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Q1 **After receiving a Medicine degree from the University of Milan, you completed a Master of Science in Clinical Medicine (Epidemiology) from the University of Oxford. What inspired this career path?**

When I graduated from Oxford in the early 80s, epidemiology was a key, innovative discipline. There were several important discoveries at that time, such as quantifying the link between tobacco, asbestos, and lung cancer and a large number of other neoplasms and diseases. The key role of time since first exposure (long latency) to asbestos on mesothelioma, the risks and benefits of oral contraceptives, and the role of human papillomavirus (HPV) on cervical cancer were also being investigated. Furthermore, there was a focus on occupational carcinogens and toxic substances. At that time, epidemiology was a key discipline from a medical and public health viewpoint. That was essentially why I chose to specialise in this field. Epidemiology was very exciting in Oxford because Richard Doll, Richard Peto, Jack Cuzick, Julian Peto, and Nick Wald, were there, so it was great to work with the major figures in the field.

Q2 **One of your most highly cited papers is an analysis of 45 epidemiological studies, including over 23,000 women, that specifically investigates the link between ovarian cancer and oral contraceptives. Could you discuss any notable findings or trends in the risk related to oral contraceptive use and its association with ovarian cancer?**

This was a major discovery in the field of epidemiology in the 80s. The first papers were published in the early 80s, with larger studies being published in early 2000. The key finding was a substantial reduction in ovarian cancer risk in women who had used oral contraceptives with a duration-risk relationship. There is approximately a 40% risk reduction in people with long-term oral contraceptive use. That is important because ovarian cancer is a very serious disease. In high-income countries, it is the major cause of cancer deaths among gynaecological neoplasms. Early diagnosis is still difficult despite various trials, and the improvements in management have been not substantial. Ovarian cancer remains a serious disease, but it is reassuring that

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mortality from ovarian cancer has been appreciably decreasing over the last several decades. A similar pattern of risk has been observed for endometrial cancer. The important message here is that the protection of oral contraceptives on these neoplasms is long-lasting. Oral contraceptives are associated with a modest excess risk of breast and cervical cancer, but that is restricted to current use. Oral contraceptives are mainly used by women aged between 18–35 years; and so, in terms of absolute risk, the excess risk of breast and cervical cancer is minor, cancer at a young age is very rare, while long-term protection against endometrial and ovarian cancer is important.

Q3 How do lifestyle factors such as diet and tobacco impact the development of ovarian and reproductive cancers, based on your extensive research in cancer epidemiology?

These factors do not have as much impact as the favourable effect of oral contraceptives. However, it is possible that dietary factors have some impact on ovarian cancers. Ovarian cancer incidence is a bit lower in Mediterranean countries and in central Northern Europe, so the Mediterranean diet and nutrition (less frequently overweight) have some favourable impact, but this is difficult to quantify and hence difficult to provide specific advice. The association with tobacco is restricted to a minority of ovarian cancers, mucinous ones. Around 20 neoplasms are associated with tobacco smoking besides lung cancer, but the ovary is not one of the most affected by tobacco. Likewise, there is not much you can do regarding diet and lifestyle to reduce cancer ovarian risk. Other reproductive cancers are more amenable to control by nutrition and diet. For example, endometrial cancer is strongly associated with overweight and obesity, so healthcare professionals can advise women to control their weight to reduce endometrial cancer risk. Cervical cancer is a viral-related disease, it is related to several types of HPV, and hence to sexual habits. However, the issue now is essentially HPV vaccination. Women in high-income countries born after the 1990s have been vaccinated, with vaccination more recently being expanded to men as well. For endometrial cancer, you can reduce your risk if you control your weight; for cervical cancer, you can get vaccinated and tested. However, for other reproductive cancers, this is not possible, with the exception of oral contraceptives to reduce the risk of ovarian cancer–a sort of hormone-prevention.

Q4 In your opinion, what are the key challenges in early detection and screening methods for ovarian cancer, and how do you propose addressing them?

Various trials have been completed over the past several decades, the major one being the PLCO, conducted in the USA. However, there no is evidence that screening can have a favourable impact on ovarian cancer mortality. We have no serum markers. The diagnosis is made when the disease has already spread to the peritoneum. Most ovarian cancers are derived from the surface of the ovary or the fallopian tube and only a few of them give rise to a large mass. This mass can be discovered either through a clinical visit or echography, but most of them are diagnosed when the disease has already spread. Unfortunately, there is not much to do now in terms of early diagnosis.

Q5 With over 2,650 publications to your name and involvement in international research consortia, what are some global trends or disparities you've observed in the incidence and mortality rates of ovarian and other reproductive cancers?

Ovarian cancer is a common disease particularly in high-income countries as it is more common in middle age. International trends have been largely affected by the wide use of contraceptives, which started with the generations born in the 30s in the UK and North America and those born in the 40s or 50s in most other European countries. That has had a substantial favourable impact on ovarian cancer mortality and these trends remain favourable. Also, we now see the impact of improved surgical management and the development of effective drugs such as chemo- and immunotherapy mainly in high-income countries.

Q6 What are the key priorities of your role as a member of the Research Project Review Panel (RP2), that assists the Sexual and Reproductive Health and Research (SRH) department of the World Health Organization (WHO)?

We essentially review protocols that are proposed. They are mostly from middle- and low-income countries, covering a wide range of topics involving reproductive health. When I started this role in the 90s, a large number of protocols involved contraception, and not only oral contraceptives

but all types of contraception. Specifically, research was focused on the advantages and risks of contraception in the population, because at that time, a major problem was overpopulation and thus the control of the population. Interestingly, we are now dealing with the opposite, as it is now that we are suffering from a decreasing fertility and number of births. So, the project has shifted from contraception to diseases, including HIV. Apart from that, the project review panel now covers all aspects of reproduction with a key focus on middle- and low-income countries.

Q7 Another of your research papers with over 3,561 citations explores hormone replacement therapy (HRT) and breast cancer. What has changed in our understanding of the link between the two since its publication in 1997?

Mainly our study, and several other observational studies, case-control studies, and cohort studies, investigated the risk of breast cancer in women who were using HRT. At the end of the 90s, our study but also a large number of other studies conducted in Northern Europe and North America, revealed that HRT, particularly combined oestrogens and progestogens, were associated with some increase in the risk of breast cancer. It is not a large increase, the risk for women using HRT for 5 years increases by around 1.2 to 1.3, and for 10 years it increases from 1.5 to 1.6. Until 2003, until the publication of the Women's Health Initiative, which was not an observational study, but a clinical trial organised and supported by the US Institutes of Health (NIH) showed that HRT, and particularly combined HRT, were not only related to excess cancer risk, which was something we already had quantified with our observational study, but also with an excess risk of thrombosis. HRT was also shown to have no real benefit, so the risk-benefit evaluation of HRT changed after 2003 and long-term use was discouraged. Now HRTs are used for a few months or a limited number of years for women with serious menopausal symptoms, but not for several years anymore.

Q8 Ahead of Ovarian Cancer Awareness Month, how can we advance our understanding of ovarian cancer, and what are the priorities for future research in this field?

In the short to medium term, I would like to prioritise innovative treatments. We have several new drugs, mainly immunotherapy, which have shown advantages across several solid cancers and that can be extended to ovarian cancer. Further, genomic characterisation of various neoplasms permits the use of personalised medicine that has been advantageous for several common cancers including lung, colorectal, and also ovarian cancer. However, further research and support is important. I am less optimistic about early diagnosis. It is conceivable that blood tests are developed, there are now several specific blood tests which are undergoing clinical trials. The idea of these tests is to detect signals of early invasive neoplasm, even in the absence of an identification of the site and type of neoplasm. Whole-body screening is then required to detect the site of origin. This may be a possibility for ovarian cancer too, but we have to wait for the results of clinical trials. We may over-diagnose several neoplasms including ovarian cancer leading to increased personal and societal burden.

Q9 Considering your hugely successful career to date, what has been your proudest achievement?

When the original findings were first reported in the mid-90s, there was an association between diabetes and colorectal and liver cancer. At that time, in Italy, we were in a very good position to study liver cancer because it was very common in Italy due to the frequency of hepatitis B and C due to high alcohol consumption. The association with diabetes was important for liver cancer. Another original contribution we published at that time revealed that there was an inverse association between coffee consumption and liver and colorectal cancer. Coffee may have a favourable effect through metabolic pathways, and this was not published before.