DEGLI STUDI DI MILANO

Department of Clinical Sciences and Community Health
PhD in Public Health Sciences
34th cycle

Final report

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Academic year 2020/2021

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Breast cancer, focus on selected epidemiological aspects

Breast cancer is the most commonly diagnosed tumour in women, accounting for a fourth of all cancer cases among women in 2020 (Sung et al. 2021), and it is still a global leading cause of cancer mortality accounting for around one sixth of female malignancy-related deaths (Malvezzi et al. 2019).

Genetic factors, including a family history of breast or ovarian cancer and inherited mutations (i.e. BRCA1, BRCA2), account for only 5% to 10% of breast cancer cases (Nielsen, van Overeem Hansen, and Sørensen 2016).

The reproductive profile and the exposure to sex hormones also explain part of the excess in risk (Boyd et al. 2005). Breast cancer risk is increased by nulliparity and late first full-term pregnancy (together they explained 38% of BC cases, in an Italian case-control study (Tavani et al. 1997)), by endogenous sex hormones intake (i.e., oral contraceptives and use of hormone replacement therapy (Corrao et al. 2008)) and by early age at menarche and late menopause (Collaborative Group on Hormonal Factors in Breast Cancer 2012), while it could be reduced by breastfeeding (Victora et al. 2016).

Mammographic breast density reflects breast tissue composition as projected on a two-dimensional mammographic image. Mammographic breast density is routinely classified, on the basis of the fibroglandular tissue proportion, into: almost entirely fat (Breast Imaging Reporting and Data System [BI-RADS] 1), scattered areas of fibroglandular density (BI-RADS 2), heterogeneously dense (BI-RADS 3), and extremely dense (BI-RADS 4) (Spak et al. 2017). Mammographic breast density is widely recognized as a strong risk factor for breast cancer (Pettersson et al. 2014) with a relative risk (RR) between the highest and lowest category over 4 according to meta-analysis (McCormack and dos Santos Silva 2006). A large US case-control study has estimated that 39% of premenopausal and 26% of postmenopausal breast cancers may be prevented if all women with high mammographic breast density (heterogeneously or extremely dense) shifted to a lower density (scattered fibroglandular) (Engmann et al. 2017).

Women with higher socioeconomic status levels, whether measured with

individual or area-based descriptors, have a higher risk of developing breast cancer (e.g., an elevated level of education accounted for 20.3% of cases in an Italian case-control study (Tavani et al. 1997)) (Baquet and Commiskey 2000). However, once diagnosed with breast cancer, these women showed greater survival rates from the disease compared to women from lower socioeconomic status levels (Kaffashian et al. 2003; Sprague et al. 2011).

Other risk factors include: excess weight in postmenopausal women (e.g., in a pooled analysis of three Italian case-control studies about 20% of all post-menopausal breast cancers were attributable to overweight and obesity (La Vecchia et al. 1997)), metabolic disorders (including perhaps diabetes (Tsilidis et al. 2015)), selected dietary exposure (Turati et al. 2018). Furthermore, active and passive smoking (Dossus et al. 2014), as well as alcohol consumption (Bagnardi et al. 2015) could explain the excess in risk of breast cancer.

Breast cancer is no longer considered a unique tumour, but rather a heterogeneous group of diseases with distinct characteristics (Holm et al. 2017). Anatomopathological breast cancer descriptors outline its multifaceted nature with respect to biological features, clinical behaviour, and prognostic implication (Carey et al. 2006). Breast cancer molecular subtypes are assessed by immunohistochemistry (IHC) and grouped, based on oestrogen and progesterone receptors, HER2 and Ki67 status, into luminal (A, BH-, BH+), HER2+and triple-negative (Goldhirsch et al. 2013).

Although breast cancer subtypes vary in biological features, clinical and prognostic implications, it is still unclear if subtypes are etiologically distinct (Kerlikowske et al. 2017). A vast amount of literature has addressed the relationship between risk factors and receptor status (Holm et al. 2017); however, whether and to which extent differences in receptor expression could be explained by these factors is still widely debated (Anderson, Schwab, and Martinez 2014). Among the most compelling evidence, Black and Hispanic ethnicities have been associated with a higher risk of developing negative oestrogen receptor breast cancer, together with younger age at diagnosis and premenopausal obesity (McCormack et al. 2013) (Pierobon and Frankenfeld

2013).

During my PhD experience, I mainly focused on breast cancer aspects following two main research lines. I initially worked on a series of breast cancer cases retrieved from the Piedmont cancer registry (Registro Tumori Piemonte-RTP). On the basis of these data, I have dealt with several aspects related to breast cancer risk factors, being involved in the drafting of five papers (three published and two under review). Starting from the mortality data provided by the World Health Organization (WHO), I co-wrote two published papers: a global overview on breast cancer mortality trend in male and a focus on female breast cancer mortality trends in Australasia. Based on this data, I'm now co-writing a global picture of soft tissue sarcomas mortality trends. In the following two paragraphs "Breast Cancer, data from Piedmont Cancer Registry" and "Breast Cancer: mortality trends and predictions" I explore in more details the two main research lines.

a. Breast Cancer, data from Piedmont Cancer Registry

My PhD main research line included an analysis on breast cancer risk factors using data from the Piedmont Cancer Registry (Registro Tumori Piemonte-RTP). We identified from this registry a series of invasive female breast cancers (n=1332) (International Classification of Disease for Oncology, 3rd edition, (ICD-O-3) site codes C50.0-50.9 ('International Classification of Diseases for Oncology, 3rd Edition (ICD-O-3)' n.d.)), diagnosed between January 2008 and December 2014 and treated at AOU (Azienda Ospedaliera Universitaria) Città della Salute e della Scienza, in Turin, Italy.

We retrieved data from the Piedmont Cancer Registry and clinical records from the hospital discharge form and reports. In particular, for each cancer case included in this study, we collected age at diagnosis, age at menarche, parity (defined as number of births), age at menopause, breast cancer family history in first- or second-degree relatives. Education was assessed as the highest educational degree obtained: primary school (at least 5 formative years), middle school (at least 8 formative years), high school (at least 13 formative years) and university (at least 18 formative years).

From pre-anaesthesia examination, additional data on tobacco smoking habits, anti-diabetes drugs, as well as on weight and height were obtained. Body mass index (BMI) was defined according to World Health Organization (WHO) criteria ('Body Mass Index (BMI)' n.d.).

Mammographic breast density was assessed from the preoperative mammogram report closest to the time of diagnosis. Density measurement was performed by a single radiologist from diagnostic digital mammograms of the unaffected breast. Mammographic breast density is routinely classified according to the Breast Imaging Reporting and Data System (BI-RADS) 5th edition into four categories: almost entirely fat, scattered areas of fibroglandular density, heterogeneously dense, and extremely dense (Spak et al. 2017).

From pathology reports we extracted information on Estrogen (ER), Androgen (AR) and Progesterone (PR) receptors, HER2 and Ki67 status and we classified it on the

basis of St. Gallen criteria and ASCO-CAP guidelines (Goldhirsch et al. 2013) (Wolff et al. 2018) (Hammond et al. 2010). In particular, ER and PR status was considered positive for a nuclear staining in at least 1% of tumour cells, while AR was considered positive for a nuclear staining in at least 10% of tumour cells. HER2 positivity (IHC result 3+) is defined as a complete, intense and in at least 10% of tumour cells membrane staining. HER2 is negative (IHC score 0 and 1+) if the membrane staining is incomplete and faint perceptible or if no staining is observed. In case of an equivocal IHC score of 2+ (weak membrane staining with circumferential distribution in at least 10% of cells) we considered the amplification test (Fluorescence in situ hybridization – FISH), which overruled results of IHC. The Ki67 index represents the percentage of positively staining cells among the total number of invasive cells in the scored area (Dowsett et al. 2011). A cut-off of 20% was used to dichotomize (low versus high) Ki67 score. Considering ER, PR, HER2 and Ki67 status together, we defined molecular subtypes as: luminal A (ER+ and/or PR+, HER2-, low Ki67), luminal BH- (ER+ and/or PR+, HER2-, Ki67 high), luminal BH+ (ER+ and/or PR+, HER2+), HER2+ (ER-, PR-, HER2+), triple negative (ER-, PR-, HER2-) (Brouckaert et al. 2012). Moreover, we retrieved information on histologic grade, pathological tumour size and lymph node status and histotype according to the American Joint Committee on Cancer (AJCC) Cancer Staging Manual criteria (Giuliano et al. 2017). Histologic grade was categorized into well differentiated and moderately-poorly differentiated, histotype into invasive ductal carcinoma (CDI), invasive lobular carcinoma (CLI) and other histotypes.
We also retrieved from the Piedmont tumour registry follow-up information.

Based on this case series, we published three papers whose abstracts are reported at the end of the paragraph. The corresponding articles are attached at the end of this report. Two more papers are still under review.

We firstly outlined a case-only study focused on breast risk factors and their association with tumour subtypes *"The impact of selected risk factors among breast cancer molecular subtypes: a case-only study"* (Pizzato et al. 2020). Using a multinomial regression model, we estimated the odds ratios (ORs) for selected

breast cancer risk factors considering luminal A as reference. We showed that triple negative, compared to luminal A, was negatively associated with higher breast density, while it was positively associated with positive family history of breast cancer, higher education, and late age at menarche. We have hence provided a further quantification of breast cancer heterogeneity, reflecting, in an etiological perspective, potential mechanisms of carcinogenesis. The abstract of this paper has been accepted at the 5th World Congress on Public Health and Health Care Management as Oral Presentation (postponed to November 2021).

Furthermore, in a subsequent paper "*Cigarettes smoking and androgen receptor-positive breast cancer*" (Pizzato et al. 2020), we explored the role of tobacco smoking on androgen receptor-positive breast cancer by analysing smoking habits in 112 women diagnosed with invasive breast cancers (selected from the original case series) according to androgen receptor status. Applying a multivariate logistic regression model, we showed that smoking-related effects on androgen hormones could play a role in the development of androgen receptor positive breast cancer.

The most recent published article is *"Mammographic breast density and characteristics of invasive breast cancer"* (M. Pizzato et al. 2021). In this case-only study, we aimed to analyse, with a case-only approach, the association between BI-RADS breast density and a wide range of breast tumour characteristics (including hormonal, proliferative and histologic aspects) in 693 breast cancers. This study provides further information on breast density-tumour characteristics relationship, showing that non-dense breasts are associated with higher grade, and thus more aggressive, breast cancers.

During this academic year, I also outlined two research articles based on breast cancer cases retrieved from the Piedmont tumour registry. The first one is entitled "*Mammographic breast density and survival in women with invasive breast cancer*" and it is still under review by "Cancer causes and control". In this paper, we analysed the impact of the breast density on survival of 693 women diagnosed with breast cancer. We estimated the overall survival in strata of breast density through the Kaplan-Meier method and we estimated the Hazard ratio of breast cancer-related

and other causes of death using the cause-specific hazards regression model. High breast density does not appear to unfavourably affect survival in women with primary invasive breast cancer, even after adjusting for several known prognostic factors. Readily available data on breast density at diagnosis may hence provide useful prognostic information.

The second paper under review, "*Association between education level and histopathological characteristics in a case series of invasive breast cancers*", is still under consideration by "The Breast". This study aims to investigate the association between an individual socioeconomic indicator, captured through the highest educational degree obtained, and selected breast cancer anatomopathological characteristics in women with invasive breast cancers, through adjusted logistic regression models. Less educated women had a higher risk to be diagnosed with a larger tumour, especially in older women. This study provides relevant, additional quantitative definition of an inverse association between education and breast cancer size in an Italian population covered by a national health service.

1. The impact of selected risk factors among breast cancer molecular subtypes: a case-only study.

Pizzato M., Carioli G., Rosso S., Zanetti R. & La Vecchia C.

Breast Cancer Research Treatment, August 2020

Purpose: Breast cancer (BC) risk factors have been differentially associated with BC subtypes, but quantification is still undefined. Therefore, we compared selected risk factors with BC subtypes, using a case-case approach.

Methods: We retrieved 1321 invasive female BCs from the Piedmont Cancer Registry. Through record linkage of clinical records, we obtained data on estrogen (Er) and progesterone (Pr) receptors, Ki67 and HER2+status, BC family history, breast imaging reporting and data system (BI-RADS) density, reproductive risk factors and education. We defined BC subtypes as follows : luminal A (Er+and/or Pr+, HER2−, low Ki67), luminal BH- (Er+and/or Pr+, HER2−, Ki67 high), luminal BH+(Er+and/or Pr+, HER2+), HER2+(Er−, Pr−, HER2+),) and triple negative (Er−,

Pr−, HER2−). Using a multinomial regression model, we estimated the odds ratios (ORs) for selected BC risk factors considering luminal A as reference.
Results: For triple negative, the OR for BC family history was 1.83 (95% confidence interval (CI) 1.13–2.97). Compared to BI-RADS 1, for triple negative, the OR for BI-RADS 2 was 0.56 (95% CI 0.27–1.14) and for BI-RADS 3–4 was 0.37 (95% CI 0.15–0.88); for luminal BH+, the OR for BI-RADS 2 was 2.36 (95% CI 1.08–5.11). For triple negative, the OR for high education was 1.78 (95% CI 1.03–3.07), and for late menarche, the OR was 1.69 (95% CI 1.02–2.81). For luminal BH+, the OR for parous women was 0.56 (95% CI 0.34–0.92).
Conclusions: This study supported BC etiologic heterogeneity across subtypes, particularly for triple negative.

2. Cigarettes smoking and androgen receptor-positive breast cancer.
Pizzato M, Carioli G, Rosso S, Zanetti R, Negri E, La Vecchia C.
European Journal Cancer Prevention, December 2020

Objectives: Cigarette smoking is related with higher levels of circulating androgens, but its association with androgen receptor (Ar) status is still unaddressed.
Methods: We analysed, with a case-only approach, smoking habits according to Ar status in 112 cases of invasive female breast cancers, from the Piedmont Cancer Registry. We applied a multivariate logistic regression model to estimate the odds ratio (OR) and the corresponding confidence interval (CI).
Results: The OR of Ar-positive breast cancer (versus Ar-negative) for ever smokers (versus never) was 2.85 (95% CI 1.02-7.96).
Conclusion: Smoking is related to Ar-positive breast cancers.

3. Mammographic breast density and characteristics of invasive breast cancer
Pizzato M., Carioli G., Rosso S., Zanetti R. & La Vecchia C.
Cancer epidemiology, February 2021

Purpose: Inconclusive data exist on the association between breast cancer characteristics and breast density. Therefore, we compared histopathological and hormonal tumour characteristics with breast density in women with invasive breast cancer.

Methods: We conducted a case-only study on 667 cases of invasive breast cancers to evaluate the association between breast density and selected breast cancer characteristics, using data from the Piedmont Cancer Registry. Breast density was classified as: low (Breast Imaging Reporting and Data System, BI-RADS, 1-2) and high (BI-RADS 3-4). We applied a multivariate logistic regression model to estimate odds ratios (ORs) and corresponding 95% confidence intervals (CIs) of high breast density (versus low) for histologic grade, pathological tumour size, pathological lymph node status, histotype, estrogen and progesterone receptor, HER2 and Ki67 status. The model included terms for age at diagnosis, education level, body mass index, parity, menopausal status, age at menarche, breast cancer family history, smoking habits and diabetes.

Results: Compared to well differentiated tumours (grade 1), the OR was 0.61 (95% CI 0.38-0.98) for moderately-poorly differentiated tumours (grade 2-3). No other associations with hormonal and histopathological characteristics were observed.

Conclusion: Our results indicate that low breast density is associated with higher grade breast cancers.

b. Breast Cancer: mortality trends and predictions

Since 2011 the mortality group of my department (i.e., Department of Clinical Sciences and Community Health) produced, based on the World Health Organization (WHO) database, annual cancer mortality predictions for selected European Union (EU) countries (Malvezzi M et al., 2011) (Carioli G et al., 2020a) and since 2017 biennial predictions for some Latin American countries (Carioli G et al., 2017b,Carioli G et al., 2020b). In 2018, this research group has also provided figures for a selection of Australasian countries and the Russian Federation (Carioli G et al., 2019). Since 2019 I started my collaboration with this group. At present, we published two papers (whose abstracts are reported in the following pages, while full papers are attached at the end of this report): "*Trends in male breast cancer mortality: a global overview*" (Pizzato et al. 2021) and "*Cancer mortality and predictions for 2020 in selected Australasian countries, Russia and Ukraine"*(Pizzato et al. 2021a).

In the first one "*Trends in male breast cancer mortality: a global overview*", we provided an updated comprehensive picture of male breast cancer mortality patterns for selected countries and some regions of the world, analysing the number of cancer deaths and mortality rates since 2000. We also predicted corresponding figures for the year 2020.Since 2000 male breast cancer mortality rates have been decreasing or levelling off globally, with however remarkable variability in rates across countries. In Central-Eastern Europe death rate during 2015-2017 was approximately five-fold higher than in Japan and about two-fold higher than in the Americas and North-Western Europe. Southern Europe showed intermediate rates between the two other European regions. Favourable mortality patterns are predicted to persist up to 2020.

In the second paper "*Cancer mortality and predictions for 2020 in selected Australasian countries, Russia and Ukraine"*, we predicted cancer mortality rates in Israel, Hong Kong, Japan, the Philippines, Korea, Australia, Russia, and Ukraine for the year 2020 using the most recent available data, focusing on breast cancer. We also considered long-term trends since 1970 and estimate avoided cancer deaths

over the last few decades. Cancer mortality in Russia, Ukraine and Australasia was predicted to decrease until 2020. Despite breast cancer remained in women the leading cause of cancer-related deaths in most countries, its predictions are favourable. About 3 million cancer deaths were avoided over 1994-2020 of which about a third in Russia.

This year, we also started working on a new publication on global mortality trend of soft tissue sarcomas, i.e., rare neoplasms arising from mesenchymal tissue. At present we went through available literature on this topic, and we mostly completed analysis. In the following months, we plan to finalise the discussion paragraph.

1. Trends in male breast cancer mortality: a global overview

Pizzato M, Carioli G, Bertuccio P, Malvezzi M, Levi F, Boffetta P, Negri E & La Vecchia C. *European Journal Cancer Prevention,* January 2021

Background: Recent trends in male breast cancer mortality have been inadequately studied.

Methods: We extracted official death certification data for male breast cancer and population estimates from the World Health Organization and the Pan American Health Organization databases, from 2000 to 2017. We computed age-standardized (world population) death rates for selected countries and regions worldwide. We used joinpoint regression analysis to identify significant changes in trends and to predict death numbers and rates for 2020.

Results: In 2015-2017, Central-Eastern Europe had a rate of 2.85/1 000 000, and Russia of 2.22, ranking among the highest. North-Western and Southern Europe and the USA showed rates ranging between around 1.5 and 2.0. Lower rates were observed in most Latin American countries, with values below 1.35/1 000 000, in Australia, 1.22, and in Japan, 0.58. Between 2000-2004 and 2015-2017, age-adjusted death rates decreased between 10 and 40% in North-Western Europe, Russia, and the USA, and between 1.5 and 25% in the other areas under study, except Latin America (+0.8%). Apart from Central-Eastern Europe, predicted rates for 2020

were favourable.

Conclusions: Advancements in management are likely the main drivers of favourable mortality trends. Delayed diagnosis may explain the higher mortality in some areas.

2. Cancer mortality and predictions for 2020 in selected Australasian countries, Russia and Ukraine.

Pizzato M, Carioli G, Bertuccio P, Malvezzi M, Levi F, Boffetta P, Negri E & La Vecchia C.

European Journal Cancer Prevention, January 2021

Objectives: Predicted cancer mortality figures are useful for public health planning. We predicted cancer mortality rates in Israel, Hong Kong, Japan, the Philippines, Korea, Australia, Russia and Ukraine for the year 2020 using the most recent available data. We focused on breast cancer. *Methods:* We obtained cancer death certification and population data from the WHO and the United Nations Population Division databases. We derived figures for 10 major cancer sites and total cancers over 1970-2017. We predicted numbers of deaths and age-standardized mortality rates for 2020 through joinpoint regression models. We calculated the number of avoided deaths from 1994-2020.

Results: Overall, total cancer mortality is predicted to decline. Russia had the highest all cancers rates in 2020, 151.9/100 000 men and 79.6 women; the Philippines had the lowest rate in men, 78.0/100 000, Korea in women, 47.5. Stomach cancer rates declined over the whole period in all countries considered, colorectal cancer since the late 1990s. Trends for pancreas were inconsistent. Predicted rates for lung and breast cancer were favourable; women from Hong Kong, Korea and Australia had lung cancer death rates higher than breast ones. Predicted rates for uterine, ovarian, prostate and bladder cancers and leukaemias were downward for most countries. Between 1994 and 2020, over 3.3 million cancer deaths were avoided in the considered countries, except for the Philippines where no reduction was observed.

Conclusion: Predicted cancer rates were lower than in the European Union and the USA, even though falls started later and were less marked.

International Agency for Research on Cancer experience

In my last PhD year (i.e., 2020-2021) I worked at the International Agency for Research on Cancer (IARC) in Lyon, France as Continuing Professional Development Trainee supervised by dott. S. Vaccarella. The aim of this training period was to gain new experience in standard epidemiological and statistical methods applied to the field of social inequalities in cancer.

Specifically, I explored the variation in the incidence of the three main lung cancer histotypes (i.e., squamous cell, small cell carcinomas and adenocarcinoma) by socioeconomic groups (i.e., upper and lower white collar, upper and lower blue collar, and farming/forestry/fishing) in the adult population of four selected Nordic countries (i.e., Sweden, Norway, Finland, and Denmark), using data from the Nordic Occupational Cancer Study (NOCCA). This prospective cohort showed a substantial socioeconomic gradient in incident lung cancer risk both in absolute and relative terms, providing a further quantification of lung cancer histotypes social inequalities. The manuscript entitled "*Socioeconomic status and risk of lung cancer by histological subtype in the Nordic countries*" has been accepted for publication by "Cancer Medicine".

Moreover, within a Globocan 2020-spin off project, we started outlining a paper entitled "*The variability of thyroid cancer incidence and mortality between and within regions of the world*"**.** Basically, we would like to point out the role of overdiagnosis for thyroid tumour, highlighting how the high global incidence variability contrasts with lower mortality variability and rates. At the moment, we went through the available material, and we started outlining the article main scheme. Within the Globocan 2020 project, we were also involved in the drafting of paper focused on lung cancer incidence and mortality, entitled *"Current situation and estimated future of lung cancer burden by world regions in consideration of the global smoking epidemic".* We are now in the closing phase, and we plan to submit the paper in the following weeks.

In the most recent months, we also wrote a project within the European

Prospective Investigation into Cancer and Nutrition (EPIC) study entitled "*Socioeconomic status and breast cancer risk by receptor status in the EPIC cohort*". EPIC is one of the largest cohort studies in the world, with more than half a million participants enrolled across 10 European countries and followed for almost 15 years. We aim to investigate the association between the socioeconomic status and breast cancer risk by receptor status and to analyse the main pathways by which socioeconomic status could be related to breast cancer receptor expression. Only a small number of studies have explored the relationship between socioeconomic status and breast cancer biological features and fewer to date have been able to explore this topic using individual-level data. This project has been recently accepted by the EPIC steering committee. We plan to define and publish a paper next year.

Other Publications

Alongside my main line of research, I worked on some other epidemiological articles. Abstracts are reported in the following pages, while full papers are attached at the end of this report.

The first two articles were born within a collaboration with other researchers of my department, and they explored the theme of secondary prevention, aiming to improve the early detection of malignancy. The first paper entitled "*Efficacy of lung cancer screening appears to increase with prolonged intervention: results from the MILD trial and a meta-analysis*" (Rota et al. 2019) is an editorial commentary on long-term Multicentric Italian Lung Detection (MILD) trial (Pastorino et al. 2019). In the second paper "*Exploring the link between diabetes and pancreatic cancer"* (Pizzato et al. 2019) we explored the complex and bidirectional connection between diabetes and pancreatic cancer, with long-standing diabetes being a predisposing factor for pancreatic cancer and new-onset diabetes an early manifestation of the tumour.

Furthermore, I was also collaborated with external departments. A systematic review with meta-analysis of randomized controlled trials about postoperative abdominal binding was born from a collaboration with Umberto I hospital (Rome) surgeons "*Evidence on postoperative abdominal binding: A systematic review with meta-analysis of randomized controlled trials*" (Ossola et al. 2021) In the most recent paper, I collaborate with an international cardiologic team in the drafting of a multicentre study (assessed in five high-volume European hospitals) addressing in-hospital mortality following percutaneous interventional procedures during the COVID-19 pandemic period compared to the non-pandemic period "*Epidemiological findings on interventional cardiology procedures during the COVID-19 pandemic: A multi-center study*" (Albani et al. 2021).

Based on the collaboration with Piedmont Tumour Registry and Ferrara Tumour Registry, I was involved in the drafting of a review about squamous vulvar cancer

promoted by the journal “Cancers”. We are at present at the closing phase, and we plan to submit the final paper by the end of the month (i.e., September 2021)

1. Efficacy of lung cancer screening appears to increase with prolonged intervention: results from the MILD trial and a meta-analysis

M. Rota, M. Pizzato, C. La Vecchia, & P. Boffetta

Annals of Oncology, May 2019

We carried out a systematic review and meta-analysis of the currently available evidence to explore the effect of LDCT (Low-dose spiral computed tomography screening) on overall and lung cancer (LC) mortality. We focused on time-related aspects considering the longest available follow up and the follow up beyond the fifth year. Incidences of early stages, adenocarcinomas and total LCs were also included as secondary outcomes. Three pilot RCTs and eight RCTs were considered eligible, including subjects at high risk of LC: 51 426 randomized to LDCT and 50 322 to the control arm (other screening techniques). The pooled estimates show in the screened arm a significant reduction of LC mortality (Relative risk (RR) 0.80) and overall mortality (RR 0.94), both greater beyond the fifth year of follow up (respectively RR 0.69 and RR 0.82). Furthermore, LCs incidence was significantly higher in the LDCT arm (RR 1.69), as well as early stages (RR 2.07) and adenocarcinomas (RR 1.20) LCs detection. These findings reflect the results of the long-term Multicentric Italian Lung Detection (MILD): screening benefits are more evident beyond the fifth year of follow up with respect to the follow up at ten years (LC mortality HR 0.42 vs 0.61 and all-cause mortality HR 0.68 vs 0.80). Results provide convincing evidence of the long-term benefit of LDCT compared with a shorter duration. New RCTs with more than five years of follow-up are essential to quantify the full effect of LDCT screening on LC mortality and develop recommendations for long-term screening of high-risk individuals.

2. Exploring the link between diabetes and pancreatic cancer

M. Pizzato, F. Turati, V. Rosato, & C. La Vecchia

Expert Review Anticancer Therapy, July 2019

Introduction: Epidemiological studies indicate an association between type 2 diabetes and pancreatic cancer but the complex and multidirectional relationship between them remains unclear.

Areas covered: We summarized epidemiological evidence on diabetes and pancreatic cancer exploring the time–risk relationship. We described mechanisms linking long- standing diabetes to pancreatic cancer. We discussed pancreatic cancer-associated diabetes and its implication in the early detection of pancreatic cancer.

Expert opinion: The markedly increased risk of pancreatic cancer in patients with new- onset diabetes compared with long-standing diabetes observed in several epidemiological studies indicates a complex and bidirectional connection, with long- standing diabetes being a predisposing factor for pancreatic cancer (increasing the risk of the malignancy 1.5- to 2-fold) and new-onset diabetes an early manifestation of the tumour. Identifying clinical features and biomarkers to distinguish pancreatic cancer- associated diabetes from type 2 diabetes is an important goal to improve management and survival of this cancer. Imaging (MRI) for middle-age patients with new-onset diabetes may be considered.

3. Evidence on postoperative abdominal binding: A systematic review with meta-analysis of randomized controlled trials.

P. Ossola, F. Mascioli, D. Coletta, M. Pizzato, & M. Bononi

Surgeon, August 2020.

Background: Midline laparotomy is an unavoidable approach to many surgical procedures. Many surgeons prescribe the use of postoperative abdominal binder during the first mobilization after surgery. The use and the cost effective of this device is still debated by many surgeons.

Methods: PubMed, EMBASE and the CENTRAL were systematically searched for

randomized controlled trials (RCT) comparing patients who wore abdominal binder ("binder") and patient who did not wear any abdominal binder ("non-binder") up to March 2020. The primary outcomes measured in the comparison were postoperative pain, pulmonary functions, the entity of physical activity, the comfort. A meta-analysis of relevant studies was performed using RevMan 5.3.
Results: wearing an abdominal binder after midline laparotomy seems to reduce postoperative pain on first and third postoperative day, to improve the physical activity on third postoperative day, and not affect pulmonary functions. Generally, an elastic abdominal binder is well tolerated during postoperative.
Conclusions: the use of elastic abdominal binder permits a comfortable early postoperative mobilization reducing pain, increases physical activity and seems to not affect pulmonary functions.

4. Epidemiological findings on interventional cardiology procedures during the COVID-19 pandemic: A multi-center study

S. Albani, H. Vinhas, G. Fuentes Ferre, S. Basavarajaiah, S. Khattak, G. Tzanis, M. Pizzato, M. Toselli, A. Khokharg, G. Musumeci, & F Giannini
IHJ, July 2021

Background: The rates of in-hospital mortality following percutaneous interventional procedures (PIP) during the COVID-19 pandemic period compared to the non-pandemic period has not been reported so far.
Methods: We retrospectively enrolled all consecutive patients admitted for PIP across five centers from February 2020 to May 2020.
Results: A total of 4092 PIP were performed during the reference periods. The total number of procedures dropped from 2380 to 1712 (28.0% reduction). Overall in-hospital mortality increased from 1.1% in 2019, to 2.6% in 2020 (63% relative increase).
Conclusion: During the COVID-19 pandemic, in-hospital all-cause mortality significantly increased in patients admitted for cardiological PIP.

Other Activities and Courses

Teaching activity

In accordance with the article n. 45 of the University General Regulations (Rectoral Decree 796/2019 of 02.2020), I obtained a collaboration for teaching activities at Dentistry and Dental Prosthodontics department in the course of Medical Statistics held by the Prof. Monica Ferraroni in the academic years 2018-2019, 2019-2020, 2020-2021. My duties included classroom exercises concerning statistical topics, student tutoring and tests grading for a total of 30 hours.

Peer Review

I was involved in peer revisions of articles for two journals. I reviewed two articles submitted to BMC Cancer and five articles submitted to Epidemiology and Biostatistics and Public Health (EPBH).

Representative in PhD Committee

I represented for three years (2018-2021) the Public Sciences PhD in the Doctoral Student committee, the highest representative council of doctoral students at university level.

Courses

Transversal competences

I attended all compulsory courses organized by the University of Milan for doctoral students. During the Academic year 2018-2019 I attended “open access, open data e il mondo delle pubblicazioni” and “la valutazione della ricerca”; In the 2019-2020 period I attended “tutelare e valorizzare sul mercato i risultati della ricerca”, “grantmanship - parte I”, “fake news, disinformazione, divulgazione e ricerca scientifica”, “research integrity - parte I/II”, “self branding”. During the 2020-2021 period, I attended “Behind the Scene of a Peer Reviewed Journal”, “Communication on new media”, “Lezione avanzata sull'utilizzo dell'IP per fare innovazione”, “Valorizzare Creando Impresa: Fare Spin off in Università degli Studi di Milano”.

PhD courses catalogue

I personalized my study plan by choosing some specific courses from the catalogue. During the Academic year 2018-2019, I attended "Disegni di studi osservazionali" held by Prof. C. La Vecchia and "Sorveglianza e dinamica delle infezioni di rilevanza in sanità pubblica" held by Prof. G. Zehender. During the Academic year 2019-2020 I attended "Valutazione dell'efficacia delle terapia dell'infertilità: un challenge statistico" held by Prof. E. Somigliana and "Modelli ad equazioni strutturali (PLS-PM)" held by Prof. F. De Battisti. During the Academic year 2020-2021 I attended "Sistema nervoso autonomo nello sport di elite e nell'esercizio" held by Prof. D. Lucini and "How to communicate your research" held by Prof. D.M. Gibelli.

Other courses

In addition to the previously mentioned courses, I attended in the year 2019 two courses concerning R software "introduzione al software r: corso base seminario di formazione metodologica" held at Università Cattolica del Sacro Cuore in Milan and "Basis Course of R" held in the informatics course of the statistics and biometry specialisation school. Furthermore, I also took part in three courses organized by the Univesity Library dedicated to bibliographic database of published literature: "Pubmed", "Embase" and "Cochrane e altre risorse EBM".

Summer School

In order to develop my epidemiologic knowledge, I attended the "Summer School advanced topics in epidemiology" held in June 2019 at S. Orsola - Malpighi University Hospital (Bologna).

HARRISON'S Principles of Internal Medicine, 20th edition

During my second PhD year, I worked on the updated edition of HARRISON'S *Principles of Internal Medicine* (20th edition) translating and editing Section 10.

Malignant sarcoma case-control study

In the context of a malignant sarcoma case-control study, I analysed and classified

about 600 cancer pathology reports, and I collaborated in the codification of about 50 questionnaires about control lifestyle habits.

Conclusions

In this final report I described the main phases on my PhD period, collecting my main research work of the last three years. I have had the possibility to explore different epidemiological themes and to collaborate with leading researchers in this field. I mainly focused on breast cancer, through Piedmont Registry data, but I had also the possibility to address epidemiological aspects of other cancers. The added value was the chance to work in an international context in Lyon at the International Agency for Research on Cancer. My career in cancer epidemiology is only at the beginning. I will be able to continue my research in the next three years, thanks to a postgraduate scholarship in health statistics.

Nul pouvoir,
un peu de savoir, un peu de sagesse,
et le plus de saveur possible.
[CdM]

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